Official Title: A Phase II, Randomized, Active-Controlled, Multicenter Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Guided by Genomic Profiling Versus Platinum-Based Chemotherapy in Patients with Cancer of Unknown Primary Site Who Have Received Three Cycles of Platinum Doublet Chemotherapy

NCT Number: NCT03498521

Document Date: Protocol Version 12: 09-Mar-2024

PROTOCOL

PROTOCOL **TITLE:**	**A PHASE II, RANDOMIZED, ACTIVE-CONTROLLED, MULTICENTER STUDY COMPARING THE EFFICACY AND SAFETY OF TARGETED THERAPY OR CANCER IMMUNOTHERAPY GUIDED BY GENOMIC PROFILING VERSUS PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH CANCER OF UNKNOWN PRIMARY SITE WHO HAVE RECEIVED THREE CYCLES OF PLATINUM DOUBLET CHEMOTHERAPY**
PROTOCOL NUMBER:	MX39795
VERSION NUMBER:	12
TEST PRODUCTS:	Alectinib (RO5424802) Atezolizumab (RO5541267) Bevacizumab (RO4876646) Cobimetinib (RO5514041) Entrectinib (RO7102122) Erlotinib (RO508231) Ipatasertib (RO5532961) Ivosidenib (RO7499824) Olaparib (RO5508245) Pemigatinib (RO7496200) Pertuzumab (RO4368451) Trastuzumab (RO0452317) Vemurafenib (RO5185426) Vismodegib (RO5450815) Carboplatin (RO4843791) Cisplatin (RO0232538) Gemcitabine (RO0249587) Paclitaxel (RO0247506) And combinations thereof
STUDY PHASE:	*Phase II*
REGULATORY AGENCY INDENTIFIERS:	IND Number: Not applicable EudraCT Number: 2017-003040-20 *EU CT Number: 2023-507580-19-00* NCT Number: NCT03498521 Performance Study Identification Number (PS ID): PLAN-00024 (FoundationOne® FMI F1CDx (tissue) test) and PLAN-00025 (FoundationOne® F1LCDx (Liquid) test)
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd. *Grenzacherstrasse 124* *4070 Basel, Switzerland*
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
12	See date on the final page of this document.	—	—	—
11	15 February 2023	Germany	11	15 February 2023
		Japan	11	15 February 2023
10	24 January 2022	Germany	10	1 February 2022
		Japan	10	4 February 2022
9.0	16 August 2021	France	9.3	01 December 2021
		Japan	9.2	31 August 2021
		Germany	9.1	16 August 2021
8.0	19 February 2021	Japan	8.2	8 March 2021
		Germany	8.1	19 February 2021
7.0	11 February 2020	Japan	7.3	30 August 2020
		Germany	7.2	6 July 2020
		Germany	7.1	11 February 2020
6.0	29 July 2019	Germany	6.1	29 July 2019
5.0	5 November 2018	Germany	5.1	5 November 2018
4.0	13 July 2018	Germany	4.1	13 July 2018
3.0	6 May 2018	—	—	—
2.1	18 April 2018	—	—	—
2.0	5 April 2018	—	—	—
1.1	13 January 2018	—	—	—
1.0	22 December 2017	—	—	—

PROTOCOL AMENDMENT, VERSION 12:
RATIONALE

Protocol MX39795 has been amended based on current experience with the trial, as well as on new advancements in the field. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

MAIN MEDICAL AND SAFETY CHANGES:

- A section for an extension part of the study for patients with no post-trial access to the investigational medicinal products (IMPs), and to provide continued access to patients until disease progression or loss of clinical benefit, has been added (Section 4.3.7). A clarification has been added stating that this extension will only be for patients with no post-trial access option outside of the study (Sections 3.2 and 4.3.7; Appendix A1-1).
- A simplified schedule of activities has been introduced for those patients that will continue receiving the study IMPs in the extension part of the study. This schedule of activities will become effective only after the end of study milestone is met (Appendix 1; Table A1-1).
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma and the adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 10; Section A10-2).

ADMINISTRATIVE CHANGES AND CLARIFICATIONS:

- The synopsis has been simplified to align with Clinical Trials Regulation (CTR) and other guidelines.
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol. Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites (front matter and Section 5.4.1).
- A section describing duration of participation has been added to align with CTR requirements (Section 3.3).
- A cross-reference to Appendix 11 has been added to clarify the identification of all IMPs, auxiliary medicinal products, and non-investigational medicinal products for this study (Section 4.3.2).
- Text has been modified to align with updates to the Roche Global Policy on Continued Access to IMPs (Section 4.3.6).
- Language has been added to clarify that, after withdrawal of consent for participation in the RBR, remaining RBR samples will be destroyed or will no longer be linked to the patient (Section 4.5.10.6).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).

- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6).
- The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in MedDRA (Appendix 4).
- The investigational, auxiliary, and non-investigational medicinal product designations for use in the European Economic Area and United Kingdom has been corrected to fully provide a full overview and separation between the products in the European Economic Area and United Kingdom (Appendix 11).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, ACTIVE-CONTROLLED, MULTICENTER STUDY COMPARING THE EFFICACY AND SAFETY OF TARGETED THERAPY OR CANCER IMMUNOTHERAPY GUIDED BY GENOMIC PROFILING VERSUS PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH CANCER OF UNKNOWN PRIMARY SITE WHO HAVE RECEIVED THREE CYCLES OF PLATINUM DOUBLET CHEMOTHERAPY**
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SPONSOR *NAME*:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

PROTOCOL **TITLE:**	**A PHASE II, RANDOMIZED, ACTIVE-CONTROLLED, MULTICENTER STUDY COMPARING THE EFFICACY AND SAFETY OF TARGETED THERAPY OR CANCER IMMUNOTHERAPY GUIDED BY GENOMIC PROFILING VERSUS PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH CANCER OF UNKNOWN PRIMARY SITE WHO HAVE RECEIVED THREE CYCLES OF PLATINUM DOUBLET CHEMOTHERAPY**
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STUDY RATIONALE:

The purpose of this study is to compare the efficacy and safety of molecularly-guided therapy versus standard platinum-containing chemotherapy in patients with poor prognosis cancer of unknown primary (CUP) site (non-specific subset) who have achieved disease control (complete response, partial response, or stable disease) after three cycles of first-line platinum-based induction chemotherapy. Molecularly-guided therapies will include 10 targeted cancer therapy regimens and 2 cancer immunotherapy regimens and will be chosen based on each patient's comprehensive genomic profile.

OBJECTIVES AND ENDPOINTS

PRIMARY OBJECTIVES	
PRIMARY EFFICACY OBJECTIVE	**CORRESPONDING ENDPOINTS**
• To evaluate the efficacy of molecularly-guided therapy versus platinum chemotherapy in term of progression-free survival in patients with CUP whose best response to three cycles of platinum induction chemotherapy was assessed CR, PR or SD	• Progression-free survival (PFS1), defined in Category 1 patients as the time from randomization to the first occurrence of disease progression, as assessed by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

SECONDARY OBJECTIVES	
SECONDARY EFFICACY OBJECTIVES	**CORRESPONDING ENDPOINTS**
• To evaluate the efficacy of molecularly-guided therapy versus platinum chemotherapy in terms of overall survival, objective response rate, duration of response and disease control rate in patients with CUP whose best response to three cycles of platinum induction chemotherapy was assessed CR, PR, or SD	• Overall survival (OS), defined as the time from randomization to death from any cause • Objective response rate (ORR1), defined in Category 1 patients as the proportion of randomized patients who exhibit a CR or PR on two consecutive occasions ≥ 4 weeks apart • Duration of response (DOR1), defined in Category 1 patients with an objective response as the time from when response (CR or PR) is first documented to disease progression or death due to any cause, whichever occurs first • Disease Control Rate (DCR1), defined as the proportion of Category 1 patients with confirmed CR, PR, SD or NA, per RECIST v1.1 Responses will be determined by the investigator according to RECIST v1.1
SAFETY OBJECTIVE	**CORRESPONDING ENDPOINTS**
• To evaluate the safety of molecularly-guided therapy in all patients with CUP who receive targeted therapy or cancer immunotherapy	• Incidence and severity of AEs, with severity determined according to NCI CTCAE v5.0 • Incidence and reasons for any dose reductions, interruptions, or premature discontinuation of any component of study treatment • Change from baseline in targeted vital signs • Incidence in clinical laboratory abnormalities

AE = adverse event; CR = complete response; CUP = cancer of unknown primary; DCR = disease control rate; DOR = duration of response; NA = not applicable; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease.
NOTE: Category 1 patients are those who achieved disease control (CR, PR, or SD) after three cycles of first-line platinum-based induction chemotherapy; Category 2 patients are those who experienced PD during three cycles of platinum induction chemotherapy (see Study Design [below] for more details).

OVERALL DESIGN AND STUDY POPULATION

This is a Phase II, randomized, open-label, active-controlled, multicenter study that compares the efficacy and safety of targeted therapy or cancer immunotherapy guided by genomic profiling versus platinum-based chemotherapy in patients with cancer of CUP site who have received three cycles of platinum doublet chemotherapy.

Several key aspects of the study design and study population are summarized below.

Phase:	*Phase II*	***Population Type:***	*Adult patients*
Control Method:	*Placebo*	***Population Diagnosis or Condition:***	*Cancer of unknown primary*
Interventional Model:	*Parallel group*	***Population Age:***	*≥18 years*
Test Product:	*Alectinib (RO5424802)* *Atezolizumab (RO5541267)* *Bevacizumab (RO4876646)* *Cobimetinib (RO5514041)* *Entrectinib (RO7102122)* *Erlotinib (RO508231)* *Ipatasertib (RO5532961)* *Ivosidenib (RO7499824)* *Olaparib (RO5508245)* *Pemigatinib (RO7496200)* *Pertuzumab (RO4368451)* *Trastuzumab (RO0452317)* *Vemurafenib (RO5185426)* *Vismodegib (RO5450815)* *Carboplatin (RO4843791)* *Cisplatin (RO0232538)* *Gemcitabine (RO0249587)* *Paclitaxel (RO0247506)* *And combinations thereof*	***Site Distribution:***	*Multi-site and multi-region*
Active Comparator:	*Carboplatin (RO4843791)* *Cisplatin (RO0232538)* *Gemcitabine (RO0249587)* *Paclitaxel (RO0247506)*	***Study Intervention Assignment Method:***	*Open-label*
Number of Arms:	*2*	***Number of Participants to Be Enrolled:***	*636 patients*

STUDY TREATMENT

The study will consist of a Screening Period, an Induction Period including an End of Induction Visit, a Treatment Period, a Safety Follow-Up Visit occurring 30 (± 7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first), and a Follow-Up Period. The first day of treatment during the Induction Period will be Day 1 (baseline) of the study.

DURATION OF PARTICIPATION

The total duration of study participation for an individual is expected to last until the enrolled patient has either died, withdrawn consent, is lost to follow-up, or has been followed for 18 months after the last study patient has been enrolled, whichever occurs first.
The patients still on treatment at the end of the study who do not have access to the IMP(s) outside of the trial will remain on study and will continue receiving the IMP(s) in a study extension part. For the patients eligible to the extension part of the study, the duration will be longer and will last until the patient having disease progression or loss of clinical benefit.

COMMITTEES

Independent Committees:	*Independent Review Committee* *Independent Data Monitoring Committee*
Other Committees:	*Eligibility Review Team* *Molecular Tumor Board* *Steering Committee*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2-HG	R(−)-2-hydroxyglutarate
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BUN	blood urea nitrogen
CCOD	clinical cut-off date
CGP	comprehensive genomic profiling
CNA	copy number alterations
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRO	contract research organization
CRS	Cytokine Release Syndrome
CT	computed tomography
ctDNA	circulating tumor DNA
CUP	cancer of unknown primary site
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-Dimension Questionnaire, 5-Level Version
ERT	Eligibility Review Team
ESMO	European Society for Medical Oncology
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy–General Questionnaire
FFPE	*formalin-fixed, paraffin-embedded*
GCP	Good Clinical Practice

Abbreviation	Definition
HADS	Hospital Anxiety and Depression Scale
HbA1c	glycated hemoglobin
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HR QoL	health-related quality of life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
ISH	In-Situ Hybridization
IV	intravenous
IxRS	interactive voice or Web-based response system
LDH	lactate dehydrogenase
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
MTB	Molecular Tumor Board
MUGA	multiple-gated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival

Abbreviation	Definition
PD	progressive disease
PD-L1	Programmed-death ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPI	Proton Pump Inhibitors
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
QD	once daily
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SC	Steering Committee
SCC	squamous cell carcinoma
SD	stable disease
TMB	tumor mutational burden
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
VAS	visual analog scale
WBC	white blood cell
WES	whole -exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON CANCER OF UNKNOWN PRIMARY

Cancer of unknown primary site (CUP) is defined as a histologically-confirmed metastatic cancer for which a standardized diagnostic work-up fails to identify the site of origin at the time of diagnosis (Pavlidis and Fizazi 2009; Massard et al. 2011; Fizazi et al. 2015).

A standardized diagnostic work-up in this context includes mainly:

- A histopathological review of biopsy material using immunohistochemistry (IHC)
- A detailed medical history of the patient
- A complete physical examination (including pelvic and rectal examination)
- A full blood count and biochemistry analysis
- Urinalysis and stool occult blood tests
- A computed tomography (CT) scan of the thorax, abdomen and pelvis
- A mammography scan (female patients)
- Additional diagnostic tests oriented by signs and symptoms, tumor location and histopathological review, typically including:
- Breast MRI (in female patients with axillary lymph nodes)
- Serum prostate-specific antigen in male patients with bone metastases
- Endoscopies directed according to clinical and immunohistochemistry context

(In the current protocol, if clinical and/or histopathological assessments in a recruited patient suggest a primary origin for the cancer, but the ESMO CUP guidelines have no guidance for its diagnosis, the most up-to-date guidance for a diagnostic work-up of the suspected tumor should apply).

CUP accounts for 3% to 5% of all malignancies (Fizazi et al. 2015). The disease has a median age of occurrence of approximately 60 years, is rare in children, and is marginally more frequent in males. Survival of patients with CUP is poor, with a median overall survival (OS) of 8–11 months and a one-year survival rate of 25% (Massard et al. 2011).

No obvious risk factors have been identified for CUP (Pavlidis and Fizazi 2009; Massard et al. 2011; Fizazi et al. 2015). By definition, early detection of patients with CUP is problematic, and screening programs for the disease are non-existent. Autopsies are performed in only a minority of patients with CUP, but even thorough post-mortem evaluations identify only 55–85% of the primaries, usually small asymptomatic tumors in the pancreas, lung, gut, and kidney (Abrams et al. 1950; Didolkar et al. 1977; Jordan and Shildt 1985; Le Chevalier et al. 1988; Mayordomo et al. 1993; Jemal et al. 2008).

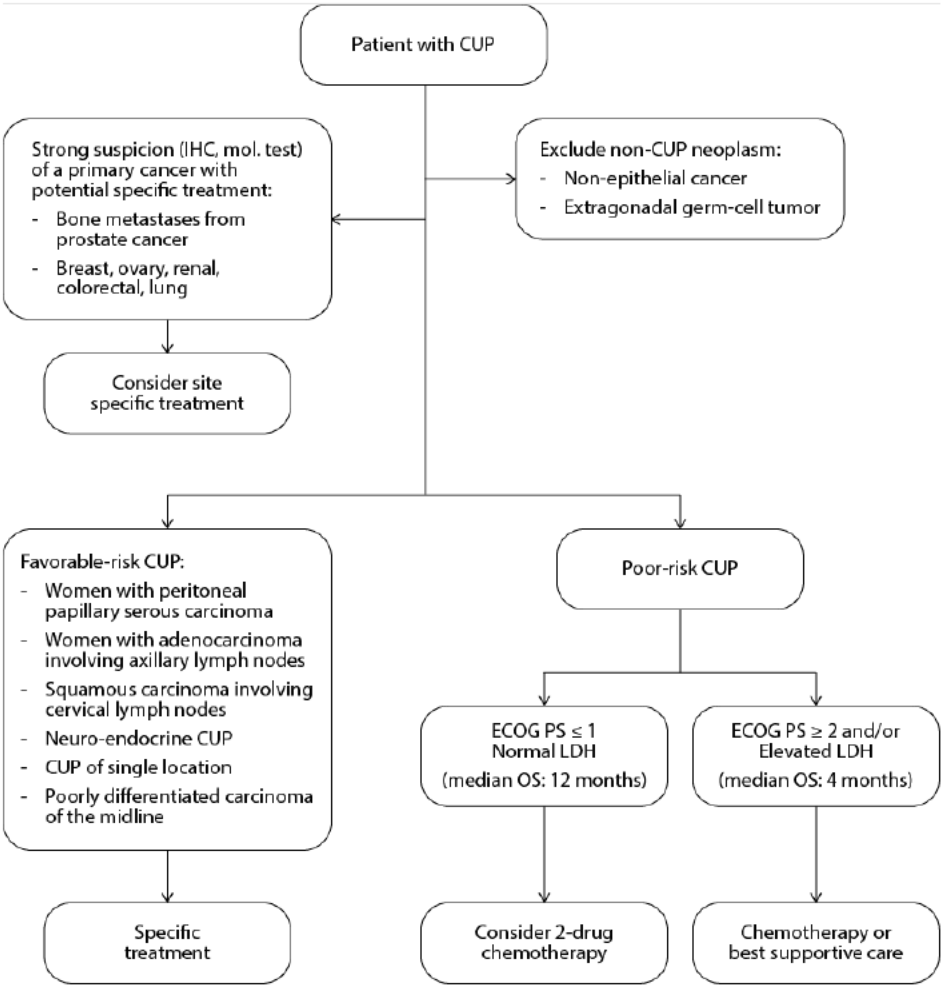
Two opposing hypotheses have been proposed for CUP pathogenesis (Busson et al. 2006; Pentheroudakis et al. 2007). One hypothesis considers CUP to be a single biological entity with unique molecular features that accounts for the absence of the primary site and for early metastatic disease. The second hypothesis posits that CUP arises from different groups of unrelated tumors, each with a primary site that escapes detection.

1.1.1 Current Treatments for Cancer of Unknown Primary Origin

The heterogeneity of CUP tumors, as well as their lack of an identified tissue of origin, imposes challenges on how the disease is treated. The European Society for Medical Oncology (ESMO) has developed a treatment algorithm for CUP that consists of two general steps (Fizazi et al. 2015) (Figure 1):

- In the first step, if examination results including clinical features, immunohistochemistry, radiology, laboratory values and additional diagnostic measures beyond those of the standard diagnostic work-up strongly suggest a tissue of origin, treatment is initiated based on known site-specific therapies for the identified cancer type
- In the second step, patients for whom a likely tissue of origin cannot be posited are classified into distinct clinic-pathological subgroups (favorable and poor prognosis CUP). Subsequent chemotherapeutic treatment is initiated based on this classification (see below)

Figure 1 Clinical Management of Patients With CUP



CUP = cancer of unknown primary; IHC = immunohistochemistry; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; OS = overall survival.
Modified from Fizazi et al. 2015.

1.1.1.1 Assessment of the Tissue of Origin

To further evaluate the potential tissue of origin of CUP, as well as to exclude chemosensitive and potentially curable tumors (e.g., lymphomas and germ-cell tumors), high-quality tumor samples are subjected to extensive IHC on multiple antigenic markers (Abbruzzese et al. 1995; Oien 2009). Patients with metastatic lesions that match one of the IHC profiles in Table 1 may be considered for treatment with standard site-specific regimens appropriate to the likely primary tissue of origin if the morphology and clinical picture are also pointing in this direction. Patients with non-specific IHC profiles or clinical pictures that do not correlate with a specific IHC profiles are candidates for non-tumor specific treatment regimens, as described in Section 1.1.1.2.

Table 1 Examples of Immunohistochemical Work-Up to Identify Tissue of Origin

	CK	PSA	ER PgR	CDX2+ CK20+ CK7–	TTF1 Napsin A CK7+	TGAB CT	NSE, CG SYP	AFP OCT4 hCG PLAP	LCA	S100 HMB45	Vim Des
Prostate cancer	+	+	–	–	–	–	–	–	–	–	–
Breast cancer	+	–	±	–	–	–	–	–	–	–	±
Colorectal cancer	+	–	–	+	–	–	–	–	–	–	–
Lung adenocarcinoma	+	–	–	–	+	–	–	–	–	–	–
Thyroid cancer	+	–	–	–	±	+	±	–	–	–	–
Neuroendocrine	+	–	–	–	±	±	+	–	–	–	–
Germ-cell cancer	+	–	–	–	–	–	–	+	–	–	±
Lymphoma	–	–	–	–	–	–	–	–	+	–	–
Melanoma	–	–	–	–	–	–	–	–	–	+	±
Sarcoma	–	–	–	–	–	–	–	–	–	±	+

AFP = alpha fetoprotein; CG = chromogranin; CK = cytokeratin; CT = calcitonin; Des = desmin; ER = estrogen receptor; hCG = human chorionic gonadotropin; LCA = leukocyte common antigen; NSE = neuron-specific enolase; PgR = progesterone receptor; PLAP = placental alkaline phosphatase; PSA = prostate-specific antigen; SYP = synaptophysin; TGAB = thyroglobulin; TTF-1 = thyroid transcription factor 1; Vim = vimentin.

The table shows general staining patterns but exceptions exist, especially for S100 and vimentin
Thyroid and neuroendocrine cancers often positive with CK7 and TTF1 but not with Napsin A.
Some lung cancers (up to 20%) may not be positive for TTF1 (Quint 2007; Travis et al. 2015).
From Fizazi et al. 2015.

1.1.1.2 Treatment of CUP

CUP is defined as a tumor without a confirmed tissue of origin. Two distinct subsets of CUP have been identified: favorable prognosis CUP, and poor prognosis CUP.

Favorable Prognosis Cancer of Unknown Primary Site

A minority (15%–20%) of patients with CUP, as defined by clinical and pathological criteria (Table 2), are referred to as having favorable prognosis disease (Fizazi et al. 2015). Within this subset, 30%–60% of patients can achieve long-term disease control if managed similarly to patients with a potentially equivalent metastatic cancer of known primary site. Retrospective analyses confirm that the clinical behavior, biology, response to treatment and outcome of patients with favorable prognosis CUP parallel those observed with metastatic tumors from a known primary site (Hainsworth and Fizazi 2009; Pavlidis et al. 2009; Spigel et al. 2009; Pentheroudakis et al. 2010; Pentheroudakis and Pavlidis 2010).

Treatment recommendations for favorable prognosis CUP, as provided in the ESMO guidelines, are shown below in Table 2.

Table 2 Therapy for Patients with Favorable Prognosis Cancer of Unknown Primary

CUP Subtype	Treatment	Potential Equivalent Tumor
Poorly differentiated neuroendocrine carcinomas of an unknown primary	Platinum + etoposide combination chemotherapy	Poorly differentiated neuroendocrine carcinomas with a known primary
Well-differentiated neuroendocrine tumor of unknown primary	Somatostatin analogs, streptozocin +5,-FU, sunitinib, everolimus	Well-differentiated neuroendocrine tumor of a known primary site
Peritoneal adenocarcinomatosis of a serous papillary histological type in females	Optimal surgical debulking followed by platinum–taxane-based chemotherapy	Ovarian cancer
Isolated axillary nodal metastases in females	Axillary nodal dissection mastectomy or breast irradiation and adjuvant chemo/hormone therapy	Breast cancer (found in 50%–70% when breast MRI is performed)
Squamous cell carcinoma involving nonsupraclavicular cervical lymph nodes	Neck dissection and/or irradiation of bilateral neck and head–neck axis. For advanced stages, induction chemotherapy with platinum-based combination or chemoradiation	Head and neck squamous cell cancer
CUP with a colorectal IHC (CK20 + CDX2 + CK7−) or molecular profile	Systemic treatment used for colorectal cancer	Metastatic colorectal cancer
Single metastatic deposit from unknown primary	Resection and/or RT ± systemic therapy	Single metastasis
Men with blastic bone metastases or IHC/serum PSA expression	Androgen deprivation therapy ± RT	Prostate cancer

5-FU = 5-fluorouracil; IHC = immunohistochemistry; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; RT = radiotherapy; CK = cytokeratin.
From Fizazi et al. 2015.

Poor-prognosis Cancer of Unknown Primary

The remaining patients (80%–85%) have more limited sensitivity to therapy.
Two prognostic groups can be identified among patients with poor prognosis disease based on the following criteria (Culine et al. 2002):

- Good performance status (0–1) and a normal lactate dehydrogenase (LDH) level
- Poor performance status, elevated serum LDH, or both

The first prognostic group has a median OS of 1 year, while the second prognostic group has a median OS of about 4 months.

Commonly used low-toxicity chemotherapy regimens for poor prognosis CUP, as described in the ESMO guidelines, are shown below in Table 3.

Table 3 Commonly Used Low-Toxicity Chemotherapy Regimens for Patients with Cancer of Unknown Primary in the Non-Specific Subset

Chemotherapy (mg/m^2)	Time	Interval	Comments
Cisplatin 60–75 + Gemcitabine 1000	Day 1 Day 1+8	q3w	Fit patients, adequate hydration
Cisplatin 75 + Etoposide 100	Day 1 Day 1–3	q3w	Fit patients with neuroendocrine-feature CUP, adequate hydration
Paclitaxel 175 + Carboplatin AUC 5	Day 1	q3w	Convenient outpatient regimen, monitor neurotoxicity
Docetaxel 75 + Carboplatin AUC 5	Day 1	q3w	Convenient outpatient regimen, monitor neurotoxicity
Irinotecan 160 + Oxaliplatin 80	Day 1	q3w	Outpatient regimen, monitor for neurotoxicity and diarrhea
Oral capecitabine 2000 ± Oxaliplatin 85–130	Days 1–14 Day 1	q3w	Outpatient regimen risk for diarrhea and neurotoxicity
Gemcitabine 1000/irinotecan 100	Day 1+8	q3w	Convenient outpatient regimen, monitor diarrhea

AUC = area under the concentration-time curve; *CUP = cancer of unknown primary*; q3w = once every 3 weeks.
From Fizazi et al. 2015.

Clinical Studies of Treatment Regimens for Poor-Prognosis CUP

A number of clinical studies/reviews have assessed the efficacy of various treatment regimens for poor-prognosis CUP. Key publications in this area include, in chronological order:

- A review published in 2009 found that poor prognosis CUP had similar outcome whether treatment was based on platinum salts, taxanes or new-generation cytotoxic compounds (gemcitabine, vinca-alkaloids or irinotecan) (Golfinopoulos et al. 2009). Hence, no single broad-based chemotherapy regimen had been identified at the time that was superior to others in this patient population. Importantly, superiority of any chemotherapy regimen over best supportive care had never been formally demonstrated either. Nevertheless, platinum-based doublet chemotherapy regimens became standard of care in the first-line treatment of poor prognosis CUP

- A meta-analysis published in 2013 confirmed the role of taxanes in the treatment of poor-prognosis CUP (Lee et al. 2013). The review of available randomized controlled trials showed that the addition of platinum, taxane, or platinum and taxane to a regimen tended to extend the survival of CUP patients. It also showed that combinations containing a taxane agent demonstrated a prolongation of the median survival times and higher 1-year survival rates following first-line treatment of poor-prognosis CUP compared with those without taxanes, although such a benefit did not seem to be sustained for 2 years
- An abstract published in 2019 described interim results from the GEFCAPI 04 study, a prospective randomized phase III trial that examined whether predicting the site of tumor origin by gene expression profiling (GEP), followed by site-specific treatment, was more effective than standard empiric treatment in patients with poor-prognosis CUP (Fizazi et al. 2019). Eligible patients were randomly assigned to receive site-specific treatment guided by GEP (n = 123) or cisplatin and gemcitabine (n = 120). Median PFS (primary endpoint) was 4.6 months in the site-specific treatment group and 5.3 months in the empiric group (HR = 0.95 [0.72–1.25]; p = 0.7). Median OS (95% CI) was 10.68 (7.33–11.93) and 9.99 (7.06–11.96) months in the site-specific and empiric treatment groups, respectively
- A study published in 2020 described another prospective randomized phase II trial in which comprehensive GEP was performed to predict tumor origin in patients with poor prognosis CUP (Hayashi et al. 2019). Following GEP, patients were randomly assigned to receive site-specific therapy (n = 50) or paclitaxel and carboplatin (n = 51). One-year survival was 44.0% and 54.9% in the site-specific and empiric treatment groups, respectively (p = 0.264). Median OS and PFS were 9.8 and 5.1 months, respectively, for site-specific treatment versus 12.5 and 4.8 months for empiric treatment, respectively (p = 0.896 and 0.550 for the comparisons)
- A meta-analysis published in 2020 identified a trend towards improved OS in patients with poor-prognosis CUP who were treated with site-specific versus empiric treatment (HR = 0.73; 95% CI: 0.52–1.02) (Rassy et al. 2020). The test for overall effect for PFS was not statistically significant (HR = 0.93; 95% CI: 0.74–1.17), with little heterogeneity between included studies

In summary, the ESMO guidelines published in 2015 recommended various chemotherapy regimens (Table 3) for the treatment of poor-prognosis CUP, consistent with studies available at the time. Newer studies examined whether genomic profiling to predict the potential origin of the tumor, followed by site-specific therapy, could provide benefit over empiric therapy. Unfortunately, little to no improvement over the regimens recommended in 2015 has yet to be demonstrated by this approach. Thus, a significant clinical need exists for new approaches that can be used to treat this relatively common and difficult-to-treat cancer type.

1.2 BACKGROUND ON TEST PRODUCTS

Please refer to the investigator's brochures for alectinib, atezolizumab, cobimetinib, entrectinib, ipatasertib, ivosidenib, pemigatinib, pertuzumab, trastuzumab, vemurafenib and vismodegib for details on nonclinical and clinical studies of the respective test products. Refer also to the local packaging information for the investigational agents bevacizumab, erlotinib and olaparib and for the control agents cisplatin, carboplatin, paclitaxel and gemcitabine for details on their clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

Treatment of cancer is generally based on the specific neoplasm's tissue of origin (National Comprehensive Cancer Network), an approach that is obviously problematic in patients with CUP. ESMO recommends standard broad-based chemotherapeutic agents for non-specific subsets of CUP, but these regimens are suboptimal in poor-prognosis disease, resulting in median OS values of 1 year in patients with good ECOG performance status (0–1) and normal LDH and approximately 4 months in patients with poor ECOG performance status (2–4), elevated LDH, or both (Fizazi et al. 2015). Whether these chemotherapy regimens prolong survival over best supportive care remains unknown. The reason(s) for the low response is unclear but might reflect the fact that any case of CUP could originate from multiple types of primary lesions (each with its own susceptibility to specific anticancer agents) or that some other unique feature(s) of CUP biology blocks response. In either case, it is clear that a high unmet need exists for new therapeutic approaches in patients with CUP who do not fall into the favorable prognosis subset.

Precision medicine is an approach for disease treatment that takes into account individual variability in genes, environment, and lifestyle for each person (National Institutes of Health). In the case of cancer, this approach typically involves: 1) delineating a patient's genetic profile via DNA sequencing methodologies (whole genome, exome, etc.); 2) using this information to identify underlying driver alterations; and 3) treating the disease with one or more of an expanding list of targeted agents that specifically counteract the effects of the identified, mutated or altered proteins.

Given the therapeutic challenges imposed when the tissue of origin is unknown, CUP would appear to be especially well suited for a precision medicine/targeted therapy approach. Indeed, beyond the theoretical underpinning described above, an increasing amount of published data suggest that such an approach may have important clinical benefits in patients with CUP, as summarized in the table below:

Study	Methodology	Outcome
(Ross et al. 2015)	• Comprehensive genomic profiling on tissue samples from 200 CUP patients using the FoundationOne® FMI F1CDx (tissue) test	• One or more potentially targetable alterations were identified in 169/200 (85%) of the specimens
(Varghese et al. 2017)	• Next-generation sequencing of 410 cancer-associated genes in tissue samples from 150 CUP patients	• Thirty percent of patients carried at least one druggable level 2 and/or level 3 alteration. An additional 25% of tumors harbored at least one potentially actionable level 4 aberration
(Kato et al. 2017)	• Next-generation sequencing of 54–70 cancer-associated genes in tissue samples from 442 patients with CUP	• Overall, 290/442 patients (66%) had one or more characterized genomic alterations (excluding variants of unknown significance). Of these, 289/290 (99.7%) exhibited targetable alterations
(Clynick et al. 2017)	• Genomic profiling on tumor tissue from 32 CUP cases	• Biologically relevant or therapeutically druggable variants were detected in 88% ($n = 28$) of cases. There were potentially actionable targets in 14/32 (44%) cases
(Krämer et al. 2018)	• Genomic profiling of 315 cancer-related genes in tumor tissue from 4650 CUP cases	• 3675 cases harbored ≥ 1 genomic alterations that were druggable with a targeted therapy and/or an immune checkpoint inhibitor • An additional 485 had genomic alterations that were druggable alterations with investigational targeted therapies
(Ross et al. 2020)	• Hybrid capture-based comprehensive genomic profiling of 303 centrally-reviewed CUP cases	• 32% of patients were potentially eligible for molecularly-guided therapy

The data presented above demonstrate the high frequency of druggable alterations in CUP tumors, supporting the idea that targeted therapy may have significant potential as a treatment approach in this setting. In further support of this hypothesis, the prospective precision oncology registry trial NCT/DKTK MASTER used a combination of whole genome sequencing, whole-exome sequencing and transcriptome analysis to examine the genetic profiles of 70 poor-prognosis CUP patients (Werner et al. 2020). Among the participants, 56 had alterations that were targetable and 20 subsequently received targeted therapy. The median PFS in the latter group after targeted therapy was 183 (50–805) days. This compared to a median PFS of 89 (31–304) days in the same group during their last prior systemic therapy, which translated into a PFS ratio 2.25 (0.16–16.43) for targeted versus systemic therapy.

Despite the high frequency of genomic alterations in CUP, a significant percentage of patients still lacks specific targetable alterations and, hence, would not be expected a priori to respond to targeted therapies. Several lines of evidence suggest that therapy with immune checkpoint inhibitors might have potential benefit in such cases, especially in patients with higher levels of tumor mutational burden (TMB):

- Tanizaki et al. performed a single-arm, non-randomized Phase II study to assess the effects of nivolumab, a PD-1 inhibitor, in 45 patients with previously treated, poor-prognosis CUP (Tanizaki et al. 2020). In this study, ORR was 24.4% (95% CI: 12.9–39.5%), DCR was 53.3% (95% CI: 37.9–68.3%), and median OS was 15.1 months (95% CI: 8.3–NR). Although the study population was not assessed for TMB, the results nonetheless the potential benefit of immune checkpoint inhibitor therapy as a general treatment modality in patients with poor-prognosis CUP.
- Gay et al. assessed TMB in 6116 CUP tumor specimens, defining high, intermediate and low TMB as ≥ 20, ≥ 6 and ≤ 20, and < 6 mutations/Mb, respectively (Gay et al. 2017). Significant numbers of patients within each tested tumor type (ACUP, CUP not otherwise specified [NOS], squamous cell CUP, neuroendocrine, neoplasm NOS, urothelial, GIST and small cell) had high TMB, with the exception of GIST. Overall, 23% of SCC tumors, 15% of malignant neoplasm NOS tumors and 13% of urothelial tumors had high TMB. For ACUP or CUP, the most common tumors, 8–11% had high TMB. In addition, 1.6% of CUP cases were found to be MSI-H. Furthermore, Varghese et al. found that about 10% of CUP tumors harbor signatures of tobacco-related or ultraviolet-induced DNA damage (Varghese et al. 2017).
- Gatalica et al. performed NGS on tumor samples from 389 CUP patients, analyzing 592 genes and 52 gene fusions (Gatalica et al. 2018). High levels of total mutation load (TML-H) were observed 11.8% (46/389) of tumors, while high levels of microsatellite instability (MSI-H) were detected in 7/384 (1.8%) of tumors. PD-L1 expression was detected in 80/362 samples (22%). Overall, therefore, 28% of CUP tumors carried one or more predictive biomarkers (MSI-H, PD-L1 and/or TML-H) to the immune checkpoint blockade.

- In non-CUP settings, high levels of TMB have been associated with favorable outcomes following therapy with immune checkpoint inhibitors (Kim et al. 2019; Schrock et al. 2019; Alborelli et al. 2020; Klempner et al. 2020; Osipov et al. 2020). For instance, in one meta-analysis of 5712 patients aggregated from 26 studies, high TMB groups exhibited better OS (HR 0.53, 95% CI: 0.42–0.67) and PFS (HR 0.52, 95% CI: 0.40–0.67) compared to low TMB groups (Kim et al. 2019). In patients with high TMB, those who received therapy with immune checkpoint inhibitors had a better OS (HR 0.69, 95% CI: 0.50–0.95) and PFS (HR 0.66, 95% CI: 0.47–0.92) compared to those who received chemotherapy alone, while the same comparisons were not statistically significant in patients with low TMB.

Combined, the above considerations clearly suggest that patients with poor-prognosis CUP might benefit from targeted therapies or immunotherapy guided by genomic profiling, but prospective clinical studies evaluating this potentially promising approach are lacking. Therefore, to test this hypothesis, Study MX39795 will directly assess whether molecularly-guided therapy based on comprehensive genomic profiling is superior to recommended systemic chemotherapy in patients with poor-prognosis CUP (non-specific subset as defined in the ESMO guidelines for CUP (Fizazi et al. 2015) who have received 3 cycles of platinum-doublet induction chemotherapy.

Choice of molecularly-guided therapy in this study will be determined based on results from patient-specific FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test reports (dependent on availability of one or both), according to the guidance provided in Table 5 (Section 3.1) and the Molecular Tumor Board Charter (see Sections 3.1 and 3.1.7 for a description of the Molecular Tumor Board [MTB]). FoundationOne® FMI F1CDx (tissue) test is a validated, comprehensive genomic profiling tool that interrogates the entire coding sequence of >300 cancer-related genes, as well as select introns from genes commonly rearranged or altered in solid tumor cancers. As described above, the FoundationOne® FMI F1CDx (tissue) test has been shown to identify, with high selectivity and sensitivity, actionable alterations in CUP tumor specimens (Ross et al. 2015). In addition to the tissue biopsy, all patients in the study will also have genomic profiling done via FoundationOne® F1LCDx (Liquid) test, a blood-based circulating tumor-DNA assay for solid tumors that interrogates >300 cancer-related genes. The gene panels used for the tissue and liquid biopsy assays are updated regularly to integrate the results of new research in cancer genomic profiling and therapy-related biomarkers. These changes are documented in the Molecular Tumor Board Charter.

Patients for whom neither a FoundationOne® FMI F1CDx (tissue) test report nor a FoundationOne® F1LCDx (Liquid) test report could be generated will be discontinued from the study.

The Molecular Tumor Board Charter provides guidance on the rationale and principles for choosing molecularly-guided therapies and on treatment assignment by the Molecular Tumor Board. For this study it is expected that choice of molecularly-guided therapies may be ambiguous in some cases (e.g., for co-occurrence of genomic alterations).

A detailed description of the study design of MX39795 is presented in Section 3.1. In brief, eligible patients with poor prognosis, non-specific CUP will receive 3 cycles of standard platinum-based chemotherapy (Fizazi et al. 2015). After this Induction Period, response to platinum-based chemotherapy will be evaluated by the investigator using RECIST v1.1 (Appendix 5). Based on these results, participants will be grouped into two categories:

- Category 1: Patients with a CR, PR or SD after 3 cycles of platinum induction chemotherapy
- Category 2: Patients with a documented PD during 3 cycles of platinum induction chemotherapy or at any time during the Induction Period

Category 1 patients will be subsequently randomized in a 3:1 ratio to receive either molecularly-guided therapy until loss of clinical benefit or additional cycles of platinum-based chemotherapy, respectively (see Section 4.3.4.7 for treatment duration). The primary and secondary efficacy endpoints will be analyzed exclusively in Category 1 patients. Category 2 patients will receive molecularly-guided therapy until loss of clinical benefit, and efficacy and safety endpoints will be assessed on an exploratory basis.

Rationales for individual features of the study design are described in Section 3.4, and include:

- Rationale for selection of CUP with poor-prognosis factors, for whom a likely tissue of origin cannot be posited (Section 3.4.1), with a restriction to cancers of epithelial origin
- Rationale for the Control Group (Section 3.4.2)
- Rationale for Three Cycles of Induction Chemotherapy (Section 3.4.3)
- Rationale for Sub-Dividing the Study Population into Two Categories of Patients (Section 3.4.4)
- Rationale for 3:1 Randomization in Category 1 Patients (Section 3.4.5)
- Rationale for Progression-Free Survival as the Primary Efficacy Endpoint (Section 3.4.6), and rationale for tumor assessments every 9 weeks
- Rationale for Combining Data from Different Experimental Treatment Cohorts for the Primary Endpoint Analysis (Section 3.4.7)
- Rationale for Investigational Medicinal Products Doses and Schedules (Section 3.4.8)

- Rationale for Patient-Reported Outcomes (Section 3.4.9)
- Rationale for Exploratory Biomarker Assessments (Section 3.4.10)

1.3.2 Benefit-Risk Assessment

1.3.2.1 Molecularly-Guided Therapy

As described in Section 1, patients with poor-prognosis CUP (non-specific subset) have poor outcomes on currently recommended treatments and, hence, have a high unmet need for new therapeutic approaches. Unfortunately, treatment options for CUP have not evolved in decades, and no drug has yet been registered specifically for the disease. This dearth of treatment options likely reflects the fact that, until recently, treatment of cancer has generally been based on the neoplasm's tissue of origin, which is obviously problematic in the case of CUP. However, with the advent of large-scale DNA sequencing technologies, and the availability of a growing collection of targeted agents and immunotherapies, a new and rationally-designed treatment paradigm may now be possible for CUP that is independent of tissue of origin (see above, Study Rationale). The potential benefits of such a molecularly-guided treatment approach provide a strong medical rationale for carrying out the current study.

With the exception of entrectinib, none of the molecularly-guided therapies examined in this study are indicated for CUP. Most of them, however, have been approved for the treatment of other cancers or are in late clinical development for non-CUP cancer indications. Consequently, all proposed treatments in this study have been shown to provide important clinical benefit in other cancers that carry the same genomic alterations examined in this study. As the molecular pathways affected by the genomic alterations examined here have been shown to operate at the molecular level in a similar fashion across different cell types (and indeed across different organisms), it is reasonable to hypothesize that the targeted agents and immunotherapy regimens comprising this study's IMPs may have significant benefit in patients with CUP.

An advantage of using agents approved in other cancer indications or in late stage of development is that their safety profiles have been assessed in great detail, at least in other cancers. Several steps will be taken to further limit the risk of participants in this study. First, administration of all IMPs will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Second, identified and potential risks associated with IMPs will be closely monitored throughout this study (Section 5.1). Third, the study will have an independent data monitoring committee (iDMC) to assess benefit-risk profiles and safety signals. Fourth, key IMP-specific eligibility criteria relating to safety in other cancers will be assessed prior to starting treatment with molecularly-guided therapy (see Sections 4.1.1.2 and 4.1.3). Finally, the study contains protocol-specified drug interruption and/or dose modification criteria designed to ensure safety (Section 5.1.2).

In view of the biological and medical rationale for using molecularly-guided therapies in patients with CUP—and with the above safety precautions in place—a favorable benefit–risk proposition exists to support the conduct of this study. This is especially true given the high unmet need for new therapeutic options in patients who have this difficult-to-treat disease.

1.3.2.2 The COVID-19 Pandemic

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of SARS-CoV-2 infection.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

<u>COVID-19 and Atezolizumab</u>

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal

association between atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2-related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

If Atezolizumab is administered in combination with chemotherapy, neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).

2. OBJECTIVES AND ENDPOINTS

Study MX39795 will compare the efficacy and safety of molecularly-guided therapy versus standard platinum-containing chemotherapy in patients with poor prognosis cancer of unknown primary site (CUP; non-specific subset) who have achieved disease control (CR, PR, or SD) after 3 cycles of first-line platinum-based induction chemotherapy. Molecularly-guided therapies will include 10 targeted cancer therapy regimens and 2 cancer immunotherapy regimens and will be chosen based on each patient's comprehensive genomic profile (see below for further details).

Specific objectives and corresponding endpoints for the study are outlined in Table 4, where "molecularly-guided therapy" refers to a pooled treatment group comprising patients who received a targeted agent or cancer immunotherapy.

Table 4 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of molecularly-guided therapy versus platinum chemotherapy in term of progression-free survival in patients with CUP whose best response to 3 cycles of platinum induction chemotherapy was assessed CR, PR, or SD	• Progression-free survival (PFS1), defined in Category 1 patients as the time from randomization to the first occurrence of disease progression, as assessed by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of molecularly-guided therapy versus platinum chemotherapy in terms of overall survival, objective response rate, duration of response and disease control rate in patients with CUP whose best response to 3 cycles of platinum induction chemotherapy was assessed CR, PR, or SD	• Overall survival (OS), defined as the time from randomization to death from any cause • Objective response rate (ORR1), defined in Category 1 patients as the proportion of randomized patients who exhibit a CR or PR on two consecutive occasions $\geq$4 weeks apart • Duration of response (DOR1), defined in Category 1 patients with an objective response as the time from when response (CR or PR) is first documented to disease progression or death due to any cause, whichever occurs first • Disease Control Rate (DCR1) defined as the proportion of Category 1 patients with confirmed CR, PR, SD, or NA, per RECIST v1.1 Responses will be determined by the investigator according to RECIST v1.1

Safety Objective	Corresponding Endpoints
• To evaluate the safety of molecularly-guided therapy in all patients with CUP who receive targeted therapy or cancer immunotherapy	• Incidence and severity of AEs, with severity determined according to NCI CTCAE v5.0 • Incidence and reasons for any dose reductions, interruptions, or premature discontinuation of any component of study treatment • Change from baseline in targeted vital signs • Incidence in clinical laboratory abnormalities
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of molecularly-guided therapy in patients with CUP who progressed (PD) during 3 cycles of platinum induction chemotherapy	• PFS2, OS2, ORR2, DOR2 and DCR2, assessed by the investigator in Category 2 patients according to RECIST v1.1 as described above
• To evaluate the mutagenic effects of 3 cycles of platinum induction chemotherapy in all patients with CUP	• Genomic profiles pre and post platinum induction chemotherapy, as assessed using FoundationOne® F1LCDx (Liquid) test
• To evaluate clonal evolution of CUP during targeted or cancer immunotherapy treatment	• Genomic profiles pre-treatment and at disease progression in patients receiving targeted therapy or cancer immunotherapy
• To characterize CUP tumors and their microenvironment on a molecular level	• Molecular profiling by, e.g., gene expression and immunohistochemistry analyses, and tumor immune signatures
• To evaluate the HRQol effects of molecularly-guided therapy in patients with CUP whose best response to 3 cycles of platinum induction chemotherapy was assessed CR, PR or SD	• Absolute change from Treatment Period Cycle 1 Day 1 in FACT-G score in Category 1 patients • Absolute change from Treatment Period Cycle 1 Day 1 in HADS score in Category 1 patients
• To evaluate health status utility of molecularly-guided therapy in patients with CUP whose best response to 3 cycles of platinum induction chemotherapy was assessed CR, PR or SD	• Absolute change from Treatment Period Cycle 1 Day 1 in EQ-5D-5L index-based score in Category 1 patients

AE = adverse event; CR = complete response; CUP = cancer of unknown primary; *DOR = duration of response; DCR = disease control rate*; EQ-5D-5L = EuroQol 5-Dimensional 5-Level questionnaire; FACT-G = Functional Assessment of Cancer Therapy: General; HADS = Hospital Anxiety and Depression Scale; HRQol = health-related quality of life; *NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0*; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease.

NOTE: Category 1 patients are those who achieved disease control (CR, PR or SD) after 3 cycles of first-line platinum-based induction chemotherapy; Category 2 patients are those who experienced PD during 3 cycles of platinum induction chemotherapy (see Study Design [below] for more details).

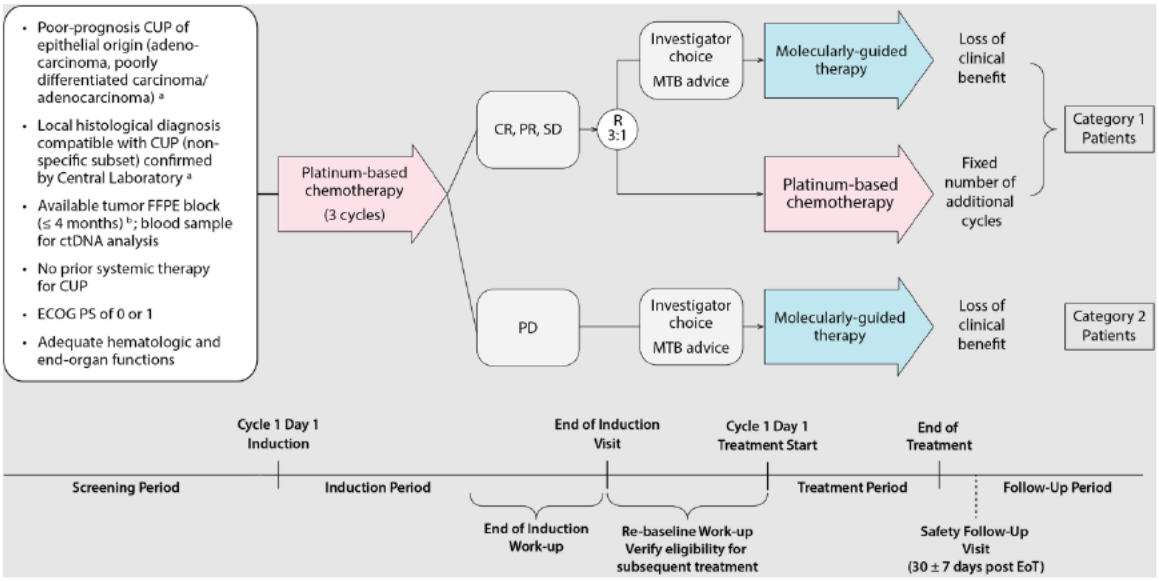
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study MX39795 is a phase II, randomized, open-label, active-controlled, multicenter trial. The study will consist of a Screening Period, an Induction Period including an End of Induction Visit, a Treatment Period, a Safety Follow-Up Visit occurring 30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first), and a Follow-Up Period. The first day of treatment during the Induction Period will be Day 1 (baseline) of the study.

The overall study design is presented in Figure 2. A Schedule of Activities is provided in Appendix 1. A timeline of key study events is summarized in Appendix 2 and further detailed below.

Figure 2 Study Design



CUP = cancer of unknown primary site; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; EoT = End of Treatment; MTB = Molecular Tumor Board; PD = progressive disease; PR = partial response; R = randomization; SD = stable disease.

[a] Confirmation according to the 2015 ESMO Clinical Practice Guidelines for CUP (Fizazi et al. 2015).

[b] A tumor tissue sample that is suitable for: 1) the initial diagnosis of CUP at the study site's local laboratory, and 2) confirmation of diagnosis compatible with CUP and generation of a comprehensive genomic profile using FoundationOne® FMI F1CDx (tissue) test at a central reference pathology laboratory. If, after local diagnosis of CUP, insufficient tumor tissue (in quantity or quality) remains for the central pathology laboratory to confirm the CUP diagnosis and generate profile using a FoundationOne® FMI F1CDx (tissue) test, then a fresh biopsy sample must be collected during the Screening Period that meets the study's requirements (refer to the Laboratory Manual for suitability details and specimen collection instructions). In exceptional cases where a repeat biopsy is not possible, or where a repeat biopsy would lead to significant delay in treatment start, the reason will be documented by the investigator and the patient will proceed through the eligibility review process without such new biopsy; in these cases, a blood sample will be used to generate a profile using the FoundationOne® F1LCDx (Liquid) test.

3.1.1 Screening Period

The population to be included in this study corresponds to patients with CUP of epithelial origin with poor-prognosis, for whom a likely tissue of origin cannot be posited.

To be eligible, patients must have a histological diagnosis compatible with CUP (non-specific subset per 2015 ESMO guidelines), with available pathology report, as determined by the study site's local laboratory on a contemporaneous tissue sample.

Only patients with the histological subtypes and the poor-prognosis subsets of CUP allowed in the study should enter the Screening Period.

The diagnosis of poor prognosis CUP must be ascertained prior to entering the Screening Period of the study, following the 2015 ESMO Clinical Practice Guidelines for CUP (Fizazi et al. 2015) and any additional protocol-specific eligibility requirements for the diagnosis of CUP. Where ESMO CUP guidelines are outdated or fail to provide guidance, an appropriate work-up using state-of the art diagnostic methods (per guidelines for the suspected tumor) should be used to exclude a potential primary origin for the cancer. All tests/examinations (e.g., pathology, clinical and imaging work-up) performed to ascertain the diagnosis of CUP and exclude a tumor of known origin must be available when entering the Screening Period.

The pre-screening tests/examinations performed to diagnose CUP will be re-assessed by an Eligibility Review Team, in consultation with a referent oncologist in complex cases (if necessary). Potential participants will be excluded from the study if their clinical presentations and pathology work-ups (including IHC) indicate primary origins for their tumors (for further information, see below ["During Screening"]).

The diagnosis of CUP according to the 2015 ESMO guidelines should have included:

Minimal basic work-up:

- Thorough physical examination (including, e.g., head and neck, rectal, pelvic and breast examination)
- Basic blood and biochemical analyses
- Computed tomography (CT) scans of thorax, abdomen and pelvis

Further work-up (including, but not limited to):

- Mammography in women
- Breast MRI in women with axillary disease
- Endoscopies guided by sign-, symptom- or laboratory abnormalities
- Serum assessment of α-fetoprotein, human chorionic gonadotropin, plasma chromogranin A and PSA suggested in male patients to exclude potentially curable extragonadal germ-cell tumors, neuroendocrine tumors and prostate cancers amenable to hormonal treatment
- Whole-body FDG–PET/CT suggested for patients with cervical adenopathies from CUP and those with a single CUP metastasis
- In situations, where clinical and histopathological pictures are suggestive of a specific primary origin for the cancer, an appropriate work-up to exclude this specific cancer should have been performed. These situations include (but are not limited to) the following:
    - Breast MRI in women with lymph nodes in the breast drainage areas in the context of IHC results suggestive of breast cancer

- High-definition CT scan of the thorax in patients with TTF-1 negative IHC in the context of poorly characterized lung masses or in the context of hilar lesions (with or without lung masses)
- MRI in patients with one or few liver lesions presenting with no extra-hepatic disease or with extra-hepatic disease limited to lung metastases and/or lesions in the upper abdomen, in the context of IHC suggestive of cholangiocarcinoma or pancreatobiliary or upper gastrointestinal disease
- Adequate abdominal and pelvic imaging in the presence of high-grade serous carcinoma
- Bosniak classification of any kidney lesion in the context of IHC suggestive of renal cell carcinoma or other kidney malignancy
- ENT (Ear-Nose-Throat) examination and MRI and/or PET imaging in patients with IHC and/or a clinical picture suggestive of salivary gland carcinoma (this includes poorly defined masses in the neck or predominance of neck lymph nodes in the clinical presentation)

Acceptable histology will include:

- Adenocarcinoma
- Poorly differentiated adenocarcinoma
- Poorly differentiated carcinoma

The following patients will not be eligible:

- Patients with squamous cell CUP
- Patients with histology and immunohistology profiles (per ESMO guidelines) that are not adenocarcinoma or poorly differentiated carcinoma/adenocarcinoma), such as but not limited to non-epithelial cancer, extragonadal germ-cell tumor, neuroendocrine tumors, sarcoma, melanoma, mesothelioma, hematologic malignancies
- Patients who can be assigned to a specific subset of CUP for which a specific treatment is recommended by the 2015 ESMO Clinical Practice Guidelines for CUP (Fizazi et al. 2015) or with a clinical and IHC profile indicative of a specific primary tumor (favorable prognosis CUP subsets). These are:
  - Poorly differentiated carcinoma with midline distribution
  - Women with papillary adenocarcinoma of the peritoneal cavity
  - Women with adenocarcinoma involving only the axillary lymph nodes
  - Squamous cell carcinoma of the cervical lymph nodes
  - Poorly differentiated neuroendocrine tumors
  - Men with blastic bone metastases and elevated PSA
  - Patients with a single, small, potentially resectable tumor

- Colon cancer-type CUP with a CK7 negative, CK20 positive, CDX-2 positive immunohistochemistry profile
- CK7 positive, CK20 negative and TTF-1 positive tumors in a context suggestive of lung adenocarcinoma or thyroid cancer (i.e., with lesions in the lung or thyroid or the lymph nodes in their drainage areas)
- IHC profile definitely indicative of breast cancer OR an IHC profile indicative of breast cancer and either a history of breast cancer or lymph nodes in the drainage areas of the breast
- High-grade serous carcinoma histology and elevated CA125 tumor marker and/or a mass in the gynecological tract or any tumor mass or lymph node in the abdominal cavity (i.e., below the diaphragm)
- IHC profile suggestive of renal cell carcinoma and renal lesions, with a Bosniak classification higher than IIF
- IHC profile compatible with cholangiocarcinoma or pancreatobiliary (or upper gastrointestinal carcinoma) AND 1 or 2 liver lesions without extrahepatic disease or with only pulmonary metastases and/or lymph nodes in the drainage areas of the liver

- Patients with a history of malignancy within 5 years prior to initiation of study treatment, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$90%).

General inclusion and exclusion criteria must also be satisfied for a patient to be considered for screening (Refer to Sections 4.1.1 and 4.1.2).

3.1.1.1 During Screening

As this study aims to direct treatment according to genomic profiles, it is further mandated that participants are willing and able to provide:

- A tumor tissue sample for generation of a comprehensive genomic profile using the FoundationOne® FMI F1CDx (tissue) test at a central reference pathology laboratory (refer to the Laboratory Manual for suitability details and specimen collection instructions)
- Archival tumor *formalin-fixed, paraffin-embedded (*FFPE) block $\leq$4 months prior to screening will be acceptable for these central analyses. However, if an acceptable archival tumor FFPE block is not available or is not suitable (in quantity and quality) at screening, an FFPE block from a freshly obtained biopsy sample must be provided that meets the study's requirements

  In cases, where the first tissue sample sent to the central laboratory is considered unsuitable for generation of a comprehensive genomic profile using the FoundationOne® FMI F1CDx (tissue) test but allows for the confirmation of CUP (or the confirmation of CUP can be ascertained on a prior sample deemed suitable by the referent pathologist), and all other eligibility criteria are met for the study, the patient may start platinum-based induction chemotherapy prior to

a fresh biopsy sample being received by the central laboratory, providing that the fresh sample has been collected (e.g., when shipment could delay an urgent start of treatment)

In exceptional cases where a repeat biopsy is not possible, or where a repeat biopsy would lead to significant delay in treatment start, the reason will be documented by the investigator and the patient will proceed through the eligibility review process without such new biopsy

Tumor FFPE blocks are preferred. In exceptional cases, 25 slides (4 μm slide thickness each) may be accepted

- The local pathology reports confirming compatibility with CUP diagnosis and the associated slides used for the diagnosis (refer to the Laboratory Manual for further details)

  Expectations are that the histology and routine immunohistochemistry performed locally are compatible with CUP following the algorithm suggested in the 2015 ESMO guidelines for CUP, which recommends CK7 and CK20 as first step markers

  If the slides used for the local test confirming local CUP diagnosis are not available, the FFPE block submitted for genomic profiling must be sufficient to allow central confirmation of CUP diagnosis (i.e., performing relevant IHC and ISH if required)

A central pathology laboratory will interpret the local histopathology results (including immunohistochemistry) and perform additional tests if required to confirm that the pathology and immunohistochemistry profiles are compatible with the diagnosis of poor prognosis CUP. The assessment performed by the central pathology laboratory will be oriented by pathological and clinical features and the choice of immunohistochemistry markers (and in-situ hybridization if required) to be reviewed and additional tests to be performed will be in line with 2015 ESMO Clinical Practice Guidelines for CUP and with the Study Laboratory Manual.

<u>NOTE</u>: The Eligibility Review Team (ERT) will review pathology and immunohistology reports from central and local laboratories, and details of the CUP work-up (as reported in the eCRF) to determine patient eligibility. Identification of acceptable poor-prognosis CUP will be carried out according to ESMO guidelines and, in cases where these guidelines may be insufficient or outdated, by adequately excluding potential primary tumors via newer genetic, immunologic, etc., methodologies. The ERT may not be able to confirm the diagnosis of poor prognosis CUP without a complete and proper pre-screening CUP work-up, i.e., one that was carried out to completion per ESMO guidelines (see beginning of this section). Therefore, failure by the investigator to provide this necessary pre-screening CUP work-up information may lead to screen failure.

In order to enter the Induction Period (see below), patients must have completed Part 1 and the RBR section of the Informed Consent Form (ICF). Since the molecularly-guided therapy eventually assigned to a patient is unknown during the Screening Period, Part 1 of the ICF will cover all aspects of the trial except for information related to any specific molecularly-guided therapies. Information related to the specific molecularly-guided therapy eventually assigned to an individual patient (e.g., identified targetable alteration, background on selected agent, and tolerability profile) will be provided in Part 2 of the ICF, which must be completed prior to the first dose of molecularly-guided therapy (see below for more detail). Patients who are randomly assigned to receive additional cycles of platinum chemotherapy will not be required to complete Part 2 of the ICF (see below).

3.1.1.2 Re-Screening and Extension of the Screening Period

The Screening Period will be 28 days (from signature of the ICF until the first dose of study treatment). Potential participants who are unable to fulfill all eligibility criteria within the Screening Period can be re-screened, provided that the reason for screen failure is one that can change over time and that all eligibility criteria will likely be fulfilled at the time of re-screening.

The 28-day Screening Period may be extended in exceptional cases:

- Up to 42 days (extension by 2 weeks) in case the first tissue submitted was not suitable or insufficient per central pathology assessment and a fresh biopsy has to be taken (see above)
- Up to 35 days (extension by 1 week):
  - If there has been a delay in the shipment of the tissue sample
  - If escalation of the eligibility review to the referent oncologist and further information are requested, or further tests are needed to determine eligibility

In cases where the Screening Period has been extended (see Section 3.1.1.2), screening assessments conducted during the initial Screening Period (e.g., CT scans) that met protocol requirements will remain valid during the Screening Period extension, with the following exceptions:

- Pregnancy tests and tests that should be repeated at baseline
- Imaging tests performed up to 49 days prior to first dose of study treatment are acceptable

3.1.2 Induction Period

All patients fulfilling eligibility criteria will enter the Induction Period.

A blood sample suitable for analysis of circulating tumor DNA using the FoundationOne® F1LCDx (Liquid) test (refer to the Laboratory Manual for specimen collection instructions) will be collected before initiation of chemotherapy.

Patients will receive 3 cycles of standard first-line platinum-based chemotherapy per investigator choice (carboplatin/paclitaxel, cisplatin/gemcitabine or carboplatin/gemcitabine) until the end of the Induction Period or documented early disease progression (Figure 2).

Patients who cannot tolerate their initial platinum-based induction therapy will be managed until the end of the Induction Period or documented early disease progression as follows:

- Patients should undergo dose reductions or interruptions of one or both components of the chosen chemotherapy regimen per institutional standards
- If dose reductions and interruptions are not sufficient or if intolerant to the initial platinum-based therapy, patients may be switched to another protocol-mandated induction chemotherapy regimen, if judged clinically relevant by the investigator
- If intolerant of the second induction chemotherapy regimen, or if switching to another platinum induction therapy is not possible, the treatment may be continued with only one component of the induction chemotherapy regimen. If treatment is reduced to one component and tolerance improves, then switching to another accepted platinum regimen will be possible if judged clinically relevant by the investigator
- If all options to manage intolerance to the induction chemotherapy are exhausted prior to Cycle 3 Day 1, the patient will discontinue from study treatment. The patient will move directly to the Safety Follow-Up Visit, receive further treatment per institutional standards, and enter the Follow-up Period (see below)

Also during the Induction Period, the patient's tumor and blood samples will be analyzed to generate comprehensive genomic profiles based on the FoundationOne® FMI F1CDx (tissue) test and FoundationOne® F1LCDx (Liquid) test respectively. Results from these analyses will be used to inform treatment decisions during the subsequent Treatment Period (see below).

In exceptional situations, where the genomic profile based on the FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test provides an indication of a non-epithelial tumor, the FoundationOne® team may inform the Sponsor. In this case, the investigator will be contacted and every effort should be made to verify the diagnosis of non-epithelial tumor. If this diagnosis is verified, the patient should be discontinued from the study.

3.1.3 End of Induction Visit

For patients, who reach Cycle 3, the End of Induction Visit will occur between Cycle 3 Day 14 and Day 21 (+3 days).

For patients who progress (PD) before Cycle 3, the End of Induction Visit will take place within 10 days of disease progression assessment.

Patients who permanently discontinue at or before the end of induction will not attend an End of Induction Visit, but instead will move directly to the Safety Follow-Up Visit.

During the End of Induction Visit:

- Response to platinum induction chemotherapy will be evaluated by the investigator according to RECIST v1.1 (Appendix 5) based on disease assessment performed between Cycle 3 Day 7 and the End of Induction Visit (except for patients with documented PD prior to Cycle 3). Based on these results, participants will be grouped into two categories (*Figure 2*):
  - Category 1: Patients with a CR, PR or SD after 3 cycles of platinum induction chemotherapy
  - Category 2: Patients with a documented PD after 3 cycles of platinum induction chemotherapy or at any time during the Induction Period

In exceptional cases, where response according to RECIST v1.1 would be Not Evaluable, the case will be referred to the referent radiologist for adjudication. Patients without a RECIST v1.1 assessment at the End of Induction Visit will discontinue from the study.

- Selected inclusion and exclusion criteria will be re-evaluated in all patients at the End of Induction Visit. This re-evaluation will include:
  - IMP-specific exclusions: to determine whether any IMP-specific restrictions have developed since Day 1, e.g., development of diabetes since start of chemotherapy, etc. Since data from this re-assessment will be used at the MTB to assign treatment (see below), each patient will be re-evaluated for all IMP-specific exclusions at the End of Induction Work-up
  - Re-assessment of general safety criteria: the purpose of this re-assessment is not to limit choice of targeted therapy, but rather to delay start of treatment or elicit a treatment discontinuation if safety criteria are not met

3.1.4 MTB and Randomization

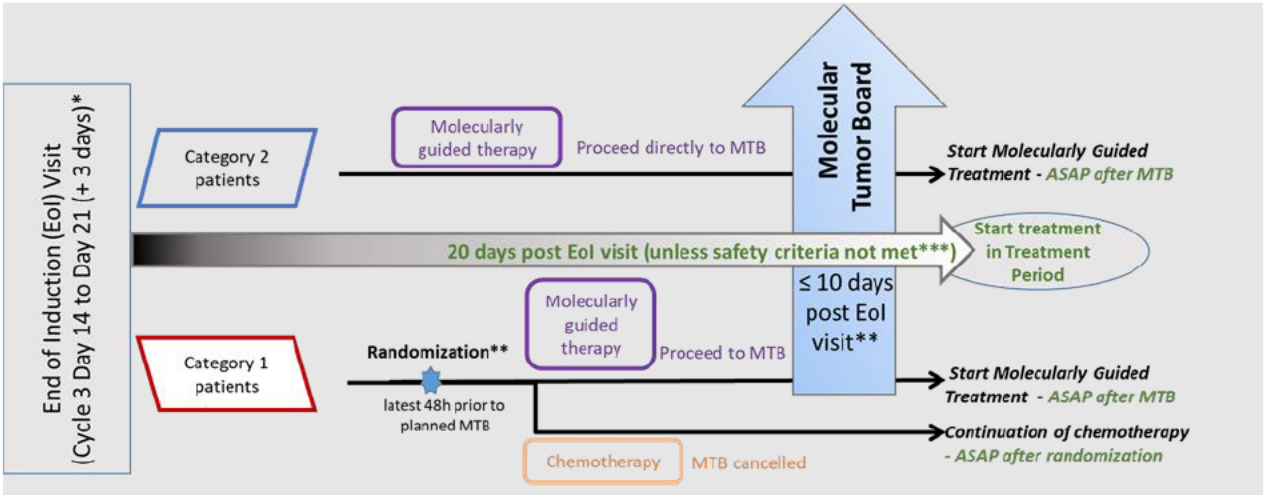
The MTB must be scheduled to take place no later than 10 calendar days after the End of Induction Visit for all patients. The MTB will be cancelled for Category 1 patients randomized to continue chemotherapy.

Randomization (for Category 1 patients only) should occur between the End of Induction Visit and no less than 48 hours before the planned MTB meeting date.

The MTB (for all patients) and randomization (for Category 1 patients) must be delayed after the End of Induction Visit if general safety criteria for entrance into the Treatment Period are not met, however the Sponsor's study team must be informed of the delay. (See below and in Sections 4.1.1.2 and 4.2). If the MTB is delayed, starting treatment in the Treatment Period of the study will be subject to verifying that the general safety criteria for entry into the study are met:

- If the MTB is delayed up to Cycle 3 Day 42 (or until 42 days after Day 1 of the last induction treatment cycle for Category 2 patients who receive less than 3 cycles), only the general safety criteria previously not met will need verifying.
- If the MTB is delayed beyond Cycle 3 Day 42 (or until 42 days after Day 1 of the last induction treatment cycle for Category 2 patients who receive less than 3 cycles), all general safety eligibility criteria must be checked, and if they are still not met, the patient will not be eligible to receive further treatment in the study. Instead, the patient will move directly to the Safety Follow-Up Visit and, then, proceed into the Follow-up Period, where he or she will receive non-IMP treatment outside of the study (see below).

Figure 3 Summary of Events on and Between the End of Induction Visit and the Start of Treatment in the Treatment Period



* If the patient experiences progressive disease before Cycle 3, the End of Induction Visit should occur within 10 days of the disease progression assessment.

** The MTB and randomization should be postponed if any re-assessed general safety eligibility criteria are not met at the End of Induction Visit.

***If start of treatment in the Treatment Period is delayed >42 days post Cycle 3 Day 1 (or 42 days post Day 1 of the last induction cycle for Category 2 patients who receive less than 3 cycles), all general safety criteria must be checked and verified prior to starting treatment in the Treatment period.

If the MTB is delayed to Day 15 or more after the End of Induction Visit, Investigator's judgment will be exercised to determine which tests need repeating prior to the MTB.

3.1.5 Treatment Period

3.1.5.1 Pre-Treatment Work-Up

As the efficacy and safety assessments for the main study endpoints are evaluated from randomization in Category 1 patients (including patients randomized to chemotherapy) and from start of molecularly-guided therapy for Category 2 patients, Treatment Period baseline assessments for efficacy and safety data will be as follows:

Tumor assessments:

- The End of Induction Visit assessment will be used for the Treatment Period baseline tumor assessment.

  In exceptional cases where the interval between end of Induction Period assessments and Day 1 of treatment in the Treatment Period are $>$42 days, tumor assessments would need repeating to ensure reliable baseline tumor assessments

- Investigators will review the CT scans and any other tests used for tumor assessment according to RECIST v1.1 to establish new baseline assessments. The target and non-target lesions chosen for baseline in the Treatment Period may differ from those chosen at baseline for the Induction Period. It is accepted that in patients with complete response and in some patients with partial response at the end of the Induction Period, there will/may not be any measurable lesion
- Physical examination, performance status, vital signs, weight and laboratory results at Day 1 of the first cycle of treatment in the Treatment Period will be used as baseline for the Treatment Period
- Any ongoing AEs from the induction chemotherapy and all concomitant medications will be reported at the End of Induction Visit and reassessed on Day 1 of the Treatment Period

The pre-treatment work-up does not require a dedicated visit, as it combines examinations performed as part of the End of induction Visit and the Cycle 1 Day 1 visit in the Treatment Period.

3.1.5.2 Category 1 Patients: Treatment Assignment and Treatment

The primary and secondary efficacy endpoints will be analyzed exclusively in Category 1 patients. Thus, patients with a CR, PR or SD during the Induction Period will be randomized in a 3:1 ratio to receive either molecularly-guided therapy or to continuation of the same chemotherapy regimen used during induction, respectively (Figure 2).
An assessment cycle will be considered to be 21 days for all treatment arms (including for cohorts with oral therapies), except for cobimetinib and vemurafenib, ipatasertib and paclitaxel, and ivosidenib, where the administration cycle will be 28 days. Administration of therapy will be according to the treatment schedules specified in Section 4.3.

To ensure balanced treatment groups, randomization will be stratified by the following factors:

- Gender
- Response to platinum induction chemotherapy (CR + PR vs. SD)

For patients randomized to the control arm: the chemotherapy will be administered per Section 4.3.4.7 of the protocol.

For patients randomized to the investigational arm, molecularly-guided therapy will be decided based on results from the FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test reports (dependent on availability of one or both) during a virtual Molecular Tumor Board (MTB), consisting of the treating investigator (or their designee), referent pathologist, referent oncologist and FoundationOne® expert (if needed).

A detailed description of the process for assigning molecularly-guided therapy is provided in the Molecular Tumor Board Charter. In brief:

- Specific therapies for potentially actionable alterations in each patient's FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test reports (dependent on availability of one or both) will be categorized for their relevance to treatment decisions in consultation with an experienced FoundationOne® pathologist (if required)
- At the same time, the FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test reports will be shared with the MTB standing members and, if required, will be discussed during preparatory MTB meetings in the absence of the investigator
- At a virtual MTB, the FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test results and relevant patient information (including exclusions criteria for specific targeted therapies) will be reviewed by all members of the MTB, and a patient-specific treatment regimen will be decided upon by the treating investigator in consultation with other board members
- It is expected that choice of molecularly-guided therapies may be ambiguous in some cases. Guidance and rationales for choosing therapy under such circumstances are presented in the Molecular Tumor Board Charter
- After the MTB, the investigator will have 24 hours to finalize the treatment choice, and if different from the MTB recommendations, a new MTB discussion will need to be organized to validate the choice

During the above process, all treatment choices will be made according to the guidance provided in Table 5 and based on exclusions criteria for specific targeted therapies.

Those Category 1 patients who are randomized to the investigational arm will complete Part 2 of the ICF and will then receive one of the molecularly-guided therapies in Table 5 until loss of clinical benefit, unacceptable toxicity, patient or investigator decision to discontinue, or death (whichever occurs first).

For Category 1 patients randomized to the investigational arm and receiving treatment given in combination with chemotherapy, the chemotherapy will be administered per Section 4.3.4.7 of the protocol.

Table 5 Identified Genomic Alterations and Corresponding Molecularly-Guided Therapies

Molecularly-Guided Therapies	Actionable Genomic Alterations
Targeted Therapies	
Alectinib	• ALK, RET fusions or rearrangements
Entrectinib	• NTRK gene fusions, ROS1 rearrangements
Ivosidenib	• IDH1 alterations
Olaparib	• BRCA1, BRCA2 • PALB2 and RAD51B/C/D • gLOH (FMI score 20 or above)
Pemigatinib	• FGFR1, FGFR2 and FGFR3 alterations
Vismodegib	• Inactivating PTCH1, SMO alterations
Erlotinib + bevacizumab	• EGFR alterations
Ipatasertib + paclitaxel	• AKT1, PIK3CA, PTEN
Vemurafenib + cobimetinib	• BRAF V600 alterations, BRAF K601E
Trastuzumab SC + pertuzumab + chemotherapy [a]	• ERBB2/ERBB3 alterations
Immunotherapy	
Atezolizumab	• TMB–High (≥ 16 mutations/Mb) or MSI-High
Atezolizumab + chemotherapy [a]	• TMB–Low or Unknown (< 16 mutations/Mb)
Other Treatment Options	**Potential Rationales for Other Options**
Alternative therapies (Only if the investigator in consultation with the MTB has strong evidence to support a therapy not represented in the investigational treatment arms above)	• Strong suspicion of a primary tumor revealed by comprehensive genomic profiling • Strong rationale for alternative, commercially-available, targeted therapy • Negative predictor of response to anti-PD-1/PD-L1 agents • Patients who do not have a genetic alteration allowing for assignment to a protocol-mandated targeted therapy and who are contraindicated for atezolizumab

TMB = tumor mutational burden; MSI = microsatellite instability.

[a] Platinum-based chemotherapy allowed per protocol (see other Sections for details).

Alternative Therapy arm:

If the investigator and MTB have strong evidence to support a therapy not represented in any of the investigational treatment arms, the investigator can choose to discontinue study treatment and allow the patient to receive an "alternative treatment option." Examples of cases suitable for an alternative treatment option include:

- Patients with a defined treatment path revealed by comprehensive genomic profiling (CGP) (e.g., prostate cancer revealed by CGP)
- Patients who have a strong rationale for an alternative targeted therapy and have access to that alternative (e.g., crizotinib for cancers with MET-amplification)
- Patients not eligible for atezolizumab plus chemotherapy (due to a safety contraindication to atezolizumab), for whom chemotherapy may remain the best treatment option
- Patients with a safety contraindication to the preferred molecularly-guided therapy and/or atezolizumab (at time of randomization) for whom chemotherapy may remain the best treatment option

Patients for whom an alternative therapy is selected by the MTB will go off study treatment. They will be managed per standard of care at their institution and will receive the alternative therapy outside of this study. They will proceed to the Safety Follow-Up Visit and post-treatment follow-up (Refer to Section 3.1.6).

Specific Scenarios:

- Reasons for a report not being generated include, but are not limited to, poor tumor tissue quantity or quality or other technical issues. Patients for whom neither a FoundationOne® FMI F1CDx (tissue) test report nor a FoundationOne® F1LCDx (Liquid) test report could be generated will be discontinued from study treatment at the end of Induction Period. These patients will not be randomized.
- Category 1 patients with a valid result from the FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test reports, but turn out to be ineligible for any molecularly-guided therapy will have the opportunity to receive the control therapy (i.e., the same platinum-based chemotherapy in place at the end of the Induction Period) for a minimum of 3 additional cycles.

Patients who show evidence of clinical benefit after meeting RECIST v1.1 criteria for progressive disease will be permitted to continue treatment with molecularly-guided therapy until loss of clinical benefit, unacceptable toxicity, patient or investigator decision to discontinue, or death (whichever occurs first), if they meet all of the following criteria:

- Evidence of clinical benefit (i.e., in the absence of symptomatic deterioration attributed to disease progression, as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], clinical status, and worsening of laboratory values)
- Absence of unacceptable toxicity

- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions (refer to Section 4.4.1)

Timelines for randomization, selection of treatment and start of treatment are described in Sections 4.2 and 4.3 and in Appendix 2.

3.1.5.3 Category 2 Patients: Treatment Assignment and Treatment

Category 2 patients, i.e., PD after or during 3 cycles of platinum induction chemotherapy, will be assigned molecularly-guided therapy by the investigator in consultation with the MTB, and will receive treatment as described for Category 1 patients, except for continuing induction chemotherapy in case of ineligibility for all molecularly-guided therapies (refer to Section 3.1.5.2).

For Category 2 patients receiving treatment given in combination with chemotherapy will be administered per Section 4.3.4.7 of the protocol.

3.1.6 Follow-Up Period

Following completion or discontinuation of all study treatments, (whether the patient discontinues after the Induction Period or After the Treatment Period), all patients will return to the clinic 30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first) for a Safety Follow-Up Visit.

After the Safety Follow-Up Visit, Patients in the control chemotherapy arm and patients who discontinue treatment for reason other than disease progression (including patient receiving alternative therapy) but who do not withdraw consent to follow-up will be assessed for progression as described during the Treatment Period (including scans) until disease progression per RECIST v1.1 (refer to Section 4.5.6).

Thereafter, all patients will be contacted by the physician by phone for survival status every 3 (±1) months until death, loss to follow-up, withdrawal of consent or end of the study. Data on nature of and response to further anticancer therapies will also be collected during the survival follow-up (refer to Appendix 1 for additional details).

3.1.7 Study Committees

A Steering Committee (SC), guided by a Steering Committee Charter, will be responsible for overseeing the general conduct of the study.

An Eligibility Review Team (ERT), guided by Eligibility Review guidelines, will be responsible for ensuring that patients who enroll in the trial have the correct diagnosis of CUP (following ESMO guidelines) (See Section 3.1.1.1). The ERT will be able to take advice from a referent oncologist, a referent radiologist and a referent pathologist,

as appropriate. In case the ERT cannot confirm a diagnosis of CUP due to an incomplete pre-screening work-up, the ERT will inform the investigator and provide the reason prior to declaring the patient ineligible.

A Molecular Tumor Board (MTB) will provide guidance to the investigator regarding the choice of molecularly-guided therapy. The MTB will be independent of the Sponsor, i.e., the Sponsor will not participate in the MTB meetings nor in the decision-making process. However, if there is a disagreement among MTB members regarding choice of molecularly-guided therapies or safety concerns associated with choice of such agents, the Sponsor should be consulted for advice. MTB members cannot grant any waiver from the protocol in regard to eligibility criteria or mandated study procedures. Further information on the MTB and the MTB process are described in the Molecular Tumor Board Charter.

An independent data monitoring committee (iDMC), guided by an iDMC Charter, will be responsible for evaluating the safety and ongoing efficacy data of trial patients at regular intervals throughout the study. This includes an ongoing evaluation of the benefit-risk balance, based on accumulating safety and, as warranted, efficacy data. The iDMC will make recommendations as to whether cohort recruitment should continue based on ongoing assessments.

If applicable, an Independent Review committee (IRC) may perform a centralized, independent review of images, and other clinical data as needed, prior to the efficacy analyses. IRC membership and procedures would be detailed in an IRC charter (see Section 4.5.6.2 for conditions of centralized independent review implementation).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study will occur when all enrolled patients have either died, withdrawn consent, are lost to follow-up, or have been followed for 18 months after the last study patient is enrolled, whichever occurs first.

If the sufficient number of events for the OS follow-up analysis is not reached (Refer to Section 6.4.2.1 of the protocol) by time of the planned end of the study as defined above, the study will be prolonged until this number is reached.

Recruitment is expected to occur over approximately 52 months. It is therefore estimated that the study will last for a total of approximately 70 months.

The study will be extended for patients still on treatment at the end of the study who do not have access to the IMP(s) outside of the trial as described in Section 4.3.6.

The extension part of the study will end when the last patient discontinues treatment (see Section 4.3.7).

3.3 *DURATION OF PARTICIPATION*

The total duration of study participation for an individual is expected to last until the enrolled patient has either died, withdrawn consent, is lost to follow-up, or has been followed for 18 months after the last study patient has been enrolled, whichever occurs first.

For the patients eligible to the extension part of the study, the duration will be longer and will last until the patient having disease progression or loss of clinical benefit.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Population Selection

The inclusion and exclusion criteria for the study are aimed at specifically selecting patients with poor-prognosis CUP, for whom a likely tissue of origin cannot be posited with the following rational:

- These patients have no customized treatment available, as opposed to patients with favorable prognosis CUP, who should receive the therapy options for their potential equivalent tumor (see Table 2, Section 1.1.1.2). It is therefore acceptable to have poor-prognosis CUP receiving a platinum-based therapy as a reference treatment in the study
- These patients have similar outcomes and constitute a rather homogeneous population, as opposed to favorable prognosis patients, among whom 30%–60% can achieve long-term disease control (see Section 1.1.1.2)
- As the tissue of origin is unknown with no potential equivalent tumor suspected and the disease is inherently heterogeneous, a therapeutic approach based on molecular profiling is particularly relevant (see Section 1.3)

Patients with squamous cell carcinoma have been excluded, as they have a different prognosis from adenocarcinoma and poorly differentiated carcinoma/adenocarcinoma of unknown primary.

3.4.2 Rationale for the Control Group

The control group in this study (Category 1 patients only) will receive 3 cycles of pre-randomization (induction) and at least 3 cycles of post-randomization platinum-based chemotherapy. This regimen is recommended by ESMO for the treatment of patients with CUP (Fizazi et al. 2015) and, hence, reflects current standard of care in this patient population. Although standard practice, superiority of chemotherapy over best supportive care has never been formally demonstrated.

3.4.3 Rationale for Three Cycles of Induction Chemotherapy

Although targeted therapy and immunotherapy may have high potential in CUP patients, effects of molecularly-guided therapy are currently unknown in this setting. In the absence of such data, the Steering Committee deemed that it was in the patient's interest to receive 3 cycles of initial induction therapy followed by a response evaluation,

consistent with ESMO guidelines for CUP, which also recommend 2 to 3 cycles of platinum-based chemotherapy followed by a response evaluation (Fizazi et al. 2015). Generally, a response in CUP patients to front-line platinum-based chemotherapy—if it is going to occur at all—is observed within 3 cycles, so the induction therapy used in this study should again be commensurate with standard of care in the study population.

3.4.4 Rationale for Sub-Dividing the Study Population Into Two Categories of Patients

The primary and secondary efficacy endpoints will be analyzed exclusively in Category 1 patients. Thus, those patients who had a CR, PR, or SD after 3 cycles of induction chemotherapy will be allocated to either molecularly-guided therapy (investigational group) or to more cycles of platinum-based chemotherapy, as recommended by the ESMO guidelines (control group). In effect, then, Study MX39795 will assess whether switching to therapy with targeted agents or cancer immunotherapy is beneficial relative to continuation of standard chemotherapy in Category 1 patients, using a standard randomized and comparative study design.

It is anticipated that a portion of the study population will have progressive disease before or at the end of the Induction Period, i.e., 3 cycles of platinum-based chemotherapy will fail to generate a response or will produce an initial response that is followed by relapse. Since response to chemotherapy is typically observed within 3 cycles for CUP, it is not in the interest of the non-responsive patients to receive additional cycles of the same chemotherapy, especially given the potential efficacy of the accessible, molecularly-guided therapies. Consequently, since they cannot be randomized to control treatment (additional cycles of chemotherapy), patients who have progressive disease following induction chemotherapy will be assigned to a separate group of patients (Category 2) and will receive only targeted therapy or immunotherapy based on their genomic profiles. Lacking a control comparator arm in the trial, or an appropriate historical control in the literature, these Category 2 patients will be analyzed on an exploratory basis.

3.4.5 Rationale for 3:1 Randomization in Category 1 Patients

Based on prior genomic profiling studies, it is estimated that approximately one quarter to one-third of CUP patients randomized to receive molecularly-guided therapy will be actually eligible for molecularly-guided therapy, leading to approximately two-thirds to three-quarters of CUP patients being candidates to receive one of the two cancer immunotherapy treatments. The number of patients in the targeted therapy cohorts will therefore be small.

In order to draw more meaningful conclusions in the individual targeted therapy arms without increasing the overall sample size, Category 1 patients will be randomized in a 3:1 fashion. The higher likelihood of receiving molecularly-guided therapies is also expected to make the study more acceptable to patients and investigators.

3.4.6 Rationale for Progression-Free Survival as the Primary Efficacy Endpoint and Frequency of Tumor Assessments

The primary efficacy endpoint in this study is progression-free survival, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit, and its determination is not generally confounded by subsequent therapies. Consequently, PFS provides an early readout of effect and is ideally suited to early-stage trials in new oncology indications.

Considering the short median progression-free survival (around 5 months) observed in this poor prognosis CUP population (Hainsworth et al. 2015; see Section 6.1), tumor assessments are planned to be done every 9 weeks (equivalent of 3 cycles of most study treatments) in order to accurately assess the primary endpoint of the study (PFS).

3.4.7 Rationale for Combining Data from Different Experimental Treatment Cohorts for the Primary Endpoint Analysis

Results will compare the pooled PFS of the different cohorts of molecularly-guided therapies plus 1 cohort of alternative therapies versus continuation of up to 3 cycles of chemotherapy in patients who exhibited disease control to an initial 3 cycles of platinum-based induction chemotherapy. Therefore, the study has been designed to assess the effects of profiling generally relative to standard chemotherapy, rather than effects within the individual therapy lines. Nonetheless, it is possible that some of the molecularly-guided treatment regimens may have benefit, whereas others may not, so the benefit of individual regimens will also be determined. The increase in statistical power afforded by combining treatment groups also made sense for this early-stage clinical trial in a new indication.

3.4.8 Rationale for Investigational Medicinal Products Doses and Schedules

While none of the IMPs in this study have been approved for CUP, all but ipatasertib have been approved for the treatment of one or more cancer types, while their development programs have included multiple cancer indications (refer to the individual agents' investigator's brochures). Consequently, a large and expanding knowledgebase of PK and safety information is available for each of the test agents in broad populations of cancer patients, allowing for reasonable extrapolation to a CUP population.

The following test agents will be administered as monotherapies: alectinib, atezolizumab (also administered in combination, see below), entrectinib, ivosidenib, olaparib, pemigatinib and vismodegib. All of these medications have been approved (pemigatinib and ivosidenib currently in the US only) for use in different non-CUP cancer indications and will be administered at the same dosages and schedules used in their

currently approved indications, as described in the current investigator's brochures and/or reference safety information for the individual IMPs:

- Alectinib will be administered as recommended for ALK-positive NSCLC in patients with ALK or RET alterations, i.e., at an oral dosage of 600 mg BID until loss of clinical benefit or unacceptable toxicity
- Atezolizumab will be administered as recommended for urinary carcinoma or NSCLC in patients with no actionable alterations and high TMB or MSI-high (also defined as mismatch repair (MMR)-deficient), i.e., as a 1200 mg intravenous infusion over 60 minutes every 3 weeks until loss of clinical benefit or unacceptable toxicity
- Entrectinib will be administered as recommended in its US label for patients with NTRK gene fusions or ROS1 gene rearrangements at an oral dosage of 600 mg QD (three 200-mg capsules per day) until loss of clinical benefit or unacceptable toxicity
- Ivosidenib will be administered as recommended in its US label for patients with newly diagnosed and relapsed or refractory acute myeloid leukemia with a susceptible IDH1 mutation, i.e., at an oral dose of 500 mg QD (with or without food) across a 28-day treatment cycle until loss of clinical benefit or unacceptable toxicity
- Olaparib will be administered until loss of clinical benefit or unacceptable toxicity, as recommended for patients with germline BRCA-mutated advanced ovarian cancer, i.e., at an oral dosage of:
  - 400 mg BID if administered as capsules
  - or 300 mg BID if administered as film-coated tablets
  - Note: After the film-coated tablets are available for use in the study,
    - patients newly randomized should start olaparib treatment with 300 mg BID using film-coated tablets.
    - patients who already started treatment with 400 mg BID using capsules should only switch to 300 mg BID using film-coated tablets, after capsules are not any more available (when the last batch of capsules expires).
- Pemigatinib will be administered as recommended for advanced or metastatic cholangiocarcinoma with FGFR2 fusions or other rearrangements, i.e., at an oral dosage of 13.5 mg QD (given in the morning with water, with or without food) across a 21-day treatment cycle until loss of clinical benefit or unacceptable toxicity. (As described in Appendix A10–11, pemigatinib may be up-titrated to 18 mg QD after one cycle of therapy if the patient does not reach the target serum phosphate level of >5.5 mg/dL at any time during Cycle 1, is compliant with taking study drug and does not experience an ongoing Grade 2 or higher treatment-related AE)
- Vismodegib will be administered as recommended for metastatic basal cell carcinoma in patients with PTCH1 or SMO alterations, i.e., at an oral dosage of 150 mg QD until loss of clinical benefit or unacceptable toxicity

- Patients with AKT1-, PIK3CA- or PTEN-altered tumors will receive the investigational agent ipatasertib either in monotherapy or in combination with paclitaxel or unacceptable toxicity
    - Ipatasertib will be administered as recommended in the current Ipatasertib Investigator's Brochure, i.e., orally at the dose of 400 mg QD on Days 1 to 21 of a 28-day cycle until loss of clinical benefit or unacceptable toxicity
    - Ipatasertib will be administered with paclitaxel at the dose of 80 mg/m^2 IV on Days 1, 8, and 15 for 3 cycles. If relevant and tolerated, it may be continued beyond 3 cycles
    - Patients (both Category 1 or 2) who have contraindications for paclitaxel, or Category 2 patients who were previously treated with paclitaxel, may receive ipatasertib monotherapy without paclitaxel at the discretion of the investigator. Likewise, patients who initiated ipatasertib without paclitaxel, as recommended in earlier versions of this protocol, may continue to receive ipatasertib monotherapy at the investigator's discretion. In all of these cases, single-agent ipatasertib will be administered as recommended in the current Ipatasertib Investigator's Brochure for patients with AKT-, PTEN- or PIK3CA-altered tumors, i.e., at a once-daily dosage of 400 mg across a 21-day treatment cycle
- Patients with BRAF V600 or BRAF K601E mutations will receive vemurafenib/cobimetinib combination therapy. The dosages and schedules for vemurafenib and cobimetinib will be the same as in the FDA- and EMA-approved melanoma indications, as described in the individual investigator's brochures:
    - Vemurafenib will be administered at an oral dosage of 960 mg BID until loss of clinical benefit or unacceptable toxicity
    - Cobimetinib will be administered at an oral dosage of 60 mg QD for the first 21 days of a 28-day treatment cycle until loss of clinical benefit or unacceptable toxicity
- Patients with EGFR alterations will receive erlotinib/bevacizumab combination therapy. The dosages and schedules for erlotinib and bevacizumab will be the same as in the EMA-approved NSCLC indications, as described in their respective *European Medicines Agency* (EMA) Summary of Product Characteristics
    - Erlotinib will be administered at an oral dosage of 150 mg QD (on an empty stomach) until loss of clinical benefit or unacceptable toxicity
    - Bevacizumab will be administered as a 15 mg/kg infusion every 3 weeks until loss of clinical benefit or unacceptable toxicity
- Patients with HER2 alterations will receive trastuzumab SC plus pertuzumab plus platinum-based chemotherapy (same as in the Induction Period) until loss of clinical benefit or unacceptable toxicity. The dosages and schedules for pertuzumab and trastuzumab will be the same as in the EMA-approved breast indications, as described in the individual investigator's brochures.

- The initial loading dose of pertuzumab will be 840 mg administered as a 60 (±10) minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 (±10) minutes. When administered with pertuzumab, the dose of trastuzumab will be 600 mg administered as a subcutaneous injection every 3 weeks. If a dose is missed (i.e., the time between two sequential infusions is 6 weeks or more), a re-loading dose of pertuzumab (840 mg) should be given as described for loading dose

- Patients with no actionable alterations and who are not TMB-high or MSI-high will receive atezolizumab 1200 mg IV every 3 weeks until loss of clinical benefit and platinum-based chemotherapy (same as in the Induction Period) for 3 cycles.
- Patients for whom an alternative therapy is selected by the MTB will go off study treatment. They will be managed per standard of care at their institution and will receive the alternative therapy outside of this study.

Category 1 patients with a valid result from the FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test reports, but turn out to be ineligible for any molecularly-guided therapy will have the opportunity to receive the control therapy, i.e., the same platinum-based chemotherapy in place at the end of the Induction Period, for a minimum of 3 additional cycles.

During the course of study, the protocol might be amended to include new treatment cohorts if additional alterations and corresponding accessible targeted therapies are identified or if new immunotherapies (as monotherapy or in combination) are identified with a rationale to use in CUP patients.

The study will also incorporate a variety of measures to ensure the safety of participants, including emergency medical facilities and staff trained to monitor for and respond to medical emergencies, an iDMC to assess safety signals on an ongoing basis, and protocol-specified drug interruption criteria designed to ensure optimal dosing (Sections 4.6.1 and 5.1.2).

3.4.9 Rationale for Patient-Reported Outcomes

Cancer treatments, particularly combination therapies, can produce significant symptomatic adverse events. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch 2010; Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting adverse event information directly from patients can provide a better understanding of treatment characteristics and their effects.

In order to evaluate the HRQol effects and the health status utility of molecularly-guided therapy in patients with CUP this study will employ the following instruments:

- The Functional Assessment of Cancer Therapy–General (FACT-G) is a widely used measure to assess health-related quality of life in patients undergoing cancer therapy (Cella et al. 1993; Luckett et al. 2011). The current instrument has 27 questions, each answered using a 5-point Likert scale. Questions measure the respondent's health status over the last 7 days in four subscales: Physical Well-Being (7 questions), Social/Family Well-Being (7 questions), Emotional Well-Being (6 questions), and Functional Well-being (7 questions). Scoring involves a simple sum of item scores
- The Hospital Anxiety and Depression Scale (HADS) is a validated self-report questionnaire used to assess patient anxiety and depression in the hospital outpatient-clinic setting (Zigmond and Snaith 1983). The HADS is a fourteen-item scale that generates ordinal data, 7 items relating to anxiety, and 7 relating to depression. This outcome measure was created to avoid reliance on symptoms of anxiety and depression that are also common symptoms of illness, e.g., fatigue, insomnia and hypersomnia. Use of the HADS scale in quantifying psychological distress among cancer patients has been assessed in several recent meta-analyses (Vodermaier and Millman 2011; Yeh et al. 2014; Wakefield et al. 2015)
- The EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L) is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status

PRO data will only be collected in Category 1 patients, i.e., in patients with a CR, PR or SD after 3 cycles of induction chemotherapy who are randomized to investigational therapy or control therapy.

PROs being only analyzed at the time of primary analysis, these questionnaires will not be collected after the clinical cut-off date *(CCOD)* for the primary analysis.

3.4.10 Rationale for Exploratory Biomarker Assessments

Exploratory biomarker assessments in this study might include, but are not limited to, the following:

- PD-L1: Expression of PD-L1 on either tumor or infiltrating immune cells, verified predominantly by immunohistochemistry (IHC) in a variety of tumors, has suggested a role for the PD-1/PD-L1 axis as a prognostic trait and therapeutic target across multiple histotypes. Several clinical studies have reported that PD-L1 overexpression is positively correlated with response to PD-1/PD-L1 targeted therapy in various indications like NSCLC, urothelial bladder cancer or renal cell carcinoma (Zou et al. 2016). Therefore, analyzing PD-L1 might elucidate PD-L1 expression patterns in CUP and correlate expression patterns with response to atezolizumab.
- RNA sequencing: RNA sequencing has changed our ability to explore the molecular mechanisms underlying complex diseases. Analyzing RNA expression will allow comprehensive molecular characterization of the underlying disease and potentially stimulate hypothesis generation on how RNA expression patterns correlate with response to targeted treatment in CUP. Gene expression analysis may also be used to predict the likely primary tumor type and how it may correlate with response to treatment.
- DNA methylation: Genome wide methylation analysis has been shown to improve classification of tumors and has the potential to predict the tissue of origin. Tumor DNA methylation analyses also allows for profiling of DNA copy number alterations (CNAs) which has been proposed as a potential predictive marker. Analyzing tumor DNA methylation profiles may allow for further classification of CUP at multiple molecular levels, assessment of potential primary tumor site and how these signatures might relate treatment response.
- Proteome analysis: Many cancer drugs specifically target proteins. Alterations on the DNA, RNA and methylation levels ultimately affect the abundance and activity of proteins expressed in tumors. Analysis of CNAs has shown relatively strong correlation with mRNA abundance, however variation in mRNA levels has shown to correlate poorly with variation in protein expression. Evolving proteome profiling technologies might help to understand posttranslational modifications of proteins much better in the future and reveal proteins whose genetic information is intact but pathogenic alterations impact functionality of respective proteins (e.g., more stable or more prone to degradation). No data are available on protein modifications and their potential relevance in CUP (Dermawan and Rubin 2020, Hayashi et al. 2020) and therefore it can be important to analyze protein expression directly in both tumor tissue and blood to identify potential predictive and prognostic proteome signatures (Dova et al. 2008).

- Immune cell infiltration: Cancer cells are heterogeneous and dynamic microenvironments that communicate with the immune system, and the immune system context of the tumor microenvironment has been shown to influence the course of the disease. Characterization of immune cell infiltration and quantification of immune cell density indicated that cytotoxic and memory T cells predict clinical outcome (Galon et al. 2006). Immune cells will be characterized (e.g., CD8-positive cells) to better understand the expression patterns in CUP.
- Germline mutation/variants: A previous genome-wide association study on CUP suggested that various germline genes (e.g., LTA4H, TIAM1) may contribute to the risk of CUP (Hemminki et al. 2016). As little is known about germline genetics in CUP, this study might help to increase the understanding of genetic variants.

It is possible that by the time tumor samples are analyzed in this study, additional molecular markers for disease characterization or efficacy correlation will emerge. Thus, during the course of this study, it may become necessary to investigate additional markers associated with disease or target signaling pathways and to reprioritize the above biomarkers.

4. MATERIALS AND METHODS

4.1 PATIENTS

The target sample for this study is 472 randomized patients with CUP who exhibited disease control (CR, PR, or SD) after 3 cycles of platinum induction chemotherapy (Category 1 patients). Assuming a 60% disease control rate at the end of induction and a 15% dropout rate, it is estimated that approximately 790 patients with CUP will need to be enrolled.

If the actual number of patients who achieve a CR, PR, or SD during induction deviates from these estimates, the study will enroll patients until 472 patients have been randomized.

In addition, if both the actual disease control and dropout rates differ from the protocol assumptions, the 330 PFS events may be reached before 790 patients are enrolled. In this case, screening will be stopped, when 330 PFS events have been observed.

4.1.1 General Inclusion Criteria

4.1.1.1 At Study Entry

Prior to eligibility review, as assessed during the Screening Period enrollment and initiation of platinum doublet chemotherapy, patients must meet the following main inclusion criteria for study entry:

- Signed Informed Consent Form
- Able and willing to comply with the study protocol
- Age ≥18 years at time of signing Informed Consent Form
- Histologically-confirmed unresectable CUP diagnosed according to the criteria defined in the 2015 ESMO Clinical Practice Guidelines for CUP (Fizazi et al. 2015). Acceptable disease includes:
  - Adenocarcinoma
  - Poorly differentiated adenocarcinoma
  - Poorly differentiated carcinoma
- Disease should not be amenable to resection and/or irradiation with curative intent during the course of the study
- At least one lesion that is measurable according to RECIST v1.1 (Appendix 5)
  - If a fresh biopsy is needed during Screening, the biopsy procedure must not affect measurability of disease
- Availability of a tumor FFPE block ≤4 months old at the start of screening that is expected to be sufficient and suitable (in quantity and quality) for generation of a comprehensive genomic profile using the FoundationOne® FMI F1CDx (tissue) test at a central reference pathology laboratory (refer to the Laboratory Manual for suitability details and specimen collection instructions)
- Availability of local pathology reports confirming compatibility with CUP diagnosis and the associated slides used for the diagnosis (histology and routine immunohistochemistry compatible with CUP; refer to the Laboratory Manual for details). If the slides used for the local test confirming CUP diagnosis are not available, an FFPE block must be submitted that is sufficient to allow for central confirmation of CUP diagnosis, i.e., performing relevant IHC and ISH if required
  - If the available tumor sample is insufficient or not suitable (in quantity and quality) to enable the above assessments, a fresh biopsy sample must be collected during the Screening Period that meets the study's requirements (refer to the Laboratory Manual for suitability details and specimen collection instructions and to Section 3.1.1 for special circumstances). There is no restriction in the number of repeat biopsies performed locally to obtain a suitable sample for a submission to the central laboratory

- No prior systemic therapy for the treatment of CUP
  - Prior local intratumoral therapy may be accepted. If prior local intratumoral therapy, at least one of the measurable lesion(s) must have not benefited from local intratumoral therapy
  - Patients who have received prior surgery and/or radiotherapy (including radioembolization of tumor) are eligible. If the patient had prior radiotherapy, the measurable lesion(s) must not have been irradiated
  - The last dose of radiotherapy must have been administered at least one week prior to the first dose of study treatment and the patient must have recovered to Grade 1 or less from any toxicity of radiotherapy

    In cases where radiotherapy has been administered for post brain surgery adjuvant treatment or as definitive intervention (e.g., stereotactic radiosurgery) for brain metastases, there must be at least 4 weeks between the end of the radiotherapy and start of study treatment
- ECOG performance status of 0 or 1
- Life expectancy ≥ 12 weeks
- Eligible for platinum-based chemotherapy (according to the reference information for the intended chemotherapy)
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to initiation of study treatment:
  - Absolute neutrophil count (ANC) $\geq 1 \times 10^9$ cells/L (1000/μL) (without granulocyte colony-stimulating factor [G-CSF] support within 2 weeks prior to the first study treatment)
  - Platelet count $\geq 100 \times 10^9$ cells/L (100,000/μL) (without transfusion within 2 weeks prior to the first study treatment)
  - Hemoglobin ≥ 90 g/L (9.0 g/dL)

    Patients may be transfused or receive erythropoietic treatment to meet this criterion
  - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 times the upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN
  - Serum bilirubin $\leq 1.5 \times$ ULN

    Patients with known Gilbert disease who have serum bilirubin $\leq 3 \times$ ULN may be enrolled
  - Creatinine clearance ≥ 30 mL/min (calculated through use of the Cockcroft-Gault formula)

    In patients who receive cisplatin, creatinine clearance must be ≥ 60 mL/min

- For patients not receiving therapeutic anticoagulation: International normalized ratio (INR) or activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN

  Patients receiving heparin treatment should have an aPTT between 1.5 to $2.5 \times$ ULN (or patient value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 to 4 days apart

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception with a failure rate of $< 1\%$ per year during the Induction and Treatment Periods and after the final dose of study treatment for at least:
  - 2 weeks for erlotinib
  - 1 month for ipatasertib and olaparib
  - 5 weeks for entrectinib and pemigatinib
  - 3 months for alectinib and ivosidenib
  - 5 months for atezolizumab
  - 6 months for bevacizumab, cobimetinib, vemurafenib, carboplatin, cisplatin, paclitaxel and gemcitabine
  - 7 months for trastuzumab and pertuzumab
  - 24 months for vismodegib
- Women must refrain from donating eggs during this same period
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations
  - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Hormonal contraceptive methods must be supplemented by a barrier method
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception
  - If required per local guidelines or regulations, locally recognized adequate periods and methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form

- Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to first dose. If the serum pregnancy test is uninterpretable (e.g., beta-HCG is elevated in the absence of other signs of pregnancy), the reason for non-interpretability should be adequately documented, and intra- or extra-uterine pregnancy should be ruled out by ultrasound within 7 days prior to the first administration of study treatment

- For male patients: acceptance that most of the study treatments require specific reliable and effective contraception measures, as well as measures related to sperm donation. This includes agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the Induction and Treatment Periods and after the final dose of study treatment for at least:
    - 2 weeks for erlotinib
    - 1 month for ipatasertib
    - 2 months for vismodegib
    - 3 months for alectinib, olaparib, entrectinib, ivosidenib and pemigatinib
    - 6 months for bevacizumab, cobimetinib, vemurafenib, carboplatin, cisplatin, paclitaxel and gemcitabine
    - 7 months for trastuzumab and pertuzumab
  - Men must refrain from donating sperm during this same period
  - With pregnant female partners, men must remain abstinent or use a condom to avoid exposing the embryo during the Induction and Treatment Periods and for at least:
    - 2 weeks for erlotinib
    - 1 month for ipatasertib
    - 2 months for vismodegib
    - 3 months for alectinib, olaparib, entrectinib, ivosidenib and pemigatinib
    - 6 months for bevacizumab, cobimetinib, vemurafenib, carboplatin, cisplatin, paclitaxel and gemcitabine
    - 7 months for trastuzumab and pertuzumab
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception
  - If required per local guidelines or regulations, locally recognized adequate periods and methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form

4.1.1.2 Prior to Start of Therapy in the Treatment Period

If any of the below criteria are **NOT** met, randomization and/or the MTB will be delayed or study treatment will be discontinued (see Section 3.1.3):

- Head CT or MRI scans must meet the following criteria:
  - Category 1 patients:
    - No change from baseline
  - Category 2 patients:
    - No change from baseline, OR:
    - Asymptomatic brain metastases (if necessary, concomitant treatment to control CNS involvement and/or provide symptom prophylaxis is allowed)
    - Patients who have had a resection of brain metastases by, for example, conventional surgery or stereotactic radiosurgery may continue into the Treatment Period, provided they have recovered from the surgery (see below) and any ongoing symptomatic therapy or prophylaxis is compatible with the treatment-specific exclusion criteria described in Section 4.1.3
- Recovery to Grade $\leq$1 of significant toxicities attributable to induction chemotherapy, with the following exceptions:
  - Alopecia of any grade is allowed
  - Neurosensory toxicity must have recovered to $\leq$Grade 2
  - Laboratory values must be as per inclusion criteria described below
- With the exception of resection of brain metastases by conventional surgery or stereotactic radiosurgery (see prior inclusion criterion), the patient must not have had a major surgical procedure within 2 weeks prior to initiation of the Treatment Period and/or there must be no anticipation of a need for a major surgical procedure during the rest of the study
  - The patient must have recovered from any major surgical procedure that occurred $\geq$2 weeks before initiation of the Treatment Period, including sufficient wound healing, with the following exceptions:

    Patients assigned to erlotinib in combination with bevacizumab, to ipatasertib (in combination with paclitaxel or as monotherapy), or to ivosidenib must have recovered from any major surgical procedure that occurred $\geq$4 weeks before initiation of the Treatment Period, including sufficient wound healing
- No history or known presence of leptomeningeal disease
- ECOG performance status of 0 or 1 for Category 1 patients
- ECOG performance status of 0, 1 or 2 for Category 2 patients

- Adequate hematologic function, defined by the following laboratory results (criteria must be verified and fulfilled prior to first dose in the Treatment Period, but will not delay randomization):
  - ANC $\geq 1.0 \times 10^9$ cells/L (1000/µL) (without granulocyte colony-stimulating [G-CSF] factor support within 2 weeks prior to planned study treatment date)
  - Platelet count $\geq 100 \times 10^9$ cells/L (100,000/µL) (without transfusion within 2 weeks prior to the planned treatment date)
  - Hemoglobin ≥ 90 g/L (9.0 g/dL)

    Patients may be transfused or receive erythropoietic treatment to meet this criterion
- Adequate end-organ function, defined by the following laboratory results:
  - AST and ALT $\leq 2.5 \times$ ULN, with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN
  - Serum bilirubin $\leq 1.5 \times$ ULN

    Patients with known Gilbert disease who have serum bilirubin $\leq 3 \times$ ULN may be randomized (Category 1 patients) or considered for molecularly-guided therapy (Category 2 patients)
  - Creatinine clearance ≥ 30 mL/min (calculated through use of the Cockcroft-Gault formula)

    In patients who receive cisplatin, creatinine clearance must be ≥ 60 mL/min
  - For patients not receiving therapeutic anticoagulation: International normalized ratio (INR) or aPTT $\leq 1.5 \times$ ULN

    Patients receiving heparin treatment should have an aPTT between 1.5 to $2.5 \times$ ULN (or patient value before starting heparin treatment)

    Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 to 4 days apart
- At least 2 weeks between the last dose of radiotherapy administered during the Induction Period and the first dose of study treatment administered during the Treatment Period.
  - Patients must have recovered from all radiation-related toxicities, must not require corticosteroids and must not have had radiation pneumonitis
- Recovery from active infections requiring intravenous antibiotics, with antibiotic therapy ceased for ≥ 7 days prior to planned start of therapy
- Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to the first dose. If the serum pregnancy test is uninterpretable (e.g., beta-HCG is elevated in the absence of other signs of pregnancy), the reason for non-interpretability should be adequately documented, and intra- or extra-uterine pregnancy should be ruled out by ultrasound within 7 days prior to the first administration of study treatment

4.1.2 Main Exclusion Criteria

- Patients who meet any of the following criteria will be excluded from study entry:
- Squamous cell CUP
- Patients with histology and immunohistology profiles (per 2015 ESMO guidelines) that are not adenocarcinoma or poorly differentiated carcinoma/adenocarcinoma), i.e., non-epithelial cancer, extragonadal germ-cell tumor, neuroendocrine tumors, sarcoma, melanoma, mesothelioma, hematologic malignancies (this list is not limitative)
- Patients who can be assigned to a specific subset of CUP for which a specific treatment is recommended by the 2015 ESMO Clinical Practice Guidelines for CUP (Fizazi et al. 2015) or with a clinical and IHC profile indicative of a specific primary tumor are also excluded (favorable prognosis CUP subsets). These are:
    - Poorly differentiated carcinoma with midline distribution
    - Women with papillary adenocarcinoma of the peritoneal cavity
    - Women with adenocarcinoma involving only the axillary lymph nodes
    - Squamous cell carcinoma of the cervical lymph nodes
    - Poorly differentiated neuroendocrine tumors
    - Men with blastic bone metastases and elevated PSA
    - Patients with a single, small, potentially resectable tumor
    - Colon cancer-type CUP with a CK7 negative, CK20 positive, CDX-2 positive immunohistochemistry profile
    - CK7 positive, CK20 negative and TTF-1 positive tumors in a context suggestive of lung adenocarcinoma or thyroid cancer (i.e., with lesions in the lung or thyroid or the lymph nodes in their drainage areas)
    - IHC profile definitely indicative of breast cancer OR an IHC profile indicative of breast cancer and either a history of breast cancer or lymph nodes in the drainage areas of the breast
    - High-grade serous carcinoma histology and elevated CA125 tumor marker and/or a mass in the gynecological tract or any tumor mass or lymph node in the abdominal cavity (i.e., below the diaphragm)
    - IHC profile suggestive of renal cell carcinoma and renal lesions, with a Bosniak classification higher than IIF
    - IHC profile compatible with cholangiocarcinoma or pancreatobiliary (or upper gastrointestinal carcinoma) AND 1 or 2 liver lesions without extrahepatic disease or with only pulmonary metastases and/or lymph nodes in the drainage areas of the liver

Note: For the aforementioned patients, but not limited to them, an escalation to a referent oncologist or radiologist may be required by the study team for adjudication

- Known presence of brain or spinal cord metastasis (including metastases that have been irradiated only), as determined by CT or magnetic resonance imaging (MRI) evaluation during screening
    - Patients who had a complete resection of brain metastases by surgery with or without a combination of stereotactic radiotherapy, whole-brain irradiation or intensity-modulated radiation therapy may be accepted, provided that there were 3 (at maximum) or less metastases resected or treated and that an MRI or high resolution CT scan of the brain not older than 3 months post intervention shows the absence of residual disease at least, no other ongoing brain metastases and no leptomeningeal carcinomatosis. Benign lesions such as meningiomas may be accepted if it can be demonstrated that they may not affect the interpretation of the study results or render the patient at high-risk from treatment complications
- History or known presence of leptomeningeal disease
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis, current alcohol abuse, or cirrhosis
- Human immunodeficiency virus (HIV) infection
- Positive for hepatitis C virus (HCV) antibody at screening
    - If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed. A patient will be excluded from the study only if the HCV antibody and the HCV RNA test are positive. If the HCV antibody test is positive, but the HCV RNA test is negative, the patient may enroll in the study
- Positive for hepatitis B surface antigen (HBsAg) at screening
    - If the HBsAg test is negative but the total hepatitis B core antibody (HBcAb) test is positive, assessment of HBV DNA must be performed. If the resulting HBV DNA test is positive, the patient will be excluded from the study
- Active tuberculosis at screening
- Active infections requiring intravenous antibiotics. If prior infection required IV antibiotic therapy, antibiotic therapy must have ceased ≥ 2 days prior to planned start of study treatment
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia (including active ventricular arrhythmia requiring medication), or unstable angina
- History of malignancy within 5 years prior to initiation of study treatment, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $> 90\%$), such as adequately treated carcinoma in-situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in-situ, or Stage I uterine cancer
- Prior allogeneic stem cell or solid organ transplantation

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high-risk from treatment complications
- Treatment with investigational therapy within 28 days or the equivalent of 5 half-lives (whichever is the longest) prior to initiation of study treatment
- Known allergy or hypersensitivity to any component of the platinum-based chemotherapy
- Pregnant or breastfeeding, or intending to become pregnant during study treatment or for up to 24 months after the final dose of treatment

4.1.3 Exclusion Criteria Specific to Molecularly-Guided Therapies

Details of exclusion criteria described below will be collected prior to study entry and re-assessed at the End of Induction Visit to capture any exclusion criteria that may have developed during the Induction Period. Meeting any of these exclusion criteria will not prevent patients from entering the study, a Category 1 patient from being randomized, or a Category 2 patient from proceeding to study treatment. Rather, if a patient does meet an exclusion criterion for a particular molecularly-guided therapy, then only that specific therapy will be excluded as a choice for this patient. This will be clearly notified to the investigator and the MTB and no patient will be allowed to start treatment with a therapy he/she is not eligible to receive within the study.

4.1.3.1 All Molecularly-Guided Therapies

- Known allergy or hypersensitivity to any component of the molecularly-guided agents
  - This includes history of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins and to Chinese hamster ovary cell products or other recombinant human or humanized antibodies for atezolizumab, bevacizumab, pertuzumab and trastuzumab.

4.1.3.2 All Oral Therapies

- History of malabsorption syndrome, lack of physical integrity of the upper gastrointestinal tract, or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills

4.1.3.3 Alectinib

- Hereditary galactose intolerance, a congenital lactase deficiency or glucose-galactose malabsorption
- Symptomatic bradycardia

4.1.3.4 Vismodegib

- Males unwilling to use condoms (with spermicide, where available), even after a vasectomy, during heterosexual intercourse while being treated with vismodegib, and for 2 months after the final dose (men must refrain from donating sperm during this same period).

4.1.3.5 Ipatasertib in Combination with Paclitaxel (or Ipatasertib Monotherapy in Patients who are not Receiving the Combination)

- Fasting total serum glucose >150 mg/dL
- Glycated hemoglobin (HbA1C) $>7.5\%$
- History of Type I or Type II diabetes mellitus requiring insulin
  - Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment
- Creatinine clearance <50 mL/min (calculated through the use of the Cockcroft-Gault formula)
- Ongoing corticosteroid therapy (use of topical steroids or inhaled steroids is acceptable) or immunosuppressants for a chronic disease
- Active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis)
- With the exception of resection of brain metastases by conventional surgery or stereotactic radiosurgery, the patient must not have had a major surgical procedure within 4 weeks prior to initiation of the Treatment Period and/or there must be no anticipation of a need for a major surgical procedure during the rest of the study
  - The patient must have recovered from any major surgical procedure that occurred ≥ 4 weeks before initiation of the Treatment Period, including sufficient wound healing
  - Patients who have received palliative radiation treatment to peripheral sites (e.g., bone metastases) for pain control and whose last treatment was completed 14 days prior to Day 1 of Cycle 1 may be enrolled in the study if they have recovered from all acute, reversible effects (e.g., resolved to Grade ≤ 1 by enrolment)
  - More guidance on permitted therapies, including palliative radiotherapy, can be found in Section 4.4

4.1.3.6 Ivosidenib

- ANC $\leq 1.5 \times 10^9$ cells/L (1500/μL)
- Creatinine clearance ≤ 50 mL/min (calculated through the use of the Cockcroft-Gault formula)
- Known medical history of progressive multifocal leukoencephalopathy (PML)
- Ongoing treatment with drugs known to be strong cytochrome P450 (CYP) 3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they can be switched to other medications within ≥ 5 half-lives prior to dosing
- Ongoing treatment with P-glycoprotein (P-gp) transporter-sensitive substrate medications with a narrow therapeutic window, unless they can be transferred to other medications within ≥ 5 half-lives prior to administration of study treatment
- LVEF $< 40\%$ by ECHO scan (or by other methods according to institutional practice) obtained within 28 days prior to the start of study treatment
- Heart rate corrected QT interval (using Fridericia's formula) (QTcF) ≥ 450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome). Bundle branch block are permitted
- Concomitant medications that are known to prolong the QT interval, unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing or unless the medications can be properly monitored during the study. (If equivalent medication is not available, QTcF should be closely monitored)
- With the exception of resection of brain metastases by conventional surgery or stereotactic radiosurgery, the patient must not have had a major surgical procedure within 4 weeks prior to initiation of the Treatment Period and/or there must be no anticipation of a need for a major surgical procedure during the rest of the study
    - The patient must have recovered from any major surgical procedure that occurred ≥ 4 weeks before initiation of the Treatment Period, including sufficient wound healing

4.1.3.7 Olaparib

- None

4.1.3.8 Pemigatinib

- Current evidence of clinically significant corneal (including, but not limited to, bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis) or retinal disorder (including, but not limited to, macular/retinal degeneration, diabetic retinopathy, retinal detachment) as confirmed by ophthalmologic examination
- Serum phosphate $>$ ULN
- Serum calcium outside of normal range, or serum-albumin-corrected calcium outside of the normal range when serum albumin is outside of the normal range

- History of calcium and phosphate homeostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues such as the skin, kidney tendon, or vessels due to injury, disease, or aging in the absence of systemic mineral imbalance)
- Use of any potent CYP3A4 inhibitors or inducers or moderate CYP3A4 inducers within 14 days or five half-lives (whichever is longer) before the first dose of pemigatinib
  - Note: Moderate CYP3A4 inhibitors are not prohibited

4.1.3.9 Atezolizumab Monotherapy or in Combination with Platinum-Based Chemotherapy

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, myocarditis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti-phospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 4 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
- Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
- Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for treatment with atezolizumab.
- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for treatment with atezolizumab provided all of following conditions are met:
  - Rash must cover $<$10% of body surface area
  - Disease is well controlled on Day 1 and requires only low-potency topical corticosteroids
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted

- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor–α[TNF-α] agents) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of atezolizumab and during treatment with atezolizumab, with the following exceptions:
    - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy or anti-emetic prophylaxis for chemotherapy) are eligible
    - Patients who received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- In patients who receive concomitant chemotherapy, all criteria for administration of chemotherapy must be verified
- Alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN, with the following exception:
    - Patients with documented liver or bone metastases must have ALP $\leq 5 \times$ ULN
    - Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium ≥ 2.9 mmol/L)

4.1.3.10 Erlotinib in Combination With Bevacizumab

- Poorly controlled hypertension (e.g., systolic > 140 mm Hg or diastolic > 90 mmHg)
- History or evidence of inherited bleeding diathesis or coagulopathy with the risk of bleeding
- History of thrombotic disorders within the last 6 months prior first dose of bevacizumab
- Patients discovered to have $\geq 2+$ proteinuria on dipstick urinalysis at end of induction work-up or at Cycle 1 Day1 assessment should undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours prior to first administration of bevacizumab
- Non-healing wound, active peptic ulcer or bone fracture at Cycle 3 of induction chemotherapy
- History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months of planned study treatment
- Recent pulmonary hemorrhage/hemoptysis ($>$ 1/2 teaspoon red blood)
- Unwillingness to stop smoking and vaping

- With the exception of resection of brain metastases by conventional surgery or stereotactic radiosurgery, the patient must not have had a major surgical procedure within 4 weeks prior to initiation of the Treatment Period and/or there must be no anticipation of a need for a major surgical procedure during the rest of the study
    - The patient must have recovered from any major surgical procedure that occurred ≥ 4 weeks before initiation of the Treatment Period, including sufficient wound healing

4.1.3.11 Vemurafenib in Combination With Cobimetinib

- LVEF below institutional LLN or below 50%, whichever is lower
- QTc > 500 msec at Cycle 3 of induction chemotherapy
- Long QT syndrome
- Uncorrectable electrolyte abnormalities
- Known risk factors for ocular toxicity, consisting of any of the following:
- History of serous retinopathy
- History of retinal vein occlusion (RVO)
- Evidence of ongoing serous retinopathy or RVO at screening
- Any Grade ≥ 3 hemorrhage or bleeding event within 28 days of Day 1 of Cycle 1
- Consumption of foods, supplements, or drugs that are strong or moderate CYP3A4 enzyme inducers or inhibitors at least 7 days prior to Day 1 of Cycle 1 and during study treatment
    - These include St. John's wort or hyperforin (strong CYP3A4 enzyme inducer) and grapefruit juice (strong cytochrome P450 CYP3A4 enzyme inhibitor)
- Poorly controlled hypertension, defined as sustained, uncontrolled, non-episodic baseline hypertension consistently above systolic > 140 mmHg or diastolic > 90 mmHg despite optimal medical management
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction
- Hereditary galactose intolerance, a congenital lactase deficiency or glucose-galactose malabsorption

4.1.3.12 Trastuzumab SC Plus Pertuzumab Plus Platinum-Based Chemotherapy

- Serious cardiac illness or medical conditions including but not confined to:
    - History of documented congestive heart failure or systolic dysfunction (baseline LVEF $< 55\%$ at Cycle 3 of induction chemotherapy, measured by echocardiography or multiple-gated radionuclide angiography (MUGA) scan prior to first dose of trastuzumab)

  - High-risk uncontrolled arrhythmias i.e., atrial tachycardia with a heart rate ≥100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block)
  - Angina pectoris requiring anti-anginal medication
  - Clinically significant valvular heart disease
  - Evidence of transmural infarction on ECG
  - Poorly controlled hypertension (e.g., systolic >140 mmHg or diastolic >90 mmHg)
- Dyspnea at rest or other diseases that require continuous oxygen therapy
- Current chronic daily treatment with corticosteroids (dose >10 mg methylprednisolone or equivalent [excluding inhaled steroids])
- Current severe, uncontrolled systemic disease that may interfere with planned treatment (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders)
- Type 1 or Type 2 diabetes mellitus requiring insulin
  - Patients who are on a stable dose of oral diabetes medication ≥4 weeks prior to initiation of trastuzumab plus pertuzumab may be eligible for treatment. Fasting total serum glucose must be ≤150 mg/dL and glycated hemoglobin (HbA1c) must be ≤7.5% at Cycle 3 of induction chemotherapy
- History of inflammatory bowel disease (e.g., Crohn disease and ulcerative colitis), active bowel inflammation (e.g., diverticulitis)
- In patients who receive concomitant chemotherapy, all criteria for administration of chemotherapy must be verified

4.1.3.13 Entrectinib

- History of prolonged QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds from ECGs performed at least 24 hours apart)
- History of additional risk factors for torsade de pointes (e.g., family history of long QT syndrome)
- History of recent (within 3 months from MTB) symptomatic congestive heart failure or ejection fraction ≤50%
- Known interstitial lung disease, interstitial fibrosis, or history of tyrosine kinase inhibitor-induced pneumonitis
- Peripheral sensory neuropathy Grade ≥2

4.2 METHOD OF TREATMENT ASSIGNMENT

This will be an open-label trial. Following screening and confirmation of the CUP diagnosis by the Eligibility Review Team, approximately 790 eligible patients will receive 3 cycles of standard first-line platinum-based induction chemotherapy (carboplatin/paclitaxel, cisplatin/gemcitabine or carboplatin/gemcitabine). If both the actual disease control and dropout rates differ from the protocol assumptions (see Section 4.1), all patients who are screened before 330 PFS events have been observed and who are eligible for the study, will start the 3 cycles induction chemotherapy.

At the end of the 3 cycles of induction chemotherapy, antitumor response will be evaluated in each patient according to RECIST v1.1 (between Cycle 3 Day 7 and Cycle 3 Day 21). The response assessment must be available at the End of Induction Visit.

- Category 1: It is estimated that approximately 60% of patients will have a CR, PR, or SD at the end of 3 cycles of induction chemotherapy. These patients will be randomly assigned in a 3:1 allocation ratio via a block-stratified randomization procedure to receive either molecularly-guided therapy or additional cycles of the same chemotherapy used during initial induction chemotherapy treatment, respectively. To assist balance, guard against systematic selection bias, and ensure comparability of treatment groups, randomization will be stratified by gender and response to platinum induction chemotherapy (CR+PR vs. SD)
- Category 2: It is estimated that approximately 40% of patients will have PD before or at the end of 3 cycles of the induction chemotherapy. These patients will have the possibility to receive molecularly-guided therapy

Central randomization and drug pack number allocations will be performed and managed by an interactive response system (IxRS); further details provided in the IxRS manual).

Choice of molecularly-guided therapy in Category 1 and Category 2 patients will be determined by the investigator in consultation with the MTB, as described in Section 3.1.

To maintain the scientific integrity of the study and the primary endpoint, genomic profiling results (FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test reports) will only be disclosed to the investigator:

- After randomization for Category 1 patients assigned to molecularly-guided therapy
- Only After disease progression per RECIST v1.1 during the Treatment Period for Category 1 patients randomized to continuing platinum-based chemotherapy
- After disease progression on platinum induction chemotherapy for Category 2 patients

- In exceptional situations during the induction period, where the genomic profile based on the FoundationOne® FMI F1CDx (tissue) test and/or FoundationOne® F1LCDx (Liquid) test provides an indication of a non-epithelial tumor (see Section 3.1.2).

4.3 STUDY TREATMENT

4.3.1 Induction Period

Platinum-based induction chemotherapy will start after the CUP diagnosis and the availability of suitable tumor tissue have been reviewed and confirmed by the Eligibility Review Team.

4.3.2 Treatment Period

Initiation of therapy should occur within 21 calendar days after the End of Induction Visit

If any of the Day 1 of the Treatment Period assessments do not meet safety criteria for starting treatment, study drug administration should be held and the tests repeated (timing of repeat testing should be based on clinical judgement).

IMPs in this study are included in the list below. Appendix 11 identifies all IMPs, auxiliary medicinal products, and non-investigational medicinal products for this study.

- Alectinib
- Atezolizumab
- Entrectinib
- Ivosidenib
- Olaparib
- Pemigatinib
- Vismodegib
- Atezolizumab + platinum-based chemotherapy
- Erlotinib + bevacizumab
- Ipatasertib ± paclitaxel
- Trastuzumab + pertuzumab + platinum-based chemotherapy
- Vemurafenib + cobimetinib
- Carboplatin + paclitaxel
- Cisplatin + gemcitabine
- Carboplatin + gemcitabine
- Paclitaxel + gemcitabine (only after induction and in exceptional circumstances)

Note: Patients for whom an alternative therapy is selected by the MTB will go off study treatment. They will be managed per standard of care at their institution and will receive the alternative therapy outside of this study.

4.3.3 Study Treatment Formulation and Packaging

Alectinib, atezolizumab, bevacizumab, carboplatin, cisplatin, cobimetinib, erlotinib, gemcitabine, ivosidenib, olaparib, paclitaxel, pertuzumab, trastuzumab, vemurafenib and vismodegib will be supplied by the Sponsor as commercially-available formulations. For information on the formulation and packaging of these marketed IMPs, refer to their respective investigator's brochures and/or reference safety information.

Ipatasertib will be supplied as 100- and 200-mg tablets. For information on the formulation and packaging of ipatasertib, refer to the Ipatasertib Investigator's Brochure.

Entrectinib will be supplied as 200-mg hard capsules. For information on the formulation and packaging of entrectinib, refer to the Entrectinib Investigator's Brochure.

Pemigatinib will be supplied as oral 4.5-mg tablets. For information on the formulation and packaging of pemigatinib, refer to the Pemigatinib Investigator's Brochure.

Alternative therapies are not part of study treatment; the patient will be discontinued from study treatment if this option is selected.

4.3.4 Study Treatment Dosage, Administration, and Compliance

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error (for IMPs site administered), overdose, medication error, drug abuse or drug misuse (for IMPs not site administered) along with any associated adverse events should be reported as described in Section 5.3.5.12.

Guidelines for dose reduction and management of specific adverse events, and treatment interruption or discontinuation for patients who experience adverse events, are available as follows (refer to Section 5.1.2 for further detail):

- The subsection of Appendix 10 (IMP-Specific Safety and Administration Information) applicable to the assigned molecularly-guided therapy
- Investigator's brochures for alectinib, atezolizumab, cobimetinib, entrectinib, ipatasertib, ivosidenib, pemigatinib, pertuzumab, trastuzumab, vemurafenib and vismodegib
- EMA Summary of Product Characteristics or local prescribing information for bevacizumab, erlotinib, olaparib, cisplatin, carboplatin, gemcitabine, and paclitaxel

4.3.4.1 Alectinib, Atezolizumab, Entrectinib, Ivosidenib, Olaparib, Pemigatinib and Vismodegib Monotherapy

These treatments will be administered, per results from comprehensive genomic profiling (see Section 3.1 and the Molecular Tumor Board Charter), as recommended in their respective investigator's brochures and/or reference safety information for currently approved (non-CUP) indications. With the exception of entrectinib, none of these agents are approved for the treatment of CUP, although all have been approved for other cancer indications:

- Alectinib will be administered as recommended for ALK-positive NSCLC (i.e., at an oral dosage of 600 mg BID) until loss of clinical benefit or unacceptable toxicity
- Atezolizumab will be administered as recommended for urinary carcinoma or NSCLC, i.e., as a 1200 mg intravenous infusion over 60 minutes every 3 weeks until loss of clinical benefit or unacceptable toxicity
- Entrectinib will be administered as recommended in its US label for patients with NTRK gene fusions or ROS1 gene rearrangements at an oral dosage of 600 mg QD (three 200-mg capsules per day) until loss of clinical benefit or unacceptable toxicity
- Ivosidenib will be administered as recommended in its US label for patients with newly-diagnosed or relapsed/refractory acute myeloid leukemia with a susceptible IDH1 mutation, i.e., at an oral dose of 500 mg QD (with or without food) across a 28-day treatment cycle until loss of clinical benefit or unacceptable toxicity
- Olaparib will be administered until loss of clinical benefit or unacceptable toxicity, as recommended for patients with germline BRCA-mutated advanced ovarian cancer, i.e., at an oral dosage of:
  - 400 mg BID if administered as capsules
  - or 300 mg BID if administered as film-coated tablets

    Note: After the film-coated tablets are available for use in the study,

    - patients newly randomized should start olaparib treatment with 300 mg BID using film-coated tablets.
    - patients who already started treatment with 400 mg BID using capsules should only switch to 300 mg BID using film-coated tablets, after capsules are not any more available (when the last batch of capsules expires).
- Pemigatinib will be administered as recommended for advanced or metastatic cholangiocarcinoma with FGFR2 fusions or other rearrangements, i.e., at an oral dosage of 13.5 mg QD (given in the morning with water, with or without food) across a 21-day treatment cycle until loss of clinical benefit or unacceptable toxicity. (As described in Appendix A10–11, pemigatinib may be up-titrated to 18 mg QD after one cycle of therapy if the patient does not reach the target serum phosphate level of $>$5.5 mg/dL at any time during Cycle 1, is compliant with taking study drug, and does not experience an ongoing Grade 2 or higher treatment-related AE)

- Vismodegib will be administered as recommended for metastatic basal cell carcinoma, i.e., at an oral dosage of 150 mg QD until loss of clinical benefit or unacceptable toxicity

Dosage modification, treatment interruption, and treatment discontinuation guidelines for alectinib, atezolizumab, entrectinib, ivosidenib, olaparib, pemigatinib and vismodegib are provided in their respective investigator's brochures and/or reference safety information. Summaries are provided in Appendices A10–1, A10–2, A10–5, A10–9, A10–10, A10–11 and A10–14, respectively.

4.3.4.2 Erlotinib/Bevacizumab Combination Therapy

Erlotinib plus bevacizumab will be administered in patients with EGFR alterations (see Section 3.1). While neither of these agents are approved for the treatment of CUP, the combination has been approved by the EMA in patients with advanced EGFR-positive NSCLC.

Erlotinib and bevacizumab will be administered as recommended in their respective EMA Summary of Product Characteristics for advanced NSCLC:

- Erlotinib will be administered at an oral dosage of 150 mg QD (on an empty stomach) until loss of clinical benefit or unacceptable toxicity
- Bevacizumab will be administered as a 15 mg/kg Q3W intravenous infusion until loss of clinical benefit or unacceptable toxicity

Dosage modification, treatment interruption, and treatment discontinuation guidelines for erlotinib and bevacizumab are provided in their respective reference safety information. Summaries are provided in Appendices A10–6 and A10–3, respectively.

In exceptional cases of patients with a contraindication to bevacizumab but not to erlotinib, erlotinib may be administered as a monotherapy.

4.3.4.3 Ipatasertib/Paclitaxel Combination Therapy

The investigational therapy ipatasertib plus paclitaxel will be administered in patients with AKT1, PTEN or PIK3CA alterations (see Section 3.1).

Ipatasertib will be administered as recommended in the current Ipatasertib Investigator's Brochure for patients with AKT-, PIK3CA- or PTEN-altered tumors, i.e., at an oral once-daily dosage of 400 mg. In combination with paclitaxel, the dosages and schedule of administration will be:

- Ipatasertib will be administered orally at a dose of 400 mg QD on Days 1 to 21 of a 28-day cycle (21 days "on", 7 days "off") until loss of clinical benefit or unacceptable toxicity. Ipatasertib will continue to be dosed as a monotherapy with the same schedule after the final administration of paclitaxel (see next bullet) until loss of clinical benefit or unacceptable toxicity

- Paclitaxel will be administered at a dose of 80 mg/m^2 IV over 1 hour on Days 1, 8, and 15 of a 28-day cycle. If the dose on Day 1, 8, or 15 is missed, it can be given on Day 22. Paclitaxel will be given for 3 cycles. If tolerated, it may be continued beyond 3 cycles (refer to Section 4.3.4.7)

Note: Ipatasertib should be administered before paclitaxel on days when patients receive both medications.

Dosage modification, treatment interruption, and treatment discontinuation guidelines for ipatasertib are provided in the Ipatasertib Investigator's Brochure. A summary of dose reductions, interruptions and discontinuation for ipatasertib and paclitaxel in combination is provided in Appendix A10–8.

Any patient who started ipatasertib monotherapy under Versions 2–5 of the protocol can be switched to ipatasertib combined with paclitaxel if judged clinically appropriate by the investigator and accepted by the patient.

Patients (both Category 1 or 2) who have contraindications for paclitaxel, or Category 2 patients who were previously treated with paclitaxel, may receive ipatasertib monotherapy without paclitaxel at the discretion of the investigator. Likewise, patients who initiated ipatasertib without paclitaxel, as recommended in earlier versions of this protocol, may continue to receive ipatasertib monotherapy at the investigator's discretion. In all of these cases, single-agent ipatasertib will be administered as recommended in the current Ipatasertib Investigator's Brochure for patients with AKT-, PTEN-, or PIK3CA-altered tumors, i.e., at a once-daily dosage of 400 mg across a 21-day treatment cycle.

4.3.4.4 Vemurafenib/Cobimetinib Combination Therapy

Vemurafenib plus cobimetinib will be administered in patients with BRAF mutations (see Section 3.1). While neither of these agents are approved for the treatment of CUP, the combination has been approved by the FDA in patients with advanced BRAF-positive melanoma.

Vemurafenib and cobimetinib will be administered as recommended in their respective investigator's brochures for advanced melanoma:

- Vemurafenib will be administered at an oral dosage of 960 mg BID until loss of clinical benefit or unacceptable toxicity
- Cobimetinib will be administered at an oral dosage of 60 mg QD for the first 21 days of a 28-day treatment cycle until loss of clinical benefit or unacceptable toxicity

Dosage modification, treatment interruption, and treatment discontinuation guidelines for vemurafenib and cobimetinib are provided in their respective investigator's brochures and/or reference safety information. Summaries are provided in Appendices A10–13 and A10–4, respectively.

In exceptional cases of patients with a contraindication to cobimetinib but not to vemurafenib, vemurafenib may be administered as monotherapy.

4.3.4.5 Trastuzumab/Pertuzumab/Platinum-Based Chemotherapy Combination

Trastuzumab SC plus pertuzumab plus platinum-based chemotherapy will be administered in patients with HER2 alterations.

While neither trastuzumab SC nor pertuzumab are approved for the treatment of CUP, the combination has been approved by the EMA in metastatic breast cancer patients with HER2 alterations, while the combination of trastuzumab, pertuzumab and chemotherapy has been approved by the EMA for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high-risk of recurrence.

Trastuzumab SC and pertuzumab will be administered as recommended in their respective investigator's brochures and/or reference safety information for advanced breast cancer with HER2 alterations:

- Pertuzumab: Initial loading dose of 840 mg administered as a 60-minute IV infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes. An observation period of 30–60 minutes is recommended after completion of each pertuzumab infusion. If a dose is delayed (i.e., the time between two sequential infusions is less than 6 weeks), the 420-mg dose of pertuzumab should be administered. If a dose is missed (i.e., the time between two sequential infusions is 6 weeks or more), a re-loading dose of pertuzumab (840 mg) should be given as described for a loading dose
- Trastuzumab: 600 mg fixed dose SC injection every 3 weeks
- Chemotherapy will be administered for a minimum of 3 additional cycles. If relevant and tolerated, the chemotherapy may be continued beyond 3 cycles with one or both drugs. Refer to Section 4.3.4.7 for details

Dosage modification, treatment interruption, and treatment discontinuation guidelines for pertuzumab and trastuzumab are provided in their respective investigator's brochures. A summary is provided in Appendix A10–12.

4.3.4.6 Atezolizumab/Platinum-Based Chemotherapy Combination

Atezolizumab plus platinum-based chemotherapy will be administered in patients with no actionable alterations and who are not TMB high or MSI-high.

The combination of atezolizumab and a platinum-based chemotherapy has been investigated in several clinical trials, including a Phase 3 study (NCT02807636) assessing the combination of atezolizumab with gemcitabine and cisplatin or carboplatin, and a Phase 3 study (NCT02367794) assessing the combination of atezolizumab with carboplatin and paclitaxel.

Atezolizumab will be administered as recommended in its investigator's brochure and/or reference safety information for urinary carcinoma or NSCLC:

- Atezolizumab: 1200 mg IV infusion over 60 minutes every 3 weeks
- Chemotherapy will be administered for a minimum of 3 additional cycles. If relevant and tolerated, the chemotherapy may be continued beyond 3 cycles with one or both drugs. Refer to Section 4.3.4.7 for details

Dosage modification, treatment interruption, and treatment discontinuation guidelines for atezolizumab are provided in the Atezolizumab Investigator's Brochure. A summary is provided in Appendix A10–2.

4.3.4.7 Platinum-Based Chemotherapy

All patients in this study will initially receive 3 cycles of platinum-based induction chemotherapy.

Three platinum-based chemotherapy regimens will be permitted in this study:

- Carboplatin/paclitaxel:
  - Paclitaxel 175 mg/m^2 + carboplatin AUC 5–6 on Day 1 of a 3-week cycle, monitoring for neurotoxicity (Fizazi et al. 2015).
  - Carboplatin AUC dose will be calculated by the Calvert formula (http://reference.medscape.com/calculator/carboplatin-auc-dose-calvert) (Calvert et al. 1989)
- Cisplatin/gemcitabine:
  - Cisplatin 60–75 mg/m^2 on Day 1
  - Gemcitabine 1000 mg/m^2 on Day 1 and Day 8 of a 3-week cycle, ensuring adequate hydration (Fizazi et al. 2015)

- Carboplatin/gemcitabine:
  - Gemcitabine 1000 mg/m^2 on Day 1 and Day 8 with carboplatin AUC 5–6 on Day 1 of a 3-week cycle (Pittman et al. 2006)
  - Carboplatin AUC dose will be calculated by the Calvert formula (http://reference.medscape.com/calculator/carboplatin-auc-dose-calvert) (Calvert et al. 1989)

The carboplatin/paclitaxel or cisplatin/gemcitabine regimens may be administered using weekly schedules as follows:

- Paclitaxel 60 mg/m^2 with carboplatin AUC 2 mg/mL every week for 9 weeks (equivalent to 3 cycles of 21 days) (Pignata et al. 2014)
- Carboplatin AUC dose will be calculated by the Calvert formula
- Cisplatin 25 mg/m² on Day 1 and Day 8 with gemcitabine 1000 mg/m² on Day 1 and Day 8 of a 3-week cycle, ensuring adequate hydration (Valle et al. 2010)

The following alternative regimen may be administered as follows (Albers et al. 2011):

- Paclitaxel: 175 mg/m^2 on Day 1 only
- Gemcitabine: 1000 mg/m^2 on Day 1 and 8

This regimen is only possible after the Induction Period, in exceptional circumstances, if the patient has contraindication to platinum-based regimens, and in association with either trastuzumab + pertuzumab or atezolizumab (not allowed for patients in the chemotherapy arm).

If an investigating site typically uses slightly different dosages or schedule of administration for a chemotherapy regimen authorized in the study (carboplatin/paclitaxel, cisplatin/gemcitabine, carboplatin/gemcitabine or paclitaxel/gemcitabine), the local regimen may be used if sufficiently close to the regimen described in the protocol (similar dose intensity and similar efficacy and safety profiles). The regimen will be used for all patients at a given site, except for management of intolerance as described in Section 3.1.2.

For Category 1 patients (randomized to the control arm, or randomized to the investigational arm and receiving treatment given in combination with chemotherapy), the same chemotherapy regimen in place at the end of the Induction Period will be continued for a minimum of 3 additional cycles:

- In exceptional circumstances, the chemotherapy may be changed, but only upon the recommendation of the MTB. Such changes in chemotherapy will be limited to the chemotherapy regimens allowed per protocol, or to any of their individual components used as single agents
- Any intolerance to the chemotherapy will be managed similarly to intolerance during the Induction Period

- After completion of 3 additional cycles, if relevant and tolerated, one of the components of the platinum-doublet therapy may be removed, and the single remaining agent may be continued beyond 3 cycles
- In selected cases, where the local practice is to give more than 6 cycles of chemotherapy for the treatment of CUP, 3 or more additional cycles of chemotherapy (same regimen as used for prior cycles, unless change is required for management of intolerance; see Section 3.1.2) may be administered, if tolerated and there is no disease progression per RECIST v1.1

For Category 2 patients receiving treatment given in combination with chemotherapy, the chemotherapy regimen in place at the end of the Induction Period may be switched to another chemotherapy regimen or continued for a minimum of 3 additional cycles. Such changes in chemotherapy regimen must be limited to the chemotherapy regimens allowed per protocol, or to any of their individual components used as single agents.

- Any intolerance to the chemotherapy will be managed similarly to intolerance during the Induction Period
- After completion of 3 additional cycles, if relevant and tolerated, one of the components of the platinum-doublet therapy may be removed, and the single remaining agent may be continued beyond 3 cycles
- In selected cases, where the local practice is to give more than 6 cycles of chemotherapy for the treatment of CUP, 3 or more additional cycles of chemotherapy (same regimen as used for prior cycles, unless change is required for management of intolerance; see Section 3.1.2) may be administered, if tolerated and there is no disease progression per RECIST v1.1

Dosage modification, treatment interruption, and treatment discontinuation guidelines for cisplatin, carboplatin, gemcitabine and paclitaxel are indicated in their respective reference information. This includes any dose or schedule adjustments at baseline that are suggested for elderly patients or any special population.

4.3.4.8 Alternative Therapy

Patients for whom an alternative therapy is selected by the MTB will go off study treatment. They will be managed per standard of care at their institution and will receive the alternative therapy outside of this study. They will proceed to the Safety Follow-Up Visit and post treatment Follow-up Period (Refer to Section 3.1.6).

4.3.5 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the Investigator's Brochure and/or or local prescribing information of each given IMP for information on IMP handling, including preparation and storage, and accountability.

4.3.6 Continued Access to Investigational Medicinal Products

After study discontinuation, the Sponsor will offer continued access to study drugs (alectinib, atezolizumab, bevacizumab, cobimetinib, entrectinib, erlotinib, ipatasertib, ivosidenib, olaparib, pemigatinib, pertuzumab, trastuzumab, vemurafenib and vismodegib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below. Access will only be given to the IMP/IMPs the patient was receiving in the study *with exception of the chemotherapy agents*.

A patient will be eligible to receive study drugs after completing the study if all of the following conditions are met:

- *The participant received any of the above listed IMPs during study conduct.*
- The patient has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.
- Treatment with study drug/drugs has not been discontinued.

Eligible participants will be provided access to Roche IMPs for up to a maximum of 24 months after entering in the extension phase of the study unless mandated otherwise by local regulations. Treatment will need to be discontinued in the event of disease progression or loss of clinical benefit.

A patient will not be eligible to receive study drugs after completing the study if any of the following conditions are met:

- *The participant was assigned to a chemotherapy treatment arm that did not include a Roche IMP during study conduct.*
- The Sponsor study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the drug or data suggest that the drug is not effective for cancer of unknown primary site.
- The Sponsor has reasonable safety concerns regarding the drug as treatment for cancer of unknown primary site.
- Provision of the drug is not permitted under the laws and regulations of the patient's country.
- *The Roche IMP is no longer manufactured.*

In these situations, the investigator and primary care physician will transition the study participant to an alternative therapy in accordance with institutional or local guidelines.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/policy_continued_access_to_investigational_medicines.pdf

4.3.7 *Extension Part of the Study*

Patients still on treatment at the end of the study who do not have access to the IMP(s) outside of the trial will remain in the study and will continue receiving the IMP(s) in a study extension part (see Section 4.3.6).

Patients will continue to be treated per protocol Section 4.3.4 and managed per the schedule of assessment in Appendix A1–1 until disease progression or loss of clinical benefit. Once the patient stops treatment, a safety follow-up visit is to be performed and this will be the final visit of the study.

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until the Safety Follow-Up Visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF according to the rules described in Section 4.5.2.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Vaccinations (such as influenza, COVID-19) are allowed during the course of this study while live, attenuated vaccines are prohibited (Section 4.3.3). SARS-CoV-2 vaccines should be administered in accordance with the approved vaccine label
- Oral contraceptives with a failure rate of $<1\%$ per year
- Hormone-replacement therapy
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain), that does not interfere with the assessment of tumor target lesions, as outlined below:
  - At any time during platinum-based induction chemotherapy, providing that the lesion to be irradiated is not a target lesion
  - After Cycle 3 of study treatment in the Treatment Period for Category 1 patients, providing that the lesion to be irradiated is not the only target lesion
  - At any time as soon as the patient has been assessed as Category 2

    There must be a 2-weeks interval between the last dose of palliative radiotherapy administered during the Induction Period and the first dose of study treatment administered during the Treatment Period. Patients must have recovered from all radiation-related toxicities, must not require corticosteroids and must not have had radiation pneumonitis

    Study drug treatment may be continued during palliative radiotherapy unless radiotherapy is part of the prohibited therapy for a specific IMP (see Appendix 10). Treatment with ipatasertib and entrectinib should be temporarily held before and after radiotherapy treatment. Please refer to the corresponding Appendix 10 for dose interruptions and specific measures for a specific IMP

- Local therapy (e.g., surgery, stereotactic radiosurgery, radiofrequency ablation) as outlined below:

  After disease progression has been reached, patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment at the investigator's discretion. These patients may then receive local therapy directed at a target lesion. Local therapy is not permitted until disease progression

- Bone-sparing agents (e.g., bisphosphonates) for palliation of bone metastases or for the treatment of osteoporosis/osteopenia are allowed
- Prophylactic use of G-CSF or initiation of erythropoietin may be instituted according to the American Society of Clinical Oncology guidelines in patients who are having difficulty with severe neutropenia or anemia.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator.

Guidelines for use of premedications are described in the respective investigator's brochures for each IMP and are summarized in Appendix 10 (if any). In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

Medications to be administered with precaution due to effects related to cytochrome P450 enzymes as well as to other potential drug interactions are presented in the individual investigator's brochures and summarized in Appendix 10 for each IMP. It is the responsibility of the investigator to identify potential drug interactions.

Treatment with strong CYP inhibitors or strong CYP inducers is to be excluded for some IMPs. It is the responsibility of the investigator to verify that none of a patient's long-term therapies are contraindicated when co-administered with a potential IMP and to communicate all contraindications at the time of the MTB.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer, with the exception of those prohibited for a specific IMP (see Section 4.4.3), may be used during the study at the discretion of the investigator.

4.4.2.3 Medications Given with Precaution Due to Potential Additive Nephrotoxicity and Ototoxicity with Platinum-Based Chemotherapy

Concomitant administration of nephrotoxic (e.g., cephalosporins, aminoglycosides, amphotericin B or contrast media) or ototoxic (e.g., aminoglycosides) medicinal products will potentiate the toxic effect of cisplatin or carboplatin on the kidneys and the auditory system and should be used with caution with platinum-based chemotherapy.

4.4.2.4 Medications Given with Precaution with Atezolizumab

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix A10–2 for details).

4.4.2.5 Medications Given with Precaution with Ipatasertib

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events (refer to Appendix A10–7 and A10–8 for details). Ipatasertib treatment should be temporarily held during systemic corticosteroids treatment.

4.4.2.6 Medications Given with Precaution with Entrectinib

Use of concomitant medications that increase or possibly increase the risk of QTc prolongation and/or induce torsades de pointes ventricular arrhythmia, congestive heart failure, syncope and cognitive disturbances (See Appendix A10–5 for details) must be used with caution or avoided if possible during treatment with entrectinib

Entrectinib should be administered with caution with cytochrome P450 enzyme-specific substrates:

CYP450 Enzyme	Sensitive Substrates	Substrates with Narrow Therapeutic Ranges
CYP2C9	Celecoxib	Warfarin
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine, pimozide
CYP3A4	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus

4.4.2.7 Medications Given with Precaution with Pemigatinib

Pemigatinib is predominantly metabolized by CYP3A4. The use of moderate CYP3A4 inhibitors is not prohibited but should involve careful monitoring, especially in relation to safety, while moderate CYP3A4 inducers and potent CYP3A4 inhibitors and inducers are prohibited (see Section 4.4.3).

Careful monitoring is required when pemigatinib is concomitantly administered with OCT2 substrates, such as dofetilide and metformin.

Proton pump inhibitors (PPIs) should be avoided with pemigatinib.

Close clinical surveillance is recommended when pemigatinib is administered with CYP2B6 substrates (e.g., methadone, efavirenz).

Co-administration of pemigatinib with P-gp substrates (e.g., digoxin, dabigatran, colchicine) may increase their exposure and thus their toxicity. Pemigatinib administration should be separated by at least 6 hours before or after administration of P-gp substrates with a narrow therapeutic index.

4.4.2.8 Medications Given with Precaution with Ivosidenib

Cytochrome P450 (CYP)-phenotyping of ivosidenib metabolism performed in human liver microsomes and recombinant CYP enzymes suggest that CYP3A4 played a major role in the oxidative metabolism of ivosidenib, while other CYP enzymes such as CYP2B6 and CYP2C8 play a minor role.

Ivosidenib induced CYP2B6, CYP2C8, CYP2C9, and CYP3A4 but not CYP1A2 in cultured human hepatocytes, and therefore, there is the possibility of drug–drug interactions upon co-administration with sensitive substrates of CYP2B6, CYP2C8, CYP2C9 and CYP3A4/5.

Co-administration will decrease concentrations of drugs that are sensitive CYP3A4 substrates and may decrease concentrations of drugs that are sensitive CYP2C9. Use alternative therapies that are not sensitive substrates of CYP3A4 and CYP2C9 during ivosidenib treatment.

Do not administer ivosidenib with itraconazole or ketoconazole (CYP3A4 substrates) due to expected loss of antifungal efficacy.

Co-administration of ivosidenib may decrease the concentrations of hormonal contraceptives, consider alternative methods of contraception in patients receiving ivosidenib.

If co-administration of ivosidenib with sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs.

Caution should be used in case of co-administration of ivosidenib with sensitive substrates of CYP2B6, CYP2C8.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited for all treatment arms as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 4 weeks prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, surgery [including radiofrequency ablation and stereotactic radiosurgery], chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy) is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2 and Appendix 10), and during study treatment, until disease progression is documented and the patient has discontinued study treatment with the exception of palliative radiotherapy under certain circumstances (see Section 4.4.1 for details).

- Live, attenuated vaccine:
  - Within 4 weeks prior to planned date for start of molecularly-guided therapy (this restriction is preventive, i.e., it is not designed to delay start of treatment; rather, this restriction is included in case a patient is subsequently found to be a candidate for an IMP that cannot be administered in combination with a live vaccine). If the selected therapies are atezolizumab or paclitaxel, carboplatin, cisplatin or gemcitabine and a live attenuated vaccine has been administered, start of treatment will be withheld until 4 weeks after the administration of the vaccine. Other therapies may start without waiting until the 4-week interval has elapsed
  - At any time during the study treatment and within 5 months after the final dose of atezolizumab
  - During study treatment for entrectinib
  - At any time during the study treatment for paclitaxel-, carboplatin-, cisplatin- or gemcitabine-containing regimens, and within 3 months after the final dose of paclitaxel, carboplatin, cisplatin, or gemcitabine
- St John's wort (Hypericum perforatum)

  At any time during study treatment with vismodegib, entrectinib or pemigatinib
- Concomitant use of moderate to strong CYP3A inhibitor and inducer medications should be avoided. This includes:

Strong Inhibitors	**Strong Inducers**
Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus

- Enzyme-Inducing Anti-Epileptic Drugs (EIAEDs) are prohibited with entrectinib
  - Carbamazepine
  - Oxcarbazepine
  - Phenytoin
  - Fosphenytoin
  - Phenobarbital
  - Primidone
- Calcium-based phosphate–binding medications are prohibited with pemigatinib, due to a concern for soft tissue mineralization. Soft tissue mineralization, including cutaneous calcification and calcinosis, may be associated with hyperphosphatemia and has been observed with pemigatinib.

- Potent CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers are prohibited with pemigatinib.
- Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.

Therapies prohibited for specific IMPs are described in the respective investigator's brochures for each IMP and summarized in Appendix 10 in subsections Prohibited Therapies and Drug Interactions.

4.4.4 Prohibited Food

Use of the following foods is prohibited as described below:

- Consumption of grapefruit or grapefruit juice, Seville oranges, pomelos, exotic citrus fruits, grapefruit hybrids or fruit juices is prohibited for 7 days before the start of the study until 30 days after the final dose of study treatment
- Patients assigned to ivosidenib or pemigatinib treatments should also refrain from consumption of red wine for 7 days before the start of study treatment until 30 days after the final dose of study treatment (see Appendices A10–9 and A10–11)
- Foods prohibited for specific IMPs are described in the respective investigator's brochures and summarized in Appendix 10

4.4.5 Additional Restrictions

Patients should not donate blood while taking vismodegib and for 24 months after the final dose.

Additional restrictions prohibited for specific IMPs are described in the respective investigator's brochures and summarized in Appendix 10.

4.5 STUDY ASSESSMENTS

A Schedule of Activities to be performed during the study is provided in Appendix 1. A timeline of key study events is summarized in Appendix 2 and further described in Section 3.1.

All activities should be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. An Eligibility Review Team (ERT), guided by Eligibility Review guidelines, will be responsible for ensuring that patients who enroll in the trial have the correct diagnosis of CUP (following ESMO guidelines). The Eligibility Review Team will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

This study will have a two-part consent process. All patients must complete Part 1 of the ICF during the Screening Period and the RBR informed consent (RBR ICF). Since the molecularly-guided therapy that will eventually be assigned to a patient is unknown at this time, Part 1 of the ICF will cover all aspects of the trial except for information related to any specific molecularly-guided therapies. Prior to post-induction study treatment, Category 1 patients who are randomized to molecularly-guided therapy, as well as all Category 2 patients, must then complete Part 2 of the ICF. Part 2 of the ICF will provide information related to the specific molecularly-guided therapy assigned to an individual patient (e.g., identified targetable alteration, background on selected agent, and tolerability profile). Category 1 patients who are randomized to 3 more cycles of chemotherapy will not have to complete Part 2 of the ICF.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including smoking history, clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and reproductive status, will be recorded during screening. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) will be recorded according to the following guidelines:

- At Screening: Any medications used by the patient within 7 days prior to initiation of study drug should be documented
- During the Induction Period: Only the medications related to the captured adverse reactions and changes to medications existing at baseline should be collected (see Section 5.2.1 for a detail of collected adverse reactions)
- At the End of Induction Visit: All ongoing medications should be collected (to allow for an appropriate assessment of the general inclusion criteria in the Treatment Period and to comply with the re-baselining activities at the start of the Treatment Period)
- At Subsequent Visits (During the Treatment Period): Changes to current medications or medications used since the last documentation of medications should be recorded

At the time of each follow-up physical examination, an interval medical history (to capture new adverse events) should also be obtained.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity will be collected (if allowed per local regulation) to allow for the assessment of potential racial or regional differences in responses or tolerance of treatment (e.g., possible differences in the toxicity of any of the IMPs relating to known differences in drug elimination).

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified visits during the Induction Period, the Treatment Period and as clinically indicated (see Appendix 1). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Patients who are assigned to vemurafenib will have additional assessments beyond those occurring during the above-mentioned complete and limited physical examinations. These additional assessments will include:

- Head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation, prior to initiation of treatment and every 3 months during treatment
- Monitoring for non-cutaneous squamous cell carcinoma (SCC) for up to 6 months after end of treatment or until initiation of another anti-neoplastic therapy
- Dermatologic evaluation prior to initiation of therapy and, then, examination for cutaneous SCC at each study visit until end of study treatment; thereafter, evaluation should occur monthly up to six months after treatment or until initiation of another anti-neoplastic therapy
- Routine monitoring of ophthalmologic reactions at each cycle (including prior to starting the first administration of vemurafenib)
- Anal examinations (for all patients) and pelvic examinations (for women) before and at the end of treatment or when considered clinically indicated

Patients who are assigned to entrectinib will have ophthalmologic exams, including at least the visual acuity and slit-lamp tests (which may be performed by an optometrist), prior to starting the first administration of entrectinib, at Day 1 of the second cycle of treatment with entrectinib, at end of treatment, and as clinically indicated.

Patients who are assigned to pemigatinib will have additional assessments beyond those occurring during the above-mentioned complete and limited physical examinations. These additional assessments will include:

- Comprehensive eye examination should be performed by a qualified ophthalmologist. The eye examination should include a visual acuity test, slit-lamp examination, and fundoscopy with digital imaging and optical coherence tomography, and is required prior to the first administration of pemigatinib, once every 3 cycles (±7 days, starting at Cycle 3), at end of treatment (not needed if completed within 28 days before the end of treatment), and more often if participants report any visual adverse events or change in visual acuity (see Appendix A10–11). An optometrist can perform the assessments if adequately trained and qualified; however, the optometrist should be supervised by an ophthalmologist, if possible, to provide the requisite clinical assessment. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist
- Nail check, due to potential nail toxicity

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

Abnormalities observed at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities should be recorded on the Adverse Event eCRF.

4.5.5 Performance Status

The patient's ability to carry out daily activities will be evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status scale (Appendix 6).

4.5.6 Tumor and Response Evaluations

4.5.6.1 Screening and Induction Periods

All known sites of disease must be documented at screening and re-assessed at the end of the Induction Period to orientate patients toward Category 1 or Category 2 for the Treatment Period.

Screening and End of Induction Period assessments must include CT scans (with oral or IV contrast unless contraindicated) of the chest, abdomen, and pelvis. CT scans of the neck should be included if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. MRI scans may be performed in lieu of CT scans, if appropriate. At the investigator's discretion and if clinically indicated, other methods of assessment of measurable disease per RECIST v1.1 may be used in addition to those listed above. All procedures for tumor assessment should be performed according to RECIST v1.1 (refer to Appendix 5).

Bone imaging may be done during the screening part of the work-up of CUP according to the 2015 ESMO Clinical Practice Guidelines for CUP.

All patients must undergo an MRI or CT scan (with contrast) of the brain at screening. In the event of an equivocal CT scan at screening, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline (refer to Section 4.1.2 for CNS-related exclusions).

Before start of the Treatment Period, a CT (with contrast) or MRI scan of the head must be included in the End of Induction tumor assessments, and results must be available at the End of Induction Visit, to exclude any CNS progression (in this case, the patient would be Category 2).

4.5.6.2 Treatment Period

All known sites of disease must be documented at the start of the Treatment Period and at each subsequent tumor evaluation. The tumor assessments obtained at the end of the Induction Period will be used for the start of Treatment Period assessments.

As with the Screening Period assessments, start of Treatment Period assessments must include CT scans (with oral/IV contrast unless contraindicated) of the chest, abdomen, and pelvis. CT scans of the neck should be included if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. MRI scans may be performed in lieu of CT scans, if appropriate. At the investigator's discretion and if clinically indicated, other methods of assessment of measurable disease per RECIST v1.1 may be used in addition to those listed above.

During the Treatment Period, tumor assessments should occur every 9 weeks ($\pm$3 days, with first assessment during the Treatment Period being made 9 weeks post C1D1) regardless of dose interruptions.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be monitored with a follow-up scan every 9 weeks until treatment discontinuation. Based on clinical judgment, the investigator can extend this period to every 12 weeks. The results from the scans from patients continuing treatment beyond progression being only analyzed at the time of primary analysis, these scans will not be collected after the $CCOD$ for the primary analysis.

The same radiographic procedure used to assess disease sites at screening (or for imaging test added at the End of Induction/start of Treatment Period assessment) should be used throughout the study (e.g., the same contrast protocol for CT scans). If the baseline imaging methods cannot be used at any point of time due to safety issues (e.g., allergy to contrast media), then every effort must be made to review all existing tumor assessments using comparable images to evaluate response (e.g., if a CT scan cannot be done with contrast, CT-images without contrast should be used from baseline

until the time point at which allergy to contrast media occurs) and further assessment methods should be aligned accordingly.

At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected. Assessments should be performed by the same individual to ensure internal consistency across visits (refer to Appendix 5).

Response will be assessed by the investigator on the basis of physical examinations, CT scans, and magnetic resonance imaging (MRI), according to RECIST v1.1 criteria as described in Appendix 5. An objective response should be confirmed by repeat assessments after initial documentation. The confirmatory assessment will be the next per protocol assessment (i.e., 9 weeks later, which complies with RECIST v1.1 criteria mandating a minimum of 4 weeks for a confirmation of response).

Evaluation of tumor response (e.g., for estimation of PFS, PFS rate, ORR, DOR, and CBR) will be completed per RECIST v1.1 per investigator's assessment. All primary imaging data used for tumor assessment may be collected by the Sponsor to enable centralized review of response endpoints by an Independent Review Committee (IRC) (e.g., to meet potential requests by a reviewing Regulatory Health Authority).

All scans and other data supporting efficacy measurements will be stored at the study site and available for subsequent collection, if necessary, for review by the Sponsor and/or independent external reviewer(s).

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Refer to the Laboratory Manual for minimum tissue specification and needs, sampling procedures, storage conditions and shipment instructions.

Refer to Appendix 3 for a summary table providing an overview of collected samples and collection time points.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate or total carbon dioxide (both optional and if considered standard of care for the region), glucose, BUN or urea, creatinine and creatinine clearance (calculated through use of Cockcroft-Gault formula), total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate and LDH.

At the End of Induction Visit, the panel will also include CPK, fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides; all performed following ≥4-hour fast prior to testing), amylase and lipase and glycated hemoglobin (HbA1c). During the Treatment Period, the panel may also include some IMP-specific exam at the timepoints indicated in the footnote r of the Schedule of Activities (Appendix 1):

- Coagulation: INR, aPTT
- Viral serology:
  - HIV

    HIV testing is mandatory for participation in the study
  - Hepatitis B surface antigen (HBsAg) and total hepatitis B core antibody (HBcAb)

    If the HBsAg test is negative but the total HBcAb test is positive, assessment of HBV DNA must be performed. If the resulting HBV DNA test is positive, the patient will be excluded from the study
  - HCV antibody serology: hepatitis C virus (HCV) antibody

    If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed. A patient will be excluded from the study only if the HCV antibody and the HCV RNA test are positive. If the HCV antibody test is positive, but the HCV RNA test is negative, the patient may enroll in the study
- Thyroid function panel: thyroid-stimulating hormone (TSH), free T3 (or total T3 for sites where free T3 is not performed), and free T4
- Lipids: cholesterol, LDL (low-density lipoprotein) cholesterol, HDL (high-density lipoprotein) cholesterol, and triglycerides
- Urinalysis: including dipstick (specific gravity, pH, glucose, protein, ketones, and blood)
- Pregnancy test (all study drugs except for vismodegib):

– All women of childbearing potential will have a serum pregnancy test ≤7 days:
  - Prior to study treatment initiation
  - Prior to starting treatment with molecularly-guided therapy

– Urine pregnancy tests will be performed
  - At each study visit (every 21 days ±3 days or every 28 days ±3 days depending on the schedule of administration of the IMP) during both Induction and Treatment Periods and no less than monthly if a study visit is delayed. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test
  - At the Safety Follow-Up Visit

- At the end of each contraception period, which corresponds to the following time points after the final dose of study treatment:

  2 weeks for erlotinib

  1 month for ipatasertib and olaparib

  5 weeks for entrectinib and pemigatinib

  3 months for alectinib and ivosidenib

  5 months for atezolizumab

  6 months for bevacizumab, cobimetinib, vemurafenib, carboplatin, cisplatin, paclitaxel and gemcitabine

  7 months for trastuzumab and pertuzumab

- Pregnancy test (for women of childbearing potential assigned to treatment with vismodegib):
  - A blood test should be performed within 7 days prior to initiating treatment
  - A supervised pregnancy test, conducted by a health care provider, should be performed:

    At each study visit during treatment. If study visits are delayed, the pregnancy tests must be performed independently of the visits and no less than monthly

    2 months and 24 months after the last administration
  - Pregnancy tests should have a minimum sensitivity of 25 mIU/mL, as per local availability
  - Patients who present with amenorrhea during treatment with vismodegib should continue monthly pregnancy testing while on treatment

Samples for the following laboratory tests will be sent to a Sponsor-designated central testing laboratory for analysis:

- Archival FFPE tumor tissue sample collected during screening for CUP confirmation and comprehensive genomic profiling using a FoundationOne® FMI F1CDx (tissue) test. If the archival tumor tissue is insufficient or not suitable (in quantity and quality) for CUP confirmation, per the specimen collection instructions provided in the Laboratory Manual, then a fresh biopsy must be collected
- Blood samples collected for FoundationOne® F1LCDx (Liquid) test genomic profiling at the timepoints indicated in the Schedule of Activities (Appendix 1)
- Optional whole blood sample on Day 1 for exploratory germline mutation analyses
- Serum sample on Day 1 for exploratory research
- Plasma blood sample at the Safety Follow-Up Visit for exploratory research

Exploratory analyses at the Sponsor-designated central testing laboratory will include the following (refer to Section 3.4.10 for rationales for choosing these biomarkers):

- PD-L1
- RNA sequencing
- DNA methylation
- Proteome analysis
- Immune cell infiltration
- Germline mutation/variants (optional)

Analysis of tumor mutations will be performed using the investigational FoundationOne® FMI F1CDx (tissue) and FoundationOne® F1LCDx (Liquid) tests. Additional information about the use of this assay can be found in the clinical performance study protocol (PLAN-00024 [FoundationOne® FMI F1CDx (tissue) test] and PLAN-00025 [FoundationOne® F1LCDx (Liquid) test]).

It Is possible that by the time of tumor sample analysis in this study, additional molecular markers for disease characterization or efficacy correlation will emerge. Thus, during the course of this study, it may become necessary to investigate additional markers associated with disease or with target signaling pathways and to reprioritize the above biomarkers.

Unless the patient gives specific consent for his or her leftover samples from Sponsor-designated central laboratories to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed 5 years after the final Clinical Study Report has been completed. Samples and derivatives thereof from patients who signed the RBR will be stored for up to 15 years or indefinitely after the final study results report has been completed (refer to Section 4.5.10).

Genomic research will aim at exploring inherited characteristics. NGS methods will not include whole genome sequencing (WGS) or whole exome sequencing (WES).

Screening samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools. Although remaining tissue blocks from screening failure patients will be returned to sites, the slides prepared from those samples and the data obtained can be used for future research and/or disease-related analysis and assay validations.

All the exploratory analyses specified above performed on screening samples may also be applicable for tissue samples of screening failure patients. The exploratory analysis on blood samples are not applicable for screening failure patients, as all blood samples collected for exploratory analysis are taken after enrolment.

NGS may be performed by FoundationOne®. If performed by FoundationOne®, the investigator may obtain an NGS report through one of the study-specific HIPAA-compliant tools (e.g., Navify). If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results will not be available for samples that do not meet criteria for testing. For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 3 months after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples should be destroyed, or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on germline mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of the exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the reports from FoundationOne®). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms and Cardiac Function Assessment

Single electrocardiogram (ECG) recordings will be obtained at specified time points, as outlined in the Schedule of Activities (Appendix 1), and may be obtained at unscheduled time points as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings and digital recordings will be kept as part of the patient's permanent study file at the site.

The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If any ECG abnormality is associated with an adverse event, it must be recorded and managed as described in the reference safety information of the respective IMP.

If at a particular post-dose time point the mean QTcF is $>$500 ms (450 ms for entrectinib) and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. Standard-of-care treatment may be instituted per the discretion of the investigator. A decision on study drug discontinuation should be made, as described in Section 4.6.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

Cardiac function assessment by echocardiogram or MUGA will be obtained at specified time points, as outlined in the Schedule of Activities (see Appendix 1) and may be obtained at unscheduled time points as indicated.

4.5.9 Clinical Outcome Assessments

Patient-reported outcome (PRO) instruments will be completed to assess the treatment benefit of targeted therapy/cancer immunotherapy in patients with CUP. In addition, PRO instruments will enable the capture of each patient's direct experience with targeted therapy/cancer immunotherapy or platinum-based chemotherapy.

PRO data will be collected through use of the following instruments: FACT-G and HADS to assess HR QoL and EQ-5D-5L to assess health status utility. Rationales for using these specific instruments and descriptions of the individual questionnaires are presented in Section 3.4.8 and Appendix 7, Appendix 8, and Appendix 9.

PRO instruments translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets to enable the instrument to be administered in the correct order at each specified timepoints during the study. The booklets will be labelled with the timepoint of administration.

PRO instruments will be self-administered at specified time points during the study (see Schedule of Activities in Appendix 1). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. PROs being only analyzed at the time of primary analysis, these questionnaires will not be collected after the $CCOD$ for the primary analysis.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 10–15 minutes at each specified visit
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers
- Site staff should not interpret or explain questions but may read questions verbatim upon request
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop new biomarker or diagnostic assays and/or validate existing diagnostic assays and to establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to CUP:

- Leftover or unused blood or tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides, slides, TMAs)
- Leftover or unused blood samples collected for optional germline mutation analyses

Note: Fresh biopsy collected as screening samples from patients who do not enroll in the study may also be stored in the RBR for future research and/or development of disease-related tests or tools. Archival tumor samples slides cut during the Screening Period may also be stored and used for future research if patient consents for the RBR ICF.

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other exploratory methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

RBR specimens are to be stored by the Sponsor for up to 15 years after the final study results or indefinitely. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable local laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

Specimens and associated data will be labelled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The Investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. *After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient.* However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in

writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a patient wishes to withdraw consent to the testing of his or her RCR samples after closure of the study site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:
global.rcr-withdrawal@roche.com

A patient's withdrawal from Study MX39795 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study MX39795.

4.5.10.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated Laboratory Information Management System, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patient Discontinuation from the Treatment:
Note: Disease progression during induction therapy is a study requirement for Category 2 patients and will not lead to study treatment discontinuation.

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues to receive study treatment. This includes discontinuations due to adverse events as described in Appendix 10
- Investigator determines it is in the best interest of the patient, which includes but is not limited to:
  - Exceptional cases, where the genomic profile based on the FoundationOne® FMI F1CDx (tissue) test and/or the FoundationOne® F1LCDx (Liquid) test provides an indication of a non-epithelial tumor (see Section 4.2) and the diagnosis of non-epithelial tumor is verified clinically or on histopathology (e.g., prior to the end of induction visit or randomization)
- Pregnancy
- Use of an anticancer therapy not required per protocol

- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to RECIST v1.1, unless the patient may benefit of treatment beyond progression as described below:
- Patients receiving molecularly-guided therapy who show evidence of clinical benefit at any time point after meeting RECIST v1.1 criteria for progressive disease will be permitted to continue treatment until loss of clinical benefit, unacceptable toxicity, patient or physician decision to discontinue, or death (whichever occurs first), if they meet all of the following criteria:

    Evidence of clinical benefit (i.e., in the absence of symptomatic deterioration attributed to disease progression, as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], clinical status, and worsening of laboratory values)

    Absence of unacceptable toxicity

    No decline in ECOG performance status that can be attributed to disease progression

    Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Following completion or discontinuation of all study treatments, (whether the patient discontinues after the Induction Period or After the Treatment Period) all patients will return to the clinic 30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first) for a Safety Follow-Up Visit.

After the Safety Follow-Up Visit, patients in the control chemotherapy arm and patients who discontinue for reason other than disease progression (including patient receiving alternative therapy) but who do not withdraw consent to follow-up will be assessed for progression as described during the Treatment Period (including scans) until disease progression per RECIST v1.1 (refer to Section 4.5.6).

Thereafter, patients will be contacted by the physician by phone for survival status every 3 (±1) months until death, loss to follow up, withdrawal of consent or end of the study. Data on nature of and response to further anticancer therapies will also be collected during the survival follow up.

Refer to the Schedule of Activities (Appendix 1) for details on follow-up assessments to be performed on patients who permanently discontinue study treatment. If a patient requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

Patient Discontinuation from the Study:
Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.
Patients may request to withdraw from treatment without withdrawing from the study (i.e., accepting study follow up). If so, this request must be documented in the source documents and signed by the investigator.

Patients who withdraw from the study (or from treatment only) will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.2 Study Discontinuation

The Sponsor has the right to terminate this study (or to close any of the molecularly-guided therapy cohorts) at any time. Reasons for terminating the study (or closing a molecularly-guided therapy cohort) may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study (or any of the molecularly-guided therapy cohorts).

4.6.3 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow or absence of recruitment
- Poor protocol adherence
- Inaccurate, repeatedly delayed or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Study medications, or the combination of study medications, analyzed in this study have not been approved for the treatment of CUP. Thus, the entire safety profile of all study medications (or their combinations) and their use by the Molecular Tumor Board are not known at this time in patients with CUP. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

Patients will be assessed by prior medical history, vital signs, weight, physical examination, *adverse events* (Aes) and concomitant medications. A complete medical history (including prior treatments for cancer) will be documented at Screening.
A complete physical exam will be performed at Screening, with symptom-directed physical exams performed throughout induction and study treatment. Changes in concomitant medication will be recorded at each study visit. Concomitant medications for treatment of Aes related to study medication will continue to be recorded while the AE is being followed. Aes will be monitored and documented continuously during the study and SAEs will also be documented and reported. See Sections 5.2.1 and 4.5.2 for a description of adverse events and concomitant medications collected during the study.

All Aes will be graded according to NCI CTCAE v5.0.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe SARS-CoV-2 infection appears to be associated with a Cytokine Release Syndrome (CRS) involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Test Agents

5.1.1.1 Alectinib, Atezolizumab, Entrectinib, Ivosidenib, Olaparib, Pemigatinib and Vismodegib Monotherapy

Alectinib, atezolizumab, entrectinib, ivosidenib, olaparib, pemigatinib and vismodegib will be administered as monotherapies in patients with the appropriate molecular profiles, as per results from comprehensive genomic profiling (see Section 3.1).

The identified and potential risks associated with alectinib, atezolizumab, entrectinib, and vismodegib are detailed in Sections 6.4 and 6.5 of their respective Investigator's Brochures. For pemigatinib, these risks can be found in Section 6 of the Pemigatinib Investigator's Brochure, for ivosidenib in Sections 6.6 and 6.7 of the Ivosidenib Investigator's Brochure, and for Olaparib in Section 4.8 of the Olaparib *EMA Summary of Product Characteristics*. Please refer to the respective reference safety information for risks associated with these IMPs in healthy volunteers and patients with diverse, non-CUP cancers.

5.1.1.2 Ipatasertib/Paclitaxel Combination Therapy

Ipatasertib plus paclitaxel will be administered in patients with AKT1, PIK3CA or PTEN alterations. The identified and potential risks associated with ipatasertib are detailed in Sections 6.4 and 6.5 of the Ipatasertib Investigator's Brochure. Please refer to the Ipatasertib Investigator's Brochure and local prescribing information for paclitaxel for risks associated with the individual components of this combination therapy in healthy volunteers and patients with diverse, non-CUP cancers.

Ipatasertib has been administered in combination with paclitaxel in a Phase I/II study of 25 patients (Study GO28341), in two Phase II studies of 62 patients (Study GO29227) and 75 patients (Study GO29505). The combination is currently being tested in a large Phase 3 trial (Study CO40016) of 450 patients, with half of the study population due to receive the combination. The data currently available show no major additional risks potentially associated with the combination (see the Ipatasertib Investigator's Brochure).

Patients (both Category 1 or 2) who have contraindications for paclitaxel, or Category 2 patients who were previously treated with paclitaxel, may receive ipatasertib monotherapy without paclitaxel at the discretion of the investigator. Likewise, patients who initiated ipatasertib without paclitaxel, as recommended in earlier versions of this

protocol, may continue to receive ipatasertib monotherapy at the investigator's discretion. In all of these cases, single-agent ipatasertib will be administered as recommended in the current Ipatasertib Investigator's Brochure for patients with AKT-, PTEN- or PIK3CA-altered tumors, i.e., at a once-daily dosage of 400 mg across a 21-day treatment cycle.

5.1.1.3 Erlotinib/Bevacizumab Combination Therapy

Erlotinib plus bevacizumab will be administered in patients with EGFR alterations (see Section 3.1). The identified and potential risks associated with erlotinib and bevacizumab are detailed in Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of their respective EMA Summary of Product Characteristics. Please refer to the Erlotinib and the Bevacizumab EMA Summary of Product Characteristics for risks associated with the individual components of this combination therapy in healthy volunteers and patients with diverse, non-CUP cancers.

There are no major additional risks potentially associated with the combination of therapies.

5.1.1.4 Vemurafenib/Cobimetinib Combination Therapy

Vemurafenib plus cobimetinib will be administered in patients with BRAF mutations (see Section 3.1). The identified and potential risks associated with vemurafenib and cobimetinib are detailed in Sections 6.4 and 6.5 of their respective Investigator's Brochures. Please refer to the vemurafenib Investigator's Brochure and the cobimetinib Investigator's Brochure for risks associated with the individual components of this combination therapy in healthy volunteers and patients with diverse, non-CUP cancers.

There are no known major additional risks potentially associated with the combination of vemurafenib and cobimetinib.

5.1.1.5 Trastuzumab/Pertuzumab/Platinum-Based Chemotherapy Combination

Trastuzumab SC plus pertuzumab plus platinum-based chemotherapy will be administered in patients with HER2 alterations. The identified and potential risks associated with trastuzumab and pertuzumab are detailed in the Sections 6.4 and 6.5 of their respective Investigator's Brochures. Please refer to the Trastuzumab Investigator's Brochure, the Pertuzumab Investigator's Brochure and local prescribing information for paclitaxel, carboplatin, cisplatin or gemcitabine (whichever are relevant) for risks associated with the individual components of this combination therapy in healthy volunteers and patients with diverse, non-CUP cancers.

There are no known additional risks potentially associated with the combination of trastuzumab, pertuzumab and platinum-based chemotherapies.

5.1.1.6 Atezolizumab/Platinum-Based Chemotherapy Combination

Atezolizumab plus platinum-based chemotherapy will be administered in patients with no actionable alterations and who are not TMB-high or MSI-high. Please refer to the Atezolizumab Investigator's Brochure and local prescribing information for paclitaxel, carboplatin, cisplatin or gemcitabine (whichever are relevant) for risks associated with the individual components of this combination therapy in healthy volunteers and patients with diverse, non-CUP cancers.

To date, no additional risks/adverse drug reactions specific to the combination of atezolizumab and other therapeutic agents have been identified.

5.1.1.7 Platinum-Based Chemotherapy

Platinum-based chemotherapy will be administered for 3 cycles in all patients and for a minimum of 3 additional cycles in patients responding to induction who are randomly allocated to the control arm. Please refer to the local prescribing information for paclitaxel, carboplatin, cisplatin or gemcitabine (whichever are relevant) for risks associated with the individual components of the platinum-based chemotherapy in patients with non-CUP cancers.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

Refer to Appendix 10 and to the individual IMPs' investigator's brochures for dose modification, dose discontinuation and specific management guidance.

5.1.2.2 Treatment Interruption

Study drug may be temporarily suspended in patients who experience toxicity considered to be related to study drug. Refer to Appendix 10 and to the individual IMPs' investigator's brochures for treatment interruption and dose discontinuation.

Study drug may be suspended for reasons other than toxicity (e.g., surgical procedures). The investigator may take advice from the Medical Monitor to determine the relevant length of treatment interruption.

5.1.2.3 Management Guidelines

Specific adverse events requiring management and their management regimens are provided for each IMP in the reference safety information. Appendix 10 lists the specific adverse events for each study treatment as of the date of this version of the protocol.

For specific adverse events for all IMPs, the following general rules should apply:

- Investigate etiology (see relevant investigator's brochure(s) for specificities)
- Initiate treatment as per institutional guidelines and check the relevant investigator's brochure(s) for any specific management
- Contact the Medical Monitor for advice as appropriate and as per investigator's brochure guidance

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present on Day 1
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
- This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- All products:
  - Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
  - Suspected transmission of an infectious agent by a study drug, as defined below

    Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected
- Individual IMPs
  - Refer to Appendix 10 for a list of additional AESIs that must be reported for individual study drugs

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug:
Only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

During the Induction Period: Only adverse events leading to dose modifications, interruption or discontinuation of the platinum-based chemotherapy and all SAEs will be captured.

At the End of Induction Visit: All ongoing adverse events will be collected (to allow for an appropriate assessment of the general inclusion criteria in the Treatment Period and to comply with the re-baselining activities at the start of the Treatment Period).

After initiation of molecularly-guided therapy (including the control arm for Category 1 patients): All adverse events, serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 30 days after the final dose of study drug or initiation of new systemic anticancer therapy, whichever occurs first, for all drugs except atezolizumab, where it will be 90 days.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points. Examples of non-directive questions include the following:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions/Administration-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion/injection should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine-release syndrome"). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF. Associated signs and symptoms of an IRR or a CRS should be recorded as free text on the additional case details section of the AE page of the eCRF.

If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms of an IRR also recorded as free text on the additional case details section of the AE page of the eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix A10–2 specifically for atezolizumab.

5.3.5.2 Diagnosis Versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF

- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of cancer of unknown primary site should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The Sponsor will consider fatal serious adverse reactions (SARs) as unexpected for regulatory reporting purpose.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Cancer of Unknown Primary Site

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of CUP on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of cancer of unknown primary").

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer
- An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:
  - Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

There are some hospitalization scenarios that do not require reporting as a serious adverse event when there is no occurrence of an adverse event. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose}
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

For alectinib, atezolizumab, bevacizumab, cobimetinib, entrectinib, erlotinib, ipatasertib, ivosidenib, olaparib, pemigatinib, pertuzumab, trastuzumab, vemurafenib and vismodegib, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes

- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes

In addition, all special situations associated with alectinib, atezolizumab, bevacizumab, cobimetinib, entrectinib, erlotinib, ipatasertib, ivosidenib, olaparib, pemigatinib, pertuzumab, trastuzumab, vemurafenib and vismodegib, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes

- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms (via PRO) with investigator reports of adverse events. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study patients, *access to Medical Monitor is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week.* The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/ Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.2.1 Events That Occur Prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies) should be reported.

5.4.2.2 Events That Occur After Study Drug Initiation

During the Induction Period: Only adverse events leading to dose modifications, interruption or discontinuation of the platinum-based chemotherapy and all SAEs will be captured.

After initiation of molecularly-guided therapy (including the control arm for Category 1 patients): All serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 30 days after the final dose of study drug or until initiation of new systemic anticancer therapy, whichever occurs first, for all drugs except atezolizumab, where it will be 90 days.

Instructions for reporting serious adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or for up to 24 months after the final dose of treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

In order to learn more about the effects of study drugs on pregnancy, additional information on any study drugs -exposed pregnancy and infant will be requested by Roche/Genentech Drug Safety at specific time points (i.e., after having received the initial report during the first trimester, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). In case of a report of pregnancy or congenital abnormality, a guided questionnaire will be sent out by Roche/Genentech Drug Safety.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or for up to 7 months after the final dose of study drug. There is no requirement for such report for atezolizumab monotherapy. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. There is no requirement for such report for male patients treated with atezolizumab monotherapy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with

additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 30 days after the final dose of study drug or until initiation of new systemic anticancer therapy for all IMPs with the exception of atezolizumab, where it will be defined as 90 days), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

Additional specific molecule-related reporting time windows for Aes after the AE reporting period (as defined above) are:

- Trastuzumab:
  - Cardiac Aes should be reported between the end of the adverse event reporting period until the end of the study
  - SAEs considered to be unrelated to trastuzumab therapy should be reported for up to 6 months after the final dose of trastuzumab, unless the patient went off study and started a new systemic anticancer treatment

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the following reference documents:

- Investigator's brochure for alectinib, atezolizumab, cobimetinib, entrectinib, ipatasertib, ivosidenib, pemigatinib, pertuzumab, trastuzumab, vemurafenib and vismodegib
- EMA Summary of Product Characteristics or locally approved label for bevacizumab, erlotinib, olaparib, cisplatin, carboplatin, gemcitabine, paclitaxel, or any alternative therapy commercially sourced

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is an open-label, randomized, multicenter study to compare the efficacy of molecularly-guided therapy versus platinum chemotherapy in patients with CUP who have received 3 cycles of platinum-based induction chemotherapy.

The analysis populations are defined as follows:

- All enrolled patients population: all patients enrolled in the study
- Intention-to-treat (ITT) population: all randomized patients, whether or not the assigned study treatment was received
- Efficacy analysis population for Category 2 patients: defined in the same way as the Safety-evaluable population: All non-randomized participants who received at least one dose of any component of study drug during the treatment period. Patients who received an alternative therapy are not part of this population
- Safety population: all patients who received at least one dose of any component of study drug
- PRO-evaluable population: all patients in the ITT population with the relevant baseline and at least one post-treatment PRO assessment

For all analyses of the ITT population, patients will be grouped according to the treatment arm assigned at randomization. For all analyses of the Safety population, patients will be grouped according to treatment actually received.

Hypothesis tests will be two-sided unless otherwise indicated. The type I error (α) for this study is 0.05 (two-sided).

Further details of the analyses will be provided in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

The sample size has been estimated based on assumptions derived from Hainsworth et al. (Hainsworth et al. 2015), giving an estimated median PFS of 5 months for CUP patients. Kaplan-Meier plots in the reference suggest that the exponential distribution is a reasonable assumption for PFS in CUP patients and, following this, we assume an estimated median PFS from randomization of 5 months for patients randomized to chemotherapy.

Based on a two-sided 5% test, 330 events will give approximately 80% power to detect an HR of 0.7 (calculated using RPACT). Randomizing 400 patients using a 3:1 ratio, and assuming a 42-month recruitment period, the time to primary analysis will occur approximately 45 months from the time of first patient randomized.

To allow for an estimated 15% dropout rate after randomization, a total of 472 patients will be randomized in the study. Assuming a 60% disease control rate at the end of induction, it is estimated that approximately 790 patients with CUP will enroll. If the actual number of patients who achieve a CR, PR, or SD during induction deviates from these estimates, the study will enroll patients until 472 patients have been randomized.

In addition, if both the actual disease control and dropout rates differ from the protocol assumptions, the 330 PFS events may be reached before 790 patients are enrolled. In this case, screening will be stopped, when 330 PFS events have been observed.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and other baseline characteristics (at patient and disease level) will be summarized using means, standard deviations (SDs), medians, inter-quartile range, minimum and maximum for continuous variables and proportions for categorical variables, as appropriate. Medical history, prior and concomitant treatments (study and non-study condition related) will also be presented.

6.4 EFFICACY ANALYSES

The primary efficacy analysis population will consist of all randomized patients, with patients grouped according to their assigned treatment arm.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study, PFS, is defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first.

The primary analysis of PFS will be based on the ITT population to evaluate the efficacy of patients randomized to molecularly-guided therapy versus patients randomized to platinum chemotherapy in patients with CUP whose response to 3 cycles of platinum induction chemotherapy was CR, PR or SD. Stratified analysis of the primary endpoint will be completed according to the pre-defined randomization stratification factors (gender and response to platinum induction chemotherapy). Results from an unstratified analysis will also be provided as a sensitivity analysis.

Data for patients without disease progression or death will be censored at the last tumor assessment date. If no tumor assessment was performed after randomization, data will be censored at the date of randomization + 1 day.

Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, together with the 95% confidence interval, and Kaplan-Meier curves will be produced. PFS will be compared between treatment arms by the stratified log-rank test. Estimates and the corresponding 95% confidence intervals will also be reported by treatment arm for the 6- and 12-month survival rates. The hazard ratio (HR) for PFS will be estimated using a Cox proportional hazards model, and the 95% confidence interval for the HR will be provided.

Additional sensitivity analyses of PFS may be conducted to assess:

- The impact of missing tumor assessments, depending on the number of patients with one or more missing tumor assessments prior to documented disease progression.
- The impact of non-protocol-specified anticancer therapy depending on the number of patients receiving a non-protocol therapy prior to a PFS event.

Details will be provided in the SAP.

Additionally, first-line PFS will be described by Kaplan-Meier methodology for each molecularly-guided therapy (targeted therapy or cancer immunotherapy) and/or for each genomic alteration, where relevant, based on the patients in the cohort-specific safety population.

The clinical cut-off date for the primary endpoint analysis will occur when approximately 330 PFS events have been observed in the ITT population. In case the recruitment is still ongoing when 330 PFS events have been observed, all patients still in screening will proceed to enrollment, if eligible, and will be included in the primary endpoint analysis. In that scenario, the clinical cut-off date for the primary endpoint analysis will be the date of randomization (or assignment in to Category 2) of the last patient enrolled.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy objectives for this study are described below. All secondary analyses will be descriptive only.

6.4.2.1 Overall Survival

Overall survival (OS) is defined as the time from randomization to death from any cause.

Data for patients with no record of death will be censored at the last date they were known to be alive. The analysis of OS will follow the same methodology as the primary endpoint.

Additional sensitivity analyses of OS will be outlined in the SAP.

A preliminary analysis of OS will be performed at the time of the primary analysis of PFS. A survival follow-up analysis will be performed once a sufficient number of death events have been observed, specifically when at least 55% of Category 1 patients (approximately 260 patients) have died.

6.4.2.2 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of randomized patients who exhibit a complete response or partial response on two consecutive per protocol disease assessment (i.e., 9 weeks later, which complies with RECIST v1.1 criteria mandating a minimum of 4 weeks for a confirmation of response), as determined by the investigator according to RECIST v1.1.

An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method.

ORR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described for the analysis of the primary endpoint of PFS. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution.

6.4.2.3 Duration of Response

Duration of Response (DOR) will be assessed in randomized patients who had an objective response as determined by the investigator according to RECIST v1.1. DOR is defined as the time from the first post-randomization occurrence of a confirmed CR or confirmed PR (whichever status is recorded first) until the first date progressive disease or death is documented, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day. DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis.

6.4.2.4 Disease Control Rate

DCR is defined as the rate of patients with confirmed CR or confirmed PR or SD, or Not Applicable (NA), as best overall response per RECIST 1.1. The analysis of DCR will follow the same methodology as ORR.

Not Applicable corresponds to patients that have Complete Response (CR) at the end of Induction. The re-baseline assessment for these patients is Not Applicable as there are no lesions to be measured anymore.

6.4.3 Exploratory Endpoints

Analyses of exploratory endpoints will be descriptive only.

Efficacy Analysis for Non-Randomized Patients Who Received Molecularly-Guided Therapy in Second Line

For Category 2 patients who received molecularly-guided therapy in second line, $PFS1_{-cat2}$ will be defined as the time from first dose of any component of platinum-based induction chemotherapy to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1. $PFS2_{-cat2}$ will be defined as the time from first dose of molecularly-guided therapy to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. For the patients in the cohort-specific safety population, second-line PFS ($PFS2_{-cat2}$) will be described by Kaplan-Meier methodology for each molecularly-guided therapy (targeted therapy or cancer immunotherapy) and a summary of $PFS2_{-cat2}/PFS1_{-cat2}$ will be presented.

For non-randomized patients who received molecularly-guided therapy in second-line, second-line OS will be defined as the time from first dose of molecularly-guided therapy to death from any cause. For the patients in the cohort-specific safety population, second-line OS will be described by Kaplan-Meier methodology for each molecularly-guided therapy (targeted therapy or cancer immunotherapy).

For non-randomized patients who received molecularly-guided therapy in second line, ORR will be defined as the proportion of patients who exhibit a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. An estimate of ORR will be calculated for each molecularly-guided therapy, and its 95% CI will be calculated using the Clopper-Pearson method. DOR and DCR will also be analyzed as described above for Category 1 patients.

6.4.4 Exploratory PRO Endpoints

The exploratory PRO objectives for this study will be assessed using the following:

- FACT-G questionnaire score
- HADS questionnaire score
- EQ-5D-5L index-based score

Analyses will be descriptive only.

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) of linear transformed scores will be reported for all scales of the questionnaires according to the scoring guidelines for each assessment time point. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be reported. Graphs depicting the mean changes (and standard errors) of items and scales over time will be provided for each treatment arm from the baseline assessment.

Completion and compliance rates will be summarized at each time point by treatment arm with reasons for missing data. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses.

The number and proportion of patients who improved, worsened, or remained stable for all of the scales of the questionnaires will be summarized at each time point.

PROs being only analyzed at the time of primary analysis, these questionnaires will not be collected after the $CCOD$ for the primary analysis.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of any component of study drug, with patients grouped according to actual treatment received. Safety will be presented by the relevant study phase: induction treatment, treatment started in first-line post-randomization (Category 1 patients), treatments started in second-line (Category 2 patients).

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

Safety endpoints will include:

- Incidence, nature and severity of Aes and SAEs with severity determined according to NCI CTCAE v5.0
- Incidence and reasons for any dose reductions, interruptions, or premature discontinuation of any component of study treatment
- Clinically significant laboratory values, ECGs and vital signs

The incidence of Aes will be summarized by frequency tables.

Dose reductions, interruptions, or premature discontinuation of any component of study treatment will be analyzed by frequency tables. Median duration of follow up and median time on treatment, with 95% CI, will be estimated by the Kaplan-Meier approach or using univariate statistics, presenting mean, median, quartiles, minimum, maximum and standard deviation.

Worst grades for laboratory parameters, and newly occurring Grade 3 and 4 laboratory values during treatment will be summarized by frequency tables. Shift in grade from baseline to worst grade during treatment will be presented in summary tables.

Changes in vital signs and physical findings from baseline will be tabulated and presented graphically when applicable.

6.6 INTERIM ANALYSES

6.6.1 Planned Interim Analysis

No interim analyses of efficacy are planned.

The iDMC will review safety data periodically during the study.

6.6.2 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an interim efficacy analysis, e.g., based on a recommendation from the iDMC and in consultation with the Steering Committee. If an interim analysis is conducted, it will be prospectively described in the SAP, and the Sponsor will remain blinded.

Provisions will be in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed. The decision to conduct the optional interim analysis, along with the rationale, timing and statistical details for the analysis, will be documented in the SAP, which will be submitted to relevant health authorities at least two months prior to the conduct of the interim analysis. In addition, the iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor based on the results of the analysis. The iDMC charter will also be made available to relevant health authorities.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The CRO will produce eCRF Specifications for the study based on Sponsor templates, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data and vendor data, including FoundationOne® FMI F1CDx (tissue) test reports, FoundationOne® F1LCDx (Liquid) test reports and IxRS, will be sent directly to the Sponsor using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the CRO.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, medication inventory records, and images, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) *or Clinical Trial Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC−approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number (including comprehensive genomic profiling services provided by the central laboratory). This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include imaging data and data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks.

Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 150 sites globally will participate to enroll approximately 790 patients. Enrollment and randomization will occur through an IxRS. The total number of patients enrolled may differ, if both the actual disease control and dropout rates differ from the protocol assumptions, as indicated in Sections 4.1 and 6.1.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests and biomarker analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/*or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

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Appendix 1
Schedule of Activities

A1–1 SCHEDULE OF ACTIVITIES AFTER THE PRIMARY ANALYSIS CUT-OFF DATE (CCOD) *AND FOR THE EXTENSION PART OF THE STUDY*

	Treatment Period First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [a]	Safety Follow-Up Visit [b] 30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	Follow-up Period [s] Every 3 (±1) months (Starting 3 months post final dose of study treatment)
Weight	X	X	
Complete physical examination [c]		X	
Limited physical examination [d]	X		
Specific physical examination [e]	X (vemurafenib patients only)		
ECOG performance status [d]	X	X	
Vital signs [f]	X	X	
12-lead ECG [d, g]	As clinically indicated or as indicated for each individual IMP	As indicated for each individual IMP	
Left ventricular ejection fraction (LVEF)	As clinically indicated or as indicated for each individual IMP	As clinically indicated or as indicated for each individual IMP	As indicated for each individual IMP
Ophthalmologic exams [h]	X (entrectinib, pemigatinib and vemurafenib only)	X	
Hematology [d, i]	X	X	
Coagulation (aPTT, INR) [d]	X	X	

Appendix 1: Schedule of Activities

	Treatment Period	Safety Follow-Up Visit [b]	Follow-up Period [s]
	First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [a]	**30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)**	**Every 3 (±1) months (Starting 3 months post final dose of study treatment)**
Thyroid function panel [d, j]	Every 9 weeks (atezolizumab only)		
Chemistry panel [d, k]	X	X	
Chemistry panel (IMP-specific) [d, l]	As indicated for each individual IMP		
Urinalysis [d, m]	X	X	
Pregnancy test [n]	Refer to Footnote n (urine)	X	Refer to Footnote n (urine)
Tumor assessment [o]	Every 9 weeks ± 3 days until PD		X [p] (as per comment)
Plasma blood sample for exploratory research		X [s]	
Concomitant medications [q]	X	X	
Adverse events [r]	X	X	X
Additional safety visits	Ipatasertib + paclitaxel only D4, 8, 15, and 22 of Cycle 1 D8 and 15 of Cycle 2 Then D15 of all cycles until paclitaxel is stopped		
Collection of information on survival and anticancer therapy		X	X

Appendix 1: Schedule of Activities

	Treatment Period	Safety Follow-Up Visit [b]	Follow-up Period [s]
	First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [a]	**30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)**	**Every 3 (±1) months (Starting 3 months post final dose of study treatment)**
Study treatment			
Molecularly-guided therapy in patients with a CR, PR or SD during induction	X [r]		
Platinum-based chemotherapy in patients with a CR, PR or SD during induction	X [r] (at least 3 cycles)		
Molecularly-guided therapy in patients with PD during induction (Category 2 patients)	X [r]		

AE =adverse event; AESI =adverse event of special interest; aPTT=activated partial thromboplastin time; C=cycle; chemo=chemotherapy; CR=complete response; CUP=cancer of unknown primary site; *cutaneous squamous cell carcinoma =cuSCC;* D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; *eCRF =electronic Case Report Form;* IMP=Investigational Medicinal Product; INR=international normalized ratio; *LDH =lactate dehydrogenase; LVEF =Left ventricular ejection fraction; MTB =Molecular Tumor Board;* PD=progressive disease; PR=partial response; *QD =once daily;* RSI=reference safety information; *SAE =serious adverse event;* SD=stable disease; *TSH =thyroid-stimulating hormone.*

Note: Unless otherwise indicated, assessments scheduled on the study treatment days should be performed prior to initiation of study treatment.

[a] 21-day cycles for all treatment arms (including for cohorts with oral therapies), except for cobimetinib and vemurafenib, ipatasertib and paclitaxel, and ivosidenib, where the administration cycle will be 28 days:
  – Assessments must be performed within 72 hours of first study treatment (Cycle 1 Day 1) and of first administration of treatment in the Treatment Period. If any of the assessments occurring within 72 hours of Cycle 1 Day 1 and of first administration of treatment in the Treatment Period are abnormal, all assessments must be repeated on the first day of study treatment and of first administration of treatment in the Treatment Period, respectively.

[b] If the timing of the Safety Follow-Up Visit overlaps with a visit already completed, e.g., the End of Induction Visit, then the Safety Follow-Up Visit may not be performed. The Safety Follow-Up Visit is applicable for all patients, whether they discontinued permanently the treatment in the Induction or in the Treatment Period.

[c] A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[d] Limited physical examination, ECOG performance status, ECG, urinalysis, and local laboratory assessments (hematology, coagulation, chemistry and thyroid function panel [when mandated]) may be obtained $\leq$72 hours before Day 1 of each cycle. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[e] In patients who are assigned vemurafenib treatment: head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation, should occur prior to initiation of treatment and every 3 months during treatment. Anal examinations (for all patients) and pelvic examinations (for women) should occur before and at the end of treatment or when considered clinically indicated. Monitoring for non-cuSCC should continue for up to 6 months after end of treatment or until initiation of another anti-neoplastic therapy. Dermatologic evaluation should occur prior to initiation of therapy, and then examination for cuSCC should occur at each study visit until end of study treatment; thereafter, evaluation should occur monthly up to six months after treatment or until initiation of another anti-neoplastic therapy.

[f] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Vital sign assessments performed on the first day of a treatment cycle should be done prior to IV study treatment (if applicable).

[g] ECG recordings will be obtained when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[h] Ophthalmologic exams should only occur in patients who are assigned to entrectinib, pemigatinib or vemurafenib treatment:
  – In patients assigned to entrectinib: Ophthalmologic exams, including at least visual acuity and slit-lamp tests (which may be performed by an optometrist), should be performed prior to starting the first administration, at Day 1 of the second cycle of treatment, at the end of treatment, and as clinically indicated.

– In patients assigned to pemigatinib: A comprehensive eye examination should be performed by a qualified ophthalmologist. The eye examination should include a visual acuity test, slit-lamp examination, and fundoscopy with digital imaging and optical coherence tomography, and is required prior to the first administration of pemigatinib, once every 3 cycles (±7 days, starting at Cycle 3), at end of treatment (not needed if completed within 28 days before the end of treatment), and more often if participants report any visual adverse events or change in visual acuity. An optometrist can perform the assessments if adequately trained and qualified; however, the optometrist should be supervised by an ophthalmologist, if possible, to provide the requisite clinical assessment. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

– In patients assigned to vemurafenib: Routine monitoring of ophthalmologic reactions should occur at each cycle.

[i] Hematology consists of CBC (including RBC count), hemoglobin, hematocrit, WBC count with *neutrophil count and platelet count. A WBC count with* differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), may be done if clinically indicated. *Abnormalities should be recorded in patient notes. Significant abnormalities should be recorded as adverse events in the Adverse Event eCRF.*

[j] Thyroid function panel includes: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4. *Abnormalities should be recorded in patient notes. Significant abnormalities should be recorded as adverse events in the Adverse Event eCRF.*

[k] Chemistry panel (serum or plasma): sodium, potassium, chloride, glucose, creatinine + creatinine clearance (calculated through use of Cockcroft-Gault formula), total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, *and* AST. *BUN or urea, urate, and LDH will be tested as clinically indicated.*

At the End of Induction Visit, the panel will also include CPK, fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides; all performed following ≥4-hour fast prior to testing), amylase and lipase and glycated hemoglobin (HbA1c). *Abnormalities should be recorded in patient notes. Significant abnormalities should be recorded as adverse events in the Adverse Event eCRF.*

During the Treatment Period, the panel may also include some IMP-specific exam at the timepoints indicated in the footnote r.

[l] The following should be tested for **specific IMPs only**

(Note: Assessments that do not coincide with planned study visits may be performed within ±3 days of the timing described below for tests planned at intervals ≤3-weekly and within ±7 days of the timing for tests planned at monthly or greater intervals):

– Alectinib: CPK levels, and liver function tests (ALT, AST, total bilirubin, alkaline phosphatase) every two weeks for 12 weeks of treatment, then every 6 weeks between weeks 12 and 48 and every 12 weeks thereafter, until week 96 (during the Treatment Period only).

– Atezolizumab: Thyroid function panel: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 every 9 weeks; ECG as clinically indicated.

– Cobimetinib: LVEF after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. CPK levels every 4 weeks during treatment and as clinically indicated in patients reporting severe myalgias.

- Entrectinib: LVEF at Cycle 3 Day 1 (±7 days), as clinically indicated, and at the Safety Follow-Up Visit (if patient experienced Grade 2 or higher ejection fraction decrease at Cycle 3 or at any time during treatment, or if clinically indicated). Safety Follow-Up LVEF is not necessary if the last LVEF assessment was performed within 1 week prior to the Safety Follow-Up Visit and if the investigator deems it not clinically indicated. Evaluation of LVEF must be performed by the same method (echocardiogram or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform echocardiogram/MUGA scans for each individual patient.

  ECGs:

  - At Day 1 of Cycles 1 to 5 of treatment with entrectinib with a single 12-Lead ECG assessment performed pre-dose and 4 hours (±15 minutes) post-dose
  - At end of treatment, and
  - As clinically indicated.

  In case of an event of QTc prolongation (Grade >1), patient should be followed more closely. In addition, the ECG should be read over for confirmation, and continuous ECG monitoring may be implemented as clinically indicated.
- Erlotinib + bevacizumab: No additional assessments.
- Ipatasertib (only if administered without paclitaxel [see next bullet if ipatasertib is administered with paclitaxel]):

  Every 3 weeks, on Day 1 of each cycle and on Day 8 of Cycle 1: Fasting blood glucose and fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides, all performed following ≥4-hour fast prior to testing); amylase and lipase; and glycosylated hemoglobin (HbA1c). In addition, on Days 4, 15 of Cycle 1 and Days 8 and 15 of Cycle 2: fasting blood glucose (patients should fast ≥4 hours prior to testing).
- Ipatasertib and paclitaxel:

  On Day 1 and 15 of each 28-day cycle, on Days 4, 8 and 22 of Cycle 1 and on Day 8 of Cycle 2: fasting blood glucose and fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides; all performed following ≥4-hour fast prior to testing), amylase and lipase, and glycosylated hemoglobin (HbA1c).

  On Days 1, 8 and 15 of each 28-day cycle (until paclitaxel is stopped): hematology including WBC count, WBC differential count (including absolute neutrophil counts, lymphocytes), hemoglobin, hematocrit, and platelet count.

  On paclitaxel dosing days, vital signs should be recorded prior to dosing and at the end of the infusion.

  Additional safety visits at Day 15 of each cycle should coincide with paclitaxel administration. These visits are necessary only until paclitaxel is stopped.
- Ivosidenib:

  ECGs: On Day 1 of each 28-day cycle, on Cycle 1 Day 15, and at the Safety Follow-Up Visit.

  LVEF: As clinically indicated and at the Safety Follow-Up Visit (ECHO or other method per institutional practice).
- Olaparib: No additional assessments.

– Pemigatinib:

Parathyroid hormone at Cycle 1 Day 1, every 3 cycles on Day 1 starting with Cycle 3, and at the Safety Follow-Up Visit
Serum phosphorus levels at:

- Day 1, Day 8 and Day 15 of Cycle 1
- Day 1 of Cycle 2 and the first day of every cycle thereafter until end of treatment
- Safety Follow-Up Visit

Note: Any patient assigned to pemigatinib who does not reach a target serum phosphate level of >5.5 mg/dL at any time during Cycle 1, is compliant with taking study drug, and does not experience an ongoing Grade 2 or higher treatment-related AE will increase the daily dose to 18 mg QD starting from Cycle 2 Day 1. Hyperphosphatemia in Cycle 1 requires Day 8 testing of serum phosphate in Cycle 2+ until phosphate is <7 mg/dL on Day 8 for at least 2 consecutive cycles on stable dose of binders.

ECGs on the first day of every cycle and at the Safety Follow-Up Visit.

Nail check, as part of the physical exam, on the first day of every cycle and at the Safety Follow-Up Visit.

– Trastuzumab + pertuzumab (± chemotherapy): LVEF at Cycle 3 Day 1, then every 3 cycles during treatment. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g., every 6–8 weeks). LVEF every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab.

– Vemurafenib: Amylase and lipase at each cycle; ECG and electrolytes (including magnesium) must be monitored in all patients before treatment, monthly for 3 months, then every third month while on study treatment and after dose modification. Note: Patients who are assigned vemurafenib will also have additional assessments during their ongoing physical examinations, as described in Footnote j.

– Vismodegib: No additional chemistry laboratory assessments.

[m] Urinalysis including dipstick: pH, glucose, protein, ketones, and blood. *Abnormalities should be recorded in patient notes. Significant abnormalities should be recorded as adverse events in the Adverse Event eCRF.*

[n] A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed prior to the first dose in the Treatment Period (see specific requirements for vismodegib). Pregnancy tests (urine) should be conducted at each study visit (every 21 days ±3 days or every 28 days ±3 days depending on the IMP schedule of administration) during both Induction and Treatment Periods and no less than monthly if a study visit is delayed. For all treatments, pregnancy tests should be conducted at the Safety Follow-Up Visit and at the end of each contraception period, which corresponds to the following time points after their final dose of study treatment: 2 weeks for erlotinib, 1 month for ipatasertib and olaparib, 5 weeks for entrectinib and pemigatinib; 3 months for alectinib and ivosidenib; 5 months for atezolizumab; 6 months for bevacizumab, cobimetinib, vemurafenib, carboplatin, cisplatin, paclitaxel and gemcitabine; 7 months for trastuzumab and pertuzumab.
Note: For vismodegib, a blood pregnancy test should be performed within 7 days prior to initiating treatment and a supervised pregnancy test, conducted by a healthcare provider, should be performed at each study visit during treatment and 2 months and 24 months after their final dose of study treatment (the 2 and 24 months post treatment tests can be performed by a local health practitioner and reported to the investigator).

If study visits are delayed, the pregnancy tests must be performed independently of the visits and no less than monthly. Pregnancy tests should have a minimum sensitivity of 25 mIU/mL, as per local availability. Patients who present with amenorrhea during treatment with vismodegib should continue monthly pregnancy testing while on treatment.

[o] The same radiographic procedure should be used throughout the study for each patient:

– Treatment Period: During the Treatment Period, tumor assessments should occur every 9 weeks (±3 days, with first assessment during the Treatment Period being made 9 weeks post C1D1) regardless of dose interruptions. Results must be reviewed by the investigator before dosing at the next cycle. *Details of tumor assessments should be recorded in patient notes, however only the overall assessment of the response will be recorded in the Tumor Assessment eCRF.*

[p] Patients who enter the Follow-up Period before PD should continue to be assessed, per protocol, until disease progression. All patients in the control arm must be followed up until disease progression. This also includes patients who discontinue to receive alternative therapy after the MTB.

[q] Concomitant medications include any prescription medications or over-the-counter medications.

– During the Treatment Period: changes to current medications or medications used since the last documentation of medications should be recorded *in the patient notes. Only medications used for the treatment of a serious adverse event will be entered on the concomitant medication eCRF.*

[r] After initiation of molecularly-guided therapy (including the control arm for Category 1 patients): all AEs, SAEs and AESIs, regardless of relationship to study drug, will be reported until 30 days after the final dose of study drug or initiation of new systemic anticancer therapy, whichever occurs first, for all drugs except for atezolizumab, where it will be 90 days. After this period, the investigator should report any SAEs or AESIs believed to be related to prior study drug treatment. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.

Note: For atezolizumab, the first Follow-Up Visit (90 days after the final dose of study drug) is regarded as the end of AE reporting period.

[s] *Not applicable for the extension part of the study.*

A1–2 SCHEDULE OF ACTIVITIES BEFORE THE PRIMARY ANALYSIS CUT-OFF DATE (CCOD)

	Screening Period [a]		Induction Period		End of Induction Visit [d]	Treatment Period	Safety Follow-Up Visit [e]	Follow-up Period
	Day –28 to Day –1	Day –14 to Day –1	Cycle 1 Day 1 [b]	First day of each 21-day cycle (±3 days) for Cycles 2 and 3 [c]	Cycle 3 Day 14 to Cycle 3 Day 21 (+3 days)	First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [c]	30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	Every 3 (±1) months (Starting 3 months post final dose of study treatment)
Informed Consent–General (Part 1) [f]	X							
Informed Consent–IMP-specific (Part 2) [f]						X		
Eligibility criteria	X		X [c]					
General and IMP-specific exclusion criteria re-evaluation					X			
Medical history and demographics [g]	X							
Weight	X		X	X		X	X	
Height	X							
Complete physical examination [h]	X				X		X	
Limited physical examination [i]			X	X		X		

Appendix 1: Schedule of Activities

	Screening Period [a]		Induction Period		End of Induction Visit [d]	Treatment Period	Safety Follow-Up Visit [e]	Follow-up Period
	Day –28 to Day –1	Day –14 to Day –1	Cycle 1 Day 1 [b]	First day of each 21-day cycle (±3 days) for Cycles 2 and 3 [c]	Cycle 3 Day 14 to Cycle 3 Day 21 (+3 days)	First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [c]	30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	Every 3 (±1) months (Starting 3 months post final dose of study treatment)
Specific physical examination [j]						X (vemurafenib patients only)		
ECOG performance status [i]	X		X	X	X	X	X	
Vital signs [k]	X		X	X	X	X	X	
12-lead ECG [l, i]	X				X	As clinically indicated or as indicated for each individual IMP	As indicated for each individual IMP	
Left ventricular ejection fraction (LVEF)					X	As clinically indicated or as indicated for each individual IMP	As clinically indicated or as indicated for each individual IMP	As indicated for each individual IMP
Ophthalmologic exams [m]						X (entrectinib, pemigatinib and vemurafenib only)	X	
HIV, HBV, HCV serology [n]	X							
Hematology [o, i]		X	X	X	X	X	X	

Appendix 1: Schedule of Activities

	Screening Period [a]		Induction Period		End of Induction Visit [d]	Treatment Period	Safety Follow-Up Visit [e]	Follow-up Period
	Day –28 to Day –1	Day –14 to Day –1	Cycle 1 Day 1 [b]	First day of each 21-day cycle (±3 days) for Cycles 2 and 3 [c]	Cycle 3 Day 14 to Cycle 3 Day 21 (+3 days)	First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [c]	30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	Every 3 (±1) months (Starting 3 months post final dose of study treatment)
Coagulation (aPTT, INR) [i]		X	X	X	X	X	X	
Thyroid function panel [p, i]		X			X	Every 9 weeks (atezolizumab only)		
Chemistry panel [q, i]		X	X	X	X	X	X	
Chemistry panel (IMP-specific) [r, i]					X	As indicated for each individual IMP		
Urinalysis [s, i]		X	X	X	X	X	X	
Pregnancy test [t]		X (serum within 7 days)		X	X (serum) (within 7 days of first dose in the treatment Period)	Refer to Footnote t (urine)	X	Refer to Footnote t (urine)
Tumor assessment [u]	X				Days 7 – 21 post C3 D1 (+3 days)	Every 9 weeks ±3 days until PD or treatment discontinuation (whichever is the later)		X [v] (as per comment)

Appendix 1: Schedule of Activities

	Screening Period [a]		Induction Period		End of Induction Visit [d]	Treatment Period	Safety Follow-Up Visit [e]	Follow-up Period
	Day –28 to Day –1	Day –14 to Day –1	Cycle 1 Day 1 [b]	First day of each 21-day cycle (±3 days) for Cycles 2 and 3 [c]	Cycle 3 Day 14 to Cycle 3 Day 21 (+3 days)	First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [c]	30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	Every 3 (±1) months (Starting 3 months post final dose of study treatment)
Archival tumor tissue [w]	X							
Tumor tissue biopsy (if insufficient or not suitable archival tissue is available) [w]	X							
Blood sample for FoundationOne® F1LCDx (Liquid) test profiling [w]			After eligibility confirmation, at C1 D1 Before starting the chemotherapy infusion		X can be taken up to C1 D1 of Treatment Period (before starting the treatment)			
Whole blood sample for exploratory research (for optional germline analyses)			X Single sample prior to infusion					
Serum blood sample for exploratory research			X Single sample prior to infusion					

Appendix 1: Schedule of Activities

	Screening Period [a]		Induction Period		End of Induction Visit [d]	Treatment Period	Safety Follow-Up Visit [e]	Follow-up Period
	Day –28 to Day –1	Day –14 to Day –1	Cycle 1 Day 1 [b]	First day of each 21-day cycle (±3 days) for Cycles 2 and 3 [c]	Cycle 3 Day 14 to Cycle 3 Day 21 (+3 days)	First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [c]	30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	Every 3 (±1) months (Starting 3 months post final dose of study treatment)
Plasma blood sample for exploratory research							X	
FACT-G HADS EQ-5D-5L [x]			X		X (Category 1 patients only)	X (Category 1 patients only)	X (Category 1 patients only)	X [y] Category 1 patients only (not applicable if visit is done by phone)
Concomitant medications [z]		X	X	X	X	X	X	
Adverse events [aa]		X	X	X	X	X	X	X
Additional safety visits						Ipatasertib + paclitaxel only D4, 8, 15, and 22 of Cycle 1 D8 and 15 of Cycle 2 Then D15 of all cycles until paclitaxel is stopped		

Appendix 1: Schedule of Activities

	Screening Period [a]		Induction Period		End of Induction Visit [d]	Treatment Period	Safety Follow-Up Visit [e]	Follow-up Period
	Day –28 to Day –1	Day –14 to Day –1	Cycle 1 Day 1 [b]	First day of each 21-day cycle (±3 days) for Cycles 2 and 3 [c]	Cycle 3 Day 14 to Cycle 3 Day 21 (+3 days)	First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [c]	30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	Every 3 (±1) months (Starting 3 months post final dose of study treatment)
Collection of information on survival and anticancer therapy [bb]							X	X
Molecular Tumor Board (MTB) and Randomization [cc]					Within 10 days of End of Induction Visit			
Study treatment								
Platinum-based induction chemotherapy			X (as per chosen treatment schedule)	X (for 2 cycles, as per chosen treatment schedule)				
Molecularly-guided therapy in patients with a CR, PR or SD during induction						X [aa] (until PD)		
Platinum-based chemotherapy in patients with a CR, PR or SD during induction						X [aa] (at least 3 cycles)		

Appendix 1: Schedule of Activities

	Screening Period [a]		Induction Period		End of Induction Visit [d]	Treatment Period	Safety Follow-Up Visit [e]	Follow-up Period
	Day –28 to Day –1	Day –14 to Day –1	Cycle 1 Day 1 [b]	First day of each 21-day cycle (±3 days) for Cycles 2 and 3 [c]	Cycle 3 Day 14 to Cycle 3 Day 21 (+3 days)	First day of each 21-day or 28-day cycle (±3 days) Dosing schedule per RSI [c]	30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	Every 3 (±1) months (Starting 3 months post final dose of study treatment)
Molecularly-guided therapy in patients with PD during induction (Category 2 patients)						X [aa] (until PD)		

AE = adverse event; AESI = adverse event of special interest; aPTT = activated partial thromboplastin time; C = cycle; chemo = chemotherapy; CR = complete response; *CT = computed tomography;* CUP = cancer of unknown primary site; *cutaneous squamous cell carcinoma = cuSCC;* D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; *eCRF = electronic Case Report Form;* FACT-G = Functional Assessment of Cancer Therapy–General; *FFPE = formalin-fixed, paraffin-embedded;* HADS = Hospital Anxiety and Depression Scale; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; *HBcAb = hepatitis B core antibody; HBsA = hepatitis B surface antigen;* HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IMP = Investigational Medicinal Product; INR = international normalized ratio; *LDH = lactate dehydrogenase; LVEF = Left ventricular ejection fraction; MRI = magnetic resonance imaging;* MTB = Molecular Tumor Board; PD = progressive disease; PR = partial response; *QD = once daily; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1;* RSI = reference safety information; *SAE = serious adverse event;* SD = stable disease; *TSH = thyroid-stimulating hormone.*

Note: Unless otherwise indicated, assessments scheduled on the study treatment days should be performed prior to initiation of study treatment.

[a] The Screening Period may be extended in exceptional cases:

- Up to 42 days (extension by 2 weeks) in case the first tissue submitted was not suitable or insufficient per central pathology assessment and a fresh biopsy has to be taken (see above).
- Up to 35 days (extension by 1 week):

  If there has been a delay in the shipment of the tissue sample.

  If escalation of the eligibility review to the referent oncologist and further information is requested or further tests are needed to determine eligibility.

[b] Assessments on Day 1 must be performed prior to study treatment. Day 1 is baseline for the study.

[c] 21-day cycles for all treatment arms (including for cohorts with oral therapies), except for cobimetinib and vemurafenib, ipatasertib and paclitaxel, and ivosidenib, where the administration cycle will be 28 days:

- Assessments must be performed within 72 hours of first study treatment (Cycle 1 Day 1) and of first administration of treatment in the Treatment Period. If any of the assessments occurring within 72 hours of Cycle 1 Day 1 and of first administration of treatment in the Treatment Period are abnormal, all assessments must be repeated on the first day of study treatment and of first administration of treatment in the Treatment Period, respectively.
- If any of the Cycle 1 Day 1 assessments do not meet eligibility criteria, study drug administration should be held and the tests repeated (timing of repeat testing should be based on clinical judgment). If eligibility criteria remain unsatisfied by the end of the initially defined Screening Period, the patient should be discontinued from the study.
- If any of the Day 1 of the Treatment Period assessments do not meet safety criteria for starting treatment in the Treatment Period, study drug administration should be held and the tests repeated (timing of repeat testing should be based on clinical judgment).

[d] For patients who reach Cycle 3, the End of Induction Visit will occur between Cycle 3 Day 14 and Cycle 3 Day 21 (+3 days). For patients who progress (PD) before Cycle 3, it will occur within 10 days of disease progression assessment.

[e] If the timing of the Safety Follow-Up Visit overlaps with a visit already completed, e.g., the End of Induction Visit, then the Safety Follow-Up Visit may not be performed. The Safety Follow-Up Visit is applicable for all patients, whether they discontinued permanently the treatment in the Induction or in the Treatment Period.

[f] Written informed consent is required for performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 (except where otherwise specified) may be used for screening assessments rather than repeating such tests, providing that these tests meet protocol requirements. The only exception to this requirement is that the imaging assessments mandatory for RECIST v1.1 (including head images) may occur up to 42 days prior to Day 1.

In cases where the Screening Period has been extended (see Section 3.1.1.2), screening assessments conducted during the initial Screening Period (e.g., CT scans) that met protocol requirements will remain valid during the Screening Period extension, with the following exceptions:

- Pregnancy tests and tests that should be repeated at baseline.
- Imaging tests performed up to 49 days prior to first dose of study treatment are acceptable.

[g] Medical history includes surgical and cancer histories. Cancer history includes stage, date of diagnosis, and prior anticancer treatment. Reproductive status and smoking history should also be captured. Demographic information includes age, sex, and self-reported race/ethnicity.

[h] A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed (see next footnote). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[i] Limited physical examination, ECOG performance status, ECG, urinalysis, and local laboratory assessments (hematology, coagulation, chemistry and thyroid function panel [when mandated]) may be obtained ≤72 hours before Day 1 of each cycle. It is not necessary to repeat these assessments again prior to Cycle 1 Day 1 of the Induction Period if they have been conducted for screening within this time period. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[j] In patients who are assigned vemurafenib treatment: head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation, should occur prior to initiation of treatment and every 3 months during treatment. Anal examinations (for all patients) and pelvic examinations (for women) should occur before and at the end of treatment or when considered clinically indicated. Monitoring for non-cuSCC should continue for up to 6 months after end of treatment or until initiation of another anti-neoplastic therapy. Dermatologic evaluation should occur prior to initiation of therapy, and then examination for cuSCC should occur at each study visit until end of study treatment; thereafter, evaluation should occur monthly up to six months after treatment or until initiation of another anti-neoplastic therapy.

[k] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Vital sign assessments performed on the first day of a treatment cycle should be done prior to IV study treatment (if applicable).

[l] ECG recordings will be obtained during screening and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[m] Ophthalmologic exams should only occur in patients who are assigned to entrectinib, pemigatinib or vemurafenib treatment:

- In patients assigned to entrectinib: Ophthalmologic exams, including at least visual acuity and slit-lamp tests (which may be performed by an optometrist), should be performed prior to starting the first administration, at Day 1 of the second cycle of treatment, at the end of treatment, and as clinically indicated.
- In patients assigned to pemigatinib: A comprehensive eye examination should be performed by a qualified ophthalmologist. The eye examination should include a visual acuity test, slit-lamp examination, and fundoscopy with digital imaging and optical coherence tomography, and is required prior to the first administration of pemigatinib, once every 3 cycles (±7 days, starting at Cycle 3), at end of treatment (not needed if completed within 28 days before the end of treatment), and more often if participants report any visual adverse events or change in visual acuity. An optometrist can perform the assessments if adequately trained and qualified; however, the optometrist should be supervised by an ophthalmologist, if possible, to provide the requisite clinical assessment. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.
- In patients assigned to vemurafenib: Routine monitoring of ophthalmologic reactions should occur at each cycle.

[n] HIV testing is mandatory for participation in the study. HBV serology includes HBsAg and total HBcAb. If the HBsAg test is negative and total HBcAb test is positive, HBV DNA must also be assessed (see Section 4.5.7). HCV antibody serology includes HCV antibody testing. If the HCV antibody test is positive, HCV RNA must also be assessed (see Section 4.5.7).

[o] Hematology consists of CBC (including RBC count), hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential may be done if clinically indicated.

[p] Thyroid function panel includes: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4

[q] Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate or total carbon dioxide (both optional and if considered standard of care for the region), glucose, BUN or urea, creatinine + creatinine clearance (calculated through use of Cockcroft-Gault formula), total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, and LDH.

At the End of Induction Visit, the panel will also include CPK, fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides; all performed following ≥ 4-hour fast prior to testing), amylase and lipase and glycated hemoglobin (HbA1c).

During the Treatment Period, the panel may also include some IMP-specific exam at the timepoints indicated in the footnote r.

[r] The following should be tested for **specific IMPs only**

(Note: Assessments that do not coincide with planned study visits may be performed within ± 3 days of the timing described below for tests planned at intervals ≤ 3-weekly and within ± 7 days of the timing for tests planned at monthly or greater intervals):

- Alectinib: CPK levels, and liver function tests (ALT, AST, total bilirubin, alkaline phosphatase) every two weeks for 12 weeks of treatment, then every 6 weeks between weeks 12 and 48 and every 12 weeks thereafter, until week 96 (during the Treatment Period only).
- Atezolizumab: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 every 9 weeks; ECG as clinically indicated.
- Cobimetinib: LVEF after the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. CPK levels every 4 weeks during treatment and as clinically indicated in patients reporting severe myalgias.
- Entrectinib: LVEF at Cycle 3 Day 1 (± 7 days), as clinically indicated, and at the Safety Follow-Up Visit (if patient experienced Grade 2 or higher ejection fraction decrease at Cycle 3 or at any time during treatment, or if clinically indicated). Safety Follow-Up LVEF is not necessary if the last LVEF assessment was performed within 1 week prior to the Safety Follow-Up Visit and if the investigator deems it not clinically indicated. Evaluation of LVEF must be performed by the same method (echocardiogram or MUGA) for each patient. It is strongly recommended that the same laboratory and operator perform echocardiogram/MUGA scans for each individual patient.

  ECGs:

  - At Day 1 of Cycles 1 to 5 of treatment with entrectinib with a single 12-Lead ECG assessment performed pre-dose and 4 hours (± 15 minutes) post-dose,
  - At end of treatment, and
  - As clinically indicated.

  In case of an event of QTc prolongation (Grade > 1), patient should be followed more closely. In addition, the ECG should be read over for confirmation, and continuous ECG monitoring may be implemented as clinically indicated.
- Erlotinib + bevacizumab: No additional assessments

- Ipatasertib (only if administered without paclitaxel [see next bullet if ipatasertib is administered with paclitaxel]):

  Every 3 weeks, on Day 1 of each cycle and on Day 8 of Cycle 1: Fasting blood glucose and fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides, all performed following ≥4-hour fast prior to testing); amylase and lipase; and glycosylated hemoglobin (HbA1c). In addition, on Days 4, 15 of Cycle 1 and Days 8 and 15 of Cycle 2: fasting blood glucose (patients should fast ≥4 hours prior to testing).
- Ipatasertib and paclitaxel:

  On Day 1 and 15 of each 28-day cycle, on Days 4, 8 and 22 of Cycle 1 and on Day 8 of Cycle 2: fasting blood glucose and fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides; all performed following ≥4-hour fast prior to testing), amylase and lipase, and glycosylated hemoglobin (HbA1c).

  On Days 1, 8 and 15 of each 28-day cycle (until paclitaxel is stopped): hematology including WBC count, WBC differential count (including absolute neutrophil counts, lymphocytes), hemoglobin, hematocrit, and platelet count.

  On paclitaxel dosing days, vital signs should be recorded prior to dosing and at the end of the infusion.

  Additional safety visits at Day 15 of each cycle should coincide with paclitaxel administration. These visits are necessary only until paclitaxel is stopped.
- Ivosidenib:

  ECGs: On Day 1 of each 28-day cycle, on Cycle 1 Day 15, and at the Safety Follow-Up Visit.

  LVEF: As clinically indicated and at the Safety Follow-Up Visit (ECHO or other method per institutional practice).
- Olaparib: No additional assessments.
- Pemigatinib:

  Parathyroid hormone at Cycle 1 Day 1, every 3 cycles on Day 1 starting with Cycle 3, and at the Safety Follow-Up Visit

  Serum phosphorus levels at:
  - Day 1, Day 8 and Day 15 of Cycle 1
  - Day 1 of Cycle 2 and the first day of every cycle thereafter until end of treatment
  - Safety Follow-Up Visit

  Note: Any patient assigned to pemigatinib who does not reach a target serum phosphate level of >5.5 mg/dL at any time during Cycle 1, is compliant with taking study drug, and does not experience an ongoing Grade 2 or higher treatment-related AE will increase the daily dose to 18 mg QD starting from Cycle 2 Day 1. Hyperphosphatemia in Cycle 1 requires Day 8 testing of serum phosphate in Cycle 2+ until phosphate is <7 mg/dL on Day 8 for at least 2 consecutive cycles on stable dose of binders.

  ECGs on the first day of every cycle and at the Safety Follow-Up Visit.

  Nail check, as part of the physical exam, on the first day of every cycle and at the Safety Follow-Up Visit.

- Trastuzumab + pertuzumab (± chemotherapy): LVEF at Cycle 3 Day 1, then every 3 cycles during treatment. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g., every 6–8 weeks). LVEF every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab.
- Vemurafenib: Amylase and lipase at each cycle; ECG and electrolytes (including magnesium) must be monitored in all patients before treatment, monthly for 3 months, then every third month while on study treatment and after dose modification. Note: Patients who are assigned vemurafenib will also have additional assessments during their ongoing physical examinations, as described in Footnote j.
- Vismodegib: No additional chemistry laboratory assessments.

[s] Urinalysis including dipstick: specific gravity, pH, glucose, protein, ketones, and blood.

[t] A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Day 1 and prior to the first dose in the Treatment Period (see specific requirements for vismodegib). Pregnancy tests (urine) should be conducted at each study visit (every 21 days ±3 days or every 28 days ±3 days depending on the IMP schedule of administration) during both Induction and Treatment Periods and no less than monthly if a study visit is delayed. For all treatments, pregnancy tests should be conducted at the Safety Follow-Up Visit and at the end of each contraception period, which corresponds to the following time points after their final dose of study treatment: 2 weeks for erlotinib, 1 month for ipatasertib and olaparib, 5 weeks for entrectinib and pemigatinib; 3 months for alectinib and ivosidenib; 5 months for atezolizumab; 6 months for bevacizumab, cobimetinib, vemurafenib, carboplatin, cisplatin, paclitaxel and gemcitabine; 7 months for trastuzumab and pertuzumab.
Note: For vismodegib, a blood pregnancy test should be performed within 7 days prior to initiating treatment and a supervised pregnancy test, conducted by a healthcare provider, should be performed at each study visit during treatment and 2 months and 24 months after their final dose of study treatment (the 2 and 24 months post treatment tests can be performed by a local health practitioner and reported to the investigator). If study visits are delayed, the pregnancy tests must be performed independently of the visits and no less than monthly. Pregnancy tests should have a minimum sensitivity of 25 mIU/mL, as per local availability. Patients who present with amenorrhea during treatment with vismodegib should continue monthly pregnancy testing while on treatment.

[u] The same radiographic procedure should be used throughout the study for each patient:

- Screening Period: A CT (with contrast) or MRI scan of the head must be included in screening tumor assessments. Imaging assessments mandatory for RECIST v1.1 (including head images) may occur up to 42 days prior to Day 1, unless the Screening Period is extended, in which case imaging tests performed up to 49 days prior to first dose of study treatment are acceptable.
- Before start of the Treatment Period: A CT (with contrast) or MRI scan of the head must be included in the End of Induction tumor assessments (results must be available at the End of Induction Visit, similar to other scans for RECIST assessment).
- Treatment Period: During the Treatment Period, tumor assessments should occur every 9 weeks (±3 days, with first assessment during the Treatment Period being made 9 weeks post C1D1) regardless of dose interruptions. Results must be reviewed by the investigator before dosing at the next cycle.

- Treatment beyond progression: Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 should be monitored with a follow-up scan every 9 weeks until treatment discontinuation. Based on clinical judgment, the investigator can extend this period to every 12 weeks.

[v] Patients who enter the Follow-up Period before PD should continue to be assessed, per protocol, until disease progression. All patients in the control arm must be followed up until disease progression. This also includes patients who discontinue to receive alternative therapy after the MTB.

[w] Refer to the Laboratory Manual for specimen collection instructions and for specific requirements for a sample to be suitable for genomic profile generation. Tumor FFPE blocks are preferred. In exceptional cases, 25 slides (4 µm slide thickness each) may be accepted. Archival tumor tissue samples and tumor biopsies should be sent to special laboratories no less than 14 days prior to planned study Day 1.

- Archival tumor tissue must not be older than 4 months at start of the Screening Period. If older, a new tissue biopsy must be obtained.
- If the tissue submitted to the central laboratory for testing does not fulfill acceptance criteria and a new tumor tissue biopsy is required, the Screening Period may be extended for up to 14 days.
- Blood sample for FoundationOne® F1LCDx (Liquid) test will be collected and sent after eligibility confirmation (collection at Cycle 1 Day 1 before starting the chemotherapy infusion).
- The local pathology reports confirming compatibility with CUP diagnosis and the associated slides used for the diagnosis must also be submitted. If the slides used for the local test reports confirming local CUP diagnosis are not available, the FFPE block submitted for genomic profiling must be sufficient to allow for central confirmation of CUP diagnosis.

[x] See Appendices 7 to 9 for the questionnaires. The baseline exam at Cycle 1 Day 1 of the Induction Period must be done prior to chemotherapy start.

[y] Only in patients who have not progressed at the Safety Follow-Up Visit. In those patients who have not progressed, PRO assessments should occur at the same times as the tumor assessments during the Follow-Up Period.

[z] Concomitant medications include any prescription medications or over-the-counter medications.

- At Screening: Any medications used by the patient within 7 days prior to initiation of study drug should be documented.
- During the Induction Period: Only the medications related to the captured adverse reactions during this period and changes to medications existing at baseline should be collected (see footnote aa for AE reporting guidelines).
- At the End of Induction Visit: all ongoing medications should be collected (to allow for an appropriate assessment of the general inclusion criteria in the Treatment Period and to comply with the re-baselining activities at the start of the Treatment Period).
- At subsequent visits (during the Treatment Period): changes to current medications or medications used since the last documentation of medications should be recorded.

[aa] After informed consent has been obtained, but prior to initiation of study drug: only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies) should be reported.

- During the Induction Period: only adverse events leading to dose modifications, interruption or discontinuation of the platinum-based chemotherapy and all SAEs will be captured.
- At the End of Induction Visit: all ongoing adverse events will be collected (to allow for an appropriate assessment of the general inclusion criteria in the Treatment Period and to comply with the re-baselining activities at the start of the Treatment Period).
- After initiation of molecularly-guided therapy (including the control arm for Category 1 patients): all AEs, SAEs and AESIs, regardless of relationship to study drug, will be reported until 30 days after the final dose of study drug or initiation of new systemic anticancer therapy, whichever occurs first, for all drugs except for atezolizumab, where it will be 90 days. After this period, the investigator should report any SAEs or AESIs believed to be related to prior study drug treatment. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.

  Note: For atezolizumab, the first Follow-Up Visit (90 days after the final dose of study drug) is regarded as the end of AE reporting period.

[bb] After treatment discontinuation, information on survival status and new anticancer therapies, including local assessment of overall tumor response and dates of progression to the following subsequent anticancer therapies, will be collected via telephone contact, patient medical records, and/or clinic visits approximately every 3 ($\pm$1) months until death, loss to follow up, end of study, patient withdrawal or study termination by the Sponsor, whichever occurs first. Patients who discontinue treatment for reason other than PD but who do not withdraw consent to follow up will be assessed for progression as described during the Treatment Period (including scans) until disease progression (refer to footnote v). After disease progression, these patients will continue with survival follow up.

[cc] The MTB must be scheduled to take place no later than 10 days after the End of Induction Visit for all patients. The MTB will be cancelled for Category 1 patients randomized to continue chemotherapy:

- Randomization (for Category 1 patients only) should occur between the End of Induction Visit and no less than 48 hours before the planned MTB meeting date.
- The MTB (for all patients) and randomization (for Category 1 patients) must be delayed after the End of Induction Visit if general safety criteria for entrance into the Treatment Period are not met, however the Sponsor's study team must be informed of the delay (Section 4.1.1.2). If the MTB is delayed, starting treatment in the Treatment Period of the study will be subject to verifying that the general safety criteria for entry into the study are met:
  - If the MTB is delayed up to Cycle 3 Day 42 (or until 42 days after Day 1 of the last induction treatment cycle for Category 2 patients who receive less than 3 cycles), only the general safety criteria previously not met will need verifying.

  - If the MTB is delayed beyond Cycle 3 Day 42 (or until 42 days after Day 1 of the last induction treatment cycle for Category 2 patients who receive less than 3 cycles), all general safety eligibility criteria must be checked, and if they are still not met, the patient will not be eligible to receive further treatment in the study. Instead, the patient will move directly to the Safety Follow-Up Visit and, then, proceed into the Follow-up Period, where he or she will receive non-IMP treatment outside of the study (see below).
- If the MTB is delayed to Day 15 or more after the End of Induction Visit, Investigator's judgment will be exercised to determine which tests need repeating prior to the MTB.

Treatment initiation must occur within 21 calendar days after the End of Induction Visit.

If any of the mandatory Day1 Treatment Period assessments do not meet the criteria for starting treatment in the Treatment Period, study drug administration should be held. If therapy is delayed beyond Cycle 3 Day 42 (or until 42 days after Day 1 of the last induction treatment cycle for Category 2 patients who receive less than 3 cycles), Medical Monitor should be informed.

Appendix 2
Timeline of Key Study Events

Study Period	Timing	Key Events
Screening Period	All patients: Day –28 to Day –1	• Complete Part 1 of the ICF • Assess patient eligibility • Collect and ship tissue sample for central laboratory: – Archival tumor tissue samples for FoundationOne® FMI F1CDx (tissue) test that meets study requirements Must not be older than 4 months at start of the Screening Period If an acceptable archival tumor FFPE block is not available or is not suitable (in quantity and quality) at screening, an FFPE block from a freshly obtained biopsy sample must be provided that meets the study's requirements – Local pathology reports confirming compatibility with CUP diagnosis and associated slides used for the diagnosis. If the slides used for confirming local CUP diagnosis are not available, the FFPE block submitted for genomic profiling must be sufficient to allow for central confirmation of CUP diagnosis The Screening Period may be extended in exceptional cases: • Up to 42 days (extension by 2 weeks) in case the first tissue submitted was not suitable or insufficient per central pathology assessment and a fresh biopsy has to be taken (see above) • Up to 35 days (extension by 1 week): – If there has been a delay in the shipment of the tissue sample – If escalation of the eligibility review to the referent oncologist and further information is requested or further tests are needed to determine eligibility Screening assessments conducted during the initial Screening Period (e.g., CT scans) that met protocol requirements will remain valid during the Screening Period extension, with the following exceptions: – Pregnancy tests and tests that should be repeated at baseline – Imaging tests performed up to 49 days prior to first dose of study treatment are acceptable

Appendix 2: Timeline of Key Study Events

Study Period	Timing	Key Events
Induction Period	All patients: Day 1 until randomization (Category 1 patients) or assignment of molecularly-guided treatment (Category 2 patients)	• Collect and ship blood sample for central laboratory: – Blood sample for FoundationOne® F1LCDx (Liquid) test after eligibility confirmation (collection at Cycle 1 Day 1 before starting the chemotherapy infusion) • Treatment will start after the CUP diagnosis and the availability of suitable tumor tissue have been reviewed and confirmed by the Eligibility Review Team – Treatment must start as soon as possible after eligibility confirmation and no later than 42 days after the start of screening (depending on screening extension) • Administer 3 cycles of platinum-based chemotherapy to all eligible patients • Assess tumor response on Cycle 3 any time after Day 7 – Tumor response results must be available for End of Induction Visit
End of Induction Visit (Part of Induction Period)	Cycle 3 Day 14 to 21 (+3 days) if no progression before Cycle 3 or within 10 days of disease progression assessment if progression before Cycle 3 [a]	• Categorize patients based on tumor assessments – Category 1: CR, PR or SD after 3 cycles of platinum induction chemotherapy – Category 2: documented PD after 3 cycles of platinum induction chemotherapy or at any time during the Induction Period • Perform or collect results for all assessments planned at End of Induction Visit • Evaluate all exclusion/inclusion criteria and safety criteria for entrance into the Treatment Period

Appendix 2: Timeline of Key Study Events

Study Period	Timing	Key Events
MTB scheduling		• A tentative date for MTB should be set at Day 1 of induction chemotherapy, and the target date should be within 10 days of the planned End of Induction Visit • Once the End of Induction Visit has taken place, the MTB date should be finalized and should be within 10 days of the End of Induction Visit • The MTB (for all patients) and randomization (for Category 1 patients) must be delayed after the End of Induction Visit if general safety criteria for entrance into the Treatment Period are not met, however the Sponsor's study team must be informed of the delay. If the MTB is delayed, starting treatment in the Treatment Period of the study will be subject to verifying that the general safety criteria for entry into the study are met: – If the MTB is delayed up to Cycle 3 Day 42 (or until 42 days after Day 1 of the last induction treatment cycle for Category 2 patients who receive less than 3 cycles), only the general safety criteria previously not met will need verifying. – If the MTB is delayed beyond Cycle 3 Day 42 (or until 42 days after Day 1 of the last induction treatment cycle for Category 2 patients who receive less than 3 cycles), all general safety eligibility criteria must be checked, and if they are still not met, the patient will not be eligible to receive further treatment in the study. Instead, the patient will move directly to the Safety Follow-Up Visit and, then, proceed into the Follow-up Period, where he or she will receive non-IMP treatment outside of the study. • MTB will be cancelled for Category 1 patients randomized to continue chemotherapy
Randomization	Category 1 patients: After End of Induction Visit and no less than 48 hours before planned MTB Category 2 patients: Not applicable	• Patients will be assigned to molecularly-guided therapy or to the control arm with chemotherapy Note: If not meeting safety criteria for entrance into the Treatment Period, the MTB and randomization will be delayed accordingly

Appendix 2: Timeline of Key Study Events

Study Period	Timing	Key Events
Molecular Tumor Board	Category 1 patients assigned to molecularly-guided therapy [b] And Category 2 patients	• Assign molecularly-guided therapy to Category 1 patients who were randomized to investigational treatment and to all Category 2 patients
Treatment Period	Initiate treatment within 21 days post End of Induction Visit	• Complete Part 2 of the ICF prior to enrollment to Treatment Period • Ensure tumor assessments have been re-assessed for re-baseline in the Treatment Period and that Treatment Period Day 1 physical evaluation, performance status, weight, vital signs and laboratory assessments are performed prior to administration of first dose to serve as baseline for the Treatment Period • Start treatment – Treat until loss of clinical benefit, unacceptable toxicity, patient or investigator decision to discontinue, or death (whichever occurs first) – An assessment cycle will be 21 days for all treatment arms (including for cohorts with oral therapies) except for cobimetinib and vemurafenib, ipatasertib and paclitaxel, and ivosidenib, where the administration cycle will be 28 days Note: If any of the mandatory Day1 Treatment Period assessments do not meet the criteria for starting treatment in the Treatment Period, study drug administration should be held. If therapy is delayed beyond Cycle 3 Day 42 (or until 42 days after Day 1 of the last induction treatment cycle for Category 2 patients who receive less than 3 cycles), Medical Monitor should be informed.
Safety Follow-Up Visit	All patients: 30 (±7) days after last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	• Refer to Appendix 1 for assessments

Appendix 2: Timeline of Key Study Events

Study Period	Timing	Key Events
Survival Follow-Up Period	All patients: Every 3 (±1) months after the final dose of treatment until death, loss to follow up, withdrawal of consent or end of the study	• Follow up for survival and further anticancer treatment (name of therapies, start and end dates, best response and date of progression) • Patients who enter the Follow-up Period before PD should continue to be assessed, per protocol, until disease progression. All patients in the control arm must be followed up until disease progression. This also includes patients who discontinue to receive alternative therapy after the MTB.

CR =complete response; CT =computed tomography; CUP =cancer of unknown primary site; FFPE =formalin-fixed, paraffin-embedded; MTB =Molecular Tumor Board; PD =progressive disease; PR =partial response; SD =stable disease.

[a] Assessments to be performed within 10 days of randomization and can start before the C3 tumor assessment to allow for planning and analysis of tests. All results must be available before randomization (Category 1 patients) or the date of the Molecular Tumor Board (Category 2 patients).

[b] Not applicable for Category 1 patients assigned to platinum-based chemotherapy.

Appendix 3
Schedule of Study Sample Collection

Visit/Period	Timing	Sample Type
Screening	Day −28 to Day –1	• For central laboratory – Archival tumor tissue sample, if available (sent no less than 14 days prior to planned Day 1) – Tumor tissue biopsy, if no archival tumor tissue is available or is insufficient or unsuitable (see Laboratory Manual for details) for study purposes (sent no less than 14 days prior to planned Day 1) – Local pathology reports confirming compatibility with CUP diagnosis and associated slides used for the diagnosis. If the slides used for confirming local CUP diagnosis are not available, the FFPE block submitted for genomic profiling must be sufficient to allow for central confirmation of CUP diagnosis • For local laboratory – Blood sample for HIV, HBV, and HCV serology
Screening	Day −14 to Day –1	• For local laboratory – Blood sample for hematology, coagulation, thyroid function panel and chemistry – Urine sample for urinalysis
	Day −7 to Day –1	• For local laboratory – Blood sample for serum pregnancy test [a]
Day 1 (Cycle 1 Day 1 of the Induction Period)	Prior to first infusion of platinum chemotherapy	• Pregnancy test – urine sample for pregnancy test • For central laboratory – Blood sample for FoundationOne® F1LCDx (Liquid) test – Serum blood sample for exploratory research – Optional: whole blood sample for exploratory germline mutation analyses • For local laboratory – Blood sample for hematology, coagulation and chemistry – Urine sample for urinalysis
Cycle 2 Day 1 (±3 days) Cycle 3 Day 1 (±3 days) of the Induction Period	Prior to infusion of platinum chemotherapy	• Pregnancy test – urine sample for pregnancy test • For local laboratory – Blood sample for hematology, coagulation and chemistry – Urine sample for urinalysis and pregnancy test

Appendix 3: Schedule of Study Sample Collection

Visit/Period	Timing	Sample Type
End of Induction Visit	Cycle 3 Day 14 to 21 (±3 days)	• For central laboratory – Blood sample for FoundationOne® F1LCDx (Liquid) test • For local laboratory – Blood sample for hematology, coagulation, thyroid function panel and chemistry (which will also include CPK, fasting lipid profile, amylase and lipase and glycated hemoglobin [HbA1c]) – Urine sample for urinalysis
Treatment Period	Prior to IMP administration on the first day (±3 days) of each treatment cycle	• Pregnancy test – Within 7 days of first dose: blood sample for serum test – At all cycles for patients randomized to chemotherapy and from 2nd cycle of molecularly guided therapy: urine sample for pregnancy test [a] • For local laboratory – Blood sample for hematology, coagulation, – Blood sample for chemistry and IMP-specific chemistry, as indicated for each individual IMP (see below) – Urine sample for urinalysis • There are additional tests for some IMPs: – Alectinib: CPK levels and liver function tests (ALT, AST, total bilirubin, alkaline phosphatase) every two weeks for the first 12 weeks of treatment, then every 6 weeks between weeks 12 and 48 and every 12 weeks thereafter, until week 96 – Atezolizumab: Thyroid function panel every 9 weeks – Cobimetinib: CPK levels every 4 weeks during treatment and as clinically indicated in patients reporting severe myalgias – Ipatasertib (only if administered without paclitaxel): Every 3 weeks, on Day 1 of each cycle and on Day 8 of Cycle 1: fasting blood glucose and fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides, all performed following ≥4 hour fast); amylase and lipase; and glycosylated hemoglobin (HbA1c). On Days 4, 8, 15 of Cycle 1 and Day 8 of Cycle 2: fasting glycemia blood glucose (patients should fast ≥4 hours prior to testing Every 3 weeks, on Day 1 of each cycle and on Day 8 of Cycle 1: Fasting blood glucose and fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides, all performed following ≥4-hour fast prior to testing); amylase and lipase; and

Appendix 3: Schedule of Study Sample Collection

Visit/Period	Timing	Sample Type
		glycosylated hemoglobin (HbA1c). In addition, on Days 4, 15 of Cycle 1 and Days 8 and 15 of Cycle 2: fasting blood glucose (patients should fast ≥4 hours prior to testing) – Ipatasertib and paclitaxel: On Day 1 and 15 of each 28-day cycle, on Days 4, 8 and 22 of Cycle 1 and on Day 8 of Cycle 2: fasting blood glucose and fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides; all performed following ≥4-hour fast prior to testing), amylase and lipase, and glycosylated hemoglobin (HbA1c) On Days 1, 8 and 15 of each 28-day cycle (until paclitaxel is stopped): hematology including WBC count, WBC differential count (including absolute neutrophil counts, lymphocytes), hemoglobin, hematocrit, and platelet count Additional safety visits at Day 15 of each cycle should coincide with paclitaxel administration. These visits are necessary only until paclitaxel is stopped. – Pemigatinib: Parathyroid hormone at Cycle 1 Day 1, every 3 cycles on Day 1 starting with Cycle 3, and at the Safety Follow-Up Visit Serum phosphorus levels at: Day 1, Day 8 and Day 15 of Cycle 1; Day 1 of Cycle 2 and the first day of every cycle thereafter until end of treatment; Safety Follow-Up Visit Note: Any patient assigned to pemigatinib who does not reach a target serum phosphate level of >5.5 mg/dL at any time during Cycle 1, is compliant with taking study drug, and does not experience an ongoing Grade 2 or higher treatment-related AE will increase the daily dose to 18 mg QD starting from Cycle 2 Day 1. In patients who up-titrate to pemigatinib 18 mg QD, two additional measurements of serum phosphate level must occur at Cycle 2 Day 8 and Cycle 2 Day 15. – Vemurafenib: amylase and lipase at each cycle

Appendix 3: Schedule of Study Sample Collection

Visit/Period	Timing	Sample Type
Safety Follow-Up Visit	30 (±7) days from last treatment or at initiation of other systemic anticancer therapy (whichever occurs first)	• For central laboratory – Plasma blood sample for exploratory research • For local laboratory – Blood sample for hematology, coagulation and chemistry – Urine sample for urinalysis and pregnancy test
Follow-up Period	As indicated for each individual IMP	• Pregnancy tests (urine; note special requirements for patients on vismodegib, including blood test prior to starting treatment and supervised pregnancy tests thereafter [b]), occurring at the end of each contraception period after the final dose of study treatment: – 2 weeks for erlotinib – 1 month for ipatasertib and olaparib – 5 weeks for entrectinib and pemigatinib – 3 months for alectinib and ivosidenib – 5 months for atezolizumab – 6 months for bevacizumab, cobimetinib, vemurafenib, carboplatin, cisplatin, paclitaxel, and gemcitabine – 7 months for trastuzumab and pertuzumab – 2 months and 24 months for vismodegib

AE = adverse event; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IMP = Investigational Medicinal Product; MTB = Molecular Tumor Board*;* *QD = once daily*.

[a] Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to first dose. If the serum pregnancy test is uninterpretable (e.g., beta-HCG is elevated in the absence of other signs of pregnancy), the reason for non-interpretability should be adequately documented, and intra- or extra-uterine pregnancy should be ruled out by ultrasound within 7 days prior to the first administration of study treatment

[b] For vismodegib, a blood pregnancy test should be performed within 7 days prior to initiating treatment and a supervised pregnancy test, conducted by a healthcare provider, should be performed at each study visit during treatment and 2 months and 24 months after their final dose of study treatment (the 2 and 24 months post treatment tests can be performed by a local health practitioner and reported to the investigator). If study visits are delayed, the pregnancy tests must be performed independently of the visits and no less than monthly. Pregnancy tests should have a minimum sensitivity of 25 mIU/mL, as per local availability. Patients who present with amenorrhea during treatment with vismodegib should continue monthly pregnancy testing while on treatment.

Appendix 4
Pre-existing Autoimmune Diseases and Immune Deficiencies Contraindicating Atezolizumab Use

Patients who are assigned atezolizumab (as monotherapy or in combination) should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias, where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anticancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Anti-phospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myelitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • *Granulomatosis with polyangiitis* • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1: Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 [1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-target Lesions" for information on lymph node measurement.

Non-measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with $\geq$10 to $<$15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, with use of calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u> Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size with use of a new modality.

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NONTARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR)**: disappearance of all target lesions
- Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline
- In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- The appearance of one or more new lesions is also considered progression.
- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to <10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis <10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the eCRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Whereas some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the time points specified in the protocol.

- **CR**: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)
- All lymph nodes must be non-pathological in size ($<$10 mm short axis).
- **Non-CR/Non-PD**: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing non-target lesions
- The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Whereas it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

When the patient has bone lesions at baseline. When a bone scan is the sole indicator of progression, progression in bone will be defined as when at least two or more new lesions are seen on bone scan compared with screening. In situations where the scan findings are suggestive of a flare reaction, or apparent new lesion(s) which may represent trauma, these results must be confirmed with other imaging modalities such as MRI or fine-cut CT to constitute progression. Only a single new bone lesion on bone scan is required for progression if the lesion can be correlated on CT, MRI or plain film.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

New osteoblastic bone lesions identified on plain films, CT, or MRI will not be considered progression in an otherwise stable or responding subject, if, in the opinion of the physician, the osteoblastic lesion appears to be healing or a response to therapy.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. Table A5-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table A5-2 is to be used.

Table A5-1 Timepoint Response: Patients with Target Lesions (with or without Non-target Lesions)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table A5-2 Timepoint Response: Patients with Non-target Lesions Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that time point.

Table A5-3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first time point, any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

NOTE: In this study, stable disease must persist for at least 6 weeks (minimum duration) to be considered a bona fide SD.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.
The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table A5-1, Table A5-2, and Table A5-3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 6
Eastern Cooperative Oncology Group (ECOG) Performance Status Scale Study

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about $>$50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair $>$50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 7
Functional Assessment of Cancer Therapy – General (FACT-G)

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family.	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed during the day	0	1	2	3	4
	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
GS7	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ?and go to the next section. I am satisfied with my sex life.	0	1	2	3	4
	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse.	0	1	2	3	4
	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (including housework)	0	1	2	3	4
GF2	My work (including housework) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I sleep well	0	1	2	3	4
GF6	I enjoy the things I usually do for fun.	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

*You will find a list of statements that other people who have the same disease as you do considered important. Please circle the number that best describes your health status during the previous 7 days.
Source: With the permission of: www.facit.com, 76 following acceptance of registration (registration number: 439)

Appendix 8
Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

Appendix 9
EQ-5D-5L Scale

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Appendix 10
IMP-Specific Safety and Administration Information

<u>NOTE</u>: For each Investigational Medicinal Product, it is the responsibility of the investigator to check for potential interactions in the investigator's brochure and local product information (if a marketed product).

This Appendix does not detail contraindications and warning and precautions that are covered by inclusion and exclusion criteria of the study protocol.

A10–1 ALECTINIB

BACKGROUND

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase that is constitutively activated in cancer due to gene alterations, such as chromosomal rearrangement.

Alectinib is a highly-selective CNS-active ALK inhibitor with a benzo[b]carbazole scaffold. In enzyme inhibition assays performed in vitro, this compound has been shown to selectively inhibit ALK. The compound also shows high antitumor activity both in vitro and in vivo against tumor cell lines with some types of ALK gene alterations, including NSCLC and anaplastic large cell lymphoma lines harboring an ALK translocation and a neuroblastoma line harboring an amplified ALK gene.

Alectinib has demonstrated antitumor activity in ALK-positive NSCLC, including in crizotinib-resistant disease and in patients with CNS metastases (Gadgeel et al. 2014; Barlesi et al. 2016; Gadgeel et al. 2016; Shaw et al. 2016; Hida et al. 2017; Peters et al. 2017; Tamura et al. 2017).

SAFETY

SAFETY PROFILE

A comprehensive description of the safety profile of alectinib is provided in the Alectinib Investigator's Brochure.

The summary information provided in the following section must always be checked against any update of the Alectinib Investigator's Brochure that may have occurred after the protocol has been issued.

Adverse reactions associated with Warning and Precautions:

- Interstitial lung disease (ILD)/pneumonitis
- Hepatotoxicity
- Severe myalgia and creatine phosphokinase (CPK) elevation
- Bradycardia
- Photosensitivity
- Hemolytic anemia

Other selected adverse reaction:

- Rash
- Anemia
- Gastrointestinal disorders (nausea, vomiting, constipation, diarrhea, stomatitis)

- Dysgeusia
- Blood alkaline phosphatase increase
- Edema
- Vision disorders
- Renal impairment (Increased blood creatinine, acute kidney injury)
- Weight increase

Management guidelines for alectinib that are applicable to this study are provided in A10–1.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For alectinib, there are no AESIs to be reported.

ADMINISTRATION

POSOLOGY

Alectinib will be administered as a 600-mg oral dose (four 150-mg capsules) taken twice daily with food (total daily dose of 1200 mg).

METHOD OF ADMINISTRATION

The hard capsules should be swallowed whole and must not be opened or dissolved. They must be taken with food.

DURATION OF TREATMENT

Treatment with alectinib should continue until loss of clinical benefit or the development of unacceptable toxicity.

DELAYED OR MISSED DOSES

If a planned dose of alectinib is missed, patients can make up that dose unless the next dose is due within 6 hours. Patients should not take two doses at the same time to make up for a missed dose. If vomiting occurs after taking a dose of alectinib, patients should take the next dose at the scheduled time.

PROHIBITED THERAPY

Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents (other than study drug treatment), ergot derivatives, probenecid, and bile acid-binding resins while on study treatment.

DOSE ADJUSTMENTS AND DISCONTINUATION

Management of adverse events may require dose reduction, temporary interruption, or discontinuation of treatment with alectinib. The dose of alectinib should be reduced in steps of 150 mg twice daily based on tolerability.

Alectinib treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

Alectinib should be permanently discontinued if the following is occurring:

- Patients are unable to tolerate the 300 mg twice-daily dose after two dose reductions due to adverse events as specified in the last section of Table A10-2
- Grade 3 or 4 events related to alectinib not improving within 21 days, as specified in the last section of Table A10-2
- Interstitial lung disease of any grade, regardless of relatedness to alectinib
- Hepatotoxicity events according to the specific criteria detailed in Table A10-2
- Abnormal kidney function AEs of Grade 4 related to alectinib
- Hemolytic anemia according to the criteria specified in Table A10-2

Bradycardia Grade 4 if no contributing concomitant medicinal product is identified, or in case of reoccurrence of bradycardia Grade 4.
The dose reduction schedule is provided in Table A10-1.

Table A10-1 Dose Reduction Schedule

Dose Reduction Schedule	Dose Level
Starting dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

Table A10-2 Dose Modification and Discontinuation Advice for Specified Adverse Drug Reactions

Event	Action to Be Taken
Interstitial lung disease /pneumonitis	• Patients should be monitored for pulmonary symptoms indicative of pneumonitis • Regardless of relatedness to alectinib, study drug should be permanently discontinued in patients diagnosed with interstitial lung disease of any grade.
Hepatotoxicity	• At any time during the study treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible. • Regardless of relatedness to alectinib, the grade-dependent rules for dose interruptions and dose modification outlined in the last section of this table must be followed. • In addition, study drug treatment has to be permanently discontinued if any of the following occurs: – First observation of ALT or AST $>8\times$ ULN – ALT or AST $>5\times$ ULN for more than 2 weeks – First observation of ALT or AST $>3\times$ ULN and total bilirubin $>2\times$ ULN – First observation of ALT or AST $>3\times$ ULN and the appearance of jaundice or signs of hepatic dysfunction or other symptoms (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [$>5\%$]) • Following study drug discontinuation, weekly monitoring of laboratory values should continue until the abnormal values have normalized to pre-treatment levels and/or an adequate explanation of the abnormal value is found • Resumption of study drug is not allowed in patients discontinuing because of any of the above criteria
Gastrointestinal tract AEs (e.g., nausea, vomiting, diarrhea)	The events are expected to be minimized by taking the study drug with meal. In case GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.

Appendix 10-1: Alectinib

Event	Action to Be Taken
Skin disorder AEs (e.g., phototoxicity, rash)	Patients should be advised to avoid prolonged sun exposure while taking alectinib and for at least 7 days after study drug discontinuation. Patients should also be advised to use a broad-spectrum sun screen and lip balm of at least SPF 50 to help protect against potential sunburn. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.
Vision disorders	Investigators should consider referring the patients for an ophthalmological evaluation according to local clinical practice guidelines if vision disorders persist or worsen in severity, and to advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.
Edema	Physical examinations will be performed routinely in clinical trials. In case edema events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.
Abnormal kidney function AEs	• If, at any time during the study treatment, eGFR decreases by $>50\%$ of the baseline visit value, the patient has to be carefully monitored. All of the underlying factors that may have acutely impacted serum creatinine levels need to be evaluated and corrected (e.g., dehydration, recent exposure to contrast media, increased amount of cooked meat in diet, concomitant medications affecting renal function as appropriate, etc.). • Any eGFR decrease by $>50\%$ of the baseline visit value requires repeat testing. • For Grade 1 and Grade 2 AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table. • For Grade 3 AEs related to alectinib, temporarily interrupt alectinib until serum creatinine recovers to Grade 1 or baseline, then resume at reduced dose. • For Grade 4 AEs related to alectinib, permanently discontinue study drug.

Event	Action to Be Taken
Severe myalgia and CPK elevations	Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.
Bradycardia [b] Grade 2 or Grade 3 (symptomatic; may be severe and medically significant, medical intervention indicated)	• Temporarily withhold for a maximum of 21 days (after which the drug must be permanently withdrawn) until recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as antihypertensive medicinal products. • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia, or to a heart rate of ≥ 60 bpm. • If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose (see Table A10-1 – Dose Reduction Schedule) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm.
Bradycardia [b] Grade 4 (life-threatening consequences; urgent intervention indicated)	• Permanently discontinue if no contributing concomitant medicinal product is identified. • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table A10-1 – Dose Reduction Schedule) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm within 21 days, with frequent monitoring as clinically indicated. • Permanently discontinue in case of recurrence.
Hemolytic anemia	• If hemoglobin concentration is < 10 g/dl (Grade ≥ 2) and hemolytic anemia is suspected, withhold alectinib and initiate appropriate laboratory testing, in accordance with local clinical practice guidelines. If hemolytic anemia is confirmed, resume alectinib at a reduced dose (refer to Table A10-1 -Dose Reduction Schedule) upon resolution with improvement of hemoglobin to Grade ≤ 1 or baseline or permanently discontinue alectinib. • In case of anemia of non-hemolytic mechanism assessed as related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.

Appendix 10-1: Alectinib

Event	Action to Be Taken
All AEs related a to alectinib (unless otherwise specified in this table) + Hepatotoxicity AEs (irrespective of relatedness)	• **Grade 4:** • Temporarily interrupt alectinib for a maximum of 21 days after which the drug must be permanently withdrawn. If improvement to Grade ≤ 1 or baseline does not occur within 3 weeks, permanently discontinue alectinib. • First episode: If improvement to Grade ≤ 1 within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID. • Second episode: If improvement to Grade ≤ 1 within 21 days, decrease the current dose of alectinib by another 150 mg (1 capsule) BID. • Third episode: Permanently discontinue alectinib. • Please note that dose should not be reduced below 300 mg BID. • **Grade 3:** • Temporarily interrupt alectinib for a maximum of 21 days after which drug must be permanently withdrawn. • First episode: If improvement to Grade ≤ 1 occurs within 10 days alectinib may be restarted at the original dose or dose reduced by 150 mg (1 capsule) as per investigator discretion. If improvement to Grade ≤ 1 or baseline occurs after 10 days but within 21 days then alectinib dose must be decreased by 150 mg (1 capsule BID). • Second episode: If improvement to Grade ≤ 1 occurs within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID. • Third episode: Permanently discontinue alectinib. • **Grade 2:** • To be managed at the investigator's discretion. Please note that alectinib cannot be interrupted for more than 21 days and cannot be dose reduced below 300 mg BID. • **Grade 1:** no action required
Sodium content	The recommended daily dose (1200 mg) of alectinib contains 2.1 mmol (or 48 mg) sodium. To be taken into consideration by patients on a controlled sodium diet.

AE = adverse event; BID = twice a day; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; ULN = upper limit of normal.

Note: Diarrhea, nausea, and vomiting should be handled with best supportive care first before considering dose modification. Pre-existing pleural effusion will not be considered as an adverse event.

[a] Please refer to Section 5.3.4 to determine whether event should be assessed as related or unrelated.

[b] Heart rate less than 60 bpm.

DRUG INTERACTIONS

No pharmacokinetic interactions with alectinib requiring dosage adjustment have been identified.

Refer to the Alectinib Investigator's Brochure for a description of drug–drug interactions other than concomitant anticancer treatment.

EFFECTS OF ALECTINIB ON OTHER DRUGS

CYP Substrates

In vitro studies indicate that neither alectinib nor its major active metabolite (M4) inhibits CYP1A2, CYP2B6, CYP2C9, CYP2C19 or CYP2D6 at clinically relevant concentrations. Alectinib and M4 showed weak time-dependent inhibition of CYP3A4. In vitro, alectinib exhibits a weak induction potential of CYP3A4 and CYP2B6 at clinical concentrations.

Results from a clinical drug–drug interaction study in ALK-positive NSCLC patients demonstrated that multiple doses of alectinib had no influence on the exposure of MDZ, a sensitive CYP3A substrate. Therefore, no dose adjustment is required for co-administered CYP3A substrates.

Although in vitro studies indicate that alectinib is an inhibitor of CYP2C8, physiologically-based pharmacokinetics (PBPK) modeling supports that alectinib does not have the potential to increase plasma concentrations of co-administered substrates of CYP2C8 at clinically relevant concentrations.

P-gp and BCRP Substrates

In vitro, alectinib and M4 are inhibitors of the efflux transporters P-gp and breast cancer resistance protein (BCRP). Therefore, alectinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp or BCRP transporters (the increase in exposure is not expected to be more than 2-fold). When alectinib is co-administered with P-gp or BCRP substrates with narrow therapeutic index (e.g., digoxin, dabigatran, methotrexate), appropriate monitoring is recommended.

Effects of Other Drugs on Alectinib

Based on in vitro data, CYP3A4 is the primary enzyme mediating the metabolism of both alectinib and its major active metabolite M4, and CYP3A contributes to 40% to 50% of total hepatic metabolism. M4 has shown similar in vitro potency and activity to alectinib against ALK.

CYP3A Inducers

Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong CYP3A inducer, with a single oral dose of 600 mg alectinib exhibited a minor effect on combined exposure of alectinib and M4 (geometric mean ratio [GMR] with/without rifampicin [90% CI]: Cmax: 0.96 [0.88–1.05], AUC_{inf}: 0.82 [0.74–0.90]). Therefore, no dose adjustments are required when alectinib is co-administered with CYP3A inducers.

CYP3A Inhibitors

Co-administration of multiple oral doses of 400 mg posaconazole BID, a strong CYP3A inhibitor, with a single oral dose of 300 mg alectinib had a minor effect on combined exposure of alectinib and M4 (GMR with/without posaconazole [90% CI]: Cmax: 0.93 [0.81–1.08], AUC_{inf}: 1.36 [1.24–1.49]). Therefore, no dose adjustments are required when alectinib is co-administered with CYP3A inhibitors.

Medicinal Products that Increase Gastric pH

Although the aqueous solubility of alectinib in vitro is pH-dependent, a dedicated clinical drug–drug interaction study with 40 mg esomeprazole once daily, a proton pump inhibitor (PPI), demonstrated no clinically relevant effect on the combined exposure of alectinib and M4. Therefore, no dose adjustments are required when alectinib is co-administered with PPIs or other drugs which raise gastric pH (e.g., H2 receptor antagonists or antacids).

Effect of Transporters on Alectinib Disposition

Based on in vitro data, alectinib is not a substrate of P-gp. Alectinib and M4 are not substrates of BCRP or organic anion transporting polypeptide (OATP) 1B1/B3. In contrast, M4 is a substrate of P-gp. Alectinib inhibits P-gp, and it is therefore not expected that co-medication with P-gp inhibitors will have a relevant effect on M4 exposure.

A10–2 ATEZOLIZUMAB

BACKGROUND

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor specific T cell responses, resulting in improved antitumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows antitumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in various countries for the treatment of urothelial carcinoma, non-small cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, melanoma*, and alveolar soft part sarcoma*.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

SAFETY

SAFETY PROFILE

A comprehensive description of the safety profile of atezolizumab is provided in the Atezolizumab Investigator's Brochure and this summary only lists specific risks, and warnings and precautions.

The summary information provided in the following section must always be checked against any update of the Atezolizumab Investigator's Brochure that may have occurred after the protocol has been issued.

Adverse reactions associated with Warnings and Precautions:

- Immune-mediated hepatitis
- Immune-mediated pneumonitis
- Immune-mediated colitis
- Immune-mediated pancreatitis

- Immune-mediated endocrinopathies (i.e., diabetes mellitus, hypothyroidism/hyperthyroidism, adrenal insufficiency, hypophysitis)
- Immune-mediated meningoencephalitis
- Immune-mediated neuropathies (i.e., myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome)
- Infusion-mediated reactions
- Immune mediated myocarditis
- Immune-mediated nephritis
- Immune-mediated myositis

Other selected adverse reactions:

- Immune-mediated uveitis
- Immune-mediated myopathies, including rhabdomyolysis

Management guidelines for atezolizumab that are applicable to this study are provided in Table A10-3 to Table A10-17.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For atezolizumab, AESIs include:

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-mediated reactions, cytokine-release syndrome, hemophagocytic lymphohistiocytosis (HLH), and macrophage activation syndrome (MAS)
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade $\geq$2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

ADMINISTRATION

POSOLOGY AND ROUTE

The dose of atezolizumab will be 1200 mg administered intravenously every three weeks.

Administration in combination with chemotherapy

For the doses of chemotherapy to be administered in combination with atezolizumab, refer to Section 4.3.4.7 in the Protocol.

METHOD OF ADMINISTRATION

The infusions must not be administered as an intravenous push or bolus.

The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

For instructions on dilution and handling of the medicinal product before administration, refer to the Atezolizumab Investigator's Brochure.

Administration in combination with chemotherapy

Atezolizumab and chemotherapy must be administered sequentially and not mixed in the same infusion bag. Chemotherapy should be administered after atezolizumab.

DURATION OF TREATMENT

Treatment with atezolizumab should continue until loss of clinical benefit or the development of unacceptable toxicity.

PROPHYLAXIS FOR ATEZOLIZUMAB (WHEN NOT ADMINISTERED WITH PACLITAXEL)

No premedication is indicated for the administration of Cycle 1 of atezolizumab.

Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

PREMEDICATION FOR ATEZOLIZUMAB + PACLITAXEL

All patients should be premedicated prior to paclitaxel administration to prevent severe hypersensitivity reactions. This premedication should consist of the institution's standard of care or one of the following premedications:

- Dexamethasone 20 mg orally approximately 12 hours prior and 6 hours prior to the paclitaxel infusion
  - Patients may be treated with dexamethasone 10−20 mg IV within 1 hour prior to paclitaxel infusion if the patient did not take the oral dexamethasone
- Diphenhydramine 50 mg IV (or equivalent) 30−60 minutes prior to paclitaxel infusion
- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30−60 minutes prior to paclitaxel infusion

DELAYED OR MISSED DOSES

If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.

PROHIBITED THERAPY

- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab

GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH ATEZOLIZUMAB

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice, unless special management is indicated, in which case management should be per protocol according to instructions provided in this appendix. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, when clinically indicated.

Although most immune-mediated adverse events observed with atezolizumab have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider *withholding* atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- *Withhold* atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day *oral* prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.

The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's *benefit–risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

DOSE MODIFICATIONS

There will be no dose reductions of atezolizumab.

Administration in combination with chemotherapy

Patients may continue therapy with atezolizumab during periods of reversible chemotherapy-induced myelosuppression, but they should be monitored carefully for complications of neutropenia and other toxicities during this time.

For platinum-based chemotherapy dose modifications, see the relevant EMA Summary of Product Characteristics.

DOSE INTERRUPTION OR DISCONTINUATION

Dose interruption and discontinuation advice are summarized in the "Management Guidelines" below (including Table A10-3 to Table A10-17).

Discontinuation

Administration in combination with chemotherapy

- After platinum-based chemotherapy is discontinued (per protocol or due to toxicity), treatment with atezolizumab will continue per protocol
- If atezolizumab treatment is discontinued prior to the planned end of concomitant chemotherapy, treatment with chemotherapy may continue in the Treatment Period per the guidance provided in Section 4.3.4.7.

Interruptions

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Summary of Reasons for Dose Discontinuation:

- Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and meningoencephalitis of any grade
- For Grade 4 toxicities except for endocrinopathies that are controlled with replacement hormones
- For Grades 3–4 pneumonitis, hepatitis, type 1 diabetes mellitus, infusion-related reactions

AND for the specific adverse reactions described in Table A10-3 to Table A10-17, atezolizumab should be permanently discontinued:

- For any recurrent event at Grade ≥ 3 severity
- If a treatment-related toxicity does not resolve to Grade 0 or Grade 1 within 12 weeks after adverse reaction onset date
- If a corticosteroid dose of >10 mg prednisone or equivalent per day is required for treatment-related toxicity beyond 12 weeks after adverse reaction onset date

MANAGEMENT GUIDELINES

ANAPHYLAXIS PRECAUTIONS

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

Required Equipment and Medication

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

Procedures

- In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:
  - Stop the study treatment administration, if possible
  - Call for additional medical assistance
  - Maintain an adequate airway
  - Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible
  - Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge
  - Continue to observe the patient and document observations

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies, such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table A10-3.

Table A10-3 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab. – *Consider resuming on radiographic evidence of improvement.*
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with *corticosteroids equivalent to* 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c, d] • For recurrent events or events with no improvement after 48−72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c, d] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL *with or without transbronchial biopsy* is recommended. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

HEPATIC EVENTS

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A10-4.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table A10-4 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events**: • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration**: • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A10-5.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table A10-5 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, *initiate* empiric IV *corticosteroids* while waiting for definitive diagnosis. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]

Event	Management
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A10-6.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table A10-6 Management Guidelines for Endocrine Events

Event	Management
Hypothyroidism, Grade 1	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Hypothyroidism, Grade 2	• Consider withholding atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Hypothyroidism, Grade 3 *or* 4	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer *patient* to endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism. [c]

Event	Management
Hyperthyroidism, Grade 1	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.
Hyperthyroidism, Grade 2	• Consider withholding atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Hyperthyroidism, Grade 3 *or* 4	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer *patient* to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

Appendix 10-2: Atezolizumab

Event	Management
Symptomatic adrenal insufficiency, Grades 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A10-7.

Table A10-7 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an of the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

In high-risk patients (including those with abnormal baseline cardiac troponin levels, when available), transthoracic echocardiogram (TTE) monitoring should be considered, as clinically indicated, and based on local clinical practice. Management guidelines for cardiac events are provided in Table A10-8.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., *troponin,* B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on *immune-mediated* pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, *a TTE for evaluation of left ventricular ejection fraction and global longitudinal strain*, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-8.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on *immune-mediated* myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer (*e.g.,* metastatic disease)*, cancer treatment (e.g.,* chest radiotherapy), cardiac injury *(e.g., injury due to* myocardial infarction or *iatrogenesis*), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, TTE, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-8. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table A10-8 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 *or* Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone $for\ 3–5\ days$ and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 24 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine-release syndrome"). Avoid ambiguous terms such as "systemic reaction". Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF. Associated signs and symptoms of an IRR should be recorded on the dedicated Infusion-Related Reaction eCRF.

If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms of an IRR also recorded separately on the dedicated Infusion-Related Reaction eCRF.

Management

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1(Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table A10-9.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and *interferon*-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table A10-9 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onse.t • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.

Event	Management
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor. [e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact the Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: These management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature $\geq 38°C$ not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio.

[f] Refer to Riegler et al. 2019.

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table A10-10.

Table A10-10 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN** • Treat as a Grade 3 event
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table A10-11.

Table A10-11 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c]

Event	Management
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based of the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. *Myasthenia may be associated with myositis (see section on immune-mediated myositis) and patients should be managed accordingly.* Management guidelines for neurologic disorders are provided in Table A10-12, with specific guidelines for myelitis provided in Table A10-13.

Table A10-12 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For facial paresis: – *Initial observation OR initiate prednisone 1–2 mg/kg/day (if progressing from mild). Initiate treatment with gabapentin, pregabalin, or duloxetine for pain.* – If event resolves fully, resume atezolizumab. [b] – If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated neuropathy including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines *and proceed as per Guillain-Barré syndrome management*.

Event	Management
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of *corticosteroids equivalent to* 1–2 mg/kg/day oral or IV prednisone. • *Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms.* • *In life-threatening cases, consider IV methylprednisolone 1 g/day for 3–5 days and consider other immunosuppressive agent.*

IVIG = intravenous immunoglobulin.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on of the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A10-13 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Investigate etiology and refer patient to neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • *Initiate non-opioid treatment (e.g., pregabalin, gabapentin, duloxetine) for pain.* • *Hospitalize patient.* – *Initiate treatment with corticosteroids equivalent to 1 g/day IV methylprednisolone.* – *If event does not improve or there is worsening of symptoms within 3 days, consider IVIG or plasmapheresis and manage as per institutional guidelines.* • *Refer patient to neurologist.*

IVIG = intravenous immunoglobulin.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-14.

Table A10-14 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-15.

Table A10-15 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function *closely*, including creatinine and urine protein, until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on of the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase*/creatine phosphokinase* increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients may initially present with low grade nondescript symptoms including mild pain and weakness; thus, there should be a low threshold for suspicion of myositis.* Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis *(see section on immune-mediated myocarditis) and myasthenia gravis (bulbar symptoms such as dysphagia, dysphonia, and dyspnea; see section on neurologic disorders).*

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A10-16.

Table A10-16 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines • Consider treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • *Consider IVIG or plasmapheresis.* • If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and contact the Medical Monitor.

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • *Consider IVIG or plasmapheresis.* • If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

IVIG = intravenous immunoglobulin.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on of the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator, The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (McClain and Eckstein 2019). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected HLH should be treated according to the guidelines in Table A10-17.

Table A10-17 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

Event	Management
Suspected HLH	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis;

DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. The drug interaction potential of atezolizumab is unknown.

A10–3 BEVACIZUMAB

Bevacizumab will be administered in combination with erlotinib—Refer to Appendix A10–6 for details on erlotinib.

BACKGROUND

Bevacizumab is a recombinant humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal immunoglobulin G1 (IgG1) antibody, produced by DNA technology in Chinese Hamster Ovary cells.

VEGF, a diffusible glycoprotein produced by normal and neoplastic cells, is an important regulator of physiologic and pathologic angiogenesis. Increased levels of VEGF expression have been found in most human malignancies examined to date [1-3]. Increased VEGF serum levels have been correlated with poor survival. Nonclinical studies have shown that the murine anti-human VEGF monoclonal antibody A4.6.1 inhibits the growth of human tumor xenografts, and a humanized variant of this antibody (bevacizumab) has therefore been developed as a treatment of various cancers.

Bevacizumab has been approved in various countries for the treatment of patients with metastatic carcinoma of the colon or rectum, unresectable, locally advanced, recurrent or metastatic non-squamous non-small-cell lung cancer; locally recurrent or metastatic breast cancer, advanced and/or metastatic renal cell cancer; epithelial ovarian, fallopian tube or primary peritoneal cancer; malignant glioma (WHO Grade IV -glioblastoma); and cervical cancer.

Bevacizumab, in combination with erlotinib, has been approved for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.

SAFETY

SAFETY PROFILE

Comprehensive descriptions of the safety profiles of bevacizumab and erlotinib are provided in their respective EMA Summary of Product Characteristics.

The summary information provided in the following section must always be checked against any update of the Bevacizumab EMA Summary of Product Characteristics that may have occurred after the protocol has been issued.

Treatment-Emergent Adverse Events

The most serious adverse reactions were:

- Gastrointestinal perforations
- Hemorrhage, including pulmonary hemorrhage/hemoptysis, which is more common in non-small cell lung cancer patients
- Arterial thromboembolism

Adverse reactions associated with Warnings and Precautions:

- Gastrointestinal perforations and fistulae
- Non-GI fistulae
- Hemorrhage
- Pulmonary hemorrhage/hemoptysis
- Hypertension
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Arterial Thromboembolism
- Venous thromboembolism events, including pulmonary embolism
- Congestive heart failure
- Wound-healing complications
- Neutropenia and infections
- Proteinuria
- Hypersensitivity reactions, infusion reactions
- Osteonecrosis of the jaw
- Ovarian failure/fertility

Management guidelines for bevacizumab that are applicable to this study are provided in Table A10-18.

Adverse Events of Special Interest

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For bevacizumab, AESIs with grades include:

- Grade ≥3 hypertension
- Grade ≥3 proteinuria
- Any grade GI perforation, abscesses, or fistulae
- Grade ≥3 wound-healing complication

- Hemorrhage
- Any grade CNS bleeding
- Grade ≥2 hemoptysis)
- Other Grade ≥3 bleeding
- Any grade arterial thromboembolic event
- Grade ≥3 venous thromboembolic event
- Any grade PRES
- Grade ≥3 CHF
- Grade ≥2 non-GI fistula or abscess

For erlotinib, AESIs include:

- Interstitial lung disease

ADMINISTRATION

POSOLOGY

When used in addition to erlotinib, bevacizumab will be administered at the dose of 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

It should not be administered as an intravenous push or bolus.

DURATION OF TREATMENT

Treatment with bevacizumab in addition to erlotinib should continue until loss of clinical benefit or the development of unacceptable toxicity.

DOSE MODIFICATIONS DURING TREATMENT

Dose Adjustments

Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended, as described in Table A10-18.

Interaction With Erlotinib

No pharmacokinetic interactions with erlotinib have been identified.

MANAGEMENT AND DISCONTINUATION ADVICE FOR SPECIFIED ADVERSE DRUG REACTIONS

Table A10-18 Guidelines for Management and Discontinuation of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Gastrointestinal (GI) perforations and fistulae	Permanently discontinue bevacizumab
Non-GI fistulae	Permanently discontinue bevacizumab if tracheoesophageal (TE) fistula or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered
Hemorrhage – especially tumor-associated hemorrhage	Permanently discontinue bevacizumab if Grade 3 or 4 bleeding during bevacizumab therapy Monitor for signs and symptoms of CNS bleeding, and discontinue treatment in cases of intracranial bleeding Exercise caution before initiating bevacizumab therapy in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism at time of initiating bevacizumab
Hypertension	Permanently discontinue bevacizumab if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy
Posterior Reversible Encephalopathy Syndrome (PRES)	PRES can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension A diagnosis of PRES requires confirmation by brain imaging, preferably MRI If developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known
Arterial thromboembolism	Permanently discontinue bevacizumab if arterial thromboembolism Patients with a history of arterial thromboembolism, diabetes or age $>$65 years have an increased risk of developing arterial thromboembolic events during bevacizumab therapy. Caution should be taken when treating such patients with bevacizumab

Event	Action to Be Taken
Venous thromboembolism events, including pulmonary embolism	Permanently discontinue bevacizumab in patients with life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism Patients with thromboembolic events ≤Grade 3 need to be closely monitored
Congestive heart failure	Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure
Wound Healing	In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed Bevacizumab therapy should be withheld for elective surgery Bevacizumab therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated
Proteinuria	Permanently discontinue bevacizumab in the event of nephrotic syndrome Testing for proteinuria is recommended prior to administration of bevacizumab therapy. If urine protein levels of ≥2g /24 hr held bevacizumab until recovery to <2g /24 hr
Hypersensitivity Reactions, Infusion Reactions	Close observation of the patient during and following the administration of bevacizumab is recommended If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered
Osteonecrosis of the jaw	Caution should be exercised when bevacizumab and intravenous bisphosphonates are administered simultaneously or sequentially A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with bevacizumab. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided

Please also refer to the Erlotinib EMA Summary of Product Characteristics and Appendix A10–6 for warnings and precautions when using bevacizumab in combination with erlotinib.

DRUG INTERACTIONS

No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered erlotinib (and its active metabolite OSI-420).

No formal pharmacokinetic drug interaction studies have been conducted with bevacizumab, other than interactions with anti-neoplastic agents.

A10–4 COBIMETINIB

Cobimetinib will be administered in combination with vemurafenib—Refer to Appendix A10–13 for details on vemurafenib.

BACKGROUND ON COBIMETINIB

Cobimetinib is a potent and highly selective small molecule inhibitor of MEK1 and MEK2, central components of the RAS/RAF pathway.

Inhibition of MEK is a promising strategy to control the growth of tumors that are dependent on aberrant signaling in the RAS/RAF pathway.

Cobimetinib is being developed for use in the treatment of cancers. Cobimetinib, in combination with vemurafenib, has been approved in various countries for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

SAFETY

SAFETY PROFILE

A comprehensive description of the safety profile of cobimetinib as monotherapy and in combination with vemurafenib is provided in the Cobimetinib Investigator's Brochure and this summary only lists specific risks, and warnings and precautions.

Identified risks with Cobimetinib are:

- Hemorrhage
- Serous retinopathy
- Left ventricular dysfunction
- Rhabdomyolysis and CPK elevations
- Pneumonitis
- Photosensitivity (when administered in combination with vemurafenib)
- Diarrhea

Potential risks with Cobimetinib are:

- Liver laboratory abnormalities

Management guidelines for cobimetinib adverse reactions that are applicable to this study are provided in Table A10-19.

The summary information provided in the following sections must always be checked against any update of the Cobimetinib Investigator's Brochure that may have occurred after the protocol has been issued.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For cobimetinib, AESIs include:

- Grade ≥1 retinal vein occlusion
- Any retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or central serous chorioretinopathy
- Rhabdomyolysis or Grade ≥3 CPK elevation
- Grade ≥3 hemorrhage or any grade cerebral hemorrhage
- Grade ≥3 rash
- Grade ≥ diarrhea
- Symptomatic heart failure or Grade ≥2 left ventricular ejection fraction reduction
- Photosensitivity
- Grade ≥3 hepatotoxicity

ADMINISTRATION OF COBIMETINIB

POSOLOGY AND ROUTE

The dose of cobimetinib will be 60 mg (3 tablets of 20 mg) once daily.

Cobimetinib is taken on a 28-day cycle. Each dose consists of three 20 mg tablets (60 mg) and should be taken once daily for 21 consecutive days (Day 1 to 21 of treatment cycle), followed by a 7-day break (Day 22 to 28 of treatment cycle). Each subsequent cobimetinib treatment cycle should start after the 7-day treatment break has elapsed.

For instructions on handling of the medicinal product, refer to the Cobimetinib Investigator's Brochure.

DURATION OF TREATMENT

Treatment with cobimetinib should continue until loss of clinical benefit or the development of unacceptable toxicity.

DELAYED OR MISSED DOSES

If a planned dose of cobimetinib is missed, it can be taken up to 12 hours prior to the next dose to maintain the once -daily regimen. If vomiting occurs after taking a dose of cobimetinib the patient should not take an additional dose on that day and treatment should be continued as prescribed the following day.

DOSE MODIFICATIONS AND DISCONTINUATION DURING TREATMENT

Dose modification of cobimetinib is independent of vemurafenib dose modification.
If doses are omitted for toxicity, these doses should not be replaced. Once the dose has been reduced, it should not be increased at a later time.

Table A10-19 below gives general cobimetinib dose modification guidance.

Table A10-19 Recommended Cobimetinib Dose Modifications

Grade (CTCAE) [a]	Recommended Cobimetinib Dose
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain cobimetinib at a dose of 60 mg once daily (3 tablets)
Grade 2 (intolerable) or Grade 3/4	
1st Appearance	Interrupt treatment until Grade ≤1, restart treatment at 40 mg once daily (2 tablets)
2nd Appearance	Interrupt treatment until Grade ≤1, restart treatment at 20 mg once daily (1 tablet)
3rd Appearance	Consider permanent discontinuation

[a] The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Summary of Dose Discontinuation Advice (see Below for Details):

Cobimetinib should be permanently discontinued for:

- Grade 4 hemorrhage events attributed to cobimetinib
- Symptomatic or asymptomatic decrease of LVEF $<40\%$ or $\geq 10\%$ absolute decrease from baseline after treatment break or recurrent symptomatic absolute decrease of LVEF $<10\%$ (see Table A10-19 for details)
- Rhabdomyolysis or symptomatic CPK elevations not improving within 4 weeks of dose interruption
- Liver laboratory abnormalities not resolving to Grade ≤ 1 within 4 weeks of dose interruption or if Grade 4 liver laboratory abnormalities recur after initial improvement
- QTc increase meets values of both >500 ms and >60 ms change from pre-treatment values or 3rd occurrence of QTc >500 ms during treatment and change from pre-treatment value remains ≤ 60 ms

Dose modification and discontinuation advice for hemorrhage

Grade 4 events or cerebral hemorrhage:

- Cobimetinib treatment should be interrupted
- Cobimetinib treatment should be permanently discontinued for hemorrhage events attributed to cobimetinib

Grade 3 events:

- Cobimetinib treatment should be interrupted during evaluation of the event
- There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events
- Clinical judgment should be applied when considering restarting cobimetinib treatment. Vemurafenib dosing can be continued when cobimetinib treatment is interrupted, if clinically indicated

Dose modification and discontinuation advice for left ventricular dysfunction

- Permanent discontinuation of cobimetinib treatment should be considered if cardiac symptoms are attributed to cobimetinib and do not improve after temporary interruption

Table A10-20 Recommended Dose Modifications and Discontinuation for Cobimetinib in Patients With Left Ventricular Ejection Fraction (LVEF) Decrease From Baseline

Patient	LVEF Value	Recommended Cobimetinib Dose Modification	LVEF Value Following Treatment Break	Recommended Cobimetinib Daily Dose
Asymptomatic	≥50% (or 40–49% and <10% absolute decrease from baseline)	Continue at current dose	N/A	N/A
	<40% (or 40–49% and ≥10% absolute decrease from baseline)	Interrupt treatment for 2 weeks	<10% absolute decrease from baseline	1st occurrence: 40 mg
				2nd occurrence: 20 mg
				3rd occurrence: permanent discontinuation
			<40% (or ≥10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	N/A	Interrupt treatment for 4 weeks	Asymptomatic and <10% absolute decrease from baseline	1st occurrence: 40 mg
				2nd occurrence: 20 mg
				3rd occurrence: permanent discontinuation
			Asymptomatic and <40% (or ≥10% absolute decrease from baseline)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

N/A = Not Applicable

Vemurafenib treatment can be continued when cobimetinib treatment is modified, if clinically indicated.

Dose modification and discontinuation advice for rhabdomyolysis and CPK elevations

Rhabdomyolysis or symptomatic CPK elevations

- Cobimetinib treatment should be interrupted
- If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, discontinue permanently cobimetinib
- If severity is improved by at least one grade within 4 weeks, cobimetinib could be restarted at a dose reduced by 20 mg, if clinically indicated. Vemurafenib dosing can be continued when cobimetinib treatment is modified, if clinically indicated.

Asymptomatic CPK elevations

Grade 4:

- Cobimetinib treatment should be interrupted. If CPK elevations do not improve to Grade $\leq$3 within 4 weeks following dose interruption, discontinue permanently cobimetinib
- If CPK improves to Grade $\leq$3 within 4 weeks, cobimetinib could be restarted, if clinically indicated, at a dose reduced by 20 mg and the cobimetinib patient should be closely monitored. Vemurafenib dosing can be continued when treatment is modified, if clinically indicated.

Grade $\leq$3:

- After rhabdomyolysis has been ruled out, cobimetinib dosing does not need to be modified

Dose modification advice for cobimetinib when used with vemurafenib

Liver laboratory abnormalities

- Grade 3:
  - Cobimetinib dose should not be modified. The dose of vemurafenib may be reduced as clinically appropriate - Refer to the vemurafenib dose modification recommendation
- Grade 4:
  - Cobimetinib treatment and vemurafenib treatment should be interrupted. If liver laboratory abnormalities improve to Grade $\leq$1 within 4 weeks, cobimetinib should be restarted at a dose reduced by 20 mg and vemurafenib at a clinically appropriate dose, per dose modification recommendation
  - Cobimetinib treatment and vemurafenib treatment should be discontinued if liver laboratory abnormalities do not resolve to Grade $\leq$1 within 4 weeks or if Grade 4 liver laboratory abnormalities recur after initial improvement

Photosensitivity

Grade ≤2 (tolerable) photosensitivity should be managed with supportive care.

If patients experience Grade 2 (intolerable) or Grade ≥3 photosensitivity, cobimetinib and vemurafenib should be interrupted until resolution to Grade ≤1. Treatment can be restarted with no change in cobimetinib dose. Vemurafenib dosing should be reduced as clinically appropriate (refer to the vemurafenib dose modification recommendations).

Rash

The dose of cobimetinib and/or vemurafenib may be either temporarily interrupted and/or reduced as clinically indicated.

Additionally:

- Grade ≤2 (tolerable) rash should be managed with supportive care. Cobimetinib dosing can be continued without modification
- Grade 2 (intolerable) or Grade ≥3 acneiform rash: General dose modification recommendations in Table A10-19 for cobimetinib should be followed. Vemurafenib dosing can be continued when cobimetinib treatment is modified (if clinically indicated)
- Grade 2 (intolerable) or Grade ≥3 non-acneiform or maculopapular rash: cobimetinib dosing can be continued without modification if clinically indicated. Vemurafenib dosing may be either temporarily interrupted and/or reduced (refer to the vemurafenib dose modification recommendations)

QT prolongation

If during treatment the QTc exceeds 500 msec, please refer to dose modifications for vemurafenib. No dose modification of cobimetinib is required when taken in combination with vemurafenib.

Please also refer to the Vemurafenib Investigator's Brochure and to its warnings and precautions when using cobimetinib in combination with vemurafenib.

INTERACTION WITH VEMURAFENIB

There is no evidence of any clinically significant drug interaction between cobimetinib and vemurafenib.

MANAGEMENT ADVICE FOR SPECIFIED ADVERSE DRUG REACTIONS

Table A10-21 Guidelines for Management and Discontinuation of Patients Who Experience Specific Adverse Events on Cobimetinib Plus Vemurafenib

Event	Action to Be Taken
Hemorrhage, including major hemorrhages, defined as symptomatic bleeding in a critical area or organ	Caution should be used in patients with additional risk factors for bleeding, and in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).
Serous Retinopathy (mostly chorioretinopathy or retinal detachment)	If reporting new or worsening visual disturbances, an ophthalmologic examination is strongly recommended. If serous retinopathy is diagnosed, vemurafenib treatment should be withheld until visual symptoms improve to Grade $\leq$1. Serious retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation. Patients should be advised to use caution when driving or using machines if their vision is impaired.
Left Ventricular Dysfunction	Decrease in LVEF from baseline can be managed using treatment interruption, dose reduction or with treatment discontinuation. All patients restarting treatment with a dose reduction of vemurafenib should have LVEF measurements taken at approximately 2 weeks, 4 weeks, 10 weeks, and 16 weeks, and then as clinically indicated until treatment discontinuation.
Rhabdomyolysis and CPK Elevations	Monitor CPK at baseline and during treatment (per protocol) or more frequently as clinically indicated.
Liver Laboratory Abnormalities (increases in ALT, AST, and ALP)	Monitor liver laboratory tests at baseline and during treatment (per protocol) or more frequently as clinically indicated. Manage Grade 3 and 4 liver laboratory abnormalities with dose interruption, reduction, or discontinuation of both cobimetinib and vemurafenib.

Event	Action to Be Taken
Hypersensitivity	In reported cases occurring in patients exposed to vemurafenib, signs and symptoms of hypersensitivity or anaphylaxis improved or resolved after treatment with steroids and/or other medications as clinically indicated.
QT prolongation ● QTc increase meets values of both >500 ms and >60 ms change from pre-treatment values ● 1st occurrence of QTc >500 ms during treatment and change from pre-treatment value remains ≤60 ms ● 2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains ≤60ms ● 3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains ≤60ms	● Discontinue permanently ● Temporarily interrupt treatment until QTc decreases below 500 ms Reduce dose by 240 mg twice daily ● Temporarily interrupt treatment until QTc decreases below 500 ms Reduce dose by 240 mg twice daily Discontinue permanently

DRUG INTERACTIONS

Effects of Concomitant Medications on Cobimetinib

CYP3A inhibitors/inducers

Cobimetinib is metabolized by CYP3A and exposures increased approximately 7-fold in the presence of a potent CYP3A inhibitor (itraconazole) in healthy subjects. Because cobimetinib is a sensitive substrate of CYP3A, it is likely that cobimetinib exposures will be significantly lower in the presence of CYP3A inducers. Therefore, concomitant administration of potent CYP3A inducers and inhibitors is not recommended. Caution should be exercised when cobimetinib is co-administered with moderate CYP3A inducers and inhibitors).

Acid reducing agents

Cobimetinib PK are not altered by the co-administration of a proton pump inhibitor. Thus, gastric pH elevations do not affect cobimetinib absorption.

Effects of Cobimetinib on Concomitant Medications

CYP Substrates

Co-administration of cobimetinib 60 mg once daily for 15 days with a single 30 mg dose of dextromethorphan (sensitive CYP2D6 substrate) or a 2 mg dose of midazolam (sensitive CYP3A substrate) to 20 patients with solid tumors did not change dextromethorphan or midazolam systemic exposure. In vitro data indicate that cobimetinib may inhibit CYP3A and CYP2D6. Cobimetinib is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9 and 2C19 or an inducer of CYP1A2, 2B6 and 3A4 at clinically relevant concentrations.

A10–5 ENTRECTINIB

BACKGROUND

Entrectinib (also known as RXDX-101) is a potent inhibitor of the receptor tyrosine kinases TrkA (encoded by the gene neurotrophic tyrosine receptor kinase NTRK1), TrkB (encoded by the gene NTRK2), TrkC (encoded by the gene NTRK3), ROS1 (encoded by the gene ROS1) and anaplastic lymphoma kinase (ALK; encoded by the gene ALK), with median inhibitory concentrations (IC_{50}) for kinase inhibition in the low nanomolar range (1.7, 0.1, 0.1, 0.2, and 1.6 nM, respectively). While these enzymes play various roles in normal cellular function, gene rearrangements (fusions) in these target kinases have the potential to be oncogenic drivers, tend to be mutually exclusive, and are present in small percentages ($<$ 10% [Vaishnavi et al. 2015]) in a variety of tumor types, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), salivary gland cancer, papillary thyroid cancer, melanoma, and sarcoma. A pan-TRK, ROS1, and ALK inhibitor such as entrectinib may have broad potential therapeutic utility.

SAFETY

SAFETY PROFILE

A comprehensive description of the safety profile of entrectinib is provided in the Entrectinib Investigator's Brochure

Identified Risks

Cognitive Disorders

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in patients treated with entrectinib in clinical trials. Patients should be monitored for signs of cognitive changes.

Based on the severity of the cognitive disorder, entrectinib treatment should be modified as described below in Table A10-23 of this Appendix.

Patients who experience symptoms of cognitive disorders should be instructed not to drive or use machines until symptoms resolve.

Congestive Heart Failure

Congestive heart failure (CHF) has been reported in patients treated with entrectinib in clinical trials. These reactions were observed in patients with or without a history of cardiac disease and resolved upon treatment with diuretics and/or dose reduction or interruption.

Patients receiving entrectinib should be carefully monitored and those with clinical signs and symptoms of CHF, including shortness of breath or edema, should be evaluated as clinically appropriate.

Based on the severity of CHF, entrectinib treatment should be modified as described below in Table A10-23 of this Appendix.

QT Interval Prolongation

QT interval prolongation has been observed in patients treated with entrectinib in clinical trials. Use of entrectinib should be avoided in patients with congenital long QT syndrome and in patients taking medications that are known to prolong QT interval.

Potential Risks (Refer to the Entrectinib Investigator's Brochure for Details)

Entrectinib-related adverse events generally occur within the first 2 cycles of treatment.

In general, the events listed below are reversible and can be managed with dose hold and/or dose reduction, as needed.

Neurologic Effects

TRK receptors are involved with neuronal development and maintenance; as such, central and peripheral neurologic events are expected. In the clinic, the following neurologic events have been reported: dysgeusia, paresthesia, and cognitive disturbance (manifested as confusion, gain disturbance, dizziness, slurred speech, muscle weakness, memory impairment and vision changes).

Weight Gain

A trend for weight gain has been observed. This is likely an on-target effect of entrectinib as TRKB is associated with appetite control; ALK and ROS1 genes may also play a role as they are part of the insulin gene family and could therefore have effects on glucose metabolism and control.

Peripheral Edema

Peripheral edema, fluid retention, and pulmonary edema have been reported. All have resolved with dose interruption and/or dose reduction, as needed.

Hypotension

Hypotension and orthostatic hypotension have been observed.

Anemia

In the clinic, Grade 1 and 2 anemia, neutropenia, and lymphocyte count decreased have been observed. Most of these adverse events do not require intervention and/or can be easily managed with dose modifications, such as short drug holidays.

Increased Creatinine

Clinically, moderate serum creatinine elevations have been observed in patients, independent of dose level that recover following entrectinib discontinuation.

Visual Effects

To date, among the eye disorders that have been reported across the ongoing studies (vision blurred, diplopia, photophobia, dry eye, abnormal sensation in eye, conjunctivitis, corneal opacity, eye irritation, eye pain, eyelid edema, halo vision, lacrimation increased, scotoma, visual acuity reduced, and vitreous floaters), vision blurred is the most likely consequence of potential corneal-related visual disturbances.

Adverse Events of Special Interest

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For entrectinib, the following AESIs are to be reported

- Grade $\geq$2 Congestive Heart Failure
- Grade $\geq$2 QT prolongation
- Any grade syncope
- Grade $\geq$2 cognitive disturbances
- Bone fracture (all grades)

ADMINISTRATION

POSOLOGY AND ROUTE

The recommended dose is 600 mg per day (three 200-mg capsules per day). Entrectinib will be self-administered orally at home, on a continuous daily dosing regimen.

The capsules of entrectinib must be swallowed intact without chewing, crushing, or opening them.

Entrectinib should be administered approximately at the same time each day.
For patients experiencing fatigue, nausea, or other mild tolerability issues, an evening time administration is recommended.

For instructions on handling of the medicinal product, refer to the Entrectinib Investigator's Brochure.

DURATION OF TREATMENT

Treatment with entrectinib should continue until loss of clinical benefit or the development of unacceptable toxicity.

DELAYED OR MISSED DOSES

If a patient misses a dose, it should be replaced only if the patient remembers within a 12-hour window. After that, patients should just take the next dose the following day, without compensating for the missed dose (including vomited doses).

DOSE MODIFICATIONS

Adverse events associated with entrectinib can often be managed with concomitant medications, supportive care and/or dose modifications, as per Table A10-23.

If toxicities that are possibly related to entrectinib are not easily managed or corrected and are not tolerable to the patient, or if there are adverse events that are not acceptable in the investigator's judgment, the patient should have study treatment interrupted until the AE resolves to Grade $\leq$1. If study treatment is interrupted, dose reduction (if mandated) should occur when study treatment is resumed. All dose reductions should be based on the most severe toxicity observed that is attributable to entrectinib.

If needed, dose reductions may occur in decrements of 200 mg and no more than 2 dose reductions will be allowed.

Table A10-22 Dose Reduction Schedule

Dose Reduction Schedule	Dose Level
Starting dose	600 mg daily
1st reduction	400 mg daily
2nd reduction	200 mg daily

Doses reduced for drug-related toxicity should generally not be re-escalated. However, intra-patient re-escalation back to the previous dose level may be permitted at the discretion of the investigator after discussion with the Sponsor.

Entrectinib treatment may be interrupted for a maximum of 28 days to allow sufficient recovery from any toxicity, if the patient is still deriving clinical benefit in the judgment of the investigator.

MANAGEMENT OF SELECTED IDENTIFIED AND POTENTIAL RISKS

Management of Entrectinib-Related Adverse Events

Table A10-23 Dose Modifications for Entrectinib-Related Adverse Events

Toxicity (treatment-related) [a]	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	• Continue at same dose level	• Continue at same dose level	• Withhold dose until toxicity is Grade 1 or has returned to baseline, then reduce by one dose level and resume treatment	• Withhold dose until toxicity is Grade 1 or has returned to baseline, then reduce by one dose level and resume treatment; or discontinue treatment as per the investigator's discretion
Cognitive disorders or intolerable CNS toxicity	• Continue at same dose level	• For Grade 2 or higher, withhold until recovery to Grade 1 or to baseline, then resume treatment at reduced dose by one level. If event recurs, further reduce dose by one level • For prolonged, severe, or intolerable events, discontinue as clinically appropriate		
Hematologic	• Continue at same dose level	• Continue at same dose level	• Withhold dose until toxicity is ≤Grade 2 or has returned to baseline, then resume treatment at the same dose level or reduce by one dose level as per investigator's discretion • Grade 3 lymphopenia without other dose limiting events (e.g., opportunistic infection) may continue study treatment without interruption	• Withhold dose until toxicity is ≤Grade 2 or has returned to baseline, then reduce by one dose level and resume treatment • Grade 4 lymphopenia without other dose limiting events (e.g., opportunistic infection) may continue study treatment without interruption

Appendix 10-5: Entrectinib

Toxicity (treatment-related) [a]	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	• Continue at same dose level	• Continue at same dose level unless patient is intolerant or symptom is recurrent	• Interrupt entrectinib until recovery to Grade 1 or better	• Interrupt entrectinib until recovery to Grade 1 or better
Prolonged QTc interval	• Continue at same dose level	• Interrupt entrectinib until recovery to baseline • Continue at same dose level	• Interrupt entrectinib until recovery to baseline • Reduce dose by one dose level and resume treatment. If an alternative cause for QTc prolongation is found and corrected, resume at same dose level • The decision to resume entrectinib treatment, without dose reduction, should be subject to a specialist opinion (cardiologist)	• Discontinue treatment permanently
Syncope	• For any grade syncope event, withhold entrectinib until recovered and then resume treatment at reduced dose by one level • If event recurs, further reduce dose by one level or consider discontinuation of entrectinib as clinically appropriate			

Toxicity (treatment-related) [a]	Grade 1	Grade 2	Grade 3	Grade 4
Congestive heart failure	• Continue at same dose level	• Continue at same dose level; may reduce by one dose level at the investigator's discretion	• Withhold dose until recovery to Grade 1 or has returned to baseline, then reduce by one dose level and resume treatment • Managing heart failure should be subject to a specialist opinion (cardiologist)	• Withhold dose until recovery to Grade 1 or return to baseline, or discontinue treatment as per the investigator's discretion. Managing heart failure and the decision to resume treatment should be subject to a specialist opinion (cardiologist). Reintroduction of entrectinib at a dose reduced by one level can be considered only for patients deriving clinical benefit
Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	• Withhold dose until toxicity is Grade 0, then resume treatment at same dose • Discontinue treatment permanently if pneumonitis recurs	• Withhold dose until toxicity is Grade 0, then resume treatment at same dose • Discontinue treatment permanently if pneumonitis recurs	• Discontinue treatment permanently	• Discontinue treatment permanently

QTc = corrected QT interval.

[a] Dose modifications are to be based on worst toxicity grade as per NCI CTCAE v5.0.

Additional Guidance on Specific Adverse Events

Congestive Heart Failure (CHF)

For Grade 3 or 4 heart failure, management of heart failure should be subject to the opinion of a cardiologist. Dose modification guidelines set forth in Table A10-23 of this Appendix should also be followed.

QTc Interval Prolongation

In cases of Grade 2 or 3 QT interval prolongation, assess and correct electrolytes and concomitant medications and follow dose modification guidelines in Table A10-23 of this Appendix. In cases of Grade 4 QT interval prolongation, entrectinib should be permanently discontinued.

For Grade 3 or 4 QTc prolongation, patient must remain hospitalized with continuous cardiac monitoring until an opinion is obtained from a cardiologist. Dose modification guidelines set forth in Table A10-23 of this Appendix should also be followed.

Cognitive Disorders

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in patients treated with entrectinib in clinical trials. Patients should be monitored for signs of cognitive changes.

Based on the severity of the cognitive disorder, entrectinib treatment should be modified as described in Table A10-23.

Patients who experience symptoms of cognitive disorders should be instructed not to drive or use machines until symptoms resolve.

Syncope

Syncope events were reported in patients treated with entrectinib in clinical trials. In some patients, syncope was reported with concurrent hypotension, dehydration, or QT prolongation and in other patients no other concurrent related conditions were reported.

Patients experiencing syncope should be evaluated and entrectinib treatment should be modified as described in Table A10-23.

Bone fractures

Entrectinib use has been associated with an increased risk of fractures. Patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures should be evaluated promptly. In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area. There are no data on the effects of entrectinib on healing of known fractures and the risk of future fractures.

Pneumonitis/Pneumonia

Investigators must thoroughly evaluate patients who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a patient has a potential diagnosis of pneumonitis or drug-related lung injury, the following evaluations/procedures should be considered to assist or exclude the diagnosis of pneumonitis during this period:

- A sputum gram stain and culture (induced sputum if needed) for bacteria, viruses, fungi, protozoa, and mycobacteria
- Blood culture for febrile patients
- Thoracentesis if pleural fluid is present (examined for same pathogens as sputum)
- Bronchoscopy with bronchoalveolar lavage (BAL), if appropriate. BAL fluid should be sent for culture and cytology (examined for same pathogens as sputum)
- Lung biopsy (e.g., open or thoracoscopic preferable; bronchoscopy with transbronchial biopsy), if appropriate
- A plasma sample for B-type natriuretic peptide to evaluate for evidence of congestive heart failure
- For Asian patients, a blood sample for β-D-glucan to evaluate for the presence of protozoal pneumonia (e.g., Pneumocystis jiroveci)

If clinically appropriate, high dose corticosteroid treatment should be initiated. Should the event be fatal, an autopsy is highly recommended to confirm/exclude the diagnosis. For any case of suspected pneumonitis, please contact the Sponsor. See Table A10-22 for appropriate dose modifications.

Nausea and Emesis

For nausea and emesis, treat with standard antiemetics; prophylactic antiemetics are permitted as necessary using institutional guidelines for treatment and/or published guidelines. Refer to Table A10-24, Table A10-25, and Table A10-26 for concomitant medications that should be administered with caution.

Diarrhea

Treatment with antidiarrheal drugs may be warranted and should follow institutional and/or published guidelines. If no guidelines exist, then the following recommendations may be instituted:

- For Grade 1 diarrhea, treat with loperamide if needed; no dose modification is necessary

- For Grade 2 diarrhea, treat with loperamide (4 mg at first onset, then 2 mg every 2–4 hours or after each loose stool, until symptom free for 12 hours). No dose modification is necessary unless the patient is intolerant or symptom is recurrent
- For Grade ≥3 (despite use of loperamide), treatment should be withheld until recovery to Grade ≤1

Concomitant Radiotherapy

In certain instances, palliative radiotherapy to specific sites is permitted if considered medically necessary by the Investigator. The Sponsor must be notified if palliative radiotherapy is started; however, the need for radiation therapy will generally be considered indicative of progressive disease.

It is recommended to avoid radiotherapy for at least 5 days after the final dose of entrectinib. The irradiated area should be as small as possible and <25% of the bone marrow reserve. Entrectinib administration should be withheld during the period of irradiation and for 2 weeks thereafter. If radiation-related toxicities (other than xerostomia) have not normalized to pre-irradiation levels after 2 weeks of rest, entrectinib should be discontinued.

Lifestyle Guidelines

Use of herbal medications (e.g., St. John's Wort) and consumption of grapefruit and/or grapefruit juice should be avoided during the Treatment Period.

MEDICATIONS TO BE GIVEN WITH PRECAUTION

Use of concomitant medications that increase or possibly increase the risk of QTc prolongation and/or induce torsades de pointes ventricular arrhythmia (see Table A10-24) must be used with caution or avoided if possible during treatment with entrectinib.

Table A10-24 Concomitant Medications to be Used with Caution

Antiarrhythmics	Amiodarone (Cordarone) Procainamide (Pronestyl) Disopyramide (Norpace) Quinidine (Quinaglute)	Dofetilide (Tikosyn) Sotalol (Betapace) Ibutilide (Corvert)
Antipsychotics	Chlorpromazine (Thorazine) Clozapine (Clozaril) Haloperidol (Haldol)	Risperidone (Risperdal) Quetiapine (Seroquel) Thioridazine (Mellaril)
Antibiotics	Azithromycin (Zithromax) Ciprofloxacin (Cipro) Clarithromycin (Biaxin) Erythromycin (Erythrocin) Fluconazole (Diflucan) Gatifloxacin (Tequin) Itraconazole (Sporanox)	Ketoconazole (Nizoral) Levofloxacin (Levaquin) Moxifloxacin (Avelox) Ofloxacin (Floxin) Sparfloxacin (Zagam) Telithromycin (Ketek) Trimethoprim-Sulfa (Bactrim)
Antidepressants	Amitriptyline (Elavil) Citalopram (Celexa) Desipramine (Pertofrane) Doxepin (Sinequan) Fluoxetine (Prozac)	Imipramine (Norfranil) Nortriptyline (Pametor) Paroxetine (Paxil) Sertraline (Zoloft) Venlaxafine (Effexor)
Antiemetics	Ondansetron (Zofran)	Prochlorperazine (Compazine)

DRUG INTERACTIONS

Antacids

Absorption of entrectinib may be pH sensitive. Patients requiring H2-receptor antagonists, proton pump inhibitors (PPIs), and/or antacids should preferentially take only H2 receptor antagonists or antacids as the duration of action of these drugs is relatively transient in contrast to PPIs, which have longer half-lives. These medications should be taken at a time point that is not proximal to entrectinib administration (at least 3–4 hours before or after administration during the day, or the night before) to minimize any potential effect on entrectinib absorption.

Cytochrome P450 Substrates

A study with recombinant human cytochrome P450 isoforms (CYP450) suggests that entrectinib is metabolized by multiple CYP450 isoforms. Entrectinib inhibited the activities of CYP2C9, CYP2D6, and CYP3A4 isoforms with IC50 values of 5.5, 5.6, and 2.8-6.3 μM, respectively. Entrectinib also exhibited the potential to induce CYP3A4, suggesting a potential for interactions with other drugs primarily metabolized by CYP3A4. Due to this potential, concomitant use of moderate to strong CYP3A inhibitor and inducer medications, including those listed in Table A10-25, should be avoided. Entrectinib should be administered with caution with the drugs listed in Table A10-26 below.

The following enzyme-inducing anti-epileptic drugs (EIAEDs) are prohibited:

- Carbamazepine
- Oxcarbazepine
- Phenytoin
- Fosphenytoin
- Phenobarbital
- Primidone

Table A10-25 Cytochrome P450 CYP3A Inhibitors and Inducers

Strong Inhibitors	Strong Inducers
Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus

Table A10-26 Cytochrome P450 Enzyme-Specific Substrates

CYP450 Enzyme	Sensitive Substrates	Substrates with Narrow Therapeutic Range
CYP2C9	Celecoxib	Warfarin
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine, pimozide
CYP3A4	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus

A10–6 ERLOTINIB

Erlotinib will be administered in combination with bevacizumab—Refer to Appendix A10–3 for details on bevacizumab.

BACKGROUND ON ERLOTINIB

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In nonclinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.

EGFR alterations may lead to constitutive activation of anti-apoptotic and proliferation signaling pathways. The potent effectiveness of erlotinib in blocking EGFR-mediated signaling in these EGFR alteration-positive tumors is attributed to the tight binding of erlotinib to the ATP-binding site in the mutated kinase domain of the EGFR. Due to the blocking of downstream-signaling, the proliferation of cells is stopped, and cell death is induced through the intrinsic apoptotic pathway. Tumor regression is observed in mouse models of enforced expression of these EGFR activating mutations.

Erlotinib is being developed for use in the treatment of cancers. Erlotinib, has been approved in various countries for the treatment of patients with non-small cell lung and pancreatic cancers.

Bevacizumab, in combination with erlotinib, has been approved for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with epidermal growth factor receptor (EGFR) activating mutations.

Rationale for the use of erlotinib in combination with bevacizumab is described in Appendix A10–3 (Bevacizumab).

SAFETY

SAFETY PROFILE

The safety profile of erlotinib as monotherapy or in combination with chemotherapy is presented in the Erlotinib EMA Summary of Product Characteristics.

Adverse reactions associated with Warnings and Precautions:

- Smokers
- Interstitial lung disease
- Diarrhea, dehydration, electrolyte imbalance and renal failure
- Hepatitis, hepatic failure
- Gastrointestinal perforation
- Bullous and exfoliative skin disorders
- Ocular disorders
- Interactions with other medicinal products

Management guidelines for erlotinib that are applicable to this study are provided in Table A10-27.

A comprehensive description of the safety profile of erlotinib in combination with bevacizumab is provided in the Bevacizumab and Erlotinib EMA Summary of Product Characteristics.

Appendix A10–3 presents a brief overview of the safety profile of bevacizumab in combination with erlotinib.

The summary information provided in the following sections must always be checked against any update of the Erlotinib EMA Summary of Product Characteristics that may have occurred after the protocol has been issued.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For erlotinib, AESIs include:

- interstitial lung disease

ADMINISTRATION OF ERLOTINIB

POSOLOGY AND ROUTE

The dose of erlotinib will be 150 mg taken at least one hour before or two hours after the ingestion of food.

For instructions on handling of the medicinal product, refer to the EMA Summary of Product Characteristics.

DURATION OF TREATMENT

Treatment with erlotinib should continue until loss of clinical benefit or the development of unacceptable toxicity.

DOSE MODIFICATIONS AND DISCONTINUATION DURING TREATMENT

When dose adjustment is necessary, the dose should be reduced in 50 mg steps (see Table A10-27).

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see Table A10-27).

Table A10-27 below gives general erlotinib dose modification guidance

Summary of Advice for Dose Discontinuation (See Table A10-27 for Details):

Erlotinib must be discontinued if:

- Interstitial lung disease
- Gastrointestinal perforation

Discontinuation: may be considered if:

- Bullous and exfoliative skin disorders
- Ocular disorders (mostly keratitis)

Please also refer to the Bevacizumab EMA Summary of Product Characteristics and to its warnings and precautions when using erlotinib in combination with bevacizumab.

MANAGEMENT ADVICE FOR SPECIFIED ADVERSE DRUG REACTIONS

Table A10-27 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Smokers	Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. The degree of reduction is likely to be clinically significant.
Interstitial Lung Disease	In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnea, cough and fever, interrupt erlotinib pending diagnostic evaluation. If ILD is diagnosed, discontinue erlotinib and initiate appropriate treatment as necessary.
Diarrhea, dehydration, electrolyte imbalance and renal failure	● Moderate or severe diarrhea Treat with e.g., loperamide. Dose reduction may be necessary. If so, reduce dose by 50 mg steps. ● Severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, Interrupt erlotinib and treat the dehydration ● If more severe or persistent cases of diarrhea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (other medications, symptoms or diseases or other predisposing conditions including advanced age). Interrupt erlotinib and take appropriate measures to intensively rehydrate the patient intravenously. Renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.
Hepatitis, hepatic failure	Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Interrupted erlotinib if changes in liver function are severe.
Gastrointestinal perforation	Discontinue erlotinib permanently. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, or who have prior history of peptic ulceration or diverticular disease are at increased risk.
Bullous and exfoliative skin disorders	Interrupt or discontinue permanently erlotinib. If bullous or exfoliative skin disorders, test patients for skin infection and treat according to local management guidelines.

Event	Action to Be Taken
Ocular disorders (mostly keratitis)	Promptly refer to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with erlotinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Exert caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.
Cutaneous Toxicity	For patients who are exposed to sun, protective clothing and/or use of sun screen (e.g., mineral containing) may be advisable.
Interactions with other medicinal products	● Potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 may lead to increased toxicity. **Concomitant treatment with these types of agents should be avoided** REFER TO THE EU SmPC FOR OTHER FORMS OF INTERACTIONS e.g., ● Medicinal products that alter the pH of the upper gastrointestinal (GI) tract, like proton pump inhibitors, H2 antagonists and antacids ● Other CYP substrates - Erlotinib is a potent inhibitor of CYP1A1, and a moderate inhibitor of CYP3A4 and CYP2C8, as well as a strong inhibitor of glucuronidation by UGT1A1 in vitro ● Coumarin-derived anticoagulants ● Statins ● P-glycoprotein inhibitors ● Medicinal products altering pH

DRUG INTERACTIONS

There is no evidence of clinically significant drug interactions between erlotinib and bevacizumab.

Erlotinib and Other CYP Substrates

Erlotinib is metabolized in the liver by the hepatic CYPs in humans, primarily CYP3A4 and to a lesser extent by CYP1A2, and the pulmonary isoform CYP1A1. Potential interactions may occur with drugs that are metabolized by or are inhibitors or inducers of these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg po BID for 5 days) resulted in increased exposure to erlotinib (86% in median erlotinib exposure [AUC] and a 69% increase in C_{max}) when compared to erlotinib alone.

When erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure (AUC) and maximum concentration (C_{max}) increased by 39% and 17%, respectively. Therefore, caution should be used when administering erlotinib with potent CYP3A4 or combined CYP3A4/CYP1A2 inhibitors. In these situations, the dose of erlotinib should be reduced if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Induction of CYP3A4 metabolism by rifampicin (600 mg po QD for 7 days) resulted in a 69% decrease in the median erlotinib AUC, following a 150 mg dose of erlotinib as compared to erlotinib alone. Pre-treatment and co-administration of rifampicin with a single 450 mg dose of erlotinib resulted in a mean erlotinib exposure (AUC) of 57.5% of that after a single 150 mg erlotinib dose in the absence of rifampicin treatment. Alternative treatments lacking potent CYP3A4-inducing activity should be considered when possible. For patients who require concomitant treatment with erlotinib and a potent CYP3A4 inducer such as rifampicin, an increase in dose to 300 mg should be considered while their safety is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Higher doses have not been studied in this setting.

Pre-treatment or co-administration of erlotinib did not alter the clearance of the prototypical CYP3A4 substrates midazolam and erythromycin. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely. Oral availability of midazolam did appear to decrease by up to 24%, which was however not attributed to effects on CYP3A4 activity.

Erlotinib and Medicinal Products Altering pH

The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Drugs that alter the pH of the upper gastrointestinal tract may alter the solubility of erlotinib and hence its bioavailability. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure (AUC) and C_{max} by 46% and 61%, respectively. There was no change to t_{max} or half-life. Concomitant administration of erlotinib with 300 mg ranitidine, an H2-receptor antagonist, decreased erlotinib exposure (AUC) and C_{max} by 33% and 54%, respectively. Therefore, co-administration of drugs reducing gastric acid production with erlotinib should be avoided where possible. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for this loss of exposure. However, when erlotinib was dosed in a staggered manner 2 hour before or 10 hours after ranitidine 150 mg twice a day, erlotinib exposure (AUC) and C_{max} decreased only by 15% and 17%, respectively. If patients need to be treated with such drugs, then an H2-receptor antagonist such as ranitidine should be considered and used in a staggered

manner. Erlotinib must be taken at least 2 hours before or 10 hours after the H2-receptor antagonist dosing.

Erlotinib and Coumarin-derived Anticoagulants

Interaction with coumarin-derived anticoagulants, including warfarin, leading to increased INR and bleeding events, which in some cases were fatal, have been reported in patients receiving erlotinib. Patients taking coumarin-derived anticoagulants should be monitored regularly for any changes in prothrombin time or INR.

Erlotinib and Statins

The combination of erlotinib and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

Erlotinib and Smokers

Cigarette smoking (a moderate CY1A2 inducer) has been shown to reduce erlotinib exposure by 50% to 60%. Smokers should be advised to stop smoking. Concomitant use of erlotinib with moderate CYP1A2 inducers should be avoided.

A10–7 IPATASERTIB

BACKGROUND ON IPATASERTIB

Ipatasertib is a potent, highly selective small-molecule inhibitor of all three isoforms of the serine/threonine kinase Akt (protein kinase B). Ipatasertib is being developed as a single agent and in combination with other therapies for the treatment of cancers in which activation of the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway may be relevant for tumor growth or therapeutic resistance.

Akt is a central node in cell signaling downstream of growth factors, cytokines, and other cellular stimuli. It plays an important role in cancer development, progression, and therapeutic resistance and is activated in most, if not all, human cancers (Altomare and Testa 2005). The ubiquity and importance of Akt activation in human cancers provide a strong rationale for developing therapeutics targeting Akt.

Ipatasertib selectively binds to the active conformation of Akt and inhibits its kinase activity (Altomare and Testa 2005). Consistent with its mechanism of action, in nonclinical studies, ipatasertib has proven to be especially effective on cells with activated Akt, including phosphatase and tensin homolog (PTEN)-null and PIK3CA-altered tumor models, resulting in G1 arrest and/or apoptosis in human cancer cells. In vivo efficacy studies support the use of ipatasertib as a single agent or in combination with chemotherapeutic, hormonal, or targeted agents for the treatment of patients with advanced or metastatic solid tumors.

SAFETY

SAFETY PROFILE

The safety profile of ipatasertib is presented in the Ipatasertib Investigator's Brochure.

The identified risks associated with ipatasertib treatment include:

- Gastrointestinal toxicities (diarrhea, nausea, vomiting and oral mucositis)
- Fatigue/asthenia
- Rash
- Erythema multiforme
- Fasting Hyperglycemia
- AST/ALT increased
- Dehydration
- Decreased appetite

- Potential risks:

The following list presents adverse events that are Adverse Drug Reactions (ADRs) of other inhibitors of the PI3K-AKT-mTOR pathway or that nonclinical data suggest could be observed in patients receiving ipatasertib. These risks are not considered ADRs:

- Hematological or Immunosuppressants effects
- Hyperlipidemia
- Hepatotoxicity
- Pneumonitis
- Colitis
- Developmental toxicity
- Drug–drug Interactions

Management guidelines for ipatasertib that are applicable to this study are provided in Table A10-28 to Table A10-36.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For ipatasertib, AESIs include:

- Grade ≥3 diarrhea
- Grade ≥3 fasting hyperglycemia
- Grade ≥3 rash
- Grade ≥ 2 pneumonitis
- Grade ≥ 2 colitis/enterocolitis
- Grade ≥3 hepatotoxicity including ALT/AST elevations

ADMINISTRATION OF IPATASERTIB

POSOLOGY AND ROUTE

The dose of ipatasertib will be 400 mg daily.

Each dose of ipatasertib should be taken with a minimum of 90 mL (3 ounces) of fluid.

Ipatasertib may be taken with or without food.

For instructions on handling of the medicinal product, refer to the Ipatasertib Investigator's Brochure.

DURATION OF TREATMENT

Treatment with ipatasertib should continue until loss of clinical benefit or the development of unacceptable toxicity.

PROPHYLAXIS

All patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Refer to Table A10-29 for further details on treatment of gastrointestinal toxicities during ipatasertib treatment.

DELAYED OR MISSED DOSES

If a dose is missed (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. If vomiting occurs after taking a dose of ipatasertib, the patient should not take an additional dose on that day and treatment should be continued as prescribed the following day.

DOSE MODIFICATIONS

Management of adverse events may require dose reduction, temporary interruption, or discontinuation of treatment with ipatasertib. The dose of ipatasertib should be reduced according to the dose reduction schedule provided in Table A10-28.

Table A10-28 Dose Reduction Schedule

Dose Reduction Schedule [a]	Dose Level
Starting dose	400 mg daily
1st reduction	300 mg daily
2nd reduction	200 mg daily
3rd reduction	Discontinue

[a] If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.

Patients may hold ipatasertib for up to 4 consecutive weeks (approximately 28 consecutive days) in order to recover from toxicity or an adverse event related to the study drug.

If the patient does not tolerate the once-daily dosing of ipatasertib, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib per patient. Dose re-escalation is not permitted for ipatasertib.

TREATMENT INTERRUPTION

Ipatasertib treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If ipatasertib has been withheld for >28 consecutive days because of treatment-related toxicity, the patient should be discontinued from ipatasertib. Ipatasertib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures)

SUMMARY OF ADVICE FOR DOSE DISCONTINUATION AND DOSE INTERRUPTION (see Table A10-28 to Table A10-36 for details):

Ipatasertib must be discontinued if:

- Grade 4 diarrhea
- Recurrent Grade 4 hyperglycemia
- Febrile and Grade 4 neutropenia if recovery to Grade 2 or better does not occur after up to 4 weeks of treatment hold
- Grade 4 and recurrent Grade 3 hepatotoxicity
- Grade 4 rash, recurrent Grade 3 rash, or Grade 3 rash that remains clinically significant for 4 weeks after treatment hold
- Grade 4 non-infectious pneumonitis, recurrent Grade 3 non-infectious pneumonitis, Grade 2 non-infectious pneumonitis if recovery to Grade 1 or better is not observed within 28 days of treatment hold
- Grade ≥3 mucositis, if recovery to Grade 2 or better does not occur within 4 weeks of treatment hold

Ipatasertib must be interrupted if:

- Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events. Ipatasertib treatment should be temporarily held during systemic corticosteroids treatment (except when corticosteroids are given as premedication to paclitaxel).

MANAGEMENT OF SELECTED IDENTIFIED AND POTENTIAL RISKS

DIARRHEA MANAGEMENT GUIDELINES

Specific guidelines for managing diarrhea to improve safety and tolerability are provided in Table A10-29. All patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance. If diarrhea occurs, it should be managed per guidelines; upon resolution or when study treatment is restarted, loperamide prophylaxis

should be considered to resume and continue based on clinical judgments (if allowed by local guidance).

Treatment modifications for diarrhea (any grade), when it occurs, should be instituted as early as possible. Guidelines for treatment of diarrhea following the prophylactic dose of loperamide (where allowed) includes use of loperamide 2 mg every 4 hours or after each loose, watery stool, up to the maximum total dose of 16 mg/day or per institutional guidelines and standard of care, including, but not limited to, additional therapy with Lomotil® (diphenoxylate and atropine), codeine, or octreotide. Duration of diarrhea may be minimized by taking ipatasertib with food, avoiding lactose-containing foods, and hydrating with 8–10 glasses per day (~12 oz/glass) of electrolyte-containing clear liquid, such as broth or low-calorie drinks.

For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib, gastroenterologists should be consulted to rule out the risk of colitis and infection (e.g., obtaining CT images or a stool culture for infectious workup [Clostridium difficile, enteric bacteria, cytomegalovirus]). Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed. Educational materials will be provided to investigators and patients outlining these guidelines.

Table A10-29 Diarrhea Management Guidelines

Severity of Diarrhea [a]	Management Guideline
Prevention	• All patients are should receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle, if allowed by local guidance or unless there is a clinical concern precluding their use. Loperamide dose adjustment may be made per investigator discretion after discussion with the Medical Monitor. • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated.
Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	• Continue study drugs at the current dose level. • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8−10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance.
Grade 2 Increase of 4−6 stools per day over baseline; moderate increase in ostomy output compared with baseline	• Rule out infectious etiology. • Manage with loperamide as early as possible 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8−10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better. • Reduce ipatasertib by one (or one additional) dose level for recurrent Grade 2 diarrhea. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.

Severity of Diarrhea [a]	Management Guideline
Grade 3 Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level when treatment is restarted. • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Permanently discontinue ipatasertib.

ADL = activities of daily living; BID = twice a day; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; QD = once a day.

[a] Diarrhea, as defined by NCI CTCAE v4.0, a disorder characterized by frequent and watery bowel movements.

FASTING HYPERGLYCEMIA

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours. The treatment goals for glycemic control should be: 1) fasting glucose under 160 mg/dL and 2) HbA1c ≤8%.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined below (see Table A10-30) and are intended to provide guidance for fasting glucose measurements assessed in the clinic. Decisions regarding study treatment should be made on fasting levels drawn in the clinic whenever possible.

In the event of ipatasertib interruption, anti-diabetic medications may need to be held or reduced (per investigator judgment) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Because the hyperglycemia observed with ipatasertib treatment is consistently associated with endogenous elevations in insulin, insulin-based therapy to manage any hyperglycemia should be used with caution because severe hypoglycemic episodes could potentially occur. Therefore, initial treatment should be considered with biguanides (preferred), sulfonylureas, and other hypoglycemic treatments.

Table A10-30 Fasting Hyperglycemia Management Guidelines

Hyperglycemia	Management Guideline
General Guidance	• Thoroughly evaluate all events of hyperglycemia for more common etiologies other than drug-induced effects. • Investigate for diabetes. If patient has Type 1 diabetes, treat as an event of fasting glucose value 250–500 mg/dL. • Workup could include confirmation of fasting blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, hemoglobin A1C, C-peptide levels, anti-islet antibodies, and anti-GAD65 antibody. • Treat hyperglycemia per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities.
Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L) *	• Continue ipatasertib. • Provide patient with education on a diabetic diet and consider home glucose monitoring. • Consider oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia.
Fasting glucose value >160 to 250 mg/dL (>8.9–13.9 mmol/L) *	• Withhold ipatasertib dosing until fasting glucose value resolves to ≤160 mg/dL. (Investigate for diabetes. If patient has Type 1 diabetes, treat as a fasting glucose value 250–500 mg/dL event. If patient does not have Type 1 diabetes, treat as per institutional guidelines). • Encourage a diabetic diet and initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia. • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level (refer to Table A10-29). • If the patient previously has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication.

Hyperglycemia	Management Guideline
Fasting glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L) *	• Withhold ipatasertib dosing until fasting glucose value resolves to ≤ 160 mg/dL and contact the Medical Monitor. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Encourage a diabetic diet and initiate home glucose monitoring. • If the patient is already on an oral anti-diabetic medication, ipatasertib should be reduced by one dose level when treatment is restarted. • If previously, the patient has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication. • If hyperglycemia 250–500 mg/dL recurs, the dose of ipatasertib should be reduced by one dose level (see Table A10-29) when treatment is restarted.
Fasting glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences *	• Withhold ipatasertib dosing until fasting glucose value resolves to ≤ 160 mg/dL. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Encourage a diabetic diet and initiate home glucose monitoring. • Upon recovery of fasting glucose to ≤ 160 mg/dL, reduce ipatasertib by one dose level (see Table A10-29) when treatment is restarted. • If glucose value > 500 mg/dL recurs, permanently discontinue ipatasertib and contact the Medical Monitor. Reduce ipatasertib by one dose level if and when treatment is restarted. • If Grade 4 hyperglycemia recurs, permanently discontinue ipatasertib.

ULN = upper limit of normal.

* For all grades, the patient should receive education on a diabetic diet.

NEUTROPENIA AND/OR THROMBOCYTOPENIA

Addition of hematopoietic growth factors is allowed. If a dose delay is required as a result of neutropenia at any grade, patients should receive prophylactic granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor per institutional standards. Patients should be counseled as to the risk of fever and infection and to the importance of contacting their treating physician immediately if these conditions occur so that they can be promptly and appropriately managed. Dosage modification guidelines for neutropenia and/or thrombocytopenia attributable to ipatasertib are outlined in Table A10-31.

Table A10-31 Neutropenia Management Guidelines

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Grade 2	• Ipatasertib may be continued at the original dose.
Grade 3	• Ipatasertib should both be held until recovery to Grade 1 and if clinically appropriate based on the investigator's medical judgment to Grade 2 as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. – First episode: If recovery is to Grade 1, resume the original dose. If recovery to Grade 1 is achieved with the use of G-CSF, then continued use of G-CSF is recommended once dosing of the study drug is resumed. If recovery is to Grade 2, follow the guidance above. – Recurrent episode: Ipatasertib should be reduced by one dose level when treatment is restarted.
Febrile neutropenia and Grade 4 neutropenia	• Ipatasertib should be held until recovery to Grade 1, and if clinically appropriate based on the investigator's medical judgment to Grade 2, as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. – First episode: Ipatasertib should be reduced by one dose level when treatment is restarted. – Recurrent episode: Ipatasertib should be discontinued. • Following a treatment hold of up to 4 weeks, if recovery to Grade 2 or better neutropenia does not occur, the patient will permanently discontinue ipatasertib treatment.

ANC = absolute neutrophil count; G-CSF = Granulocyte-colony stimulating factor.

NAUSEA AND/OR VOMITING

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other antiemetics (i.e., prochlorperazine or metoclopramide per institutional guidelines; see Table A10-32). For persistent nausea and/or vomiting attributable to ipatasertib, dosage modification guidelines are outlined in Table A10-29.

Table A10-32 Nausea and Vomiting Guidelines

Severity of Nausea and /or Vomiting	Management Guideline
Grade 1	• Provide supportive care as needed.
Grade 2	• Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron.
Grade ≥3	• Interrupt ipatasertib until nausea or vomiting resolves to Grade 2 or better. • Provide maximum supportive care per local guidelines, with a minimum of two anti-emetics, including ondansetron. • If Grade ≥3 nausea or vomiting recurs, ipatasertib should be reduced by one dose level when treatment is restarted.

HEPATOTOXICITY

Permanently discontinue ipatasertib for any patients who develop a concurrent elevation of ALT and/or AST greater than 3 × ULN and total bilirubin greater than 2 × ULN and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria. Dosage modification and symptom management guidelines for hepatotoxicity, attributable to study treatment are shown below (see Table A10-33).

Table A10-33 Hepatotoxicity Management Guidelines

Severity of LFT Elevation	Management Guideline
Grade 1 AST or ALT > baseline −3 × ULN or T bilirubin > baseline −1.5 × ULN	Continue study drugs.
Grade 2 AST or ALT > 3–5 × ULN or T bilirubin > 1.5–3.0 × ULN	Continue study drugs. The frequency of liver function test monitoring should be increased as clinically indicated if the investigator judges that the laboratory abnormalities are potentially related to study medication.
Grade 3 AST or ALT > 5–20 × ULN or T bilirubin > 3–10 × ULN	Immediately interrupt ipatasertib. On return of LFTs to baseline or to AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib/ at previous dose level (refer to Table A10-28). Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter. If another Grade 3 event occurs, interrupt ipatasertib/. On return of LFTs to baseline or AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib/, reducing the dose by one level. Further Grade 3 occurrences must result in permanent discontinuation of ipatasertib.
Grade 4 AST or ALT > 20 × ULN or T bilirubin > 10 × ULN	Permanently discontinue ipatasertib.

LFT = liver function test; QD = once daily; ULN = upper limit of normal.

RASH

Treatment-related rash, has occurred in patients receiving ipatasertib treatment particularly when ipatasertib has been used certain combinations (e.g., ipatasertib in combination with paclitaxel and atezolizumab or with abiraterone). The following prophylaxis measures can be considered, in particular for combinations with overlapping skin toxicity.

- Unless contraindicated, daily PO antihistamine prophylaxis can be considered for at least the first cycle. It is suggested that a non-sedating longer-acting oral antihistamine be used (such as 10 mg of cetirizine PO QD or comparable dose of other antihistamines, e.g., loratadine, fexofenadine).

Ipatasertib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity, including erythema multiforme, attributable to ipatasertib are shown below in Table A10-34.

Table A10-34 Rash Management Guidelines

Severity of Rash	Management Guideline
Grade 1	• Continue study drugs. • Consider topical corticosteroids.
Grade 2	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids.
Grade 3	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If the skin toxicity resolves to Grade 1 or better or is no longer clinically significant within 28 days, following completion of the steroid taper, ipatasertib may be resumed at one dose level below the previous dose. • If recovery of the skin toxicity to Grade 1 or better does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib.
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. Ipatasertib should be permanently discontinued.

PNEUMONITIS

Pneumonitis is not known to be causally related to ipatasertib; however, it has been observed with other drugs treating pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see Table A10-35).

Table A10-35 Pneumonitis Management Guidelines

Severity of Pneumonitis	Management Guideline
Grade 1	• Continue study drugs. • Perform CT scan and PFTs. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment until improvement to Grade 1 or better. Consider resuming ipatasertib at same dose level or one dose level below per investigator's assessment. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • For recurrent Grade 2 pneumonitis, ipatasertib must be resumed at one dose level below the previous dose. • Discontinue ipatasertib if recovery to Grade 1 or better is not evident within 28 days.
Grade 3	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment until improvement to Grade 1 or better. Resume ipatasertib at one dose level below previous dose per investigator's assessment. If recovery to Grade 1 or better is not evident within 28 days, discontinue study treatments. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • For recurrent non-infectious Grade 3 pneumonitis events, ipatasertib should be permanently discontinued.
Grade 4	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Permanently discontinue ipatasertib. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

CT = computed tomography; PFT = pulmonary function test.

MUCOSITIS

Mouthwash such as magic mouth wash (if inaccessible, warm salt or bicarbonate water) should be used as supportive care per institution guidelines. Brushing teeth after meals, keeping lips moisturized with non-Vaseline® products, and avoiding alcohol, spicy food, and smoking have all been shown to reduce pain and infection related to mucositis. Ranitidine or omeprazole may be helpful if patients have epigastric pain. Dosage modification guidelines for mucositis attributable to study treatment are outlined in Table A10-36.

Table A10-36 Mucositis Management Guidelines

Severity of Mucositis	Management Guidelines
Grade 1 or 2	• Manage with maximum supportive care. • If Grade ≥ 2 mucositis recurs in subsequent 4 week cycles, despite maximal supportive care, the dose of ipatasertib should be reduced by one dose level.
Grade ≥ 3	• Hold ipatasertib until recovery to Grade 2 or better. If the mucositis resolves to Grade 2 or better during the current cycle, the dose of ipatasertib should be reduced by one dose level. • If recovery of mucositis to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue ipatasertib.

OTHER NON-HEMATOLOGIC TOXICITIES

If other Grade ≥ 3 non hematologic toxicities not described above develop in patients, treatment with ipatasertib may be held, depending on the attribution of the toxicity, at the discretion of the investigator. Ipatasertib should be discontinued for any non-hematologic Grade 4 adverse event considered related to ipatasertib.

If the toxicity resolves to Grade 1 or better within 2 weeks, treatment may resume with the attributable agent.

If the toxicity resolves to Grade 1 or better in 2–4 weeks, the dose of the attributable drug should be reduced by one level per the suggested guidelines.

Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes > 4 weeks, treatment may resume with the attributable agent with dose reduction, or the attributable agent may be permanently discontinued, at the discretion of the investigator based on clinical judgement.

SURGERY AND PALLIATIVE RADIOTHERAPY

Patients who require radiotherapy or surgery as part of medical treatment in the absence of radiographic disease progression must exercise caution: ipatasertib should be temporarily withheld for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For minor surgeries or single-day radiotherapy, this hold of ipatasertib may be shorter, upon clinical judgment. After the temporary treatment hold is complete, study treatment may be re-initiated when the patient has sufficiently recovered.

DRUG INTERACTIONS

A clinical study in patients showed that ipatasertib at a dose of 600 mg QD is a moderate inhibitor of CYP3A, which resulted in a 2.22-fold increase in midazolam (sensitive CYP3A substrate) exposures. Ipatasertib is primarily metabolized by CYP3A and, hence, strong inhibitors and inducers of CYP3A may result in increased or decreased ipatasertib exposures, respectively. Therefore, the following drugs should be avoided, or used with caution when administering ipatasertib. If using of one of these drugs is necessary, the risks and benefits should be evaluated prior to its concomitant use with ipatasertib per protocol guidelines:

- Strong CYP3A inhibitors, such as but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, and/or grapefruit juice or grapefruit supplements
- Strong CYP3A inducers, such as but not limited to rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- CYP3A4 substrates with a narrow therapeutic index, such as but not limited to alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine

A10–8 IPATASERTIB IN COMBINATION WITH PACLITAXEL

BACKGROUND ON IPATASERTIB

Ipatasertib is a potent, highly selective small-molecule inhibitor of all three isoforms of the serine/threonine kinase Akt (protein kinase B). Ipatasertib is being developed as a single agent and in combination with other therapies for the treatment of cancers in which activation of the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway may be relevant for tumor growth or therapeutic resistance.

Akt is a central node in cell signaling downstream of growth factors, cytokines, and other cellular stimuli. It plays an important role in cancer development, progression, and therapeutic resistance and is activated in most, if not all, human cancers (Altomare and Testa 2005). The ubiquity and importance of Akt activation in human cancers provide a strong rationale for developing therapeutics targeting Akt.

Ipatasertib selectively binds to the active conformation of Akt and inhibits its kinase activity (Altomare and Testa 2005). Consistent with its mechanism of action, in nonclinical studies, ipatasertib has proven to be especially effective on cells with activated Akt, including phosphatase and tensin homolog (PTEN)-null and PIK3CA-altered tumor models, resulting in G1 arrest and/or apoptosis in human cancer cells. In vivo efficacy studies support the use of ipatasertib as a single agent or in combination with chemotherapeutic, hormonal, or targeted agents for the treatment of patients with advanced or metastatic solid tumors.

Recent research has demonstrated that considerable cross talk occurs in the PI3K/AKT signaling pathway, which may limit the action of PI3K/AKT pathway inhibitors like ipatasertib, particularly when used as single agents. Combination of ipatasertib with several cytotoxic agents, however, has shown synergistic effects. For instance, ipatasertib enhanced the in vitro efficacy of the taxane paclitaxel in a human breast cancer model system (Morgillo et al. 2017). This may be of significant clinical import in the case of CUP, as a meta-analysis of 32 trials found that taxane-based regimens prolonged median survival time and improved 1-year survival rates among CUP patients (Lee et al. 2013). Based on these considerations, patients in the current study with AKT1, PTEN or PIK3CA alterations who are assigned to molecularly-guided treatment will receive a combination of ipatasertib and paclitaxel (any patient who started ipatasertib monotherapy under Versions 2–5 of the protocol can be switched to ipatasertib combined with paclitaxel if judged clinically appropriate by the investigator and accepted by the patient).

SAFETY

SAFETY PROFILE

The safety profile of ipatasertib as monotherapy and in combination with paclitaxel is presented in the Ipatasertib Investigator's Brochure.

The identified risks associated with ipatasertib treatment include:

- Gastrointestinal toxicity (diarrhea, nausea, vomiting and oral mucositis)
- Fatigue/asthenia
- Rash
- Erythema multiforme
- Fasting Hyperglycemia
- AST/ALT increased
- Dehydration
- Decreased appetite

- Potential risks:

The following list presents adverse events that are Adverse Drug Reactions (ADRs) of other inhibitors of the PI3K-AKT-mTOR pathway or that nonclinical data suggest could be observed in patients receiving ipatasertib. These risks are not considered ADRs:

- Hematological or Immunosuppressants effects
- Hyperlipidemia
- Hepatotoxicity
- Pneumonitis
- Colitis
- Developmental toxicity
- Drug–drug interactions

RISKS ASSOCIATED WITH IPATASERTIB IN COMBINATION WITH PACLITAXEL

Data for ipatasertib in combination with paclitaxel come primarily from 61 cancer patients in Study GO29227, where patients were randomized to ipatasertib + placebo or ipatasertib + paclitaxel.

- Adverse events related to ipatasertib which incidences were higher by > 10% in patients receiving ipatasertib + paclitaxel versus placebo + paclitaxel were diarrhea (88.5% vs. 16.1%) and nausea (41.0% vs. 19.4%)

- The Grade ≥3 adverse events reported more frequently in the ipatasertib+paclitaxel arm versus the placebo+paclitaxel arm were diarrhea (23.0%, all Grade 3, vs. 0), neutropenia (9.8% vs. 1.6%], and decreased neutrophil count (8.2% vs. 6.5%)
- The incidence of overall neutropenia was similar in both arms (34% in the ipatasertib+paclitaxel arm vs. 39% in the placebo+paclitaxel arm), but Grade ≥3 neutropenia was higher in the ipatasertib+paclitaxel arm (18% vs. 8%)

Management guidelines for ipatasertib that are applicable to this study are provided in Table A10-37 to Table A10-46.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For ipatasertib, AESIs include:

- Grade ≥3 diarrhea
- Grade ≥3 fasting hyperglycemia
- Grade ≥3 rash
- Grade ≥2 pneumonitis
- Grade ≥2 colitis/enterocolitis
- Grade ≥3 hepatotoxicity including ALT/AST elevations

ADMINISTRATION OF IPATASERTIB IN COMBINATION WITH PACLITAXEL

POSOLOGY AND ROUTE

The dose of ipatasertib will be 400 mg daily on Day 1 to 21 of a 28-day cycle. There is no administration of ipatasertib on Day 22 to 28. Ipatasertib will continue to be dosed as a monotherapy after the final administration of paclitaxel (see below) until loss of clinical benefit.

Each dose of ipatasertib should be taken with a minimum of 90 mL (3 ounces) of fluid.

Ipatasertib may be taken with or without food.

Paclitaxel will be administered at a dose of 80 mg/m^2 IV over 1 hour on Days 1, 8, and 15 of a 28-day cycle. If the dose on Day 1, 8, or 15 is missed, it can be given on Day 22. Paclitaxel will be given for 3 cycles. If relevant and tolerated, it may be continued beyond 3 cycles (refer to Section 4.3.4.7).

Note: On days when patients are to receive both medications, ipatasertib should be administered before paclitaxel infusions.

For instructions on handling of ipatasertib, refer to the Ipatasertib Investigator's Brochure. For instructions on handling of paclitaxel, refer to the local reference information.

DURATION OF TREATMENT

Treatment with ipatasertib should continue until loss of clinical benefit or the development of unacceptable toxicity.

Paclitaxel in combination with ipatasertib will be administered for 3 cycles. If relevant and tolerated, it may be continued beyond 3 cycles.

PROPHYLAXIS

All patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Refer to Table A10-39 for further details on treatment of gastrointestinal toxicities during ipatasertib treatment.

PREMEDICATION FOR IPATASERTIB + PACLITAXEL

All patients should be premedicated prior to paclitaxel administration to prevent severe hypersensitivity reactions. This premedication should consist of the institution's standard of care or one of the following premedications:

- Dexamethasone 20 mg orally approximately 12 hours prior and 6 hours prior to the paclitaxel infusion
  - Patients may be treated with dexamethasone 10−20 mg IV within 1 hour prior to paclitaxel infusion if the patient did not take the oral dexamethasone
- Diphenhydramine 50 mg IV (or equivalent) 30−60 minutes prior to paclitaxel infusion
- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30−60 minutes prior to paclitaxel infusion

DELAYED OR MISSED DOSES

If a dose is missed (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. If vomiting occurs after taking a dose of ipatasertib, the patient should not take an additional dose on that day, and treatment should be continued as prescribed the following day.

If a dose of paclitaxel is missed on Day 1, 8, or 15, it can be given on Day 22.

DOSE MODIFICATIONS

Management of adverse events may require dose reduction, temporary interruption, or discontinuation of treatment with ipatasertib.

The doses of ipatasertib and paclitaxel should be reduced according to the dose reduction schedules provided in Table A10-37 and Table A10-38.

Table A10-37 Dose Reduction Schedule for Ipatasertib

Dose Reduction Schedule [a]	Dose Level
Starting dose	400 mg daily
1st reduction	300 mg daily
2nd reduction	200 mg daily
3rd reduction	Discontinue

[a] If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.

Patients may hold ipatasertib for up to 4 consecutive weeks (approximately 28 consecutive days) in order to recover from toxicity or an adverse event related to the study drug.

If the patient does not tolerate the once-daily dosing of ipatasertib, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib per patient. Dose re-escalation is not permitted for ipatasertib.

Table A10-38 Dose Reduction Schedule for Paclitaxel

Dose Reduction Schedule	Dose Level
Starting dose	80 mg/m^2
1st reduction	65 mg/m^2
Further reduction	Not permitted

TREATMENT INTERRUPTION

Ipatasertib treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If ipatasertib has been withheld for $>$28 consecutive days because of treatment-related toxicity, the patient should be discontinued from ipatasertib. Ipatasertib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures).

SUMMARY OF ADVICE FOR DOSE DISCONTINUATION AND DOSE INTERRUPTION (see Table A10-39 to Table A10-46 for details):

Ipatasertib must be discontinued if:

- Grade 4 diarrhea
- Recurrent Grade 4 hyperglycemia
- Febrile and Grade 4 neutropenia if recovery to Grade 2 or better does not occur after up to 4 weeks of treatment hold
- Grade 4 and recurrent Grade 3 hepatotoxicity
- Grade 4 rash, recurrent Grade 3 rash, or Grade 3 rash that remains clinically significant for 4 weeks after treatment hold
- Grade 4 non-infectious pneumonitis, recurrent Grade 3 non-infectious pneumonitis, Grade 2 non-infectious pneumonitis if recovery to Grade 1 or better is not observed within 28 days of treatment hold
- Grade $\geq$3 mucositis, if recovery to Grade 2 or better does not occur within 4 weeks of treatment hold

Ipatasertib must be interrupted if:

- Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events. Ipatasertib treatment should be temporarily held during systemic corticosteroids treatment (except when corticosteroids are given as premedication to paclitaxel).

MANAGEMENT OF SELECTED IDENTIFIED AND POTENTIAL RISKS OF IPATASERTIB AND PACLITAXEL

DIARRHEA MANAGEMENT GUIDELINES

Specific guidelines for managing diarrhea to improve safety and tolerability are provided in Table A10-39. All patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance. If diarrhea occurs, it should be managed per guidelines; upon resolution or when study treatment is restarted, loperamide prophylaxis should be considered to resume and continue based on clinical judgments (if allowed by local guidance).

Treatment modifications for diarrhea (any grade), when it occurs, should be instituted as early as possible. Guidelines for treatment of diarrhea following the prophylactic dose of loperamide (where allowed) includes use of loperamide 2 mg every 4 hours or after each loose, watery stool, up to the maximum total dose of 16 mg/day or per institutional

guidelines and standard of care, including, but not limited to, additional therapy with Lomotil® (diphenoxylate and atropine), codeine, or octreotide. Duration of diarrhea may be minimized by taking ipatasertib with food, avoiding lactose-containing foods, and hydrating with 8–10 glasses per day (~12 oz/glass) of electrolyte-containing clear liquid, such as broth or low-calorie drinks.

For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib, gastroenterologists should be consulted to rule out the risk of colitis and infection (e.g., obtaining CT images or a stool culture for infectious workup [Clostridium difficile, enteric bacteria, cytomegalovirus]). Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed. Educational materials will be provided to investigators and patients outlining these guidelines.

Table A10-39 Diarrhea Management Guidelines

Severity of Diarrhea [a]	Management Guideline
Prevention	• All patients are should receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle, if allowed by local guidance or unless there is a clinical concern precluding their use. Loperamide dose adjustment may be made per investigator discretion after discussion with the Medical Monitor. • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated.
Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	• Continue study drugs at the current dose level. • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8–10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance.

Severity of Diarrhea [a]	Management Guideline
Grade 2 Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline	• Rule out infectious etiology. • Manage with loperamide as early as possible 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8-10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better. • Reduce ipatasertib by one (or one additional) dose level for recurrent Grade 2 diarrhea. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.
Grade 3 Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level when treatment is restarted. • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Permanently discontinue ipatasertib.

ADL = activities of daily living; BID = twice a day; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; QD = once a day.

[a] Diarrhea, as defined by NCI CTCAE v4.0, a disorder characterized by frequent and watery bowel movements.

FASTING HYPERGLYCEMIA

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours. The treatment goals for glycemic control should be: 1) fasting glucose under 160 mg/dL and 2) HbA1c $\leq$8%.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined below (see Table A10-40) and are intended to provide guidance for fasting glucose measurements assessed in the clinic. Decisions regarding study treatment should be made on fasting levels drawn in the clinic whenever possible.

In the event of ipatasertib interruption, anti-diabetic medications may need to be held or reduced (per investigator judgment) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Because the hyperglycemia observed with ipatasertib treatment is consistently associated with endogenous elevations in insulin, insulin-based therapy to manage any hyperglycemia should be used with caution because severe hypoglycemic episodes could potentially occur. Therefore, initial treatment should be considered with biguanides (preferred), sulfonylureas, and other hypoglycemic treatments.

Table A10-40 Fasting Hyperglycemia Management Guidelines

Hyperglycemia	Management Guideline
General Guidance	• Thoroughly evaluate all events of hyperglycemia for more common etiologies other than drug-induced effects. • Investigate for diabetes. If patient has Type 1 diabetes, treat as an event of fasting glucose value 250–500 mg/dL. • Workup could include confirmation of fasting blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, hemoglobin A1C, C-peptide levels, anti-islet antibodies, and anti-GAD65 antibody. • Treat hyperglycemia per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities.
Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L) *	• Continue ipatasertib. • Provide patient with education on a diabetic diet and consider home glucose monitoring. • Consider oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia.
Fasting glucose value > 160 to 250 mg/dL (> 8.9–13.9 mmol/L) *	• Withhold ipatasertib dosing until fasting glucose value resolves to ≤ 160 mg/dL. (Investigate for diabetes. If patient has Type 1 diabetes, treat as a fasting glucose value 250–500 mg/dL event. If patient does not have Type 1 diabetes, treat as per institutional guidelines). • Encourage a diabetic diet and initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia. • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level (refer to Table A10-37). • If the patient previously has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication.

Hyperglycemia	Management Guideline
Fasting glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L) *	• Withhold ipatasertib dosing until fasting glucose value resolves to ≤ 160 mg/dL and contact the Medical Monitor. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Encourage a diabetic diet and initiate home glucose monitoring. • If the patient is already on an oral anti-diabetic medication, ipatasertib should be reduced by one dose level when treatment is restarted. • If previously, the patient has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication. • If hyperglycemia 250–500 mg/dL recurs, the dose of ipatasertib should be reduced by one dose level (see Table A10-37) when treatment is restarted.
Fasting glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences *	• Withhold ipatasertib dosing until fasting glucose value resolves to ≤ 160 mg/dL. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Encourage a diabetic diet and initiate home glucose monitoring. • Upon recovery of fasting glucose to ≤ 160 mg/dL, reduce ipatasertib by one dose level (see Table A10-37) when treatment is restarted. • If glucose value > 500 mg/dL recurs, permanently discontinue ipatasertib and contact the Medical Monitor. Reduce ipatasertib by one dose level if and when treatment is restarted. • If Grade 4 hyperglycemia recurs, permanently discontinue ipatasertib.

ULN = upper limit of normal.

* For all grades, the patient should receive education on a diabetic diet.

NEUTROPENIA AND/OR THROMBOCYTOPENIA

Addition of hematopoietic growth factors is allowed. If a dose delay is required as a result of neutropenia at any grade, patients should receive prophylactic granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor per institutional standards. Patients should be counseled as to the risk of fever and infection and to the importance of contacting their treating physician immediately if these conditions occur so that they can be promptly and appropriately managed. Dosage modification guidelines for neutropenia and/or thrombocytopenia attributable to ipatasertib are outlined in Table A10-41.

Table A10-41 Neutropenia Management Guidelines

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Grade 2	• Ipatasertib may be continued at the original dose.
Grade 3	• Ipatasertib should both be held until recovery to Grade 1 and if clinically appropriate based on the investigator's medical judgment to Grade 2 as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. – First episode: If recovery is to Grade 1, resume the original dose. If recovery to Grade 1 is achieved with the use of G-CSF, then continued use of G-CSF is recommended once dosing of the study drug is resumed. If recovery is to Grade 2, follow the guidance above. – Recurrent episode: Ipatasertib should be reduced by one dose level when treatment is restarted.
Febrile neutropenia and Grade 4 neutropenia	• Ipatasertib should be held until recovery to Grade 1, and if clinically appropriate based on the investigator's medical judgment to Grade 2, as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. – First episode: Ipatasertib should be reduced by one dose level when treatment is restarted. – Recurrent episode: Ipatasertib should be discontinued. • Following a treatment hold of up to 4 weeks, if recovery to Grade 2 or better neutropenia does not occur, the patient will permanently discontinue ipatasertib treatment.

ANC = absolute neutrophil count; G-CSF = Granulocyte-colony stimulating factor.

NAUSEA AND/OR VOMITING

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other antiemetics (i.e., prochlorperazine or metoclopramide per institutional guidelines; see Table A10-42). For persistent nausea and/or vomiting attributable to ipatasertib, dosage modification guidelines are outlined in Table A10-37.

Table A10-42 Nausea and Vomiting Guidelines

Severity of Nausea and/or Vomiting	Management Guideline
Grade 1	• Provide supportive care as needed.
Grade 2	• Provide maximum supportive care as needed per local guidelines, with a minimum of two antiemetics, including ondansetron.
Grade ≥3	• Interrupt ipatasertib until nausea or vomiting resolves to Grade 2 or better. • Provide maximum supportive care per local guidelines, with a minimum of two antiemetics, including ondansetron. • If Grade ≥3 nausea or vomiting recurs, ipatasertib should be reduced by one dose level when treatment is restarted.

HEPATOTOXICITY

Permanently discontinue ipatasertib for any patients who develop a concurrent elevation of ALT and/or AST greater than 3 × ULN and total bilirubin greater than 2 × ULN and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria. Dosage modification and symptom management guidelines for hepatotoxicity, attributable to study treatment are shown below (see Table A10-43)

Table A10-43 Hepatotoxicity Management Guidelines

Severity of LFT Elevation	Management Guideline
Grade 1 AST or ALT > baseline −3 × ULN or T bilirubin > baseline −1.5 × ULN	Continue study drugs.
Grade 2 AST or ALT > 3–5 × ULN or T bilirubin > 1.5–3.0 × ULN	Continue study drugs. The frequency of liver function test monitoring should be increased as clinically indicated if the investigator judges that the laboratory abnormalities are potentially related to study medication.
Grade 3 AST or ALT > 5–20 × ULN or T bilirubin > 3–10 × ULN	Immediately interrupt ipatasertib. On return of LFTs to baseline or to AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib at previous dose level (refer to Table A10-37) Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter. If another Grade 3 event occurs, interrupt ipatasertib/. On return of LFTs to baseline or AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib, reducing the dose by one level Further Grade 3 occurrences must result in permanent discontinuation of ipatasertib.
Grade 4 AST or ALT > 2 × ULN or T bilirubin > 10 × ULN	Permanently discontinue ipatasertib.

LFT = liver function test; QD = once daily; ULN = upper limit of normal.

RASH

Treatment-related rash, has occurred in patients receiving ipatasertib treatment particularly when ipatasertib has been used certain combinations (e.g., ipatasertib in combination with paclitaxel and atezolizumab or with abiraterone). The following prophylaxis measures can be considered, in particular for combinations with overlapping skin toxicity.

- Unless contraindicated, daily PO antihistamine prophylaxis can be considered for at least the first cycle. It is suggested that a non-sedating longer-acting oral antihistamine be used (such as 10 mg of cetirizine PO QD or comparable dose of other antihistamines, e.g., loratadine, fexofenadine).

Ipatasertib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity, including erythema multiforme, attributable to ipatasertib are shown below in Table A10-44.

Table A10-44 Rash Management Guidelines

Severity of Rash	Management Guideline
Grade 1	• Continue study drugs. • Consider topical corticosteroids.
Grade 2	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids.
Grade 3	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If the skin toxicity resolves to Grade 1 or better or is no longer clinically significant within 28 days, following completion of the steroid taper, ipatasertib may be resumed at one dose level below the previous dose. • If recovery of the skin toxicity to Grade 1 or better does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib.
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. Ipatasertib should be permanently discontinued.

PNEUMONITIS

Pneumonitis is not known to be causally related to ipatasertib; however, it has been observed with other drugs treating pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see Table A10-45).

Table A10-45 Pneumonitis Management Guidelines

Severity of Pneumonitis	Management Guideline
Grade 1	• Continue study drugs. • Perform CT scan and PFTs. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment until improvement to Grade 1 or better. Consider resuming ipatasertib at same dose level or one dose level below per investigator's assessment. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • For recurrent Grade 2 pneumonitis, ipatasertib must be resumed at one dose level below the previous dose. • Discontinue ipatasertib if recovery to Grade 1 or better is not evident within 28 days.
Grade 3	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment until improvement to Grade 1 or better. Resume ipatasertib at one dose level below previous dose per investigator's assessment. If recovery to Grade 1 or better is not evident within 28 days, discontinue study treatments. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • For recurrent non-infectious Grade 3 pneumonitis events, ipatasertib should be permanently discontinued.
Grade 4	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Permanently discontinue ipatasertib. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

CT = computed tomography; PFT = pulmonary function test.

MUCOSITIS

Mouthwash such as magic mouth wash (if inaccessible, warm salt or bicarbonate water) should be used as supportive care per institution guidelines. Brushing teeth after meals, keeping lips moisturized with non-Vaseline® products, and avoiding alcohol, spicy food, and smoking have all been shown to reduce pain and infection related to mucositis. Ranitidine or omeprazole may be helpful if patients have epigastric pain. Dosage modification guidelines for mucositis attributable to study treatment are outlined in Table A10-46.

Table A10-46 Mucositis Management Guidelines

Severity of Mucositis	Management Guidelines
Grade 1 or 2	• Manage with maximum supportive care. • If Grade ≥ 2 mucositis recurs in subsequent 4 week cycles, despite maximal supportive care, the dose of ipatasertib should be reduced by one dose level.
Grade ≥ 3	• Hold ipatasertib until recovery to Grade 2 or better. If the mucositis resolves to Grade 2 or better during the current cycle, the dose of ipatasertib should be reduced by one dose level. • If recovery of mucositis to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue ipatasertib.

OTHER NON-HEMATOLOGIC TOXICITIES

If other Grade ≥ 3 non hematologic toxicities not described above develop in patients, treatment with ipatasertib may be held, depending on the attribution of the toxicity, at the discretion of the investigator. Ipatasertib should be discontinued for any non-hematologic grade 4 adverse event considered related to ipatasertib.

If the toxicity resolves to Grade 1 or better within 2 weeks, treatment may resume with the attributable agent.

If the toxicity resolves to Grade 1 or better in 2–4 weeks, the dose of the attributable drug should be reduced by one level per the suggested guidelines.

Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes > 4 weeks, treatment may resume with the attributable agent with dose reduction, or the attributable agent may be permanently discontinued, at the discretion of the investigator based on clinical judgement.

SURGERY AND PALLIATIVE RADIOTHERAPY

Patients who require radiotherapy or surgery as part of medical treatment in the absence of radiographic disease progression must exercise caution, and paclitaxel and ipatasertib should be temporarily withheld for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For minor surgeries or single-day radiotherapy, this hold of paclitaxel and ipatasertib may be shorter, upon clinical judgment. After the temporary treatment hold is complete, study treatment may be re-initiated when the patient has sufficiently recovered.

DRUG INTERACTIONS

A clinical study in patients showed that ipatasertib at a dose of 600 mg QD is a moderate inhibitor of CYP3A, which resulted in a 2.22-fold increase in midazolam (sensitive CYP3A substrate with a narrow therapeutic window) exposures. Ipatasertib is primarily metabolized by CYP3A and, hence, strong inhibitors and inducers of CYP3A may result in increased or decreased ipatasertib exposures, respectively. Therefore, the following drugs should be avoided, or used with caution when administering ipatasertib. If using of one of these drugs is necessary, the risks and benefits should be evaluated prior to its concomitant use with ipatasertib per protocol guidelines:

- Strong CYP3A inhibitors, such as but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, and/or grapefruit juice or grapefruit supplements
- Strong CYP3A inducers, such as but not limited to rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- CYP3A4 substrates with a narrow therapeutic index, such as but not limited to alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine

A10–9 IVOSIDENIB

BACKGROUND ON IVOSIDENIB

Isocitrate dehydrogenase (IDH) catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate and CO_2. Three isoforms of IDH exist in human cells: IDH1, IDH2 and IDH3. Although alike in enzymatic activity, the three isoforms can be distinguished, in part, on the basis of cellular localization. Specifically, IDH1 is found in peroxisomes and the cytosol, while IDH2 and IDH3 are found within mitochondria.

A mutation in IDH1 that replaces arginine at position 132 with histidine (R132H) has been shown to be associated with various types of cancer, including acute myeloid leukemia, cholangiocarcinoma, chondrosarcoma, glioma, myelodysplastic syndromes, and others. The R132H mutation results in an enzyme that has lost the wild-type ability to convert isocitrate to α-ketoglutarate (Yan et al. 2009; Zhao et al. 2009), while gaining a new ability to catalyze the reduction of α-ketoglutarate to R(−)-2-hydroxyglutarate (2-HG) (Dang et al. 2009). 2-HG is an onco-metabolite that has been shown to be associated with elevated risks of brain tumors and other types of cancer (Kolker et al. 2002; Wajner et al. 2004; Aghili et al. 2009). High levels of 2-HG inhibits enzymes involved in DNA and histone methylation (Yan et al. 2009; Gross et al. 2010; Ward et al. 2010; Borger et al. 2012; Fan et al. 2017), which in turn blocks cellular differentiation and promotes tumorigenesis in both hematologic and non-hematologic malignancies (Chowdhury et al. 2011; Xu et al. 2011; Koivunen et al. 2012).

Ivosidenib is a potent and selective inhibitor of the IDH1 mutant protein; no significant off-target activity has been identified to date (see Ivosidenib Investigator's Brochure). The compound has been demonstrated to reduce 2-HG levels by $>95\%$, to reverse growth factor-independent growth in vitro, and to induce differentiation in cancer cell models. The US Food and Drug Administration has approved ivosidenib for the treatment of acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test in: adult patients with newly diagnosed AML who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy; and adult patients with relapsed or refractory AML.

SAFETY

The safety profile of ivosidenib is detailed in the Ivosidenib Investigator's Brochure.

Identified or potential risks associated with ivosidenib treatment are described immediately below. Management guidelines for these and other adverse reactions are provided in a later section of this Appendix (see Table A10-47).

QT PROLONGATION

Prolongation of heart-rate corrected QT (QTc) interval has been observed in monkeys at relatively high doses of ivosidenib, as well as in patients while receiving ivosidenib. Please refer to the current Ivosidenib Investigator's Brochure for detailed information.

Subjects may be at increased risk for the development of QT prolongation when treated with ivosidenib in combination with fluoroquinolones, azole antifungal agents, or serotonin (5-HT3) antagonists. Investigators need to be vigilant regarding concomitant medications associated with QT prolongation, and if no other therapeutic options are available, monitor subjects receiving ivosidenib with the combination of these drugs, and evaluate ECG and electrolytes (including potassium, magnesium, and calcium) particularly in subjects presenting with nausea, vomiting, or diarrhea.

LEUKOENCEPHALOPATHY

Leukoencephalopathy is a potential risk associated with ivosidenib treatment based on clinical safety findings observed across the ivosidenib clinical development program. Progressive multifocal leukoencephalopathy (PML) and posterior reversible encephalopathy syndrome (PRES), both Grade 3 SAEs, have each been reported in 1 subject.

The signs and/or symptoms of PML may begin gradually, usually worsen rapidly, and vary depending on which part of the brain is infected. Signs and symptoms may include difficulty with walking and other movements, progressive weakness, decline in mental function, visual field deficits, and speech and language disturbances. Rarely, headaches and seizures occur. Subjects should be monitored for onset of signs or symptoms suggestive of PML. Diagnostic evaluations may include consultation with a neurologist, MRI of the brain, lumbar puncture, and/or brain biopsy as clinically warranted. Treatment with ivosidenib should be suspended in the setting of suspected PML and permanently discontinued in subjects with confirmed PML.

PRES is a rare clinico-radiological neurological syndrome (Linda and von Heijne 2015). Clinical characteristics may include sub-acute onset of headache, hypertension, seizures, altered mental status, visual disturbances, and occasionally other focal neurological signs. Radiologically, signs of vasogenic edema are usually seen bilaterally in the white mater of the parieto-occipital lobes, but changes can also be seen in frontal and temporal lobes, brainstem, cerebellum, and in cortical as well as deep gray matter. Subjects should be monitored for onset of neurological signs and/or symptoms that are clinically associated with PRES. Diagnostic evaluations may include consultation with a neurologist, MRI of the brain, and other recognized standard of care measures as clinically warranted.

Refer to Section 6.6.2.1 (PML) and Section 6.6.2.2 (PRES) in the Ivosidenib Investigator's Brochure for further details on these events.

SENSORIMOTOR NEUROPATHY/POLYNEUROPATHY

Sensorimotor neuropathy/polyneuropathy is a potential risk associated with ivosidenib treatment based on safety findings observed across the ivosidenib clinical development program. Guillain-Barre syndrome (Grade 2 SAE in one subject; Grade 3 SAE in one subject) and lumbosacral plexopathy (Grade 2 SAE in one subject) are rare, serious syndromes that affect the central and peripheral nervous systems.

Subjects should be monitored for onset of new signs or symptoms or motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. If a subject experiences signs or symptoms suggestive of sensorimotor neuropathy, Guillain-Barre syndrome, or lumbosacral plexopathy, diagnostic evaluation may include a consultation with a neurologist, lumbar puncture, and electromyography. Ivosidenib should be permanently discontinued in subjects with a confirmed diagnosis of Guillain-Barre syndrome.

Refer to Section 6.6 (Potential Risks) in the Ivosidenib Investigator's Brochure for further details on these events.

IDH INHIBITOR-INDUCED DIFFERENTIATION SYNDROME

Subjects with hematologic malignancies receiving treatment ivosidenib have developed signs and symptoms of IDH differentiation syndrome as early as 1 day and as late as 3 months while on treatment. The median time to onset was approximately 30 days after treatment initiation.

Clinical features may include some or all of the following: respiratory compromise, interstitial pulmonary infiltrates, pleural and/or pericardial effusion, hypoxia, unexplained fever, rash, weight gain, and clinical deterioration. Laboratory features may include an increase in absolute neutrophil count (ANC) and/or platelets. An increase in mature leukocytes may be observed in the bone marrow aspirate differential if a bone marrow biopsy is conducted during this time. However, no single sign or symptom may be considered per se as diagnostic of the syndrome, and other causes should be sought and excluded. In addition, clinical and/or laboratory features may require further medical intervention and could be life-threatening or fatal if left untreated.

LEUKOCYTOSIS

Ivosidenib may be associated with leukocytosis that can occur without progression of AML.

It is recommended that the prophylactic and therapeutic measures indicated below are undertaken at the earliest manifestations of leukocytosis:

Temporary hold of study treatment only if symptoms cannot be medically managed with the following:

- Prompt initiation of hydroxyurea at up to a dose of 2,000 or 3,000 mg PO BID
- Prompt initiation of leukapheresis, if required

Treatment with hydroxyurea is allowed during treatment with ivosidenib for control of peripheral leukemic blasts in subjects with leukocytosis (WBC $>$30,000/µL). Once the signs and symptoms resolve and the subject's clinical condition improves, ivosidenib may be re-initiated if study treatment was held.

Refer to Section 6.6 (Potential Risks) in the Ivosidenib Investigator's Brochure for further details on these events.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For ivosidenib, AESIs include:

- Grade $\geq$3 QT / QTc prolongation
- Any Grade Leukoencephalopathy
- Grade $\geq$2 Sensorimotor Neuropathy/Polyneuropathy
- Any Grade Leukocytosis
- Any Grade Differentiation syndrome

ADMINISTRATION OF IVOSIDENIB

POSOLOGY AND ROUTE

Ivosidenib will be administered continuously at an oral dosage of 500 mg once daily across a 28-day treatment cycle.

Patients should refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices for 7 days before the start of study treatment until 30 days after the final dose, as this can affect the metabolism of the study drug.

Ivosidenib should be administered at about the same time each day. Ivosidenib may be administered with or without food, although it should NOT be administered with a high-fat meal because of an increase in ivosidenib concentration. Ivosidenib tablets should not be split or crushed.

DURATION OF TREATMENT

Treatment with ivosidenib should continue until loss of clinical benefit or the development of unacceptable toxicity. Patients without disease progression or unacceptable toxicity should be treated for a minimum of 6 months to allow time for clinical response.

DELAYED OR MISSED DOSES

If a dose of ivosidenib is vomited, a replacement dose should not be administered. Instead, wait until the next scheduled dose is due.

If a dose of ivosidenib is missed or not taken at the usual time, the dose should be administered as soon as possible and at least 12 hours prior to the next scheduled dose. Return to the normal schedule on the following day. Two doses of ivosidenib should not be administered within 12 hours of each other.

DOSE MODIFICATIONS OR DISCONTINUATION DURING TREATMENT

Table A10-47 Guidelines for Management (Including Discontinuation) of Patients Who Experience Specific Adverse Events

IDH Differentiation Syndrome	• Initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until symptoms resolution and for a minimum of 3 days. • If concomitant non-infectious leukocytosis is observed, initiate treatment with 2–3 g/day hydroxyurea or leukapheresis, as clinically indicated. • Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. • If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt ivosidenib until signs and symptoms are no longer severe. • Resume ivosidenib when signs and symptoms improve to Grade 2 or lower.

QTc Prolongation	<u>QTc interval >480 msec to ≤ 500 msec</u> • Monitor and supplement electrolyte levels as clinically indicated. Review and adjust concomitant medications with known QTc interval-prolonging effects. • The dose of ivosidenib may be reduced without interruption of dosing. The ivosidenib dose may be re-escalated to the prior dose in ≥ 14 days after QT prolongation has decreased to Grade ≤ 1. • Restart at 500 mg once daily after the QTc interval returns to less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation.
	<u>QTc interval >500 msec</u> • Monitor and supplement electrolyte levels as clinically indicated. • Hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. • Review and adjust concomitant medications with known QTc interval-prolonging effects (see Appendix). • Dosing with ivosidenib will be interrupted. If QTcF returns to within 30 msec of baseline or <450 msec within 14 days, treatment may be resumed at a reduced dose. Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. • The ivosidenib dose cannot be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormality or concomitant medication.
	<u>QTc interval prolongation with signs/ symptoms of life-threatening arrhythmia</u> • Discontinue ivosidenib permanently.
Non-infectious Leukocytosis (White blood cell [WBC] $>25\times10^9$/L or an absolute increase in total WBC of $>15\times10^9$/L from baseline)	• Initiate treatment with hydroxyurea, as per standard institutional practices, and leukapheresis if clinically indicated. • Taper hydroxyurea only after leukocytosis improves or resolves. • Interrupt ivosidenib if leukocytosis is not improved with hydroxyurea, and then resume ivosidenib at 500 mg daily when leukocytosis has resolved.

Guillain-Barré Syndrome	• Discontinue ivosidenib permanently.
Other Grade 3 or higher toxicities considered related to ivosidenib treatment	• Interrupt ivosidenib until toxicity resolves to Grade 2 or lower. • Resume ivosidenib at 250 mg once daily; may increase to 500 mg once daily if toxicities resolve to Grade 1 or lower. • If Grade 3 or higher toxicity recurs, discontinue ivosidenib.

DRUG INTERACTIONS

Table A10-48 Effects of Other Drugs on Ivosidenib

Strong or Moderate CYP3A4 Inhibitors	
Clinical Impact	• Co-administration of ivosidenib with strong or moderate CYP3A4 inhibitors increased ivosidenib plasma concentrations. • Increased ivosidenib plasma concentrations may increase the risk of QTc interval prolongation.
Prevention or Management	• Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors during treatment with ivosidenib. • If co-administration of a strong CYP3A4 inhibitor is unavoidable, reduce ivosidenib to 250 mg once daily. • Monitor patients for increased risk of QTc interval prolongation.
Strong CYP3A4 Inducers	
Clinical Impact	• Co-administration of ivosidenib with strong CYP3A4 inducers decreased ivosidenib plasma concentrations.
Prevention or Management	• Avoid co-administration of strong CYP3A4 inducers with ivosidenib.
QTc Prolonging Drugs	
Clinical Impact	• Co-administration of ivosidenib with QTc prolonging drugs may increase the risk of QTc interval prolongation.
Prevention or Management	• Avoid co-administration of QTc prolonging drugs with ivosidenib or replace with alternative therapies. • If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation.

Effect of Ivosidenib on Other Drugs

Cytochrome P450 (CYP)-phenotyping of ivosidenib metabolism performed in human liver microsomes and recombinant CYP enzymes suggest that CYP3A4 played a major role in the oxidative metabolism of ivosidenib, while other CYP enzymes such as CYP2B6 and CYP2C8 play a minor role.

Ivosidenib induced CYP2B6, CYP2C8, CYP2C9, and CYP3A4 but not CYP1A2 in cultured human hepatocytes, and therefore, there is the possibility of drug−drug interactions upon co-administration with sensitive substrates of CYP2B6, CYP2C8, CYP2C9 and CYP3A4/5.

Co-administration will decrease concentrations of drugs that are sensitive CYP3A4 substrates and may decrease concentrations of drugs that are sensitive CYP2C9. Use alternative therapies that are not sensitive substrates of CYP3A4 and CYP2C9 during ivosidenib treatment. Do not administer ivosidenib with itraconazole or ketoconazole (CYP3A4 substrates) due to expected loss of antifungal efficacy. Co-administration of ivosidenib may decrease the concentrations of hormonal contraceptives; consider alternative methods of contraception in patients receiving ivosidenib. If co-administration of ivosidenib with sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs.

Caution should be used in case of co-administration of ivosidenib with sensitive substrates of CYP2B6, CYP2C8.

A10–10 OLAPARIB

BACKGROUND ON OLAPARIB

Olaparib is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3).

PARP are required for the efficient repair of DNA single strand breaks. An important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When OLAPARIB is bound to the active site of DNA-associated PARP, it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells, this leads to DNA double strand breaks (DSBs) when replication forks meet the PARP-DNA adduct. In normal cells, homologous recombination repair (HRR), which requires functional BRCA1 and 2 genes, is effective at repairing these DNA double-strand breaks. In the absence of functional BRCA1 or 2, DNA DSBs cannot be repaired via HRR. Instead, alternative and error-prone pathways are activated, such as the non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells have a high DNA damage load relative to normal cells.

Olaparib is being developed for use in the treatment of cancers. Olaparib has been approved in various countries as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic), high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

SAFETY

The safety profile of olaparib is presented in the Olaparib EMA Summary of Product Characteristics.

Adverse reactions associated with Warnings and Precautions:

- Hematological toxicity
- Myelodysplastic syndrome/acute myeloid leukemia
- Pneumonitis
- Interactions with other drugs

Management guidelines for olaparib adverse reactions that are applicable to this study are provided in Table A10-49.

The summary information provided in the following sections must always be checked against any update of the olaparib local prescription guidelines/EMA Summary of Product Characteristics that may have occurred after the protocol has been issued.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For olaparib, no AESI needs reporting.

ADMINISTRATION OF OLAPARIB

POSOLOGY AND ROUTE

The dose of olaparib will be either:

- 400 mg (eight 50 mg capsules) taken twice daily, equivalent to a total daily dose of 800 mg.
- or 300 mg (two 150 mg film-coated tablets) taken twice daily, equivalent to a total daily dose of 600 mg.
  - Note: After the film-coated tablets are available for use in the study,
    - patients newly randomized should start olaparib treatment with 300 mg BID using film-coated tablets.
    - patients who already started treatment with 400 mg BID using capsules should only switch to 300 mg BID using film-coated tablets, after capsules are not any more available (when the last batch of capsules expires).

Due to the effect of food on olaparib absorption, patients should take olaparib at least one hour after food, and refrain from eating preferably for up to 2 hours afterwards.

For more details and instructions on handling of the medicinal product, refer to the Olaparib Summary of Product Characteristics from the EMA.

DURATION OF TREATMENT

Treatment with olaparib should continue until loss of clinical benefit or the development of unacceptable toxicity.

DELAYED OR MISSED DOSES

If a dose is missed, the next normal dose should be taken at its scheduled time.

DOSE MODIFICATIONS OR DISCONTINUATION DURING TREATMENT

Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhea, and anemia and dose reduction can be considered.

For Treatment with capsules:
The recommended dose reduction is to 200 mg twice daily (equivalent to a total daily dose of 400 mg).

If a further final dose reduction is required, then reduction to 100 mg twice daily (equivalent to a total daily dose of 200 mg) could be considered.

For Treatment with film-coated tablets:
The recommended dose reduction is to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily (equivalent to a total daily dose of 500 mg).

If a further dose reduction is required, then reduction to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended.

Renal Impairment

For Treatment with capsules:
For patients with moderate renal impairment (creatinine clearance 31 to 50 mL/min), the recommended dose of olaparib is 300 mg twice daily (equivalent to a total daily dose of 600 mg).

For Treatment with film-coated tablets:
For patients with moderate renal impairment (creatinine clearance 31 to 50 mL/min) the recommended dose is 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg).

Dose Adjustments for Co-administration With CYP3A Inhibitors

Concomitant use of strong and moderate CYP3A inhibitors is not recommended and alternative agents should be considered.

For Treatment with capsules:
If a strong or moderate CYP3A inhibitor must be co-administered, the recommended olaparib dose reduction is to 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a strong CYP3A inhibitor or 200 mg taken twice daily (equivalent to a total daily dose of 400 mg) with a moderate CYP3A inhibitor. It is also not recommended to consume grapefruit juice while on olaparib therapy as it is a CYP3A inhibitor.

For Treatment with film-coated tablets:
If a strong or moderate CYP3A inhibitor must be co-administered, the recommended Lynparza dose reduction is to 100 mg taken twice daily (equivalent to a total daily dose of 200 mg) with a strong CYP3A inhibitor or 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a moderate CYP3A inhibitor. It is also not recommended to consume grapefruit juice while on olaparib therapy as it is a CYP3A inhibitor.

Summary of Advice for Dose Discontinuation (see Table A10-49 for Details):

Olaparib must be discontinued if:

- Myelodysplastic syndrome/acute myeloid leukemia
- Pneumonitis

Table A10-49 Guidelines for Management (Including Discontinuation) of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Hematological toxicity	Follow up of hematological parameters per protocol. If severe hematological toxicity or blood transfusion dependence, treatment with olaparib should be interrupted and appropriate hematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of olaparib dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.
Myelodysplastic syndrome/acute myeloid leukemia	If MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that the patient be treated appropriately. Treatment with olaparib will be discontinued.
Pneumonitis	If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.
Interactions	Olaparib co-administration with strong or moderate CYP3A inhibitors is not recommended (see SPC). If a strong or moderate CYP3A inhibitor must be co-administered, the dose of olaparib should be reduced (see SPC and section Dose adjustments for co-administration with CYP3A inhibitors above). Olaparib co-administration with strong or moderate CYP3A inducers is not recommended (see section SPC). In the event that a patient already receiving olaparib requires treatment with a strong or moderate CYP3A inducer, the efficacy of olaparib may be substantially reduced (see section SPC). In the event that a patient already receiving olaparib requires treatment with a P-gp inhibitor, careful monitoring of olaparib associated adverse events and management of those events via the dose reduction strategy is recommended (see SPC section Dose Adjustments for co-administration with CYP3A inhibitors above). SEE SPC FOR FULL DETAILS ON INTERACTIONS

SPC = EMA Summary of Product Characteristics

DRUG INTERACTIONS

Pharmacodynamic Interactions

Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these drugs are co-administered with olaparib and patients should be closely monitored.

Pharmacokinetic Interactions

Effect of other drugs on olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. A clinical study to evaluate the impact of rifampicin, a known CYP3A inducer has shown that co-administration with olaparib decreased olaparib mean C_{max} by 71% (treatment ratio: 0.29; 90% CI: 0.24–0.33) and mean AUC by 87% (treatment ratio: 0.13; 90% CI: 0.11–0.16). Therefore, known strong inducers of this isozyme (e.g., phenytoin, rifampicin, rifapentine, carbamazepine, nevirapine, phenobarbital and St John's Wort) are not recommended with olaparib, as it is possible that the efficacy of olaparib could be substantially reduced. The magnitude of the effect of moderate to strong inducers (e.g., efavirenz, rifabutin) on olaparib exposure is not established, therefore the co-administration of olaparib with these drugs is also not recommended.

A clinical study to evaluate the impact of itraconazole, a known CYP3A inhibitor has shown that co-administration with olaparib increased mean olaparib mean C_{max} 1.42-fold (90% CI: 1.33-1.52) and mean AUC 2.70-fold (90% CI: 2.44-2.97). Therefore, known strong (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, boceprevir, telaprevir) or moderate (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of this isozyme are not recommended with olaparib If the strong or moderate CYP3A inhibitors must be co-administered, the dose of olaparib should be reduced. The recommended olaparib dose reductions are described above.

In vitro olaparib is a substrate for the efflux transporter P-gp and therefore P-gp inhibitors may increase exposure to olaparib.

Effect of olaparib on other drugs

Olaparib inhibits CYP3A4 in vitro and is predicted to be a mild CYP3A inhibitor in vivo. Therefore, caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g., simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine) are combined with olaparib. Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.

Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP2B6 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp can also not be excluded. Therefore, olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.

In vitro, olaparib inhibits the efflux transporter P-gp (IC50 = 76µM), therefore it cannot be excluded that olaparib may cause clinically relevant drug interactions with substrates of P-gp (e.g., simvastatin, pravastatin, dabigatran, digoxin and colchicine). Appropriate clinical monitoring is recommended for patients receiving this type of medication concomitantly.

In vitro, olaparib has been shown to be an inhibitor of OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. It cannot be excluded that olaparib may increase the exposure to substrates of OATP1B1 (e.g., bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (e.g., metformin), OCT2 (e.g., serum creatinine), OAT3 (e.g., furosemide and methotrexate), MATE1 (e.g., metformin) and MATE2K (e.g., metformin). In particular, caution should be exercised if olaparib is administered in combination with any statin.

A10–11 PEMIGATINIB

BACKGROUND ON PEMIGATINIB

Pemigatinib is a potent inhibitor of the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases and is being developed for use in the treatment of solid tumor malignancies with activating FGFR gene mutations or chromosomal translocations.

The mammalian FGFR family is composed of four highly conserved receptors (FGFR1, FGFR2, FGFR3, and FGFR4) that have an extracellular ligand-binding domain, a single transmembrane domain and an intracellular tyrosine kinase domain. Eighteen FGFR ligands, divided into canonical and hormonal FGFRs, bind to FGFRs, leading to receptor dimerization, activation of the kinase domain and transphosphorylation of the receptors (Eswarakumar et al. 2005). Subsequent signal transduction occurs through phosphorylation of substrate proteins, such as FGFR substrate 2, which leads to activation of the RAS–mitogen-activated protein kinase, the phosphoinositide 3-kinase-protein kinase B pathway and phospholipase Cγ, which activates the protein kinase C pathway.

There is strong genetic and functional evidence that dysregulation of FGFR can lead to the establishment and progression of cancer (Knights and Cook 2010; Turner and Grose 2010). Moreover, a substantial body of evidence indicates that genetically activated FGFR pathways sensitize FGFR-altered cancer cells to knockdown or inhibition of these receptors (Kunii et al. 2008; Qing et al. 2009; Weiss et al. 2010; Lamont et al. 2011). Consistent with these molecular studies, pemigatinib has been shown to produce significant anticancer response in patients with previously treated, locally advanced or metastatic cholangiocarcinoma with and without FGFR2 fusions (Abou-Alfa et al. 2020), leading the US FDA to grant accelerated approval to pemigatinib as a treatment in this setting (https://bit.ly/3eQVuzc).

SAFETY

The safety profile of pemigatinib is presented in the Pemigatinib Investigator's Brochure.

Management guidelines for pemigatinib adverse reactions that are applicable to this study are provided in Table A10-50 to Table A10-53 (see below).

The most frequently serious adverse events occurring in greater than 2% of patients included urinary tract infection, acute kidney injury, abdominal pain, pneumonia, pyrexia, back pain, hyponatremia, and general physical health deterioration. Rare but significant AEs associated with pemigatinib use include serous retinal detachment and soft tissue mineralization including calcinosis and calciphylaxis.

WARNINGS AND PRECAUTIONS

Hyperphosphatemia

Data from clinical studies of selective FGFR inhibitors, including the ongoing studies of pemigatinib, have indicated that hyperphosphatemia is an on-target pharmacologic effect of FGFR inhibition. Therefore, participants must be monitored closely for hyperphosphatemia. Hyperphosphatemia (defined as >5.5 mg/dL) can be managed appropriately with low-phosphate diet, phosphate-lowering medication, dose interruptions and dose reductions (see Table A10-51, below).

Serous Retinal Detachment

Treatment-emergent AEs, which may represent serous retinal detachment (including PTs chorioretinal folds, chorioretinal scar, chorioretinopathy, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, macular detachment, macular edema, maculopathy, retinal detachment, retinal disorder, retinal exudates, retinal edema, retinal pigmentation, retinal thickening, serous retinal detachment and subretinal fluid) have been reported in 9.1% of patients with advanced malignancies who received pemigatinib as monotherapy (N=592).

Serous retinal detachment is due to subretinal fluid accumulation and is caused by some tyrosine kinase inhibitors. Most cases are self-limiting, frequently without treatment discontinuation (Arkenau et al. 2014; Duncan et al. 2015; Urner-Bloch et al. 2016; Saka et al. 2017). Nevertheless, participants should be monitored for signs and symptoms of serous retinal detachment, and the retina should be assessed with optical coherence tomography. Mild and moderate intensity events should be monitored with ophthalmology examination and, in case of worsening of vision and in severe (Grade 3) cases of serous retinal detachment, pemigatinib treatment should be interrupted.

Effects on Embryo/Fetal Development

Pemigatinib has been shown to affect embryo/fetal development in rats.

Pemigatinib must not be used by female participants who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking pemigatinib in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For pemigatinib, no AESI needs reporting.

ADMINISTRATION OF PEMIGATINIB

POSOLOGY AND ROUTE

Pemigatinib will be administered at a continuous oral dosage of 13.5 mg QD (given in the morning with water) across a 21-day treatment cycle.

Pemigatinib may be administrated with or without food. Patients should refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices for 7 days before the start of study treatment until 30 days after the final dose, as this can affect the metabolism of the study drug.

Any patient who does not reach a target serum phosphate level of $>$5.5 mg/dL at any time during Cycle 1, is compliant with taking study drug and does not experience an ongoing Grade 2 or higher treatment-related AE will increase the daily dose to 18 mg starting from Cycle 2 Day 1.

Patients who are titrated up to 18 mg QD will begin the next cycle at the new dose level. Up-titration may occur no earlier than on Day 1 of Cycle 2, so that participants are observed for phosphate level and AEs for at least for 1 cycle.

For instructions on handling of the medicinal product, refer to the Pemigatinib Pharmacy Manual.

DURATION OF TREATMENT

Treatment with pemigatinib should continue until loss of clinical benefit or the development of unacceptable toxicity.

DELAYED OR MISSED DOSES

Treatment with pemigatinib may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator should contact the Sponsor to discuss the case of any participant whose treatment has been delayed for more than 14 days before restarting treatment with pemigatinib.

If a dose of pemigatinib is missed by 4 or more hours or vomiting occurs after taking a dose, an additional dose should not be administered and dosing should be resumed with the next scheduled dose.

DOSE MODIFICATIONS OR DISCONTINUATION DURING TREATMENT

A maximum of two reductions in dose level are allowed with pemigatinib for patients dosed at 13.5 mg. Thus, for these patients, pemigatinib can be decreased to 9 mg and, if additional dose reduction is required, further to 4.5 mg. Dose reductions below 4.5 mg are not allowed.

The frequency and schedule of pemigatinib administration (continuous once-daily dosing) should remain the same following dose reduction.

A maximum of three reductions in dose level are allowed with pemigatinib for patients who are up-titrated from 13.5 mg to 18 mg (see above). Thus, for these patients, pemigatinib can be decreased to 13.5 mg, and if additional dose reductions are required, to 9 mg and then to 4.5 mg.

AST and/or ALT Elevations

Table A10-50 Guidelines for Management (Including Discontinuation) of Patients With AST and/or ALT Elevations

Event	Action to Be Taken
• AST and/or ALT > 5.0 × ULN Note: In patients with liver metastases-related elevations at baseline, contact the Sponsor to discuss clinical management and possible dose reductions	Step 1: Interrupt pemigatinib up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1. Step 2: Restart pemigatinib at same dose. If assessed as related to pemigatinib, restart pemigatinib at next lower dose; monitor as clinically indicated.

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

Hyperphosphatemia

Hyperphosphatemia is an expected on-target pharmacologic effect of FGFR inhibition. Hyperphosphatemia should be managed with diet modifications, phosphate binders and diuretics, or a dose reduction per the recommendations in Table A10-51. For grading of hyperphosphatemia, please note that CTCAE v5.0 now has a category for hyperphosphatemia.

The use of diet modifications alone include food exchanges from high-phosphate foods to low-phosphate foods and can be implemented once serum phosphate levels are above the ULN but do not exceed 7.0 mg/dL. Diet modification should continue with the inclusion of phosphate binders once serum phosphate levels exceed 7.0 mg/dL. Examples of phosphate binders are sevelamer HCl (examples of brand names: Renegel® or Renvela®) or lanthanum HCl.

Administration of phosphate binders should be 3 times per day (e.g., with each meal) to reduce absorption of phosphate. Doses and frequency of doses should be based on the participant's tolerance for the binder and the control of serum phosphate. If binders are used to manage hyperphosphatemia during treatment, it is recommended to stop binders at the same time pemigatinib is stopped to reduce the risk of hypophosphatemia.

Table A10-51 Guidelines for Management (Including Discontinuation) of Patients with Hyperphosphatemia

Serum Phosphate Level	Supportive Care	Guidance for Interruption/ Discontinuation of Pemigatinib	Guidance for Restarting Pemigatinib
>5.5 mg/dL and ≤ 7 mg/dL	Initiate a low-phosphate diet.	No action.	Not applicable.
>7 mg/dL and ≤ 10 mg/dL	Initiate/continue a low-phosphate diet and initiate phosphate-binding therapy. Monitor serum phosphate approximately twice a week and adjust the dose of binders as needed; continue to monitor serum phosphate at least twice a week until level returns to ≤ 7 mg/dL.	If serum phosphate level continues to be >7 mg/dL and ≤ 10 mg/dL with concomitant phosphate-binding therapy for 2 weeks, or if there is recurrence of serum phosphate level in this range, interrupt pemigatinib for up to 2 weeks.	Restart at the same dose when serum phosphate is <7 mg/dL. If serum phosphate level recurs at >7 mg/dL, restart pemigatinib with dose reduction.
>10 mg/dL	Continue to maintain a low-phosphate diet, adjust phosphate-binding therapy, and start/continue phosphaturic agent. Continue to monitor serum phosphate approximately twice a week until level returns to ≤ 7 mg/dL.	If serum phosphate level is >10 mg/dL for 1 week following phosphate-binding therapy and low-phosphate diet, interrupt pemigatinib. If there is recurrence of serum phosphate level in this range following two dose reductions, permanently discontinue pemigatinib.	Restart pemigatinib at reduced dose with phosphate binders when serum phosphate is <7 mg/dL.

QT Interval Prolongation

Table A10-52 Guidelines for Management (Including Discontinuation) of Patients with QT Interval Prolongation

Event	Action to Be Taken
• QT/QTc to >500 msec or to >60 msec over baseline	Discontinue pemigatinib administration.

Other Toxicities

Table A10-53 Guidelines for Management (Including Discontinuation) of Patients with Other Toxicities

Event	Action to Be Taken
• Any Grade 1 or 2 toxicity	Continue pemigatinib treatment and treat toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	Step 1: Interrupt pemigatinib up to 2 weeks (14 days) until toxicity resolves to ≤Grade 1. Step 2: Restart pemigatinib at same dose. If assessed as related to pemigatinib, restart pemigatinib at next lower dose; monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after two dose reductions	Discontinue pemigatinib administration.
• Any Grade 4 toxicity	Discontinue pemigatinib administration.

DRUG INTERACTIONS

Pemigatinib is predominantly metabolized by CYP3A4.

- Potent CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers are prohibited with pemigatinib. Concomitant use of pemigatinib with St John's wort (CYP3A4 inducer) is contraindicated
- Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole

The use of moderate CYP3A4 inhibitors is not prohibited but should involve careful monitoring, especially in relation to safety.

Careful monitoring is required when pemigatinib is concomitantly administered with OCT2 substrates, such as dofetilide and metformin.

The gastric pH-modifying agents esomeprazole and ranitidine have a modest effect on the overall exposure of pemigatinib when co-administered.

Proton pump inhibitors (PPIs) should be avoided with pemigatinib.

Close clinical surveillance is recommended when pemigatinib is administered with CYP2B6 substrates (e.g., methadone, efavirenz).

Co-administration of pemigatinib with P-gp substrates (e.g., digoxin, dabigatran, colchicine) may increase their exposure and thus their toxicity. Pemigatinib administration should be separated by at least 6 hours before or after administration of P-gp substrates with a narrow therapeutic index.

A10–12 PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB

BACKGROUND

Pertuzumab and trastuzumab bind to distinct epitopes on the HER2 receptor without competing with each other, and have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity in vitro and in vivo when pertuzumab and trastuzumab are given in combination.

In various countries, trastuzumab is indicated for the treatment of metastatic or operable early breast cancers that overexpress the HER2 protein, as monotherapy or in combination with aromatase inhibitors or chemotherapy. It is also indicated for the treatment of metastatic gastric cancers that overexpress the HER2 protein.

In various countries pertuzumab is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease and in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer as part of a complete treatment regimen for early breast cancer.

In this study pertuzumab will be administered as an intravenous infusion and trastuzumab will be administered as a subcutaneous injection in combination with a platinum-based chemotherapy (see Section 4.3.4.5 of the protocol).

SAFETY

SAFETY PROFILE

A comprehensive description of the safety profile of pertuzumab in combination with trastuzumab and cytotoxic agents in metastatic breast cancer and for the neoadjuvant treatment of breast cancer is provided in the Pertuzumab Investigator's Brochure. This summary only lists specific risks, warnings and precautions.

The summary information provided in the following section must always be checked against any update of the Pertuzumab Investigator's Brochures that may have occurred after the protocol has been issued. Please also refer to the Trastuzumab Investigator's Brochure and to its warnings and precautions when using pertuzumab in combination with trastuzumab.

Adverse reactions associated with Warnings and Precautions (common to pertuzumab, trastuzumab and their combination):

- Cardiac dysfunction
- Infusion-related reactions (IRRs)/administration-related reactions (ARRs) and hypersensitivity/anaphylaxis
- Pulmonary events

Other selected adverse reactions:

- Hematotoxicity

Management guidelines for pertuzumab in combination with trastuzumab that are applicable to this study are provided in Table A10-54.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For pertuzumab, AESIs include:

- Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of monoclonal antibodies

For trastuzumab, AESIs include:

- Congestive heart failure

ADMINISTRATION

POSOLOGY

Pertuzumab will be administered as initial loading dose of 840 mg administered as a 60 (±10) minute IV infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 (±10) minutes. If a dose is delayed (i.e., the time between two sequential infusions is less than 6 weeks), the 420 mg dose of pertuzumab should be administered. If a dose is missed (i.e., the time between two sequential infusions is 6 weeks or more), a re-loading dose of pertuzumab (840 mg) should be given as described for loading dose.

Trastuzumab will be administered at a dose of 600 mg fixed dose SC injection over 2 to 5 minutes every 3 weeks.

For the doses of chemotherapy to be administered in combination with pertuzumab and trastuzumab, see Section 4.3.4.7 of the protocol.

METHOD OF ADMINISTRATION

Pertuzumab and trastuzumab must be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available.

Trastuzumab, pertuzumab, and chemotherapy must be administered sequentially and not mixed in the same infusion bag. Trastuzumab and pertuzumab can be given in any order. Chemotherapy should be administered after trastuzumab and pertuzumab. An observation period of 30 to 60 minutes is recommended after each trastuzumab infusion and before commencement of any subsequent infusion of pertuzumab or chemotherapy.

Pertuzumab is administered intravenously by infusion. It should not be administered as an intravenous push or bolus. For the initial dose, the recommended infusion period is 60 (±10) minutes. If the first infusion with the initial loading dose was well tolerated, subsequent infusions may be administered over a period of 30 minutes to 60 (±10) minutes.

Patients should be observed for at least one hour after the end of the first administration of pertuzumab (intravenously) and trastuzumab (subcutaneously) and for 30 minutes after the end of the subsequent administrations for symptoms like fever and chills or other infusion-related symptoms. Interruption or slowing the rate of the infusion of pertuzumab may help control such symptoms. The infusion of pertuzumab may be resumed when symptoms abate. The observation period should be completed prior to any subsequent infusion of trastuzumab or chemotherapy.

DURATION OF TREATMENT

Treatment with pertuzumab in combination with trastuzumab and a platinum-based chemotherapy should continue until loss of clinical benefit or the development of unacceptable toxicity. The administration of the chemotherapy must be limited to the number of chemotherapy cycles described in Section 4.3.4.7 of the protocol.

DOSE MODIFICATIONS DURING TREATMENT

Dose reductions of pertuzumab or trastuzumab are not recommended.

Patients may continue therapy with pertuzumab and trastuzumab during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia and other toxicities during this time. For platinum-based chemotherapy dose modifications, see the relevant EMA Summary of Product Characteristics.

DOSE DELAY OR DISCONTINUATION

If pertuzumab treatment is discontinued, treatment with trastuzumab should be discontinued. If trastuzumab treatment is discontinued, treatment with pertuzumab should be discontinued.

After platinum-based chemotherapy is discontinued (per protocol or due to toxicity), treatment with pertuzumab and trastuzumab will continue per protocol.

If pertuzumab and trastuzumab treatment is discontinued prior to the planned end of concomitant chemotherapy, treatment with chemotherapy may continue in the Treatment Period per the guidance provided in Section 4.3.4.7.

Dose delay and discontinuation advice are summarized in Table A10-54. See also Table A10-55 for management of specific toxicities, according to special warnings and precautions.

Summary of Advice for Dose Discontinuation (See Table A10-54 for Details):

Pertuzumab and trastuzumab must be discontinued if:

- Hypersensitivity reactions/anaphylaxis
- LVEF decrease with symptomatic heart failure
- LVEF $<$ 50% or LVEF of 40%–45% associated with a fall of $\geq$ 10% points below pre-treatment values not improving after a 3 week dose interruption

Table A10-54 Dose Delay and Discontinuation Advice

Adverse Reaction	Severity	Treatment Modification
Hypersensitivity reactions/anaphylaxis	Grade 4 (anaphylaxis), bronchospasm or acute respiratory distress syndrome	Discontinue immediately and permanently.
Infusion reactions (pertuzumab)		Slow or the infusion rate or interrupt infusion of pertuzumab. The infusion may be resumed when symptoms abate. Treatment including oxygen, beta agonists, antihistamines, rapid IV fluids and antipyretics may also help alleviate symptoms.
Left ventricular dysfunction including any of the following: signs and symptoms suggestive of congestive heart failure drop in left ventricular ejection fraction (LVEF) to less than 50% LVEF of 40%–45% associated with a fall of $\geq$ 10% points below pre-treatment values		Withheld pertuzumab and trastuzumab for at least 3 weeks. Discontinue pertuzumab and trastuzumab if symptomatic heart failure is confirmed. Resume pertuzumab and trastuzumab if the LVEF has recovered to $>$50% or 40–45% associated with $<$ 10% points below pre-treatment value. If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinue pertuzumab and trastuzumab, unless the benefits for the individual patient are deemed to outweigh the risks (Medical Monitor advice should be sought). Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g., every 6–8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of trastuzumab therapy has been seen.

MANAGEMENT ADVICE FOR SPECIFIED ADVERSE DRUG REACTIONS

Table A10-55 Management Advice for Specified Adverse Drug Reactions

Adverse Reaction	Severity	Treatment Modification
Exacerbation of chemotherapy associated neutropenia		Hematological monitoring for neutropenia per protocol.
Diarrhea		To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication should be considered and patients treated with fluids and electrolyte replacement, as clinically indicated.
Rash		Treatment recommendations include topical or oral antibiotics, topical pimecrolimus, topical or (for severe reactions) systemic steroids.
Mucositis		Mucositis is generally not considered preventable although for some cytotoxic agents, mucositis may be reduced by cooling the mouth using ice chips before and during the infusion.

DRUG INTERACTIONS

Pertuzumab

A sub-study in 37 patients in the pivotal trial CLEOPATRA showed no evidence of drug–drug interaction between pertuzumab and trastuzumab and between pertuzumab and docetaxel. In addition, no clinical relevant pharmacokinetic interaction of co-administered docetaxel or trastuzumab on pertuzumab was evident, based on the population pharmacokinetics analysis. The lack of drug–drug interaction between pertuzumab and trastuzumab and between pertuzumab and docetaxel was further confirmed by pharmacokinetic data from the WO209697 (NEOSPHERE) trial.

Four studies have evaluated the effects of pertuzumab on the pharmacokinetics of co-administered cytotoxic agents, docetaxel, gemcitabine, erlotinib and capecitabine, respectively. There was no evidence of any pharmacokinetics interaction between pertuzumab and any of these agents. The pharmacokinetics of pertuzumab in these studies was comparable to those observed in single agent studies.

Trastuzumab

There have been no formal drug interaction studies performed with trastuzumab in humans. Clinically significant interactions between trastuzumab and the concomitant medications used in clinical trials have not been observed.

- Effect of trastuzumab on the pharmacokinetics of other anti-neoplastic agents
- Study BO15935 found no observable drug–drug interaction between trastuzumab and paclitaxel
- Study M77004 was a study of trastuzumab and doxorubicin plus paclitaxel followed by qW paclitaxel and trastuzumab in women with HER2-positive MBC. There was no observable drug–drug interaction between trastuzumab and paclitaxel and doxorubicin (and their major metabolites) in this study
- Study JP19959 was a randomized study in male and female Japanese patients with AGC to investigate potential changes to capecitabine or cisplatin pharmacokinetics when administered either together or in the presence of trastuzumab. Comparisons of plasma concentrations and PK parameters of capecitabine and its metabolites (5'-deoxy-5-fluorocytidine, 5'-deoxy-5-fluorouridine, 5-FU and α-fluoro-β-alanine) and plasma concentration of cisplatin (total platinum in plasma and unbound platinum in ultrafiltered plasma) suggest that the pharmacokinetics of these two chemotherapy agents are not altered by concomitant trastuzumab treatment
- Study H4613g (Her-Q-Les), a Phase Ib, single-arm, open-label clinical trial evaluated corrected QT interval and drug–drug interaction of trastuzumab with carboplatin in the presence of docetaxel in patients with HER2-positive metastatic or locally advanced inoperable cancer. Trastuzumab administration had no impact on the pharmacokinetics of carboplatin, and carboplatin had no impact on the pharmacokinetics of trastuzumab. No new safety signals were identified
- In a published study in patients with NSCLC where trastuzumab was administered in combination with gemcitabine and cisplatin, trastuzumab did not appear to alter the kinetics of either gemcitabine or cisplatin, and trastuzumab serum levels did not appear to be altered by these agents

A10–13 VEMURAFENIB

Vemurafenib will be administered in combination with cobimetinib—Refer to Appendix A10–4 for details on cobimetinib.

BACKGROUND

Vemurafenib is a selective inhibitor of oncogenic BRAF kinase. Oncogenic mutations in BRAF kinase, predominantly V600E, have been observed in approximately 8% of all solid tumors. Such mutations result in constitutive activation of BRAF kinase, which causes dysregulated downstream signaling via MEK and ERK, leading to excessive cell proliferation and survival.

Inhibition of MEK1/2 (MAPK/ERK kinase) is a potential strategy to control the growth of tumors that are dependent on aberrant MAPK pathway signaling. Clinical and preclinical data have demonstrated that the addition of a MEK inhibitor can delay or overcome BRAF inhibitor (BRAFi) resistance, which supports the clinical evaluation of combination therapeutic strategies incorporating MEK inhibition with BRAF inhibition.

Vemurafenib is being developed for use in the treatment of cancers. Cobimetinib, in combination with vemurafenib, has been approved in various countries for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

SAFETY

SAFETY PROFILE

A comprehensive description of the safety profile of vemurafenib as monotherapy is provided in the Vemurafenib Investigator's Brochure and a comprehensive description of the safety profile of vemurafenib in combination with cobimetinib is provided in the Cobimetinib Investigator's Brochure.

Adverse reactions associated with Warnings and Precautions:

- Cutaneous squamous cell carcinoma (cuSCC)
- Non-cutaneous squamous cell carcinoma (non-cuSCC)
- New primary melanoma
- Other malignancies
- Potentiation of radiation toxicity
- Hypersensitivity reactions
- Dermatologic reactions
- Risk of Ventricular Arrhythmia

- Liver injury
- Photosensitivity
- Ophthalmologic reactions

Other selected adverse reactions:

- Pancreatitis
- Colorectal polyps
- Acute kidney injury

Management guidelines for vemurafenib adverse reactions that are applicable to this study are provided in Table A10-56. For management of adverse events of cobimetinib in combination with vemurafenib.

The summary information provided in the following sections must always be checked against any update of the Vemurafenib and Cobimetinib Investigator's Brochures that may have occurred after the protocol has been issued.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For vemurafenib, AESIs include:

- Acute kidney injury
- Bone marrow toxicity
- Cutaneous squamous cell carcinoma
- Hypersensitivity
- Severe cutaneous reactions (cutaneous reactions reported as severe or Grade 3 or Grade 4)
- New/second primary melanoma
- Non cutaneous squamous cell carcinoma
- Pancreatitis
- Photosensitivity
- Potentiation of radiation toxicity
- Progression of RAS mutant malignancy
- QT Prolongation
- Retinal vein inclusion
- VII nerve paralysis

- Liver injury
- Uveitis
- GI polyps

ADMINISTRATION

POSOLOGY AND ROUTE

The recommended dose of vemurafenib is 960 mg (4 tablets of 240 mg) twice daily (equivalent to a total daily dose of 1,920 mg). Vemurafenib may be taken with or without food, but consistent intake of both daily doses on an empty stomach should be avoided.

For instructions on handling of the medicinal product, refer to the Vemurafenib Investigator's Brochure.

DURATION OF TREATMENT

Treatment with vemurafenib should continue until loss of clinical benefit or the development of unacceptable toxicity.

DELAYED OR MISSED DOSES

If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. Both doses should not be taken at the same time.

In case of vomiting after vemurafenib administration, the patient should not take an additional dose of the medicinal product. Instead, the treatment should be continued as usual.

DOSE MODIFICATION OR DISCONTINUATION

Dose modification of vemurafenib is independent of cobimetinib dose modification.
If doses are omitted for toxicity, these doses should not be replaced. Once the dose has been reduced, it should not be increased at a later time.

Table A10-56 below gives general vemurafenib dose modification guidance.

Management of Adverse Drug Reactions or QTc prolongation may require dose reduction, temporary interruption and/or treatment discontinuation (see Table A10-56 and Table A10-57). Posology adjustments resulting in a dose below 480 mg twice daily are not recommended.

In the event the patient develops cutaneous squamous cell carcinoma (cuSCC), it is recommended to continue treatment without modifying the dose of vemurafenib.

Summary of Advice for Dose Discontinuation (see Table A10-56 for Details):

Vemurafenib must be discontinued if:

- Second (2nd) occurrence of Grade 4 adverse event or 3rd occurrence of Grade 2–3 adverse event
- QTc increase meets values of both $>$500 ms and $>$60 ms change from pre-treatment values or 3rd occurrence of QTc $>$500 ms during treatment and change from pre-treatment value remains $\leq$60ms
- Hypersensitivity reaction (including Stevens-Johnson syndrome, generalized rash, erythema or hypotension)
- Dermatologic reactions (including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms)

Discontinuation of vemurafenib may be considered for

- First (1st) occurrence of Grade 4 adverse event

Table A10-56 Dose Modification or Discontinuation Schedule Based on the Grade of any Adverse Events

Grade (CTCAE) [a]	Recommended Dose Modification
Grade 1 or Grade 2 (tolerable)	Maintain vemurafenib at a dose of 960 mg twice daily.
Grade 2 (intolerable) or Grade 3	
1st occurrence of any Grade 2 or 3 AE	Interrupt treatment until Grade 0–1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of any Grade 2 or 3 AE or persistence after treatment interruption	Interrupt treatment until Grade 0–1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of any Grade 2 or 3 AE or persistence after 2nd dose reduction	Discontinue permanently.
Grade 4	
1st occurrence of any Grade 4 AE	Discontinue permanently or interrupt vemurafenib treatment until Grade 0–1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
2nd occurrence of any Grade 4 AE or persistence of any Grade 4 AE after 1st dose reduction	Discontinue permanently.

AE = adverse event.

[a] The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label phase II study in previously treated patients with metastatic melanoma. Management of QTc prolongation may require specific monitoring measures.

Table A10-57 Dose Modification Schedule Based on Prolongation of the QT Interval

QTc Value	Recommended Dose Modification
QTc > 500 ms at baseline	Treatment not recommended.
QTc increase meets values of both > 500 ms and > 60 ms change from pre-treatment values	Discontinue permanently.
1st occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains < 60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in Section 4.4. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains < 60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. See monitoring measures in Section 4.4. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains < 60 ms	Discontinue permanently.

Table A10-58 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Cutaneous squamous cell carcinoma (cuSCC) (which includes keratoacanthoma or mixed keratoacanthoma subtype)	Dermatologic evaluation prior to initiation of therapy. During treatment, examination for cuSCC at each study visit until end of study treatment. Thereafter evaluation monthly up to six months after treatment or until initiation of another anti-neoplastic therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per local standard of care. In patients, who develop cuSCC, continue treatment without dose adjustment. Patients should be instructed to inform their physicians upon the occurrence of any skin changes.

Event	Action to Be Taken
Non-cutaneous squamous cell carcinoma (non-cuSCC)	Perform head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation prior to initiation of treatment and every 12 weeks during treatment. Anal examinations (for all patients) and pelvic examinations (for women) are before and at the end of treatment or when considered clinically indicated. Monitoring for non-cuSCC should continue for up to 6 months after end of treatment or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.
New primary melanoma	Monitor for skin lesions should occur as outlined above for cutaneous squamous cell carcinoma.
Other malignancies	Carefully consider benefits and risks before administering vemurafenib to patients with a prior or concurrent cancer associated with RAS mutation.
Potentiation of radiation toxicity	Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment.
Hypersensitivity reaction (including Stevens-Johnson syndrome, generalized rash, erythema or hypotension)	Permanently discontinue vemurafenib.
Dermatologic reactions (including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, and Drug reaction with eosinophilia and systemic symptoms)	Permanently discontinue vemurafenib.
QT prolongation (may lead to an increased risk of ventricular arrhythmias including Torsade de Pointes)	Monitor of ECG and electrolytes (including magnesium) per protocol. If during treatment the QTc exceeds 500 ms, vemurafenib treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur once the QTc decreases below 500 ms and at a lower dose as described in Table A10-57. Permanent discontinuation of vemurafenib treatment is recommended if the QTc increase meets values of both $>$500 ms and $>$60 ms change from pre-treatment values.

Event	Action to Be Taken
Liver injury	Monitoring of liver enzymes and bilirubin per protocol and management if laboratory abnormalities per Table A10-56.
Photosensitivity	Advise patients to minimize sun exposure and use sun block and lip balm with broad-spectrum, UVA and UVB protection (minimum of SPF 30, re-applied every 2 to 3 hours) during vemurafenib treatment and for at least 5 to 10 days after study drug discontinuation. For photosensitivity, Grade 2 (intolerable) or greater AEs, dose modifications are recommended (see Table A10-56).
Ophthalmologic reactions (including uveitis)	Monitor routinely for ophthalmologic reactions.
Pancreatitis	Investigate unexplained abdominal pain (including measurement of serum amylase and lipase). Close monitored when restarting vemurafenib after an episode of pancreatitis.

Please also refer to the Cobimetinib Investigator's Brochure and to its warnings and precautions when using vemurafenib in combination with cobimetinib.

DRUG INTERACTIONS

Concomitant Use with Other Medications

Effects of vemurafenib on drug metabolizing enzymes

Results from an in vivo drug–drug interaction study in metastatic melanoma patients demonstrated that vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer. Concomitant use of vemurafenib with agents with narrow therapeutic windows that are metabolized by CYP1A2 and CYP3A4 is not recommended as vemurafenib may alter their concentrations. If co-administration cannot be avoided, exercise caution and consider a dose reduction of the concomitant CYP1A2 substrate drug.
Co-administration of vemurafenib increased the AUC of caffeine (CYP1A2 substrate) 2.6-fold, while it decreased the AUC of midazolam (CYP3A4 substrate) by 39%.
In another clinical trial, vemurafenib increased AUC_{last} and AUC_{inf} of a single 2-mg dose of tizanidine (CYP1A2 substrate) approximately 4.2 and 4.7 fold, respectively. The AUC of dextromethorphan (CYP2D6 substrate) and its metabolite dextrorphan were increased by approximately 47%, indicating an effect on dextromethorphan kinetics that may not be mediated by inhibition of CYP2D6.

Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.

Vemurafenib moderately inhibited CYP2C8 in vitro. The in vivo relevance of this finding is unknown, but a risk for a clinically relevant effect on concomitantly administered CYP2C8 substrates cannot be excluded. Concomitant administration of CYP2C8 substrates with a narrow therapeutic window should be made with caution since vemurafenib may increase their concentrations.

Drugs that inhibit or induce CYP3A4

Based on in vitro data, vemurafenib is a substrate of CYP3A4, and concomitant administration of strong CYP3A4 inhibitors or inducers may therefore alter vemurafenib concentrations. Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) should be used with caution when co-administered with vemurafenib.

Interaction of vemurafenib with drug transport systems

In vitro studies have demonstrated that vemurafenib is both a substrate and an inhibitor of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In vitro studies have also demonstrated that vemurafenib is a weak inhibitor of the bile salt export pump (BSEP). A clinical study (Study GO28394) demonstrated that multiple oral doses of vemurafenib (960 mg BID) increased the AUC of a single 0.25 mg oral dose of digoxin approximately 1.8-fold.

INTERACTION WITH COBIMETINIB

There is no evidence of any clinically significant drug interaction between vemurafenib and cobimetinib in unresectable or metastatic melanoma patients.

A10–14 VISMODEGIB

BACKGROUND

The Hedgehog signaling pathway presents a novel and potentially beneficial target for cancer therapy. The secreted Hedgehog ligands (Desert Hedgehog, Indian Hedgehog and Sonic Hedgehog) bind to PTCH1, a 12-pass transmembrane receptor on the surface of cells. Binding of Hedgehog to PTCH1 relieves the catalytic inhibitory effect of PTCH1 on SMO, a 7-pass transmembrane domain protein with homology to the G-protein coupled receptor superfamily.

Hedgehog signaling regulates epithelial and mesenchymal interactions in a variety of tissues during mammalian embryogenesis (Ingham and McMahon 2001). The outcome of Hedgehog signaling varies according to the receiving cell type, but it can include upregulation of D-type cyclins (resulting in cell proliferation); upregulation of anti-apoptotic proteins such as B-cell lymphoma 2 (mediating cell survival); production of vascular endothelial growth factor and angiopoietins (regulating angiogenesis); and transcription of SNAIL (initiating the epithelial-mesenchyme transition in metastasis) (Scales and de Sauvage 2009).

Vismodegib (vismodegib is a small-molecule inhibitor of the Hedgehog signal pathway that binds to and inhibits SMO (Zhang et al. 2001). Vismodegib is currently indicated for the treatment of symptomatic metastatic basal cell carcinoma and locally-advanced basal cell carcinoma that is inappropriate for surgery or radiotherapy.

SAFETY

SAFETY PROFILE

A comprehensive description of the safety profile of vismodegib is provided in the Vismodegib Investigator's Brochure.

Adverse reactions associated with Warnings and Precautions:

- Embryofetal death or severe birth defects

Refer to the Vismodegib Investigator's Brochure for guidance on the use of vismodegib in women of childbearing potential and in men. There are specific recommendations for contraception for both women and men.

The summary information provided in the following sections must always be checked against any update of the vismodegib local prescription guidelines and the EMA Summary of Product Characteristics that may have occurred after the protocol has been issued.

ADVERSE EVENTS OF SPECIAL INTEREST

Non-serious AESIs follow the same process flow as SAEs and require immediate reporting in a clinical trial.

For vismodegib, there are no AESIs to report

ADMINISTRATION

POSOLOGY AND ROUTE

The recommended dose is one 150 mg capsule taken once daily.

Vismodegib may be taken with or without food. Capsules should be swallowed whole; capsules should not be crushed.

For instructions on handling of the medicinal product, refer to the Vismodegib Investigator's Brochure.

DURATION OF TREATMENT

Treatment with vismodegib should continue until loss of clinical benefit or the development of unacceptable toxicity.

DELAYED OR MISSED DOSES

If a dose is missed, patients should be instructed not to take the missed dose but to resume with the next scheduled dose.

Treatment interruptions of up to 4 weeks are allowed based on individual tolerability.

DOSE MODIFICATION

Dose modification of vismodegib is not recommended.

CONTRAINDICATIONS

Vismodegib is contraindicated in nursing mothers during the course of treatment and for 9 months after the final dose because of the potential to cause serious development defects in breastfed infants and children.

DRUG INTERACTIONS

In vitro, vismodegib is an inhibitor of OATP1B1. It cannot be excluded that vismodegib may increase the exposure to substrates of OATP1B1, e.g., bosentan, ezetimibe, glibenclamide, repaglinide, valsartan and statins. In particular, caution should be exercised if vismodegib is administered in combination with any statin.

In vitro studies indicate that vismodegib also has the potential to act as an inhibitor of breast cancer resistance protein.

No other clinically relevant pharmacokinetic reactions between vismodegib and other drugs have been identified.

Appendix 11
Investigational, *Auxiliary,* and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A11-1 **Investigational, *Authorized Auxiliary, and Unauthorized Auxiliary* Medicinal Product Designations for European Economic Area**

Product Name	IMP/*AxMP* Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Alectinib (RO5424802)	IMP (test product)	Authorized	No [a]
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No [a]
Bevacizumab (RO4876646)	IMP (test product)	Authorized	No [a]
Cobimetinib (RO5514041)	IMP (test product)	Authorized	No [a]
Entrectinib (RO7102122)	IMP (test product)	Authorized	No [a]
Erlotinib (RO508231)	IMP (test product)	Authorized	No [a]
Ipatasertib (RO5532961)	IMP (test product)	Unauthorized	Not applicable
Ivosidenib (RO7499824)	IMP (test product)	Unauthorized	Not applicable
Olaparib (RO5508245)	IMP (test product)	Authorized	No [a]
Pemigatinib (RO7496200)	IMP (test product)	Authorized	No [a]
Pertuzumab (RO4368451)	IMP (test product)	Authorized	No [a]
Trastuzumab (RO0452317)	IMP (test product)	Authorized	No [a]

Table A11-1 Investigational, *Authorized Auxiliary, and Unauthorized Auxiliary* Medicinal Product Designations for European Economic Area

Product Name	IMP/*AxMP* Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Vemurafenib (RO5185426)	IMP (test product)	Authorized	No [a]
Vismodegib (RO5450815)	IMP (test product)	Authorized	No [a]
Carboplatin (RO4843791)	IMP (test product)	Authorized	No [a]
Cisplatin (RO0232538)	IMP (test product)	Authorized	No [a]
Gemcitabine (RO0249587)	IMP (test product)	Authorized	No [a]
Paclitaxel (RO0247506)	IMP (test product)	Authorized	No [a]
Loperamide	*AxMP* (premedication)	Not applicable	Not applicable
Dexamethasone	*AxMP* (premedication)	Not applicable	Not applicable
Diphenhydramine	*AxMP* (premedication)	Not applicable	Not applicable
Cimetidine	*AxMP* (premedication)	Not applicable	Not applicable
Acetaminophen	*AxMP* (premedication) [b]	Not applicable	Not applicable

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.

[a] No molecules are approved for the treatment of cancer of unknown primary.

[b] If needed.

Table A11-2 Investigational and Non-Investigational Medicinal Product Designations for United Kingdom

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in U.K.*	*Used within Marketing Authorization*
Alectinib (RO5424802)	*IMP (test product)*	*Authorized*	*No* [a]
Atezolizumab (RO5541267)	*IMP (test product)*	*Authorized*	*No* [a]
Bevacizumab (RO4876646)	*IMP (test product)*	*Authorized*	*No* [a]
Cobimetinib (RO5514041)	*IMP (test product)*	*Authorized*	*No* [a]
Entrectinib (RO7102122)	*IMP (test product)*	*Authorized*	*No* [a]
Erlotinib (RO508231)	*IMP (test product)*	*Authorized*	*No* [a]
Ipatasertib (RO5532961)	*IMP (test product)*	*Unauthorized*	*Not applicable*
Ivosidenib (RO7499824)	*IMP (test product)*	*Unauthorized*	*Not applicable*
Olaparib (RO5508245)	*IMP (test product)*	*Authorized*	*No* [a]
Pemigatinib (RO7496200)	*IMP (test product)*	*Authorized*	*No* [a]
Pertuzumab (RO4368451)	*IMP (test product)*	*Authorized*	*No* [a]
Trastuzumab (RO0452317)	*IMP (test product)*	*Authorized*	*No* [a]
Vemurafenib (RO5185426)	*IMP (test product)*	*Authorized*	*No* [a]

Table A11-3 Investigational and Non-Investigational Medicinal Product Designations for United Kingdom (cont.)

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in U.K.*	*Used within Marketing Authorization*
Vismodegib (RO5450815)	*IMP (test product)*	*Authorized*	*No* [a]
Carboplatin (RO4843791)	*IMP (test product)*	*Authorized*	*No* [a]
Cisplatin (RO0232538)	*IMP (test product)*	*Authorized*	*No* [a]
Gemcitabine (RO0249587)	*IMP (test product)*	*Authorized*	*No* [a]
Paclitaxel (RO0247506)	*IMP (test product)*	*Authorized*	*No* [a]
Loperamide	*NIMP (premedication)*	*Not applicable*	*Not applicable*
Dexamethasone	*NIMP (premedication)*	*Not applicable*	*Not applicable*
Diphenhydramine	*NIMP (premedication)*	*Not applicable*	*Not applicable*
Cimetidine	*NIMP (premedication)*	*Not applicable*	*Not applicable*
Acetaminophen	*NIMP (premedication)* [b]	*Not applicable*	*Not applicable*

IMP =investigational medicinal product; NIMP =non investigational medicinal product.

[a] *No molecules are approved for the treatment of cancer of unknown primary.*

[b] *If needed.*

Signature Page for Protocol - MX39795 - TECENTRIQ - v12 - Global/Core - Publishe
System identifier: RIM-CLIN-523951

Approval Task	[redacted] Company Signatory 09-Mar-2024 17:18:05 GMT+0000