CLINICAL STUDY PROTOCOL

Protocol Title: Phase 1b/2a safety and tolerability study of bemcentinib with pembrolizumab/carboplatin/pemetrexed in subjects with untreated advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) without/with a STK11 mutation.

Protocol Number: BGBC016

Substance: Bemcentinib

Study Phase: Phase 1b/2a

Short Title: A study to investigate the safety, tolerability, and preliminary anti-tumor activity of bemcentinib in combination with pembrolizumab plus pemetrexed and carboplatin in adult subjects with untreated non-squamous non-small cell lung cancer.

Sponsor Name: BerGenBio ASA

Legal Registered Address: Mollendalsbakken 9, 5009 Bergen, Norway

Regulatory Agency Identifier Numbers:

IND number: 124645

EudraCT: 2019-003806-28

Amendment no.: 4

Version: V3.0

Scope: Global

Approval Date: 07-Jul-2023

Replaces protocol version: V2.0 (Global), 07-Dec-22

V2.0 (EU), 11-Jan-23

V2.2 (France), 04-Jul-23

CONFIDENTIALITY STATEMENT

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws and regulations or without prior written authorization from BerGenBio ASA (BGB). In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you, which is indicated as privileged or confidential.

COMPLIANCE STATEMENT

This study will be conducted in compliance with the protocol, the International Council on Harmonization of technical requirements for pharmaceuticals for human use (ICH) guidelines on Good Clinical Practice (GCP) E6(R2) (ICH, 2016), the Declaration of Helsinki (World Medical Association, 2013), and in accordance with local legal and regulatory requirements including the Clinical Trial Directive 2001/20/EC (European Parliament and Council of the European Union, 2001).

Refer to Appendix 1 for compliance related to data protection.

CONTACT DETAILS

Contact details for the Medical Monitor, the Clinical Project Manager, and appointed Clinical Research Associates are provided to the study sites as a separate contact list.

Document History

Version	Date	Description of change
1.0	30-Jun-2022	Original version
2.0 (Global) 2.0 (Europe)	07-Dec-2022 11-Jan-2023	• Sponsor signature page was updated • An Investigator's statement signature page was added • Pembrolizumab, carboplatin and pemetrexed defined as Investigational Medicinal Products (V2.0 Europe only) • Added bemcentinib 50 mg capsules • Added bemcentinib 125 mg as an alternative dose cohort • Updated eligibility criteria: o Inclusion criteria no. 1, 14: minor clarifications o Inclusion criteria no. 5: Treatment free interval update o Exclusion criteria no. 1, 2, 5, 6, 11, 13, 14, 22: Minor clarifications o Exclusion criteria no. 3: Prior malignancy free period updated o Exclusion criteria no. 4: Steroid free period updated o Exclusion criteria no. 12: Information regarding inclusion of HIV positive subjects updated • Definition of End of Study was updated • Clarifications were made to the descriptions of the follow-up periods following treatment discontinuation, i.e., safety follow-up period, progression free survival (PFS) follow-up period, survival follow-up • Clinical data from other bemcentinib studies were updated following the annual IB update • The risk benefit section was updated • To align the protocol to the Clinical Trial Regulation (Regulation (EU) No 536/2014), the following key updates were made: o Addition of relevant nonclinical data o Addition of relevant clinical data o The protocol synopsis was shortened Minor editorial changes to improve clarity and language have been made throughout the document
2.1 (France) 2.2 (France) 3.0 (Global)	04-Apr-2023 04-Jul-2023 07-Jul-2023	Note that updates in V2.1 (France), V2.2 (France) and V3.0 (Global) overlap; updates specific to V3.0 Global have been identified in parentheses. • Included an updated study schema (Figure 1) (V3.0 Global only) • Updated eligibility criteria: o Inclusion criterion no. 8: updated to include the required duration of contraception measures after the last dose of chemotherapeutic agents to align with the carboplatin and pemetrexed SmPCs/USPIs (US)

		○ Inclusion criterion no. 13: updated to define the acceptable screening QTcF interval separately for male and female subjects ○ Exclusion criterion no. 4: added "Subjects who have experienced an acute neurological event (e.g. intracranial or subarachnoid haemorrhage, stroke, intracranial trauma) within 6 months prior to study enrolment will be excluded" ○ Exclusion criterion no. 5: included "prior to first dose" in part b (V3.0 Global only), "or history of cardiomyopathy or left ventricular hypertrophy" in part c and "any conduction disorder within 6 months prior to dosing" in part e ○ Exclusion criterion no. 10: updated to include "hereditary problem of galactose intolerance, LAPP-lactase deficiency or glucose-galactose malabsorption" ○ Exclusion criterion no. 16: updated to include "has a bleeding tumor" (Note: this was included as a new criterion in V2.1 France and included as part of criterion no. 16 in V3.0 Global) ○ Exclusion criterion no. 17: updated to included "stomach or duodenal ulcer" ○ Exclusion criterion no. 21: updated to include hypersensitivity to "pemetrexed, carboplatin or pembrolizumab" • Updated to include the required duration of contraception measures after the last dose of chemotherapeutic agents to align with the carboplatin and pemetrexed SmPCs/USPIs (US) • Updated to include risks of gonadal suppression with amenorrhea or azoospermia associated with carboplatin. Men are advised to seek advice on sperm preservation before starting therapy due to the possibility of irreversible infertility after treatment with carboplatin (V3.0 Global only) • Clarified that access to bemcentinib via an alternative access program or study is not applicable in France • Included a list of prohibited medications for study drugs in a new appendix • Pembrolizumab, carboplatin and pemetrexed defined as Investigational Medicinal Products in Europe and standard of care in the United States (V3.0 Global only) • Updated the details in Table 2 Study Medication Provided by Sponsor (V3.0 Global only) • Alimta (brand name) was replaced with pemetrexed in Table 3, and dose formulation updated for pemetrexed and carboplatin (V3.0 Global only) • Updated to include pemetrexed and carboplatin effects on ability to drive and operate machinery (V3.0 Global only) • Added a footnote to Table 10 to specify "diarrhea that requires hospitalization"

		• Updated wording for dose limiting toxicities:
		  ○ Thrombocytopenia previously captured under hematologic toxicity now captured as a separate toxicity;
		  ○ Exceptions for Any Grade 3 or Grade 4 non-hematologic laboratory value revised to add that imaging will be performed at the investigator's discretion to rule out pancreatitis for asymptomatic Grade 3 or Grade 4 amylase or lipase increase.
		• Clarified that the DSMB will recommend the bemcentinib dose for the phase 2a expansion cohort (V3.0 Global only)
		• Clarified in the protocol compliance section that the policy of BerGenBio is that no waivers will be issued (V3.0 Global only)

SPONSOR SIGNATORY PAGE

The signatures below document the Sponsor approval of this clinical study protocol.

Sponsor approval, BerGenBio ASA

[redacted]

[redacted]

Name and Title

Date

[redacted]

INVESTIGATOR SIGNATURE PAGE

Protocol Title: Phase 1b/2a safety and tolerability study of bemcentinib with pembrolizumab/carboplatin/pemetrexed in subjects with untreated advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) without/with a STK11 mutation

Protocol Number: BGBC016

Confidentiality, Good Clinical Practice and Compliance Statement:

- I, the undersigned, have reviewed this protocol and amendment, including appendices, and I will conduct the study as described in compliance with this protocol and amendment, International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH) guidelines on Good Clinical Practice (GCP) E6(R2) and other relevant guidelines. All subjects will be informed comprehensively about the nature of the study and will give their written consent to participate before entry into the study. They will be informed that they may withdraw from the study at any time. I will use only the consent and information form approved by BerGenBio ASA (hereafter referred to as BGB) and the independent ethics committee (IEC)/institutional review board (IRB), for this study.
- I am thoroughly familiar with the appropriate use of the study drug as described in this protocol and any other information provided by BGB including, but not limited to, the current Investigator's Brochure.
- I ensure that all persons or parties assisting me with the study are adequately qualified, trained, and informed about the study drug and of their delegated study-related duties and functions as described in the protocol. I ensure that source documents and study records that include all pertinent observations on each of the site's study subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subject's state of health will be regarded as confidential. No subjects personal identifying information will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Should it be requested by government regulatory agencies, I will make available additional background data from my records, and where allowed, from the hospital or institution where the study was conducted.
- I understand that the case report forms and other data pertinent to this study are the property of BGB and are confidential. I will supply BGB (or their delegates) with the study data in such a way that the patient cannot be personally identified.

<Name>

_____

<Title> Investigator Signature

<Institution>

_____

Date (DD-Mmm-YYYY)

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1 PROTOCOL SUMMARY

1.1 Synopsis

<table>
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<tr><td>Investigational Medicinal Products (IMPs):

bemcentinib

IMPs in Europe/standard of care (SOC) in the United States:
pembrolizumab
carboplatin
pemetrexed</td><td>Drug class:

small molecule, AXL kinase inhibitor

monoclonal antibody, PD-1 inhibitor
antineoplastic, platinum analogue
antineoplastic, folate analogue</td></tr>
<tr><td>Protocol number: BGBC016</td><td>Indication: non-squamous NSCLC</td></tr>
<tr><td>Study Phase: 1b/2a</td><td>Version: V3.0 (Global), 07-Jul-2023</td></tr>
<tr><td colspan="2">EudraCT number/EU Trial number/IND number: 2019-003806-28/NA/124645</td></tr>
<tr><td colspan="2">Study Rationale:
The combination of platinum-based chemotherapy, pemetrexed and pembrolizumab has become the standard of care as first line (1L) treatment in NSCLC. However, despite an increase in response rates and survival, the emergence of chemoresistance highlights the unmet medical needs in these patients. STK11 mutations (STK11m) are common (~20%) in NSCLC and promote immunosuppression by activation of AXL signaling. Inhibition of AXL has the potential to improve the efficacy of chemo-immunotherapy (CIT) and therefore bemcentinib, a selective AXL inhibitor, may improve the outcome of chemo-immunotherapy in NSCLC patients with STK11m.</td></tr>
<tr><td colspan="2">Objectives and Key Endpoints
<table>
<tr><th>Primary Objective</th><th>Primary Endpoint</th></tr>
<tr><td>Phase 1b: To determine the safety and tolerability of the combination of bemcentinib with CIT to identify the recommended phase 2 dose (RP2D) when administered as 1L treatment in subjects with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC with no actionable mutations.</td><td>Phase 1b: The incidence of dose limiting toxicities (DLTs) during a 21-day assessment period in treatment cycle 1 (i.e., the first 21 days from Cycle 1 Day 1 (C1D1) for each subject).</td></tr>
<tr><td>Phase 2a: To determine the anti-tumor activity of the combination of bemcentinib with CIT when administered as 1L treatment in subjects with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC with STK11 mutation and no actionable mutations.</td><td>Phase 2a: Response per "Response Evaluation Criteria in Solid Tumors 1.1" (RECIST):

Objective response rate (ORR) (complete response and partial response) at 6 and 12 months.</td></tr>
<tr><th>Secondary Objective</th><th>Secondary Endpoints</th></tr>
<tr><td>Phase 1b: To assess the anti-tumor activity of the combination of bemcentinib with CIT when administered as 1L treatment.</td><td>Phase 1b: Response per RECIST 1.1: ORR, Disease control rate (DCR), Duration of response (DOR), Overall survival (OS).</td></tr>
</table></td></tr>
</table>

Phase 2a: To further assess the anti-tumor activity as well as the safety and pharmacokinetic profile of the combination bemcentinib with CIT when administered as 1L treatment.	**Phase 2a**: The frequency and percentage of Adverse Events (AEs) and Serious Adverse Events (SAEs); assessment of safety laboratory parameters, vital signs, and electrocardiograms (ECGs). Response per RECIST 1.1: DCR, DOR, Progression free survival (PFS), Time to progression, OS, pharmacokinetic (PK) exposure.

Study Design:
This is an open-label, multi-center, phase 1b/2a clinical study to assess the safety, tolerability, and preliminary anti-tumor activity of bemcentinib in combination with CIT comprising pembrolizumab plus pemetrexed and carboplatin as 1L treatment in subjects with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC without actionable mutations. In the phase 2a only subjects with a STK11m will be enrolled. All subjects will receive bemcentinib once daily in combination with CIT, which is administered on Day 1 of each 21-day treatment cycle. After the completion of 4 cycles of CIT + bemcentinib, study subjects will receive maintenance treatment with bemcentinib in combination with pemetrexed plus pembrolizumab.

Phase 1b follows a standard 3+3 design: 3 subjects will receive bemcentinib + CIT at one of 3 dose levels: Cohort 1=75 mg daily dose of bemcentinib; Cohort 2=100 mg daily dose of bemcentinib; or Cohort 3=150 mg daily dose of bemcentinib. An independent data safety monitoring board (DSMB) will review the safety data from each cohort at the end of the DLT assessment period (the first 21 days from C1D1 for each subject of each cohort) and based on overall safety and tolerability, the DSMB will recommend the bemcentinib dose for the phase 2a expansion. The clinical study consists of a screening period (up to 28 days), and a treatment period up to 24 months for each subject. All subjects will be followed for OS.

Number of subjects:
Phase 1b: 9-24 DLT-evaluable subjects. Phase 2a: 40 efficacy-evaluable subjects. Assuming a 30% screening failure rate, up to 92 subjects will be screened to achieve the planned 64 evaluable subjects.

Patient population:
Adult subjects with advanced or metastatic non-squamous NSCLC.

Key inclusion:

- Have a histologically- or cytologically confirmed diagnosis of advanced (Stage IIIb/IIIc) or metastatic (Stage IV) (AJCC Edition 8) non-squamous NSCLC not amenable to curative therapy without actionable mutations. In phase 2a, the subjects must also have a STK11m.
- Have not received prior systemic treatment for their advanced/metastatic NSCLC.
- Have measurable disease per RECIST 1.1 as assessed by the Investigator.
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 and adequate organ function.

Main Assessments:
The safety assessments include collection of AEs, SAEs, safety laboratory parameters, vital signs, and ECG changes. Efficacy will be assessed based on tumor scan evaluation by RECIST 1.1., chest, abdomen, and pelvis. Additionally, x-ray and bone scans, as well as imaging of other sites of disease will be used as appropriate.

Ethical considerations and risk-benefit:
As of July 2022, 543 subjects have been dosed with bemcentinib with diarrhea, nausea, and fatigue being the most commonly reported AEs; the reported liver AEs have resolved with steroid therapy. Subjects will be closely monitored, and the risk-benefit profile of bemcentinib is considered positive in subjects with advanced or metastatic disease with poor prognosis and limited treatment options.

1.2 Flowchart

The Flowchart displaying the assessments and visit schedule is available in Section 8, Table 11.

2 INTRODUCTION

2.1 Study Rationale

Indication:

Phase 1b: Previously untreated advanced (Stage IIIb/IIIc)/metastatic (Stage IV) non-squamous NSCLC without actionable mutations (for phase 1b)

Phase 2a: Previously untreated advanced (Stage IIIb/IIIc)/metastatic (Stage IV) non-squamous NSCLC having a serine/threonine kinase 11 (STK11) mutation as identified by Next Generation Sequencing (NGS) and without actionable mutations.

Rationale:

Non-small cell lung cancer (NSCLC) is a life-threatening condition with a clear unmet need, particularly for subjects diagnosed with advanced or metastatic non-squamous NSCLC without a driver mutation, who represent the majority of NSCLC patients. Despite constant advances in therapy, the 5-year survival of NSCLC is approximately 20-30% (Min & Lee, 2021).

Brain metastases are a common consequence of advanced lung cancer with currently no effective therapeutic options, due to a lack of actionable targets and a failure of systemic therapies to penetrate the blood-brain barrier (BBB). Studies have shown that the brain metastasis rate of NSCLC is approximately 10-20% (Bajard et al., 2004, Smith et al., 2019, Waqar et al., 2018) with a higher incidence rate (approximately 30-50%) in patients with advanced NSCLC (Waqar et al., 2018, Ceresoli et al., 2002, Robnett et al., 2001, Chen et al., 2007).

Current developments for first-line (1L) treatment of NSCLC define a widening role for chemo-immunotherapy (CIT) regardless of programmed death-ligand 1 (PD-L1) status, with approval for the combination of platinum, pemetrexed, and pembrolizumab in 1L, which has become the standard of care (SOC) (Planchard et al., 2018, Ettinger et al., 2022) in non–oncogene addicted NSCLC. However, despite an initial improvement in response rates and survival, the emergence of chemoresistance poses a significant obstacle to the management of NSCLC and highlights the unmet medical need in these patients (Min & Lee, 2021).

Of the currently non-actionable mutations, STK11 mutations (STK11m) occur in ~20% of NSCLC subjects and recent evidence suggests that STK11m NSCLC patients have a minimal response to checkpoint inhibitors and to chemo-immunotherapy in the first line setting (Shire et al., 2020, Perez Parente et al., 2022). STK11 alterations drive an immunosuppressed tumor microenvironment (TME) by activation of AXL signaling.

AXL suppresses anti-tumor innate immune cell responses, thus driving an immunosuppressive TME and promoting tumorigenicity and chemoresistance in tumor cells (Shire et al., 2020). AXL is a recognized driver of chemoresistance and AXL inhibition has been shown to prevent and reverse chemoresistance (Wilson et al., 2014, Wnuk-Lipinska et al., 2014, Wu et al., 2014, Brand et al., 2015, Wang et al., 2016, Lin et al., 2017, Ludwig et al., 2018). Moreover, AXL is a recognized driver for tumor metastases, with TAZ-AXL-ABL2 signaling axis promoting brain metastases in lung

cancer (Hoj et al., 2019) and AXL targeting by genetic silencing or pharmacological inhibition has been shown to prevent cancer metastasis in numerous mouse models (Auyez et al., 2021) An enhanced AXL expression in lung adenocarcinoma brain metastases relative to primary tumors was reported to be prognostic of poor survival outcomes (Wu et al., 2017).

Analysis of patients with lung adenocarcinoma correlating gene expression to patient survival revealed that high expression of AXL, ABL2, or WWTR1 (TAZ) individually predicted reduced overall survival (OS) and progression free survival (PFS) (Hoj et al., 2019).

Importantly, AXL inhibition potentiated the efficacy of combined chemo-immunotherapy in models of NSCLC (Lee et al., 2022) as well as in models of breast cancer and melanoma (Dhakal et al., 2021, Dhakal et al., 2022). Enhanced T cell immunity was observed following AXL inhibition in the chemo-immunotherapy combination treatment in NSCLC models (Lee et al., 2022) and it was demonstrated that bemcentinib enhanced the Type 1 interferon (IFN) response following chemotherapy as well as reduced the tumor epithelial-mesenchymal transition (EMT) (Dhakal et al., 2021, Dhakal et al., 2022).

Analyses of subjects receiving pembrolizumab, ipilimumab/nivolumab, and durvalumab/tremelimumab have shown that STK11m subjects respond poorly to checkpoint inhibitors (CPIs) with a shorter PFS and OS as compared with STK11 wild-type (STK11wt) subjects (Shire et al., 2020).

Bemcentinib is a potent and highly selective, orally bioavailable, inhibitor of AXL tyrosine kinase. Bemcentinib potentiates the anti-tumorigenic activity of innate immune cells through regulation of myeloid suppressor activation, prevents and reverses aggressive EMT driven phenotypes in NSCLC cells, therefore potentiating the immune therapy through tumor EMT modulation, enhanced Type 1 IFN response and modulation of the immune cell landscape.

Moreover, pharmacokinetic studies showed that bemcentinib crosses the BBB in mice (Meel et al., 2020) and readily distributes with higher concentrations in brain tumor issue in recurrent glioblastoma patients following oral administration (Nabors et al., 2021).

Recent preclinical data in syngeneic STK11m NSCLC mouse models refractory to pembrolizumab has demonstrated that the addition of bemcentinib to pembrolizumab in this setting re-instated checkpoint inhibition with strong synergistic responses to the combination *in vivo* (Li et al., 2022). It was observed that STK11m NSCLC mouse tumors drove AXL upregulation within the tumor microenvironment (rather than on the cancer cells) and AXL expression was identified on immunosuppressive macrophages and dendritic cells. This correlated with a more suppressive T cell composition in the tumor microenvironment. Furthermore, it was shown that bemcentinib, through inhibition of AXL expressed on the immunosuppressive dendritic cells, induced Type 1 IFN secretion and expansion of tumor associated TCF1+programmed cell death protein 1 (PD-1)+CD8 T cells therapeutically sensitive to anti-PD-1 targeting and restoration of cytotoxic T cell antitumor response (Li et al., 2022).

The doses of bemcentinib to be used in the clinical study have been selected to provide exposure levels of bemcentinib which are both safe and biologically active. As this is the first time bemcentinib is being dosed in combination with a chemotherapy doublet and CPI, bemcentinib will be started at a lower dose than previously dosed in clinical studies

(75 mg) and will be escalated in a step-wise approach. Refer to Section 4.7 for a dose justification.

In summary, based on supportive *in vitro* and *in vivo* pharmacology in NSCLC cells and animal models, as well as preliminary clinical data, there is a scientific rationale for the combination of bemcentinib with pembrolizumab plus pemetrexed and carboplatin in previously untreated advanced (Stage IIIb/IIIc)/metastatic (Stage IV) non-squamous NSCLC with no actionable mutations, including those with STK11m.

2.1.1 BGBC008 – second line NSCLC study combination with pembrolizumab

BGBC008 (NCT03184571) is a Phase II, open-label, single-arm study to assess the efficacy and safety of bemcentinib in combination with pembrolizumab in subjects with previously treated, advanced adenocarcinoma of the lung. By 30 July 2022, 138 subjects have been enrolled, of which 99 have been assigned to treatment with 400 mg loading dose of bemcentinib for 3 days followed by a daily maintenance dose of 200 mg in combination with 200 mg pembrolizumab every 3 weeks. At the data cut-off, 95 subjects have discontinued bemcentinib treatment, 34 (34.3%) due to progression of disease, 30 (30.3%) due to the Investigator's decision, 23 (23.2%) due to adverse events (AEs), five have died (5.1%) and 3 (3.0%) due to withdrawal of consent.

A total of 1327 treatment emergent AEs were reported in 101 subjects (73.2%). The most frequently reported AEs were diarrhea (29.7%), blood creatinine increased (21.7%), decreased appetite (21.7%), alanine aminotransferase (ALT) increased (21.0%) and aspartate aminotransferase (AST) increased (21.0%). An increased incidence of liver-related events had been observed in BGBC008 with the combination therapy of bemcentinib and pembrolizumab compared to monotherapy with bemcentinib or pembrolizumab alone. However, all reported events responded well to treatment with steroids and were reversible. This study is ongoing, and the safety data should therefore be considered as preliminary.

An earlier report from six evaluable subjects with STK11m showed clinical benefit in three, when receiving the combination of bemcentinib and pembrolizumab, thus providing proof of concept and supporting the above *in vivo* preclinical data. In these six evaluable STK11m patients (four CPI-naïve and two CPI-progressed) the PFS ranges between 3.5 and >44 months and the OS between 10 months to >44 months. These initial observations compare favorably with the median progression free survival (mPFS) and median OS reported in second line (2L) STK11m NSCLC patients (2.2 months and 6.3 months, respectively) (Shire et al., 2020) and that was indeed observed in those patients during their prior therapies.

2.1.2 BGBIL005 – 2L NSCLC combination with docetaxel

Clinical data generated from an ongoing Phase Ib/II Investigator-led 2L NSCLC clinical study (BGBIL005 [NCT02922777]) of bemcentinib in combination with docetaxel showed encouraging clinical benefit when bemcentinib was given in combination with docetaxel with preliminary objective response rate (Ludwig et al., 2018) of 35%, which is higher than previously seen with docetaxel monotherapy or in combination with targeted therapies and provide proof of concept around the ability of bemcentinib to prevent and reverse chemoresistance (Bhalla et al., 2022).

2.2 Background

2.2.1 Non-Small Cell Lung Cancer

Lung cancer is the second most common cancer and the leading cause of cancer death in the USA. Approximately 247,270 new cases of lung cancer are estimated to occur in 2020, with 130,340 male cases and 116,930 female cases (Siegel et al., 2020) Prior studies have reported that lung cancer resulted in more deaths than breast cancer, prostate cancer, colorectal cancer, and leukemia combined in men ≥40 years old and women ≥60 years old. With the introduction of screening guidelines and decrease in tobacco use, the mortality rate for lung cancer has recently decreased by 48% in males and 23% in females. Despite this decrease in mortality rate, approximately 140,730 deaths are estimated to be secondary to lung cancer in 2020 (Siegel et al., 2020).

While progress has been made in the clinical management of early-stage NSCLC by establishing comprehensive, multi-modality treatment regimens, the prognosis for advanced disease has not improved substantially. Chemotherapy with a platinum-based doublet is SOC for patients with advanced NSCLC and pembrolizumab is considered the SOC for patients with advanced non-squamous NSCLC with a median overall survival (mOS) of 22.0 months (Gray et al., 2021). However, the emergence of chemoresistance poses a significant obstacle to the management of NSCLC and highlights the unmet medical need in these patients (Min & Lee, 2021).

With the introduction of molecular testing, targeted therapy has improved clinical outcomes in a significant proportion of NSCLC patients with advanced disease and actionable mutations, however some mutations, such as STK11 mutation, in non-squamous NSCLC remain non-actionable mutations at present. STK11m is a tumor suppressor serine/threonine kinase that functions as master regulator of cell growth, metabolism, survival and polarity by interacting with downstream mediators. STK11m is present in up to ~20% of non-squamous NSCLC and is a recognized resistance mechanism for anti-PD-1/PD-L1 monotherapy with low response rates (2-3%) and limited clinical efficacy (mPFS 2-3 months). Moreover, recent evidence suggests that the levels of STK11m increase on immunotherapy treatment (Ricciuti et al., 2022).

STK11m patients are characterized by reduced CD8+/PD-L1+ T cell infiltration, low PD-L1 expression, increased AXL expression on dendritic cells and relatively low level of actionable co-mutations (ALK, EGFR, etc.) (Li et al., 2022).

Clinical data indicate that 1L NSCLC STK11m patients treated with PD-1/L1 blockade have shorter mPFS, mOS, and reduced response rates (objective response rate [ORR] 33% vs 44%) compared to STK11wt NSCLC (Hellmann et al., 2018, Skoulidis et al., 2018, Pore et al., 2021). Moreover, the addition of pembrolizumab to doublet chemotherapy in 1L STK11m NSCLC patients showed no added benefit [(mPFS 4.8 months vs 4.3 months) and mOS (10.6 months vs 10.3 months)] compared to chemotherapy alone. This subgroup of patients, therefore, represents a high unmet medical need where the currently available therapies offer suboptimal benefit.

Bemcentinib has the potential to restore immune checkpoint response and to delay chemoresistance. Encouraging data have been observed in clinical study BGBC008 (NCT03184571) in 2L NSCLC treated with pembrolizumab and bemcentinib. In the six evaluable STK11 mutated patients (four CPI-naïve and two CPI-progressed) the PFS ranges between 3.5 and >44 months and the OS from 10 months to >44 months, which compared very favorably with the poor outcome reported in literature where mPFS and

mOS for 2L STK11m NSCLC patients following immune-oncology monotherapy was found to be 2.2 months and 6.3 months, respectively (Shire et al., 2020) and that was observed in those patients during their prior therapies.

Based on the mode of action of bemcentinib and the encouraging data generated in 2L NSCLC indicating that bemcentinib has the potential to both reverse chemoresistance in combination with chemotherapy as well as target immunosuppression in combination with immunotherapy, there is potential for bemcentinib to provide additional clinical benefit when combined with the chemo-immunotherapy currently administered as 1L treatment for NSCLC patients.

2.2.2 Experience with Bemcentinib

Bemcentinib is a small molecule, orally bioavailable, highly specific inhibitor of AXL kinase.

2.2.2.1 Combination of Bemcentinib with Targeted Therapy and Chemotherapy

Bemcentinib prevented chemoresistance to erlotinib in NSCLC HCC8277 (study 060-SR-324), sensitized A549 NSCLC cells to erlotinib (study 041-SR-324) and potentiated the anti-tumorigenic effect of docetaxel in the NSCLC H1299 (study 059-SR-324) xenograft models. Bemcentinib as a single agent and in combination with gemcitabine reduced spleen, small intestine and liver metastasis (study 054-SR-324; Ludwig et al., 2018) and enhanced the effect of gemcitabine in reducing primary tumor growth in pancreatic cancer models. There are several reports showing bemcentinib improved sensitivity to platinum and taxane in ovarian cancer (Quinn et al., 2019) restored paclitaxel sensitivity in uterine serous cancer (Palisoul et al., 2017) and helped overcome docetaxel resistance in advanced prostate cancer (Seymour et al., 2017).

2.2.2.2 Combination of Bemcentinib and Checkpoint Inhibition

Bemcentinib has been shown to potentiate the activity of immune checkpoint blockade using antibodies targeting PD-1/programmed death-ligand 1 (PD-L1) and/or cytotoxic T-lymphocyte antigen-4 (CTLA-4) in syngeneic models of triple negative breast cancer (TNBC) (studies 102-SR-324; 153-SR-502P1MS6.2_Ver4; 348-TR-502; 368-TR-502) (Davidsen et al., 2019), lung cancer (study 179-SR-502P1MS10.2_Ver2), colorectal cancer (study 216-SR-502P1MS16) and melanoma (study 151-SR-502-P1MS3.3_Ver2), as well as breast cancer and glioblastoma (Sadahiro et al., 2018; Guo et al., 2017). Bemcentinib enhances immune checkpoint inhibition by influencing the tumor EMT status, by modulating the inflammatory cytokine profile and by modulating the presence and activation status of anti-tumorigenic immune cells in the tumors (Davidsen et al., 2019; Ludwig et al., 2018) study 349-TR-502; study 179-SR-502P1MS10.2_Ver2; (Goyette et al., 2021; Li et al., 2022); study 422-TR-502). Moreover, bemcentinib increases the expression of surface receptors, thus facilitating tumor-NK and -CTL effector cell interaction and enhancing apoptosis (Terry et al., 2019).

2.2.2.3 Bemcentinib in STK11 Mutant NSCLC Model

Mutations in Kirsten rat sarcoma virus (KRAS) and STK11/LKB1 have been reported to correlate with a more immunosuppressive TME, which may account for the limited response to anti-PD-1/PD-L1 treatment (Kadara et al., 2017; Koyama et al., 2016; Skoulidis et al., 2018). NSCLC mouse models with mutant KRAS/Tp53 knockout and STK11/LKB1 mutations (KPL) were used to determine if systemic AXL inhibition enhances the efficacy of anti-PD-1 therapy (Li et al., 2022). The combination of

bemcentinib with anti-PD-1 showed sustained control of tumor progression, indicating the therapeutic effect seen was dependent on the adaptive immune system (Li et al., 2022). Mechanistically, bemcentinib facilitated increased type I IFN secretion and expansion of tumor-associated TCF1+ PD-1+ CD8 T cells resulting in restored therapeutic response to anti-PD-1 in both syngeneic immunocompetent mouse models and in humanized mice bearing STK11/LKB1 mutant NSCLC human tumor xenografts.

2.2.2.4 Combination of Bemcentinib, chemotherapy, and checkpoint inhibition

In *in vivo* syngeneic mouse models of chemo-immunotherapy refractory tumor types, including those with low mutational burden or oncogenic drivers, bemcentinib potentiated the effect of immune checkpoint inhibitors in combination with chemotherapy and significantly enhanced survival (422-TR-502) (Dhakal et al., 2022). A recent paper showed that bemcentinib in combination with immune checkpoint therapy and chemotherapy produced the best anti-tumor effect in mouse models of lung adenocarcinoma and lung 1 cell carcinoma (Lee et al., 2022).

For more details on the nonclinical data, refer to the bemcentinib Investigator's brochure (IB) for a compilation of clinical and nonclinical data including pharmacokinetics (PK).

2.2.3 Overview of Clinical Studies

To date, three company-Sponsored clinical studies have been completed - a phase 1 (BGBC001) study in healthy volunteers, a phase 1/2 study in NSCLC (BGBC004) and a study (BGBC020) evaluating bemcentinib plus standard of care in subjects hospitalized with COVID-19.

Previous and ongoing studies with bemcentinib, used a fasted dose of bemcentinib of 400 mg loading dose and 200 mg maintenance dose.

A phase 1 food and gastric effect study (BGBC018) has completed patient recruitment and has concluded and is in the final stages of reporting.

Two phase 1b/2 company-Sponsored clinical studies (BGBC003 [NCT02488408] and BGBC008 [NCT03184571]) are currently ongoing in subjects with advanced cancers.

One phase 2 clinical study (BGBC007 [NCT03184558]) evaluating bemcentinib in combination with pembrolizumab in patients with TNBC was terminated due to predefined futility.

A further five Investigator-led studies (ILS) in the oncology setting are ongoing (BGBIL005 [NCT02922777], BGBIL006 [NCT02872259], BGBIL010, BGBIL011 [NCT03654833], and BGBIL013 [NCT03965494]) and two studies (BGBIL009 and BGBIL019) have the clinical study report (CSR) under preparation (studies in advanced cancer and COVID-19). The ILS BGBIL006 is enrolling subjects with advanced non-resectable (Stage IIIc) or metastatic (Stage IV) melanoma. ILS BGBIL011 (mesothelioma stratified therapy [MiST]) is enrolling subjects with relapsed malignant mesothelioma, and ILS BGBIL013 is enrolling subjects with recurrent glioblastoma. The ILS BGBIL009 (NCT03824080) has enrolled subjects with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) that fail or are refractory to hypomethylating agent treatment (Gadgeel et al., 2020).

The ILS BGBIL005 has enrolled subjects with previously treated advanced NSCLC and BGBIL010 has enrolled subjects with metastatic or recurrent pancreatic adenocarcinoma.

There is also one ILS (BGBIL019), evaluating bemcentinib plus SOC in patients hospitalized with COVID-19 for which the final CSR is being developed.

Preliminary data from the ongoing phase 2 combination clinical study with pembrolizumab in previously treated NSCLC (BGBC008) is presented in Section 2.1.

2.2.3.1 Exposure and Safety Evaluation

As per the cut-off date of 30 July 2022, 61 healthy subjects and 630 patients (AML, MDS, NSCLC, TNBC, melanoma, pancreatic cancer, glioblastoma, and COVID-19) have been included in the studies and 543 subjects in total have been dosed with bemcentinib in the seven company-Sponsored (BGBC001, BGBC003, BGBC004, BGBC007, BGBC008, BGBC018, and BGBC020; 405 patients included/348 patients dosed) and the seven Investigator-led (BGBIL005, BGBIL006, BGBIL009, BGBIL010, BGBIL011, BGBIL013, and BGBIL019; 225 patients included/195 patients dosed) clinical studies (NCT numbers are provided in Section 2.2.3).

Overall, the most commonly reported treatment emergent AEs were diarrhea (38.4%), nausea (27.2%), and fatigue (23.8%). A total of 13 deaths were reported (12 in the company-Sponsored bemcentinib clinical studies and 1 in the ILS) between 31 July 2021 and 30 July 2022. Of the 12 deaths reported in the company-Sponsored studies, one occurred in clinical study BGBC003 (cause of death was unknown but possibly due to an infarction), 11 occurred in clinical study BGBC008. The one death reported in the ILS occurred in BGBIL010. The cause of death was not provided.

In the company-Sponsored bemcentinib clinical studies up to the cut-off date, 52 deaths have been reported in the safety database as a result of serious AEs (SAEs). A comprehensive review of all deaths did not show any trends and the majority of the deaths were attributable to the disease under study.

In the ILSs, 22 subjects have died due to SAEs (2 in BGBIL005, 3 in BGBIL006, 15 in BGBIL009, 1 in BGBIL010, and 1 in BGBIL013). Two deaths, one in BGBIL009 and another in BGBIL010 were assessed as related to study treatment. In total four deaths were assessed to be related to bemcentinib across all company-Sponsored and Investigator-led clinical studies.

2.2.3.2 Safety Parameters

Overall, 106 patients in clinical studies BGBC003, BGBC004, BGBC007, and BGBC008 were reported to have 195 events of QTcF (QT interval corrected for heart rate using Fridericia's formula) prolongation, the majority of which were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 or not assessed as clinically significant. None of the patients experienced Grade 4 QTcF prolongation. It is of note the majority of the raised QTcF events were findings on scheduled electrocardiograms (ECGs). It is also important to note that there have been no cases of fatal arrhythmias reported in the bemcentinib development program to date.

Low levels of magnesium (hypomagnesemia) were seen in a high proportion of patients in study BGBC008 (79.5% in Cohort A, 65.5% in Cohort B and 45.0% in Cohort C), however, it should be noted that the magnesium levels were elevated at baseline in most patients.

Liver toxicity/elevated liver function test (LFT) were commonly reported events with the combination treatment of bemcentinib and pembrolizumab. Events of liver toxicity/elevated LFTs were reversible, and all events resolved when treated with corticosteroids. Most cases were reported as elevation of ALT and AST with normal bilirubin. Diagnoses of hepatotoxicity/immune hepatitis were made based on exclusion and none of the cases had confirmed liver damage from liver biopsies. Enhanced

monitoring of LFTs in the BGBC008 clinical study resulted in a reduction of the severity of the AEs reported with only a small number of patients reporting Grade 3 or Grade 4 liver-related AEs.

Preliminary safety data from the BGBC008 clinical study show that the combination treatment of bemcentinib (400 mg loading dose for 3 days followed by 200 mg daily as a maintenance dose) and pembrolizumab (200 mg every 3 weeks) in 2L NSCLC subjects had a favorable safety profile.

There are several key safety events such as changes to liver enzymes and QTcF intervals that will be monitored closely in this clinical study to better characterize the risk-benefit profile of bemcentinib.

2.2.4 Chemo-immunotherapy

In patients without targetable genetic alteration and no contraindication to the use of PD-1/PD-L1 inhibitors, immunotherapy, either as monotherapy or in combination, has become the SOC in the front-line setting for advanced squamous and non-squamous lung cancer (Ettinger et al., 2022).

Pembrolizumab has demonstrated superior efficacy versus chemotherapy in untreated Stage IV NSCLC patients enrolled in KEYNOTE-024, a phase 3 randomized clinical study comparing single agent pembrolizumab against platinum chemotherapy. In this clinical study, patients with tumors expressing PDL-1 tumor proportion score (TPS) >50% demonstrated superior response rate with pembrolizumab monotherapy over chemotherapy (44.8% vs 27.8%, respectively), and OS (mOS 30.0 months vs 14.2 months, respectively) (Reck et al., 2016).

In KEYNOTE-189, a phase 3 clinical study in patients with non-squamous NSCLC regardless of TPS, study subjects were randomized to cisplatin or carboplatin plus pemetrexed with pembrolizumab or placebo followed by pemetrexed and pembrolizumab or placebo maintenance therapy (Gandhi et al., 2018). Overall survival was superior in the chemo-immunotherapy group for all subgroups of PD-L1 TPS, including patients with a score of less than 1%, a population for which single agent PD-1 and PD-L1 inhibition has a small benefit rate. In a recent update (Gray et al., 2021) the 4-year follow-up data from KEYNOTE-189 confirmed the superiority of the pembrolizumab-based combination. The median (95% CI) OS was 22.0 (19.5–24.5) months with pembrolizumab plus pemetrexed-platinum vs 10.6 (8.7–13.6) months with placebo plus pemetrexed-platinum (hazard ratio [HR], 0.60; 95% CI, 0.50–0.72). The 3–year OS rate was 31.3% vs 17.4% with a median (95% CI) PFS of 9.0 (8.1–10.4) months vs 4.9 (4.7–5.5) months, respectively (HR,0.50; 95% CI, 0.41–0.59).

Based on the benefit observed in KEYNOTE-189, the combination of pembrolizumab plus platinum and pemetrexed is recommended in the international guidelines (i.e. European Society for Medical Oncology [ESMO], American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Network [NCCN]) for the treatment of patients with previously untreated metastatic non-squamous NSCLC without sensitizing EGFR/ALK alterations, irrespective of PD-L1 expression (Planchard et al., 2018, Planchard et al., 2020; Gadgeel et al., 2020; NCCN, 2022).

2.3 Bemcentinib Benefit-Risk Assessment

Based on the emerging data (cut-off date of 30 July 2022), with 604 subjects exposed to bemcentinib either as monotherapy or in combination with other anticancer agents as discussed in Section 2.2.3, as well as the nonclinical toxicological and pharmacological

safety, the benefit-risk ratio is considered favorable and supports the development of bemcentinib for the treatment of cancers where there are limited treatment options or short life expectancy.

Bemcentinib is a selective tyrosine kinase AXL inhibitor and there is a known class effect in relation to prolongation of QT/QTc. In the studies conducted so far, the majority of QT/QTcF prolongations were CTCAE Grade 1 or 2 or not assessed as clinically significant, identified during screening. None of the patients experienced Grade 4 QTcF prolongation. There have been no cases of fatal arrhythmias reported in the bemcentinib development program to date. The treatments that are given in combination with bemcentinib, pembrolizumab, pemetrexed, and carboplatin, are all well-known anti-neoplastic drugs that are widely used since many years, in different indications. New combinations always add a risk of synergetic effects to the safety profile of the individual drugs. Out of the 604 subjects exposed to bemcentinib, 160 subjects with lung cancer have been treated with bemcentinib in combination with either pembrolizumab, targeted therapy (erlotinib) or chemotherapy (docetaxel). The combination with pembrolizumab showed an increased incidence of liver-related events compared to monotherapy with bemcentinib or pembrolizumab alone. However, all reported events responded well to treatment with steroids and were reversible. There were no reports of increased incidence of QT/QTcF prolongation with any NSCLC combination compared to bemcentinib monotherapy.

Appropriate measures have been incorporated into this clinical study to safeguard subjects from potential risks and to closely monitor each subject throughout the clinical study, such as:

- Close monitoring of subjects during the treatment period with 4 visits during the first treatment cycle as described in Table 11.
- Exclusion of subjects with pre-existing cardiac conditions due to the potential risk associated with bemcentinib administration of prolongation of cardiac ventricular repolarization. Mitigation strategies such as: cardiac exclusion criteria (i.e. screening ECG with a mean QTcF interval ≤470ms [for women] and ≤450 ms [for men]), specific monitoring requirements which includes ECG in triplicate, and instructions concerning dose modification if QTcF prolongation is observed, have been incorporated.
- Diarrhea is a commonly reported event during bemcentinib treatment. All patients participating in the clinical study will be made aware of this potential reaction and will be instructed to contact their treating center at the first sign of increased stool frequency. Early treatment with loperamide or another anti-diarrheal agent is recommended.
- Measures in the clinical study to address the risk of elevated LFTs include:
    - Frequent monitoring of LFTs to enable the treating physician to identify any deterioration at an early stage and take appropriate action.
    - Inclusion criteria to only allow participation of subjects with adequate hepatic function defined as:
        - Total bilirubin <1.5 ×ULN (<3 x ULN for participants with liver metastases).
        - AST (serum glutamic oxaloacetic transaminase [SGOT]) (AST [SGOT]) and ALT (serum glutamic pyruvic transaminase [SGPT]) <2.5 × ULN (<5 × ULN for participants with liver metastases).

- Dose modification guidance of bemcentinib for potential toxicities, Section 6.7.

For inclusion of elderly subjects, the benefit/risk is also considered favorable. Inclusion of patients ≥65 years is based on emerging safety information from previous and ongoing studies, the thorough baseline/screening inclusion/exclusion criteria and safety monitoring in place for the study.

Altogether, the risks associated with participating in this clinical study are considered to be outweighed by the potential clinical benefit for untreated advanced or metastatic non-squamous NSCLC patients enrolled in the clinical study.

3 OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary objectives	**Primary endpoints**
Phase 1b To determine the safety and tolerability of the combination of bemcentinib with CIT to identify the RP2D when administered as 1L treatment in subjects with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC with no actionable mutations.	**Phase 1b** • The incidence of DLTs during a 21-day assessment period in treatment cycle 1 (i.e. the first 21 days from Cycle 1 Day 1 [C1D1] for each subject).
Phase 2a To determine the anti-tumor activity of the combination of bemcentinib with CIT when administered as 1L treatment in subjects with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC with STK11 mutation and no actionable mutations.	**Phase 2a** • ORR (complete response and partial response per RECIST 1.1) (Eisenhauer et al., 2009) at 6 and 12 months.
Secondary objectives	**Secondary endpoints**
Phase 1b To assess the anti-tumor activity of the combination of bemcentinib with CIT when administered as 1L treatment in subjects with locally advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC with no actionable mutations.	**Phase 1b** • ORR (complete response and partial response per RECIST 1.1). • Disease control rate (DCR) (complete response, partial response, and stable disease per RECIST 1.1). • Duration of response (DOR) Time of first response to progressive disease as assessed per RECIST 1.1). • OS.
Phase 2a To further assess the anti-tumor activity as well as the safety and pharmacokinetic profile of the combination bemcentinib with CIT when administered as 1L treatment in subjects with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC with STK11 mutation and no actionable mutations.	**Phase 2a** • The frequency and percentage of AEs; assessment of safety laboratory parameters, vital signs, and ECGs per CTCAE. • DCR (complete response, partial response, and stable disease). • DOR. • PFS. • Time to progression. • Overall survival. • PK exposure (C_{max}, AUC, and $t_{½}$).
Explorative	
Exploratory objectives To assess the association between biomarkers and response and/or immune status.	**Exploratory endpoints** Correlation between biomarker signatures and response and/or immune status by way of genomic, transcriptomic and protein analyses.

Abbreviations: 1L=first line; AE=adverse event; C1D1=Cycle1 Day1; CIT=Chemo-immunotherapy; DCR=disease control rate; DLT=dose limiting toxicity; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression free survival; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended phase 2 dose.

The analysis of all endpoints is described in Section 9.4.

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, multi-center, phase 1b/2a clinical study to assess the safety, tolerability, and preliminary anti-tumor activity of bemcentinib in combination with CIT comprising pembrolizumab plus pemetrexed and carboplatin as 1L treatment in subjects with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC without actionable mutations, irrespective of PD-L1 status, with or without STK11m depending on the study phase.

All subjects will receive bemcentinib once daily in combination with CIT, which is administered on Day 1 of each 21-day treatment cycle.

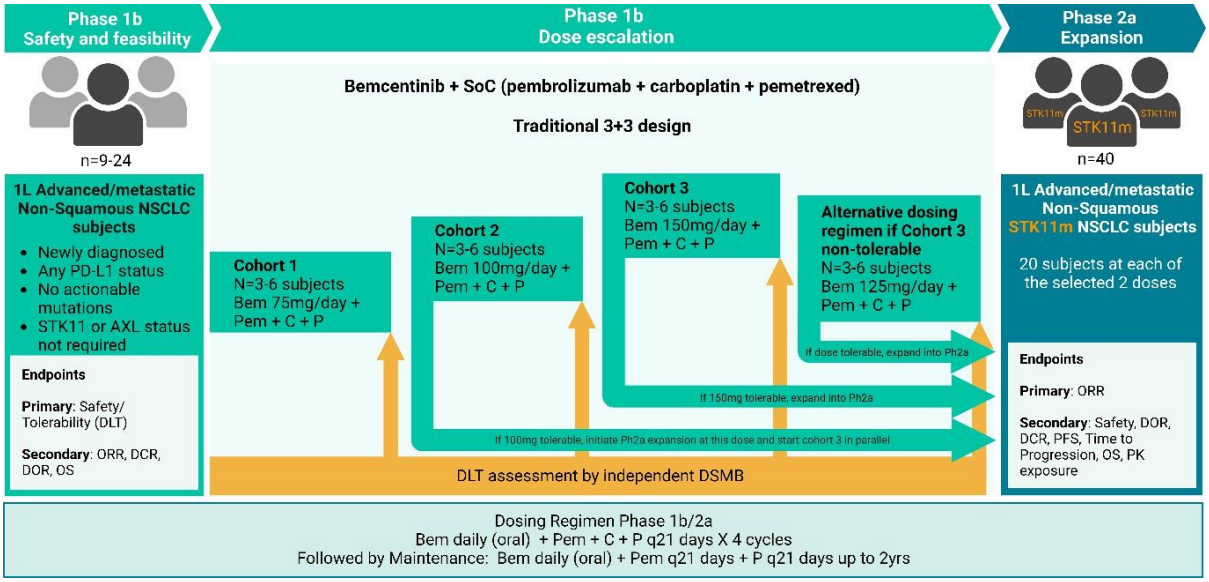
- **Phase 1b:** Previously untreated locally advanced (Stage IIIb/IIIc)/metastatic (Stage IV) non-squamous NSCLC without actionable mutations.
- **Phase 2a:** Previously untreated advanced (Stage IIIb/IIIc)/metastatic (Stage IV) non-squamous NSCLC having a serine/threonine kinase 11 (STK11) mutation as identified by NGS and without actionable mutations.

A schema of the study design is provided in Figure 1. A schedule of all study visits and procedures is provided in Table 11 and all study-related assessments are described in Section 8.

Phase 1b follows a standard 3+3 design: 3 subjects will receive bemcentinib + CIT at one of 3 dose levels: Cohort 1=75 mg daily dose of bemcentinib; Cohort 2=100 mg daily dose of bemcentinib; or Cohort 3=150 mg daily dose of bemcentinib. An alternative dose level, i.e., Cohort 4, 125 mg, will be added in case of unacceptable toxicities in Cohort 3. An independent data safety monitoring board (DSMB) will be responsible for reviewing the safety data from each cohort at the end of the dose limiting toxicity (DLT) assessment period of each cohort and will provide recommendations to the Sponsor on dose cohort management. Further, based on overall tolerability, the DSMB will recommend the bemcentinib dose for the phase 2a expansion cohort.

Subjects will take bemcentinib capsules daily and will continue until a reason for discontinuation has been met (see Section 7 for reasons for discontinuation) or for up to 2 years, whichever occur first. Subjects will receive CIT on Day 1 of each 21-day treatment cycle for a maximum of 4 cycles. After completion of the 4 cycles of CIT, subjects will receive maintenance bemcentinib, pembrolizumab, and pemetrexed for up to 2 years. Any subjects still ongoing at 2 years after the start of treatment who continue to derive clinical benefit from the treatment, will be offered access to bemcentinib via an alternative access program or study (not applicable in France).

Figure 1 Overall Study Design



Abbreviations: 1L=first line; Bem=bemcentinib; C=carboplatin; DC=doublet chemotherapy; DCR=disease control rate; DLT=dose limiting toxicity; DOR=duration of response; DSMB=data safety monitoring board; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; Pem=pembrolizumab; P=pemetrexed; PFS=progression free survival; PK=pharmacokinetics; SOC=standard of care.

The primary endpoint for phase 1b will be assessed after the first 21 days from C1D1 for each subject. To be DLT-evaluable, the subject must have received at least 80% of the bemcentinib dose (at least 17 of 21 days, with no more than 2 consecutive days of dosing missed) and completed evaluation for DLT in Cycle 1 or developed DLT during Cycle 1.

The primary endpoint for phase 2a of the study is the ORR calculated from start of treatment (C1D1) to confirmation of response per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 at 6 and 12 months.

In the phase 2a expansion there will be an interim analysis after 20 study subjects have completed 2 treatment cycles (no earlier than Day 42) with the purpose of identifying potential early efficacy signals.

The clinical study consists of a screening period (up to 28 days), a treatment period (up to 24 months), a post-treatment safety follow-up period (30 days) and a survival follow-up phase for at least 2 years. For each subject, the expected duration of the clinical study when visits to the clinic are needed will be no more than 26 months. After the safety follow-up period and final study visit all subjects will be followed at ≤3-monthly intervals to confirm their survival status following the final study visit until death unless they withdraw consent or are lost to follow-up, see Figure 2 and Figure 3.

4.2 Number of Subjects

For phase 1b of the clinical study, 9 to 24 DLT-evaluable subjects (defined as subjects who have received at least 80% of the bemcentinib dose [at least 17 of 21 days, with no more than 2 consecutive days of dosing missed] and completed evaluation for DLT in Cycle 1 or developed DLT during Cycle 1) will be enrolled.

For phase 2a of the clinical study, 40 efficacy-evaluable subjects (defined as subjects who do not discontinue study medication or withdraw from the clinical study before a post-baseline disease assessment has been completed) will be enrolled.

Assuming a 30% screening failure rate, approximately 92 subjects will be screened to achieve the planned 64 evaluable subjects.

4.3 Study Flow

Screening period:
The screening period (Day -28 to -1) has a maximum of 28 days and includes a single screening visit.

Treatment period
Following the screening period, eligible subjects will enter the open cohort:

Phase 1b

- Cohort 1: Bemcentinib 75 mg daily dose + CIT.
- Cohort 2: Bemcentinib 100 mg daily dose + CIT.
- Cohort 3: Bemcentinib 150 mg daily dose + CIT.
- Alternative dose level: Cohort 4: Bemcentinib 125 mg daily dose + CIT.

Phase 2a

- Expansion cohort(s) at the recommended dose(s).

The phase 2a expansion part of the study implements the dose(s) selected according to the methodology described in Figure 1. The selected dose(s) recommended for phase 2a will be the Maximum Tolerated Dose (MTD), (defined as the highest dose of a drug or treatment that does not cause unacceptable side effects), and, if applicable, the MTD-1 dose, i.e., the dose level below MTD.

The treatment period will continue for up to 24 months or until disease progression, withdrawal of consent, pregnancy, or introduction of other anticancer therapy. Any subjects still ongoing at 2 years after the start of treatment who continue to derive clinical benefit from the treatment, will be offered access to bemcentinib via an alternative access program or study (not applicable in France).

Subjects who discontinue bemcentinib (for reasons other than disease progression) may continue CIT treatment, on study, for PFS follow-up see Figure 3, if this is considered in the best interest of the subject, as determined by the Investigator. The subject should continue according to the Flowchart of visits and assessments with the exception of ECGs. Once the subject is off bemcentinib treatment, one more ECG will be performed, at the next visit.

The CIT treatment regimen is detailed in Section 6.1.2.

Dose modifications will follow the standard guidelines for this regimen and will include dose reductions of bemcentinib for specified events (e.g., QTc events and liver function abnormalities). The dose reduction (and/or interruption or discontinuation) of bemcentinib will need to be performed as per guidance in the respective dose modification tables for toxicity, Section 6.7.

Safety follow-up period
All subjects will enter a safety follow-up period after bemcentinib discontinuation. The safety follow-up visit will occur 30 days after the last dose of bemcentinib, regardless of whether CIT is ongoing at that stage.

Disease progression follow-up

Subjects who discontinue any of the 4 drugs in the treatment combination (but not all) for reasons other than "disease progression", will continue to be followed up as described in Section 7.1 until disease progression, initiation of subsequent antineoplastic therapy, withdrawal of consent, death, or study closure, whichever occurs first.

Survival follow-up

All subjects will be followed for survival for at least 2 years or until withdrawal of consent, lost to follow-up, or death, whichever occurs first. The survival status should be assessed every third month by the method of choice of the Investigator, e.g., telephone contact or assessing the medical or official records, according to local practice.

Patients lost to follow-up should be recorded as such on the electronic case report form (eCRF). For patients who are lost to follow-up, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient (e.g., dates of telephone calls, registered letters, etc.).

Figure 2 Study flow for subject discontinuing CIT before or at the same time as bemcentinib

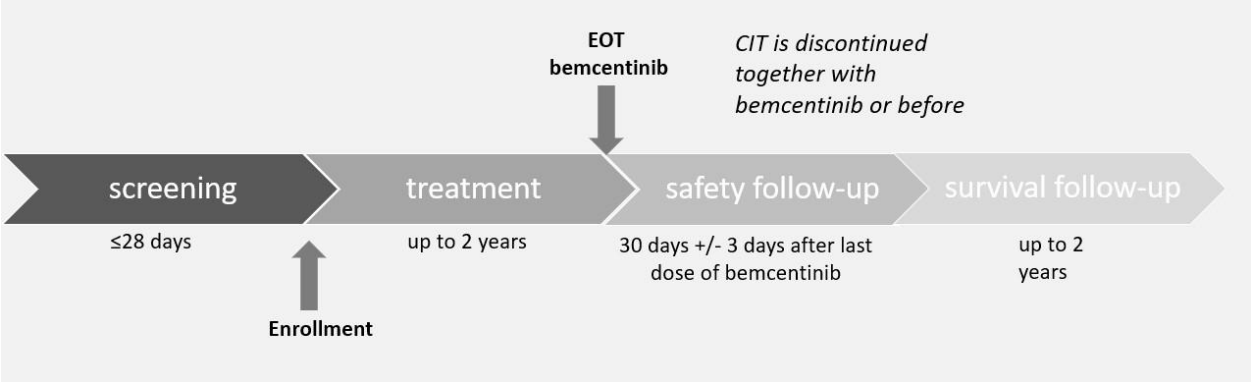
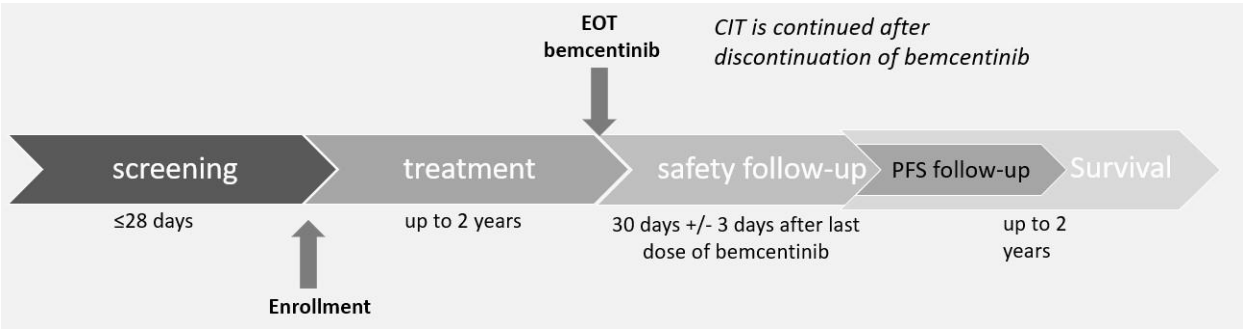


Figure 3 Study flow for subject continuing CIT after End of Treatment (EoT); PFS follow-up



All subsequent therapies should be recorded in the eCRF if the subject receives further treatment for NSCLC following the end of study visit.

4.4 Definition of the End of Study

- The overall End of Study and study closure is defined in Section 4.8.
- For the individual subject, the study is considered completed when all phases of the clinical study including the Safety follow-up and the Survival follow-up phases are completed or until withdrawal of consent, lost to follow-up or death, whichever occurs first.

4.5 Scientific Rationale for Study Design

The rationale for the clinical study is provided in Section 2.1. An uncontrolled, open-label design is chosen, as the purpose of the clinical study is to evaluate the safety and tolerability of bemcentinib in combination with CIT as 1L treatment in subjects with advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC with no actionable mutations The design is regarded as scientifically justified and adheres to the ethical standards ensuring the rights, safety, and wellbeing of the subjects.

The rationale for the CIT combination treatment is provided in Section 6.1.2.

The combination of pembrolizumab plus pemetrexed and carboplatin has not previously been used in conjunction with bemcentinib in subjects (in any indication) and therefore a dose escalation design was chosen for the phase 1b part of the clinical study.

4.6 Ethical considerations

Children, women who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled in the clinical study. To participate in the clinical study, subjects (both male and female) of reproductive potential must be willing to practice highly effective methods of contraception throughout the clinical study and for an additional 4 months after the last dose of pembrolizumab, 6 months after the last dose of chemotherapeutic agents or 30 days after the last dose of bemcentinib whichever is the later. In addition, women of childbearing potential will have a pregnancy test done before, during, and after end-of treatment to ensure no fetuses are exposed to bemcentinib.

In this clinical study, subjects will be treated with bemcentinib in addition to CIT. If subjects discontinue bemcentinib, they may continue CIT treatment at the discretion of the Investigator and hence will not be deprived from effective therapy.

In accordance with the current version of the ICH-GCP guidelines, qualified medical personnel employed by Sponsor will be readily available to advise on study-related medical questions. Medical monitoring will be performed throughout the clinical study and safety data will be reviewed regularly by medically qualified staff by the Sponsor or designee to ensure that prompt action is taken, if needed, to maximize the safety of study subjects. Furthermore, an independent DSMB will be responsible for reviewing the safety data from each cohort and will provide recommendations to the Sponsor on the dose cohort management and recommend dose for the expansion cohort.

4.7 Justification for Dose

4.7.1 Rationale for Bemcentinib Dose and Schedule Selection

The selection of the planned doses for the phase 1b/2a clinical study in 1L NSCLC patients has been centered around achieving a concentration at the target site that would engage and inhibit the biological target AXL with an acceptable benefit-risk profile. Bemcentinib is a competitive, reversible inhibitor of AXL with a Ki of 6 nM and a short

residence time of approximately 2 mins, so the minimum effective concentration to achieve [redacted] occupancy is approximately 24 nM, which is equivalent to a plasma total concentration of [redacted].

A preliminary population PK model for bemcentinib has been developed from PK data derived from healthy- and oncology-subjects. The full dataset included 281 individual subjects (31 healthy subjects and 250 subjects with solid tumors and myeloid malignancies) containing 4149 PK sample results. This evaluation was based on single doses of bemcentinib of up to [redacted] in healthy subjects (C_{max} range of [redacted]) and repeat doses of up to [redacted] in oncology subjects with C_{max} range of [redacted], all dosed in a fasted state. The PK variability was found to be [redacted] in the fasted state.

Data generated from a food and gastric pH study (BGBC018) indicate that the C_{max} and AUC are increased by [redacted] in the presence of food, whereas the variability in PK exposure was reduced by [redacted].

Bemcentinib is a selective tyrosine kinase AXL inhibitor and there is a known class effect in relation to prolongation of QT/QTc. As a result of the known class effect the Sponsor has conducted extensive modelling of the relationship between exposure and QT/QTc change by using PK and ECG data from 59 healthy subjects and over 149 patients. It is understood that the QT/QTc change as measured by the 90% CI will start to change at or around [redacted]. The Grade 3 AE incidence of QTcF following a loading dose of [redacted] for 3 days followed by [redacted] of bemcentinib in monotherapy was found to be [redacted], a reflection of the high variability in PK exposures in the fasted state.

The increased exposure of bemcentinib ([redacted]) and reduced PK variability ([redacted]) when given with food provides the opportunity to generate exposures of bemcentinib similar to those generated in the fasted state at higher doses (approximately [redacted] seen with the 400 mg loading/200 mg maintenance dose) but with reduced potential to cause QT/QTc prolongation.

The modelled C_{av} at steady state generated by the doses of 75 mg, 100 mg, and 150 mg will be [redacted], respectively when dosed in the fed state. The pharmacokinetic-pharmacodynamic (PK-PD) analysis exploring the relationship of bemcentinib exposure with QTc change indicates that the concentrations of [redacted] and [redacted] will produce a D-QT/QTc change of 19ms and 29ms, respectively, based on a 90% CI calculation.

Bemcentinib has been safely dosed in combination with chemotherapies as well as immune-checkpoint inhibitors at multiple doses up to 400 mg loading for 3 days followed by 200 mg maintenance. As this is the first time bemcentinib is being dosed in combination with pembrolizumab plus the chemotherapy doublet pemetrexed and carboplatin, the initial dose of bemcentinib in the phase 1b will be at a daily dose of 75 mg followed by a stepwise increase in dose utilizing a 3+3 approach to assess the safety of the combination. There will be no loading dose employed in this clinical study, in order to reduce any early potential AEs when combining bemcentinib with pembrolizumab plus pemetrexed and carboplatin. As bemcentinib will be dosed chronically in the 1L setting, it is not believed that the efficacy of bemcentinib (achievement of primary endpoints in phase 2a and secondary endpoints in phase 1b) will be affected by dropping the loading dose from the dosing regimen. A loading dose was originally used in prior bemcentinib clinical studies as bemcentinib has a long elimination half-life (steady state concentrations will be reached in 14 days when dosed without loading dose in this clinical study as opposed to 10 days with the loading dose).

4.7.2 Rationale for Chemo-Immunotherapy Dose

The US Food and Drug Administration (FDA)/EMA approved combination of pembrolizumab with pemetrexed and platinum as 1L treatment of patients with metastatic, non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations, has become the SOC.

Clinical benefit of the combination was demonstrated by the KEYNOTE-189 clinical study (Gandhi et al., 2018) and the dosing regimen in the present clinical study is based on this.

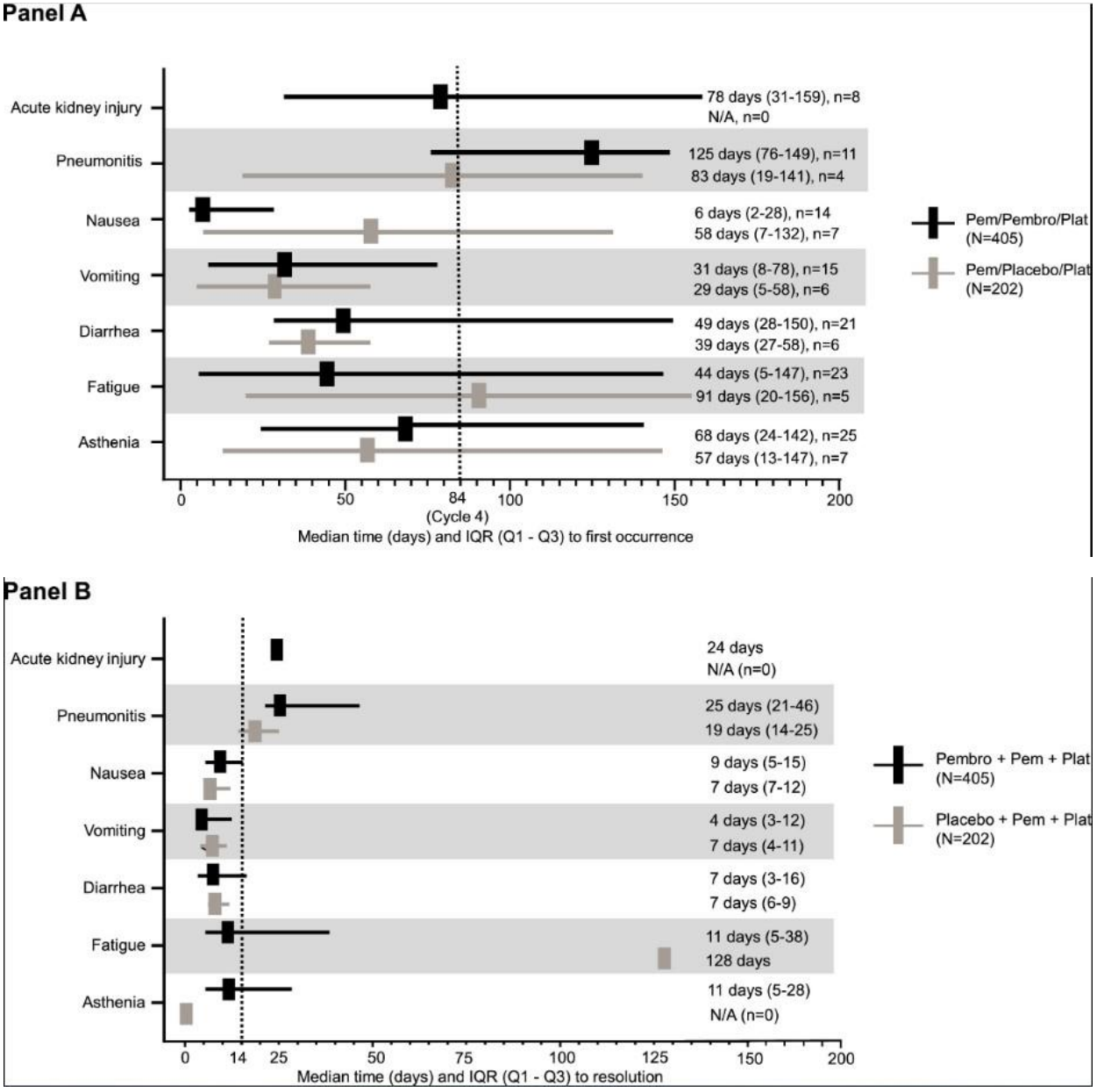
See Section 6.1.2 for a rationale using this CIT combination of medicinal products in the clinical study.

All subjects will receive a) pembrolizumab at 200 mg Day 1 intravenous (IV); b) pemetrexed 500 mg/m^2 body surface area (BSA) IV Day 1 and c) carboplatin (area under the concentration– time curve, 5 mg per milliliter per minute) IV after completion of the pemetrexed IV infusion Day 1 of a 21-day treatment cycle for a maximum of 4 cycles.

The safety of the combination of pemetrexed and platinum-based chemotherapy with pembrolizumab in 405 NSCLC patients was presented as a post-hoc analysis of the KEYNOTE-189 clinical study (Garon et al., 2021). A total of 334/405 (82.5%) subjects completed all 4 cycles of platinum-based chemotherapy. In summary, AEs Grade >3 were reported in 272 patients (67.2%) with non-hematological AEs (nausea, vomiting, diarrhea, and asthenia) having a median time-to-onset within the first 4 cycles of treatment and a median time to resolution of <2 weeks (Figure 4). Thirty-seven patients (9%) discontinued pemetrexed or pembrolizumab during the first 4 cycles and 31 (7.7%) of patients required platinum treatment discontinuation.

It was concluded that the KEYNOTE-189 regimen is safe to use in clinical practice.

Figure 4 Non-Hematologic Grade ≥3 AEs pembrolizumab/platinum



Time-to-Onset (Panel A) and Time-to-Resolution (Panel B) of Non-Hematologic Grade ≥3 AEs that Occurred in ≥2 % of the All-Subjects-as Treated Population. Source: Garon et al., 2021

Abbreviations: IQR=interquartile range; N/A=not applicable; Pem=pemetrexed; Pembro=pembrolizumab; Plat=platinum, Q1=quartile 1; Q3=quartile 3.

4.8 End of Study and Study Closure Definition

- **End of study** is defined by the date of Last Subject Last Visit (LPLV) including the survival follow-up phase.
- **Study closure** is defined by end of study and occurs when the database is locked and the CSR has been produced (excluding any CSR addendum).

5 STUDY POPULATION

In order to be eligible for this clinical study, the subjects must meet ALL the inclusion and NONE of the exclusion criteria as detailed below.

5.1 Inclusion Criteria

To participate in this clinical study, the subject must fulfil ALL the below inclusion criteria:

1. The subject (or legally acceptable representative, if applicable) must provide written informed consent for the study prior to any screening procedures.
2. Be ≥18 years of age on the day of signing the informed consent.
3. Have a histologically- or cytologically-confirmed diagnosis of advanced (Stage IIIb/IIIc) or metastatic (Stage IV) (AJCC Edition 8) non-squamous NSCLC not amenable to curative therapy, irrespective of PD-L1 status and without actionable mutations **(phase 1b).**
4. Have a histologically- or cytologically-confirmed diagnosis of advanced (Stage IIIb/IIIC) or metastatic (Stage IV) (AJCC Edition 8) non-squamous NSCLC with STK11m, not amenable to curative therapy, irrespective of PD-L1 status and without actionable mutations (**phase 2a**).
5. Participants who received prior neo-adjuvant or adjuvant/consolidation treatment (radiotherapy, chemotherapy, immunotherapy) or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months since the last dose of chemotherapy, immunotherapy and/or radiotherapy before enrollment.
6. Have measurable disease per RECIST 1.1 as assessed by the Investigator. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Have diagnostic/archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks and/or slides with tumor will be requested. In the absence of adequate tumor material from the FFPE diagnostic block, fresh tissue biopsies will be requested. If it is not feasible to obtain a fresh biopsy, discuss with the Sponsor prior to excluding the subject from the study.
   Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the laboratory manual).
8. Subjects (both male and female) of reproductive potential must be willing to practice highly effective methods of contraception throughout the clinical study and for 4 months after the last dose of pembrolizumab, 6 months after the last dose of chemotherapeutic agents or 30 days after the last dose of bemcentinib, whichever is later.
9. A female subject is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
   a. Note a woman of childbearing potential (WOCBP) if they have a history of surgical sterility (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or evidence of post-menopausal status (no menses for 12 months without any alternative medical cause – Follicle Stimulating

Hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy).

b. A WOCBP must have a negative urine or serum pregnancy test within 72 hours prior to the first dose of study treatment. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
11. Have a life expectancy of at least 3 months.
12. Be able to swallow and tolerate oral medication.
13. Have a screening 12-lead ECG (in triplicate) with a mean QTcF interval ≤470 ms (for women) and ≤450 ms (for men).
14. Have adequate organ function as defined in the table overleaf.

System	Laboratory value
Hematological	
Absolute neutrophil count	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Measured or calculated[2] creatinine clearance (eGFR can also be used in place of creatinine or CrCl)	Calculated creatinine clearance ≥45 mL/min (by Cockcroft Gault formula)
Hepatic	
Total bilirubin	<1.5 × ULN (<3 x ULN for subjects with liver metastases)
AST (SGOT) and ALT (SGPT)	<2.5 × ULN (<5 × ULN for subjects with liver metastases)
Coagulation (Optional)	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=creatinine clearance; DLT=dose limiting toxicity; DSMB=data safety monitoring board; GFR=glomerular filtration rate; PT=prothrombin time; ULN=upper limit of normal.

[1]Criteria must be met without packed red blood cell transfusion within one week of screening. Subjects can be on stable dose of erythropoietin (≥approximately 3 months).

[2]CrCl should be calculated by Cockcroft Gault formula.

Notes: This table includes eligibility defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Note: AST and ALT may have their limits increased in cases of liver metastases; however enrolling subjects with elevated values at baseline may be inviting DLTs, therefore this should be discussed with the DSMB.

5.2 Exclusion Criteria

A subject will not be eligible for enrollment into the clinical study if they meet ANY of the following exclusion criteria:

1. Has received any prior chemotherapy or biological therapy for advanced (Stage IIIb/IIIc) or metastatic (Stage IV) non-squamous NSCLC.
2. Has any actionable mutation that is considered targetable with first-line treatment.
3. Has a known history of prior malignancy except if the subject has undergone potentially curative therapy with no evidence of disease recurrence for 3 years since initiation of that therapy.
   Note: The time requirement for no evidence of disease for 3 years does not apply

to the NSCLC tumor for which a subject is enrolled in the clinical study. The time requirement also does not apply to subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

4. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate, provided they are radiologically stable, i.e. without evidence of progression for at least 2 weeks and have no evidence of new or enlarging brain metastases and are off steroids 7 days prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of study medication. Subjects with asymptomatic brain metastases (i.e. no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease. Subjects who have experienced an acute neurological event (e.g. intracranial or subarachnoid haemorrhage, stroke, intracranial trauma) within 6 months prior to study enrolment will be excluded.
5. History of the following cardiac conditions:
    a. Congestive cardiac failure of >Grade II severity according to the New York Heart Association (NYHA) or resistant or inadequately treated heart failure.
    b. Ischemic cardiac event including myocardial infarction prior to first dose or hospitalization for unstable angina within 3 months prior to first dose.
    c. Abnormal left ventricular ejection fraction on echocardiography or multi-gated acquisition scan (MUGA) (less than the lower limit of normal for a subject of that age at the treating institution or <45%, whichever is lower), or history of cardiomyopathy or left ventricular hypertrophy.
    d. Uncontrolled cardiac disease, including unstable angina, uncontrolled hypertension (i.e., sustained systolic blood pressure (BP) >160 mmHg or diastolic BP >90 mmHg), or need to change medication due to lack of disease control within 12 weeks prior to the provision of consent.
    e. History or presence of sustained bradycardia (≤55 bpm) or history of symptomatic bradycardia, left bundle branch block, cardiac pacemaker, significant arrhythmias or any conduction disorder within 6 months prior to dosing as defined by the need for treatment.
    f. Family history of long QTc syndrome or ventricular arrhythmias; personal history of long QTc syndrome or previous drug induced QTc prolongation of at least Grade 3 (QTc >500 ms).
    g. Presence of any other risk factors that increase the risk of QTc prolongation, specifically, hypokalemia or hypomagnesemia (if corrected the subject may be enrolled) or inadequately treated hypothyroidism (defined as thyroid stimulating hormone [TSH] below the expected range).
    h. Current treatment with any agent known to cause QT prolongation and have a risk for Torsades de pointes (TdP), which cannot be discontinued at least 5 and ½ half-lives or 2 weeks prior to the first dose of study treatment, with the exception of antiemetics (e.g. ondansetron) which may be required. Please see https://crediblemeds.org for a list of

medications with known TdP risk that need to be excluded (also included in Appendix 6).

6. Received radiation therapy for brain metastasis within 2 weeks prior to starting study treatment or has not recovered (i.e., ≤Grade 1 at baseline) from AEs due to a previous radiation therapy.
7. Major surgery within 28 days prior to start of study treatment and failure to have recovered adequately from the complications of the surgery/intervention prior to the first dose of study treatment.
   Note: Major surgery does not include procedures for insertion of venous catheters or biopsies.
8. Has had an allogeneic tissue/solid organ transplant or an allogeneic hematopoietic stem cell transplantation (alloHSCT) within the last 5 years.
   Note: Subjects who had an alloHSCT >5 years ago are eligible only if there are no symptoms of Graft vs Host Disease (GVHD).
9. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., required use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
   Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy [no >10 mg prednisolone or equivalent] for adrenal or pituitary insufficiency, etc.) or inhaled corticosteroids (e.g. for asthma) are not considered a form of systemic treatment.
10. Has a known lactose intolerance, hereditary problem of galactose intolerance, LAPP-lactase deficiency or glucose-galactose malabsorption.
11. Is currently participating and receiving another study therapy or have participated in a clinical study with an investigational medicinal agent and received study therapy or used an investigational device within 28 days or within 5 half-lives, whichever is longer, of the first dose of study treatment.
12. Subjects with known human immunodeficiency virus (HIV) infection are eligible if they have a CD4+ T cell (CD4+) counts ≥350 cells/uL; in addition, subjects on established anti-retroviral treatment for at least 4 weeks who have an HIV viral load less than 400 copies/mL prior to enrollment may also be eligible. No HIV testing is required, unless mandated by the local health authority. Subjects on atazanavir or tenofovir therapy must be excluded due to the risk of drug-drug interactions.
13. Has known active Hepatitis B infection (e.g., Hepatitis B surface antigen [HbsAg] reactive and/or detectable Hepatitis B virus [HBV] deoxyribonucleic acid [DNA] viral load) or Hepatitis C (e.g., Hepatitis C virus (HCV) ribonucleic acid [RNA] [qualitative] is detected).
    Note: Subjects with a history of hepatitis B infection are eligible provided they are HbsAg negative and have an undetectable HBV DNA viral load; Subjects with a history of hepatitis C infection are eligible provided they have no evidence of HCV RNA using a quantitative polymerase chain reaction (qPCR) test at least 6 months after completing treatment for hepatitis C infection.
14. Has received a live-virus vaccine within 30 days of treatment start.
    Note: Seasonal flu vaccines that do not contain live virus and messenger RNA (mRNA) COVID-19 vaccines are permitted.

15. Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.
16. Has an active infection requiring systemic treatment or has a bleeding tumor.
17. Existing stomach or duodenal ulcer, gastrointestinal disease affecting drug absorption (e.g. Celiac disease, Crohn's disease, etc.) or previous bowel resection which is considered clinically significant or could interfere with absorption.
18. Is unable or unwilling to take folic acid or vitamin B12 supplementation.
19. Requires vitamin K antagonists.
    Note: Factor Xa antagonists are permitted if clinically required or required to maintain the patency of venous access.
20. Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index.
21. Known severe hypersensitivity (≥Grade 3) to bemcentinib, pemetrexed, carboplatin or pembrolizumab and/or any of the excipients.
22. Has received radiation to the lung of >30 Gray within 6 months of study entry.
23. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the clinical study, interfere with the subject's participation for the full duration of the clinical study, or means it is not in the best interest of the subject to participate, in the opinion of the Investigator.
24. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the clinical study.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not eligible for participation according to inclusion/exclusion criteria. The minimal information required to be collected includes informed consent date, demography, screen failure reason(s), eligibility criteria, and any SAE. A screen failure rate of 30% is expected.

Any screen failure subject should be registered as such in the interactive response technology system (Rave RTSM) and in the eCRF.

Individuals who do not meet the criteria for participation in this clinical study (screen failure) at the end of the 28-day screening period, may be rescreened after discussion with the Medical Monitor. If the subject has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is allowed only once per subject within a 28-day window from the point of screen failure. In case of technical issues (e.g. hemolyzed or lost samples), re-sampling is allowed for the affected parameters. Rescreened subjects should be assigned the same subject number as for the initial screening.

6 TREATMENTS

6.1 Treatments Administered

6.1.1 Investigational Medicinal Product (Bemcentinib)

The Investigator must document that instructions for bemcentinib administration are given to the subject verbally and in writing at the first dispensing visit (C1D1).

Bemcentinib will be provided by Sponsor according to the details presented in Table 2.

The administration of bemcentinib is described in Section 6.1.3.

Table 2 Study Medication Provided by Sponsor

Study Medication Name	Bemcentinib (investigational medicinal product [IMP])
Dose Formulation	Size 0, Swedish Orange, HPMC capsule
Unit Dose Strengths	50 mg, 75 mg or 100 mg
Dosage Levels	75 mg, 100 mg, 125 mg, or 150 mg Daily within 4 hours of consuming food
Route of Administration	Per oral
Use	Experimental
Packaging and Labelling	The capsules are supplied in multidose 50 mL HDPE bottles, each containing 22 capsules and closed with a child-resistant, tamper-evident screw cap Each container will be labelled as required per country requirement
Storage	Stored at or below 25°C/77°F

Abbreviations: HMPC=hydroxypropyl methylcellulose; HDPE high density polyethylene

6.1.2 Investigational Medicinal Products (Europe)/Standard of Care (United States) (Pembrolizumab, Pemetrexed and Carboplatin)

The products pembrolizumab and pemetrexed have market authorizations across US, EU, and UK corresponding to the use in the study.

Pembrolizumab, pemetrexed and carboplatin will be classified as IMPs and supplied by the Sponsor in Europe and prescribed as SOC in the US through the clinical study. They will be administered according to Table 3 and further detailed in Section 6.1.3.

Carboplatin has a market authorization across US, EU, and UK for ovarian cancer and SCLC, i.e., it is not specifically authorized for the combination treatment for non-squamous NSCLC specified in the protocol. However, pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is indicated for the 1L treatment of metastatic non-squamous NSCLC in adults whose tumors have no EGFR or ALK positive mutations. The most frequently used platinum-agent in this target population is carboplatin. The combination of pembrolizumab plus platinum and pemetrexed is recommended in the international guidelines, (i.e. ESMO, ASCO, and NCCN) for the treatment of patients with previously untreated metastatic non-squamous NSCLC without sensitizing EGFR/ALK alterations, irrespective of PD-L1 expression. In the KEYNOTE-021 study, patients with advanced non-squamous NSCLC were treated with pemetrexed and carboplatin with or without pembrolizumab. Response (ORR and PFS) and OS were improved in the pembrolizumab combination versus chemotherapy,

regardless of PD-L1 status (Awad et al., 2021). These recommendations were confirmed based on data from the phase 3 KEYNOTE-189 study, where the patients treated with pembrolizumab, pemetrexed, and platinum-based chemotherapy compared with chemotherapy alone had significantly improved the survival outcomes (Gadgeel et al., 2020; NCCN, 2022; Planchard et al., 2018; Planchard et al., 2020). Most of the patients included in these trials were treated with carboplatin, and only some of them were treated with cisplatin as the platinum-containing part of the combination. Furthermore, real world data from the SEER registry also found that in practice most patients undergoing treatment for stage IV NSCLC received carboplatin, while only 4.5% of patients received cisplatin. Carboplatin is used more commonly than cisplatin because it has less non-hematologic toxicity and is easier to administer in the outpatient setting, because it does not require vigorous hydration regimens (Zhu et al., 2013). Altogether, this supports the use of carboplatin in SOC across US, EU, and UK.

Table 3 Chemo-Immunotherapy

Study Medication Name	**Pembrolizumab**	**Pemetrexed**	**Carboplatin**
Dose Formulation	Concentrate for solution for infusion	Powder or concentrate for solution for infusion	Concentrate for solution for infusion
Dosage Levels	200 mg Administration on Day 1 of each 21-day cycle prior to chemotherapy	500 mg/m^2 BSA Administration on Day 1 of each 21-day cycle	AUC5* Administration after completion of the pemetrexed infusion on Day 1 of each 21-day cycle*
Route of Administration	IV infusion	IV infusion	IV infusion
Use	CIT	CIT	CIT
Storage	As per prescribing information	As per prescribing information	As per prescribing information
Market authorization in US, EU, and UK	Keytruda® **Label: US, EU, UK** In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations	Pemetrexed **Label: US** In combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations **Label: EU, UK** In combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology	Carboplatin **Label: US** Ovarian cancer **Label: EU, UK** Ovarian cancer and SCLC

* Carboplatin dose calculated using the Calvert equation: Carboplatin dose (mg)=AUC x (CrCl +25) or a maximum of 4 cycles.
Abbreviations: BSA=body surface area; CIT=chemo-immunotherapy; CrCL=creatinine clearance; IV=intravenous

6.1.3 Treatment Regimen

Subjects will receive bemcentinib once daily at one of 3 dose levels as per cohort (see below) in combination with CIT.

Bemcentinib will be taken orally within 4 hours of consuming food. On visits when CIT and bemcentinib are given on the same day, bemcentinib must be given first and the

subject observed for 1 hour prior to administration of CIT during the first 4 administrations.

DLTs will be assessed on the first complete 21-day treatment cycle of the combination therapy.

An independent DSMB will be responsible for reviewing the safety data from each cohort at the end of the DLT assessment period of that dose level and will provide recommendations to the Sponsor on the dose cohort management.

Cohort 1: The first 3 subjects will be enrolled at 75 mg bemcentinib daily dosing.

- If 0/3 subjects experience a DLT, initiate Cohort 2.
- If 1/3 subjects experience a DLT, add 3 additional subjects at the same dose level.
- If 1/6 subjects experience a DLT, initiate Cohort 2.
- If 2/6 subjects experience a DLT, stop the clinical study.

Cohort 2: 3 subjects will be enrolled at 100 mg bemcentinib daily dosing.

- If 0/3 subjects experience a DLT, proceed to phase 2a expansion at this dose level and start Cohort 3 dose level in parallel.
- If 1/3 subjects experience a DLT, add 3 additional subjects at the same dose level.
- If 1/6 subjects experience a DLT, proceed to phase 2a expansion at this dose level and start Cohort 3 dose level in parallel.
- If 2/6 subjects experience a DLT, de-escalate to Cohort 1 dose.

Cohort 3: 3 subjects will be enrolled at 150 mg bemcentinib daily dosing.

- If 0/3 DLTs, proceed to phase 2a expansion.
- If 1/3 DLTs, add 3 additional subjects at this dose level.
- If 1/6 DLTs, proceed to phase 2a expansion with this dose level.
- If 2/6 DLTs, start alternative dosing regimen.

Cohort 4: Alternative dose level if 2/6 experience DLTs in Cohort 3: 3 subjects will be enrolled at 125 mg bemcentinib daily dosing.

- If 0/3 DLTs, proceed to phase 2a expansion with this dose level.
- If 1/3 DLTs, add 3 additional subjects at this dose level.
- If 1/6 DLTs, proceed to phase 2a expansion with this dose level.
- If 2/6 DLTs, stop escalation.

6.1.3.1 Chemo-immunotherapy

Chemo-immunotherapy should be administered on Day 1 of each 21-day treatment cycle after all procedures and assessments have been completed. The treatment can be administered +/- 3 days of the targeted Day 1 for each cycle, except Cycle 1 where treatment can only be administered + 3 days of the targeted Day 1.

Subjects should receive CIT treatment in the following order:

- Pembrolizumab infusion over 30 minutes followed by

- Pemetrexed infusion over 10 minutes followed by
- Carboplatin infusion over 30-60 minutes.

All subjects should receive antiemetic therapy according to local guidelines for the use of pembrolizumab plus pemetrexed and carboplatin. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 to 4.

Pembrolizumab
Pembrolizumab dose of 200 mg will be administered per institutional practice on the first day of each 21-day treatment cycle.

Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (except Cycle 1, see above).

Pembrolizumab will be administered as 30-minute IV infusion every 3 weeks (Q3W). Sites should make every effort to target infusion timing to be as close to 30-minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30-minutes: -5 min/+10 min).

Pemetrexed
Pemetrexed dose of 500 mg/m^2 BSA will be administered as an IV infusion per institutional practice on the first day of each 21-day treatment cycle. Pemetrexed will be administered as an IV infusion over 10 minutes Q3W until progression or unacceptable toxicity. All subjects should receive the appropriate supplementation of vitamin B12 and folic acid as well as corticosteroid prophylaxis as listed below:

- At least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 9 weeks thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg, orally twice per day (or equivalent). Taken the day before, day of, and day after pemetrexed administration.

Carboplatin
Carboplatin AUC5 (=area under the concentration– time curve, 5 mg per milliliter per minute) will be administered per institutional practice after completion of the pemetrexed infusion on the first day of each 21-day treatment cycle for a maximum of 4 cycles.

Study subjects must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving carboplatin.

Carboplatin AUC 5 mg/mL/min will be administered as an IV infusion over 30-60 minutes Q3W for 4 cycles immediately after pemetrexed as per local practice.

6.2 Preparation/Handling/Storage/Accountability

Only subjects enrolled in the clinical study may use study medication and only delegated site staff may handle, dispense and/or administer study medication.

6.2.1 Preparation of Study Medication

6.2.1.1 Bemcentinib

Each site will be supplied with sufficient bemcentinib for the clinical study on an ongoing basis. Bemcentinib will be distributed to the sites according to screening numbers.

Bemcentinib is provided in bottles containing a specified number of capsules per bottle to dispense to the clinical study subjects. The subjects will be asked to take the specified number of capsules for their prescribed dose within 4 hours of food intake. For rescue therapy, see Section 6.5.

On visits when CIT and bemcentinib are given on the same day, bemcentinib must be given first and the subject observed for 1 hour prior to the start of CIT administration during the first 4 administrations.

6.2.1.2 Pembrolizumab, carboplatin, and pemetrexed

Pembrolizumab, carboplatin, and pemetrexed will be prepared as per institutional practice.

6.2.2 Handling and Storage

Acceptable temperature ranges and conditions for storage and handling of the IMPs (Europe [CIT and bemcentinib]/US [bemcentinib only]) are described in the pharmacy manual (Europe)/IMP manual (US).

The Sponsor will provide the IMPs (Europe)/bemcentinib (US) for each subject for the duration of their participation in the clinical study.

The Investigator, or designee will dispense bemcentinib on Day 1 of each treatment cycle. A sufficient quantity of bemcentinib will be dispensed to assure that the subject has sufficient supply to last at least until the next scheduled drug dispensing visit. The Investigator must ensure that no subject uses expired bemcentinib at any time.

Subjects will be familiarized with bemcentinib administration prior to the first administration, and as needed, at the site. The Investigator must document that instructions for use are given to the subject verbally, and in writing.

- The Investigator must confirm that appropriate temperature conditions have been maintained during transit for all IMPs (Europe)/bemcentinib (US) received, and that any discrepancies are immediately reported to the Sponsor and the IMPs (Europe)/bemcentinib (US) quarantined separately at recommended storage condition and resolved before release from quarantine and use.
- IMPs (Europe)/bemcentinib (US) must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and delegated site staff.
- The Investigator must inform the Sponsor immediately if any IMP (Europe)/bemcentinib (US) has been stored outside of the specified conditions (exposed to light or outside recommended temperature). IMPs (Europe)/bemcentinib (US) must be quarantined separately at the recommended storage condition and must not be dispensed or administered to any subject before the storage excursion has been evaluated and approved for release from quarantine and further use by Sponsor. Additional details regarding handling of temperature deviations can be found in the pharmacy manual.

6.2.3 Investigational Medicinal Products (Europe)/Bemcentinib (US) Accountability

The Investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final dispensation records). The Investigator must ensure that a designated person receives the IMPs (Europe)/bemcentinib (US) deliveries from the Sponsor or designee and that all such deliveries are:

- Recorded.
- Handled and stored safely and properly.
- Returned to Sponsor or designee, as required.

The Investigator or designee must keep drug inventory and accountability logs of which a copy must be given to the Sponsor at the end of the clinical study. An accurate record of the date and amount of IMP (Europe)/bemcentinib (US) dispensed to and returned from each subject must be available for inspection at any time. The inventory logs will include details of IMPs (Europe)/bemcentinib (US) received and dispensed to the subject. All opened and unopened bottles of bemcentinib must be kept and returned to site. The clinical research associate (CRA) will perform reconciliation of delivery records and accountability logs for all IMPs (Europe)/bemcentinib (US). Discrepancies between the amount of IMP (Europe)/bemcentinib (US) received, dispensed, and returned will be verified.

Subjects should be instructed to bring all their bemcentinib to Day 1 of each treatment cycle. Investigator or delegated staff must perform drug accountability with the subject on Day 1 of each treatment cycle.

In case the Investigator, the site staff, or the CRA suspect that any IMP (Europe)/bemcentinib (US) is defective or potentially defective, the Sponsor should be contacted immediately, and a complaint raised.

6.2.4 Return and Destruction of Investigational Medicinal Products (Europe)/Bemcentinib (US)

- Returned bemcentinib must be stored separately from non-allocated bemcentinib.
- Destruction/return of IMPs (bemcentinib and CIT [Europe]/bemcentinib [US]) (used and unused) must be approved by the Sponsor.
- At the conclusion of the clinical study (or by agreement with Sponsor during the clinical study if e.g. storage capacity at site is limited) the Investigator will return/destroy locally all used and unused IMPs (Europe)/bemcentinib (US) following authorization from the Sponsor.
- Destruction/return of bemcentinib can be performed on an ongoing basis, following authorization from the Sponsor, and will be done according to local procedures after accountability is finalized by the site and reconciled by the CRA.
- Destruction of used/expired CIT IMPs (Europe) can be performed without authorization from the Sponsor as per local procedures. Evidence of destruction and completed accountability will be reviewed by the CRA.
- All returned, un-used, expired or damaged IMPs (bemcentinib and CIT [Europe]/bemcentinib [US]) must be stored separately from non-allocated IMPs (Europe)/bemcentinib (US). No temperature monitoring is required (for technical complaint, see Section 6.2.5).

- Non-allocated IMPs (bemcentinib and CIT [Europe]/bemcentinib [US]) including expired or damaged product must be accounted as unused, at the latest at closure of the site.

6.2.5 Reporting Product Complaints

Pharmaceutical technical complaints associated with Sponsor-provided IMPs (Europe)/bemcentinib (US) must be reported to the Sponsor immediately. The same reporting timelines as for SAEs apply.

6.3 Treatment Compliance

6.3.1 Bemcentinib

- The subject will be asked to bring all bottles, including the empty ones, with them to Day 1 of each treatment cycle to check compliance and for the Drug Accountability and Dose Log to be completed in the eCRF.

6.3.2 All Clinical Study Medications

- Administration, missed doses, or failures in compliance will be recorded in the subject's file and eCRF. The subject will be instructed as to the importance of taking their bemcentinib in accordance with instructions.
- If it is discovered that an overdose has or may have been administered and the subject has experienced an adverse outcome as a consequence, the Investigator should complete the designated AE or SAE eCRF page. Expeditious handling and reporting is required.

Throughout the clinical study, the Investigator will remind the subjects to follow the study procedures and requirements to encourage subject compliance.

When subjects are dosed at the site, they will receive bemcentinib directly from the Investigator or designee, under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents.

When subjects self-administer bemcentinib at home, compliance with bemcentinib administration will be assessed and recorded in source documents at each visit where information is available. If any suspicion of non-compliance arises, apart from occasionally missed doses, the site must enter into a dialogue with the subject, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use (include at least 2 methods):

- Drug accountability information; counting returned bemcentinib.
- Questioning of subject.
- Other.

Treatment start and stop dates will be recorded in the eCRF.

6.4 Concomitant Therapy

In general, no concomitant therapy should be started before consulting with the Investigator.

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) other than bemcentinib and CIT that the subject is

receiving at the screening visit or receives during the clinical study must be recorded in the eCRF along with:

- Generic name.
- Indication.
- Dates of administration including start and stop dates.
- Additional information, such as dose and unit, frequency, start time, stop time and route of administration, should be recorded.

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 6.5. The Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

Changes in concomitant medication must be recorded at each visit. If changes occur during the clinical study period, documentation of drug dosage, frequency, route, and date may also be included on the eCRF.

If a change is due to an AE, then this must be reported according to Section 10.3.3.

6.4.1 Premedication

Anti-emetic premedication and additional supportive medication should be administered per local guidelines.

All subjects should receive premedication with folic acid, vitamin B12, and corticosteroid administered according to local guidelines for pemetrexed use.

6.5 Prohibited Medication

In general, medications or vaccinations specifically prohibited in the exclusion criteria are not allowed for the entire duration of the clinical study. Treatment with antacids, proton pump inhibitors, and histamine receptor 2 inhibitors can be initiated as rescue therapy after subjects have been receiving bemcentinib for one week, provided they are taken in the evening.

If there is a clinical indication for any medication or vaccination specifically prohibited during the clinical study, discontinuation from the clinical study may be required. The Investigator should discuss any questions regarding this with the Medical Monitor. The final decision on any supportive therapy or vaccination remains with the Investigator and/or the subject's primary physician. However, the decision to continue the subject on study medication requires the mutual agreement of the Investigator, the Sponsor, and the subject.

For easy reference, a copy of medications that carry the risks of QT prolongation and must be avoided have been included in Appendix 6. A list of prohibited medications is provided in Appendix 7.

6.6 Effects on the Ability to Drive and Use Machines

Pemetrexed can cause fatigue and carboplatin can cause acute hypersensitivity reactions with a drop in blood pressure in some subjects. Therefore, subjects must be cautioned against driving or the operation of machines if these effects occur.

6.7 Treatment Dose Modification

If appropriate, the Investigator may attribute each toxicity event to carboplatin, pemetrexed, pembrolizumab, bemcentinib alone, or to the combination and use a stepwise dose reduction according to Table 4, Table 5, Table 6, and Table 7. Dose modifications must be based on the maximum toxicity experienced during a treatment cycle. Toxicity needs to resolve to Grade ≤1 or baseline prior to resuming subsequent cycle. For individual subjects requiring a dose modification, treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to Grade ≤1 or the baseline status of the subject.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of chemotherapy agents, all drugs should be reduced according to recommended dose modifications.

Chemotherapy may be interrupted for a maximum of 6 weeks; pembrolizumab may be interrupted for a maximum of 12 weeks. Bemcentinib may be interrupted for a maximum of 2 weeks (applicable only for phase 2a of the clinical study).

The following dose modifications guidelines help guide modification of treatment doses of bemcentinib and CIT depending on the nature of toxicity reported.

Table 4 Bemcentinib Daily Dose Modification for Potential Toxicities

Grade (CTCAE v5.0)	Recommended Dose Modification
Grade 1	
Any occurrence	No dose modification required.
Grade 2	
Any occurrence	Interrupt treatment (maximum of 2 weeks) until toxicity returns to baseline or Grade 1 then resume bemcentinib at [redacted] daily (depending on cohort daily dose). If the subject develops the same toxicity at Grade 2, please discuss with Medical Monitor.
Grade 3	
Any occurrence	Interrupt treatment (maximum of 2 weeks) until toxicity returns to baseline or Grade 1. Restart bemcentinib at [redacted] daily for 1 cycle, then titrate up to [redacted] daily for subjects on a [redacted] daily dose. If the subject was on [redacted] daily dose, titrate up to this dose ([redacted]) if subject tolerates [redacted] daily for 1 cycle. If the subject was on [redacted] daily dose, titrate up to this dose ([redacted]) if subject tolerates [redacted] daily for 1 cycle. If [redacted] daily dose is not tolerated, reduce the dose to [redacted]. If [redacted] daily dose is not tolerated, reduce the dose to [redacted] daily. If [redacted] daily dose is not tolerated, reduce the dose to [redacted] daily. *If the subject was on [redacted] daily dose, please discuss with the Medical Monitor before restarting.* If the subject develops the same toxicity at Grade 3, please discuss with Medical Monitor.
Grade 4	
1st occurrence	Discontinue permanently or discuss with Medical Monitor.

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events
Notes: Treatment interruption for bemcentinib-related toxicity is allowed for a maximum of 2 weeks. Subjects being considered for dose reduction or permanent discontinuation of bemcentinib, may be discussed with the Medical Monitor.

Table 5 Dose Modification of Bemcentinib for Risk Management of QTcF Prolongation

QTcF	Recommended Bemcentinib Dose Modification
Grade 1 (451-480 ms)	
Any occurrence	No dose modification required
Grade 2 (481-500 ms)	
1st and 2nd occurrence	Continue dosing and conduct weekly ECGs: i) if QTcF reduces to ≤Grade 1 within 14 days from initial recording, no dose modification is required ii) if QTcF does not reduce to ≤Grade 1 by 14 days from initial recording, reduce dose to [redacted] daily (for all dosing regimen) and titrate to [redacted] (depending on daily dose in [redacted] increments every 1 cycle), if possible If the patient was on [redacted] daily dose, please discuss treatment options with the Medical Monitor
3rd and subsequent occurrence	At 3rd occurrence, interrupt bemcentinib dosing for ≤14 days and conduct weekly ECGs: i) if QTcF reduces to ≤Grade 1 within 14 days, restart bemcentinib at [redacted] dose and maintain at [redacted] for the remainder of the clinical study (discuss with Medical Monitor prior to restart if subject is on daily dose of [redacted]) ii) if QTcF does not reduce to ≤Grade 1 within 14 days, discontinue treatment permanently or discuss with Medical Monitor. At any subsequent occurrence, discontinue treatment permanently or discuss with Medical Monitor
≥Grade 3 (>501 ms)	
Any occurrence	For 1st occurrence, interrupt treatment for ≤14 days: - if QTcF reduces to ≤Grade 1, reduce dose to [redacted] daily (for those on [redacted] daily dose) and discuss with Medical Monitor prior to restarting patients on [redacted] dose; discontinue treatment if dose reduction is not possible or discuss with Medical Monitor - if QTcF does not reduce to ≤Grade 1, discontinue treatment or discuss with Medical Monitor For 2nd occurrence, discontinue treatment or discuss with Medical Monitor
Ventricular arrhythmia	
Any occurrence	Discontinue permanently

Abbreviations: ECG=electrocardiogram; QTc=corrected QT interval; QTcF=QT interval corrected for heart rate using Fridericia's formula.
Notes: Electrolytes should be measured at the time of reporting QTc prolongation, and regularly until the QTc has returned to baseline. Any clinically significant electrolytes should be corrected. The mean QTcF value from triplicate ECG readings should be used when considering dose modification.
Treatment interruption for bemcentinib-related QTcF prolongation is only allowed for 14 days.

Table 6 Recommended Dose Modification for Bemcentinib and CIT for Liver-Related Events

Dosing regimen: Daily dose of 75 mg, 100 mg, 125 mg, or 150 mg				
Increased AST and/or ALT with or without increased bilirubin	**Pembrolizumab**	**Bemcentinib**	**Pemetrexed**	**Carboplatin**
Grade 1	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Grade 2	Withhold for up to 12 weeks of last dose If resolved to Grade 0 or 1, restart pembrolizumab If not discontinue treatment	For 1st occurrence withhold bemcentinib for up to 2 weeks. If improved to Grade 1 or baseline within 2 weeks without steroids restart at [redacted] (depending on daily dose). If improved to Grade 1 or baseline within 2 weeks with steroids, restart at [redacted] daily for 1 cycle, then titrate up to [redacted] daily for subjects on a [redacted], [redacted] daily dose. If the subject was on [redacted] daily dose, titrate up to this dose if subject tolerates [redacted] daily for 1 cycle. If the subject was on [redacted] daily dose, titrate up to this dose if subject tolerates [redacted] daily for 1 cycle. Discuss with Medical Monitor before restarting subjects on daily [redacted] dose If not improved in 2 weeks (with or without steroids), discontinue or discuss with the Medical Monitor For 2nd occurrence, discontinue or discuss with Medical Monitor	No dose modification needed	No dose modification needed

Dosing regimen: Daily dose of 75 mg, 100 mg, 125 mg, or 150 mg				
Increased AST and/or ALT with or without increased bilirubin	**Pembrolizumab**	**Bemcentinib**	**Pemetrexed**	**Carboplatin**
Grade 3	Permanently discontinue	For 1st occurrence, withhold bemcentinib for up to 2 weeks and start steroids If resolved within 2 weeks with or without steroids restart at [redacted] (discuss with Medical Monitor before restarting subjects on daily [redacted] dose) If not improved in 2 weeks (with or without steroids), discontinue permanently or discuss with the Medical Monitor For 2nd occurrence, discontinue or discuss with Medical Monitor	Reduce dose of pemetrexed to 375 mg/m^2	Reduce dose of carboplatin to achieve AUC 3.75 (maximum dose 562.5 mg)
Grade 4	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase
Notes: Treatment interruption for bemcentinib-related QTcF prolongation is only allowed for 14 days.
Gandhi et al, 2018

Table 7 Dose Modifications for Chemo-Immunotherapy

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Pembrolizumab	200 mg fixed dose.	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue
Carboplatin	AUC5 Maximum dose 750 mg	AUC3.75 Maximum dose 562.5 mg	AUC2.5 Maximum dose 375 mg	Discontinue

Source: Gandhi et al., 2018

AEs (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 8 below.

Table 8 Dose Modification Guidelines for Pembrolizumab Drug-Related AEs

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or increased bilirubin	2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or hyperglycemia	Type 1 diabetes mellitus or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when subjects are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal failure or nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All other drug- related toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) pembrolizumab-related AE that recurs or any life-threatening event.

[a.] For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.

[b.] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.

[c] Subjects with intolerable or persistent Grade 2 drug-related AE may hold pembrolizumab at physician discretion. Permanently discontinue pembrolizumab for persistent Grade 2 adverse reactions for which treatment with pembrolizumab has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Source: Gandhi et al., 2018

Recommended dose modifications for key pemetrexed and carboplatin toxicities are outlined in Table 9 and Table 10. These serve as a guide and do not replace Investigator judgment and applicable local label recommendations if more stringent.

Table 9 Recommended Dose Modifications for Key Pemetrexed and Carboplatin Hematological Toxicity

		Pemetrexed	Carboplatin
Platelets	**ANC**	**Dose level (DL) from Table 7**	
≥50 AND	≥0.5	DL 0	DL 0
≥50 AND	<0.5	DL -1	DL -1
<50 without bleeding AND	ANY	DL -1	DL -1
<50 with Grade ≥2 bleeding AND	ANY	DL -2	DL -2
ANY AND	<1.0 + fever ≥38.5°C (101°F)	DL -1	DL -1

Source: Gandhi et al., 2018

Table 10 Recommended Dose Modifications for Pemetrexed and Carboplatin Non-Hematological Toxicity

		Pemetrexed	Carboplatin
Event	**CTC Grade**	**Dose level (DL) from Table 7**	
Nausea or vomiting	Grade 3 or 4	DL 0	DL 0
Diarrhea*	Grade 3 or 4	DL -1	DL 0
Mucositis	Grade 3 or 4	DL -2	DL 0
Neurotoxicity	Grade 2	DL 0	DL 0
	Grade 3 or 4	DL -1	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1
	Grade 4	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	DL -1	DL -1

*requires hospitalization
Source: Gandhi et al., 2018

Management of Creatinine Clearance with Pemetrexed and Carboplatin
Creatinine Clearance (CrCl) will be calculated on the original weight-based Cockcroft Gault formula (CrCl must be ≥45 mL/min prior to the administration of chemotherapy). Pemetrexed and/or carboplatin may be delayed for up to 42 days to allow the subject time to recover from the toxicity. If a subject's CrCl value has not returned to ≥45 mL/min within 42 days after the previous dose, carboplatin and/or pemetrexed must be discontinued.

6.8 Treatment After the End of the Clinical Study

Subjects who are ongoing and continuing to derive clinical benefit from bemcentinib after 2 years will be offered access to bemcentinib via an alternative access program/study until disease progression (not applicable in France).

7 TEMPORARY STUDY HALT/DISCONTINUATION OF STUDY MEDICATION AND SUBJECT WITHDRAWAL

7.1 Discontinuation of Study Medication

Treatment of a subject may be discontinued at any time during the clinical study at the discretion of the Investigator and Sponsor for safety, compliance, or administrative reasons.

A subject must be discontinued from study medication if:

- Any safety concerns or AEs that in the opinion of the Investigator might place the subject at unacceptable risk, including any deterioration of a subject's health state.
- Pregnancy or intention to become pregnant.
- Simultaneous use of an approved or non-approved IMP in another clinical study.
- Confirmed disease progression.
- The subject withdraws consent.
- The subject is lost to follow up.

Subjects can be discontinued from study medication if:
If a subject prematurely discontinues study medication, the primary reason must be specified in the eCRF. If the subject continues in the clinical study without one or more of the study medications, the intent should be to follow the subject to the extent possible according to the planned visit schedule and assessments with the purpose of following the safety and efficacy of the subjects. Reason for visits not having been performed must be documented.

The primary reason for discontinuation of study medication must be specified in the end-of-treatment-form in the eCRF. Final drug accountability must be performed.

The following options are available:

- AE (a reason must be provided).
- Death.
- Lost to follow up.
- Lack of efficacy (defined as confirmed disease progression).
- Withdrawal of consent by subject.
- Pregnancy.
- Other (a reason must be provided).

Subjects who discontinue bemcentinib (for reasons other than disease progression) may continue CIT treatment, if this is considered in the best interest of the subject, as determined by the Investigator.

Following permanent discontinuation of bemcentinib, the subject will attend an EoT visit, and will then be followed for safety evaluation during 30 days counting from the bemcentinib treatment discontinuation date, i.e., the safety follow-up phase, Figure 2. If the subject discontinued for any reason other than disease progression, the subject will remain on study but off bemcentinib and be followed for PFS, Figure 3. The subject must

continue to follow the schedule of assessments for CIT as applicable. All subsequent therapies must be recorded in the eCRF.

Safety data will no longer be collected beyond the 30-day safety follow-up period after the last dose of bemcentinib.

Efficacy data collection must continue as planned for as long as the subject remains on CIT treatment (for a maximum of 2 years) or until discontinuation, withdrawal of consent, lost to follow up or death has occurred.

7.2 Subject Withdrawal from the Clinical Study

A subject may withdraw from the clinical study at any time at his/her own request (withdrawal of consent). The subject's request to withdraw from the clinical study must always be respected.

If a subject withdraws consent, the Investigator must ask the subject if he/she is willing, as soon as possible, to have an assessment performed according to the EoT visit. See the Flowchart for data to be collected.

A subject must be withdrawn if any of the following applies:

- Withdrawal of informed consent.
- Safety concerns or AEs that in the opinion of the Investigator might place the subject at unacceptable risk for further participation in this clinical study or would likely make the subject unable to carry out the full clinical study.
- Sponsor closure of the clinical study.
- Pregnancy or intention to become pregnant.

All efforts should be made for subjects to attend the EoT visit where all general, safety, and laboratory assessments should be performed as detailed in the Flowchart.

Final drug accountability must be performed even if the subject is not able to come to the site.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the clinical study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Although a subject is not obliged to give his/her reasons for withdrawing, the Investigator should make a reasonable effort to ascertain the reasons, while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the End of Study form in the eCRF.

7.2.1 Replacement of subjects

In phase 1b of the clinical study, subjects who are <u>not</u> DLT evaluable will be replaced.

To be DLT-evaluable, the subject must have received at least 80% of the bemcentinib dose (at least 17 of 21 days, with no more than 2 consecutive days of dosing missed) and completed evaluation for DLT in Cycle 1 or received a partial dose of bemcentinib and developed DLT during Cycle 1.

In phase 2a, subjects will not be replaced, unless they are not efficacy-evaluable (defined as subjects who discontinue study medication or withdraw from the study before a post-baseline disease assessment has been completed) to ensure at least 20 efficacy-evaluable subjects are available at each dose level studied in phase 2a.

7.2.2 Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a subject fails to return to the site for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and remind the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the clinical study.
- Before a subject is deemed "lost to follow-up", the Investigator must make every effort to regain contact with the subject (where possible, at least 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable, he/she will be considered `lost to follow-up'.

7.3 Clinical Study or Site Termination

If the Sponsor or their representatives, Investigator, or Competent Authority officials discover conditions during the clinical study that indicate that the clinical study or site involvement should be terminated, this action may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the clinical study or involvement of a site include, but are not limited to:

The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the clinical study.

The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of bemcentinib.

Failure of the Investigator to comply with pertinent clinical trial regulations.

Submission of knowingly false information from the research facility to the Sponsor, CRA, or Competent Authority.

Insufficient adherence to protocol requirements.

Clinical study termination and follow-up will be performed in accordance with applicable local regulations.

8 STUDY ASSESSMENTS AND PROCEDURES

The following sections describe the assessments and procedures, while their timing is summarized in the Flowchart, Table 11. The assessment schedule is the same for phase 1b and 2a.

- Informed consent must be obtained before any study-related activity, using the current version of the subject information sheet informed consent form (ICF), see Section 10.1.4. Re-consenting of subjects is required to ensure the subject is consented to the latest version of the ICF.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all inclusion criteria and none of the exclusion criteria and the data must be supported in the subjects' source documentation.
- The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- Re-screening is allowed once per subject.
- At Screening, subjects will be provided with a card stating that they are participating in a clinical study and provided with contact details of relevant site staff that can be contacted in case of emergency.
- Adherence to the study design requirements, including those specified in the Flowchart, is essential and required for study conduct.
- Please refer to Section 6.3 for treatment compliance.
- Review of ECG, laboratory reports etc. must be documented either on the documents or in the subject's source documents.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 for further details on laboratory samples.
- On visit days, assessments should be performed prior to dosing unless specified otherwise.
- Additional assessments may be carried out at any point in the clinical study where clinically indicated.

Visit Windows

A tolerance window of ± 3 days is permitted. Other tolerance windows for specific assessments are described in the footnotes of Table 11.

Table 11 Flowchart – Assessment and Visit Schedule

Visit Name	**Screening**	**Treatment (21-day cycles)**										**EoT[19]**	**Safety follow-up[20]**	**PFS follow-up[21]**	**Survival follow-up[22]**
Treatment Cycle	Screening	1				2	3	4	5	6	>7				
Cycle day	-28 to -1	1	2	8	15	1	1	1	1	1	1				
Informed consent	X														
Informed consent for biomarkers	X														
Inclusion/exclusion criteria	X														
Demographics[1]	X														
Medical/surgical history	X														
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
NSCLC diagnosis[2]	X														
Prior anticancer treatments	X														
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X			
Echocardiogram or MUGA	X														
12-Lead ECG in triplicate[5]	X	X	X	X	X	X	X	X	X	X	X	X	(X)[5]		

Visit Name	**Screening**	**Treatment (21-day cycles)**										**EoT[19]**	**Safety follow-up[20]**	**PFS follow-up[21]**	**Survival follow-up[22]**
Treatment Cycle	Screening	1				2	3	4	5	6	>7				
Cycle day	-28 to -1	1	2	8	15	1	1	1	1	1	1				
Hematology[6]	X	X	X	X	X	X	X	X	X	X	X	X		X	
Clinical chemistry[6]	X	X		X	X	X	X	X	X	X	X	X		X	
PT/INR and aPTT[6]		X				X	X	X	X	X	X	X		X	
Urinalysis[7]	X	X			X		X		X		X	X		X	
Pregnancy test[8]	X	X				X	X	X	X	X	X			X	
Bemcentinib[9]		X---------- X													
Pembrolizumab[10]		X				X	X	X	X	X	X			(X)	
Pemetrexed[11]		X				X	X	X	X	X	X			(X)	
Carboplatin[12]		X				X	X	X						(X)	
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor imaging[13]	X						X		X		X	X		X	
Subsequent antineoplastic therapy details[14]													X	X	(X)
Blood sample for genomic DNA	X														
Blood sample for serum biomarkers	X						X		X			X[15]			
PK[16]		X	X	X	X										

Visit Name	**Screening**	**Treatment (21-day cycles)**										**EoT[19]**	**Safety follow-up[20]**	**PFS follow-up[21]**	**Survival follow-up[22]**
Treatment Cycle	Screening	1				2	3	4	5	6	>7				
Cycle day	-28 to -1	1	2	8	15	1	1	1	1	1	1				
Tumor Tissue sample [17]	X														
Liquid biopsy[18]	X											X			
Survival															X

Footnotes:

1. Demography - race, ethnicity, gender, and age (birth month and year)
2. NSCLC diagnosis details including date of initial diagnosis, date of advanced/metastatic disease, histological diagnosis, clinical staging, details on any non-actionable mutations noted.
3. Vital signs will include temperature, systolic BP, diastolic BP, heart rate and respiratory rate. On pembrolizumab dosing days, vital signs will be taken both pre-dose and at the end of infusion.
4. Physical examination includes height at Screening only and weight at Screening and at the start of each cycle. After the screening assessment, the physical examination may be reduced to a symptom-directed assessment.
5. For each ECG assessment, triplicate 12-lead ECGs must be taken less than 5 minutes apart, with the subject having rested for at least 10 minutes in the supine position prior to assessment. On Cycle 1 Day 1 (C1D1), ECGs should be taken prior to the bemcentinib dose and 6 hours post-dose. All other timepoints are pre-dose only, unless clinically indicated. If a subject has bemcentinib interrupted for 14 days for toxicity, an ECG will be conducted twice weekly for the following 2 weeks once a subject restarts daily dosing. If a subject permanently discontinues bemcentinib (but continues any of the CIT drugs), the last ECG will be performed at the next visit, or at the safety follow-up visit. ECGs are not required for EoT of CIT drugs if bemcentinib was discontinued earlier and a final ECG assessment was performed.
6. Hematology, clinical chemistry and coagulation to be assessed prior to administration of study medications; a sample draw window of max. 3 days is allowed to ensure results are available prior to Day 1 dosing.
7. Urinalysis should be performed at Screening, C1D1, Cycle 1 Day 15 (C1D15) and then every other cycle thereafter.
8. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of study medication. A serum test can be considered if urine is not appropriate. Monthly pregnancy testing should be conducted as per local regulations, before Day 1 of each cycle.
9. Bemcentinib will be taken orally OD within 4 hours of consuming food. On visits when pembrolizumab and bemcentinib are given on the same day, bemcentinib must be given first and the subject observed for 1 hour prior to administration of pembrolizumab during the first 4 treatment cycles.
10. Pembrolizumab dose of 200 mg will be administered IV per institutional practice on the first day of each 21-day cycle (timing window ± 3 days).
11. Pemetrexed 500 mg/m^2 BSA will be administered as an IV infusion per institutional practice on the first day of each 21-day cycle.
12. Carboplatin AUC5 will be administered IV per institutional practice after completion of the pemetrexed infusion on the first day of each 21-day cycle for a maximum of 4 cycles (note: subjects must receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving carboplatin).

13. The same imaging method (CT or MR scan) should be used throughout the clinical study (timing window ± 7 days). Disease assessments should use the RECIST 1.1. iRECIST is to be used only if a subject is clinically stable and a pseudo-progression is suspected. A tumor response or disease progression should be confirmed no less than 28 days after the initial finding. If treatment administration is misaligned with weeks (e.g. because of treatment delay), the tumor imaging schedule should be maintained by week number.
14. Details of any anticancer therapies received after the last dose of bemcentinib will be collected.
15. Blood sample for serum biomarkers should be collected only at end of bemcentinib treatment.
16. The maximum PK sampling timepoints for the measurement of bemcentinib in blood will be C1D1 pre-dose and 2- and 6-hours post-dose; Cycle 1 Day 2 (C1D2) pre-dose; Cycle 1 Day 8 (C1D8) pre-dose; and C1D15 pre-dose. Samples should be taken contemporaneously with the ECG assessments and be marked with actual times. In the event of unit closures or holidays (or pandemic restrictions) PK samples can be missed with the prior approval of the Sponsor. All sample times are approximate, but every effort must be made to take PK samples at the specified times. Please refer to Table 12 and the local laboratory manual for full details on PK sample collection, timepoints, processing, storage, and shipment.
17. All subjects must have histological confirmation of the diagnosis. Fresh or diagnostic/archival tumor tissue must be available (or expected from another institution) at the time of enrollment. Suitable diagnostic/archival biopsy material may also be obtained at Screening. NB: The biopsies should not be performed solely for study purposes, but it is expected that subjects will have biopsies performed as a part of their SOC procedure at the time of diagnosis. In the absence of adequate diagnostic/archival tumor material, study-specific biopsies will be requested. If it is not feasible to obtain a fresh study-specific biopsy, discuss with the Sponsor prior to excluding the subject from the study.
18. Blood for liquid biopsy will be collected at 2 timepoints i.e. Screening and End of bemcentinib Treatment. In phase 1b, the enrollment of the patients onto the clinical study will be independent of the STK11m status (all comers). Phase 2a part of the clinical study, will, however, enroll only those patients who have a STK11m at Screening that is detected in the liquid and/or solid tumor biopsies.
19. End of Treatment visit to be conducted within 14 days of last dose of each of the 4 drugs.
20. Safety follow-up visit to be conducted 30 days (± 3 days) from the last dose of bemcentinib. AEs and concomitant medications must be assessed to 30 days.
21. PFS follow-up is only for subjects who have discontinued any treatment (but not all 4) without progression.
22. The survival follow-up will be conducted virtually (via a phone call) approximately every 3 months. The survival follow-up phase will start once the subject has discontinued ALL 4 drugs and not before.

8.1 Demographics and Other Baseline Characteristics

8.1.1 Demographics

Demographic information to be collected includes race, ethnicity, gender, and age (birth month and year).

8.1.2 Medical History/Concomitant Illness

Medical history information to be collected includes all ongoing conditions and relevant/significant medical history including all major hospitalizations and surgeries as well as prior anticancer treatment for any malignancy, as applicable.

Medical history is a medical event that the subject experienced prior to the time point from which AEs are collected.

A concomitant illness is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other study procedures performed before exposure to study medication.

Concurrent illnesses recorded at Screening (excluding the primary disease under evaluation), that worsen in severity or frequency from the time of signing the consent form, but before treatment is initiated need to be reported as an AE if the event causes the patient to be excluded from the trial or is a result of a protocol specific intervention.

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the Investigator must record the finding on the Medical History/Concomitant Illness form.

8.1.3 Physical Examinations

A full physical examination will include assessment of the following categories: head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, musculoskeletal, extremities, neurological, lymph nodes, and 'other'. After the screening assessment, the physical examination may be reduced to a symptom-directed assessment.

Body measurements (e.g. height and weight) will also be measured and recorded as specified in the Flowchart, see also Section 8.3.1.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.1.4 ECOG Performance Score

Details of the ECOG performance score categories are presented in Appendix 8. Subjects must be confirmed as ECOG performance score 0 or 1 at Screening to be eligible for study participation.

8.1.5 NSCLC Diagnosis

Details of the NSCLC diagnosis including date of initial diagnosis, date of advanced/metastatic disease, histological diagnosis, clinical staging, and details of any non-actionable mutations will be recorded.

8.1.6 Tumor Tissue Sample

All subjects must have tumor tissue available (or expected from another institution) at the time of enrollment. It is expected that subjects will have suitable biopsies performed

as part of their SOC, but in the absence or insufficiency of such material, study-specific biopsies will be requested. However, if the archival sample is not available or if it contains minimal tumor tissue and it is not feasible to collect a fresh biopsy, it should be discussed with the Sponsor prior to excluding subjects from the clinical study.

8.1.7 Liquid Biopsy NGS

NGS analysis of a liquid biopsies (i.e., blood sample) will be performed to evaluate if the subject is harboring a mutation in the STK11 gene.

For phase 1b, analysis may be carried out retrospectively as subjects will be included in the study independently of their mutational status in the STK11 gene.

For phase 2a, prospective NGS will be carried out during Screening to identify subjects who harbor mutations in STK11 gene as only patients harboring a STK11 mutation will be enrolled to phase 2a. However, if during Screening for phase 2a, the STK11 gene is already known to harbor mutations, the subject will be enrolled to the study and NGS analysis maybe carried out retrospectively.

Liquid biopsy samples will also be collected at the end of bemcentinib treatment for all subjects.

8.2 Efficacy Assessments

Planned time points for all efficacy assessments are provided in Table 11.

8.2.1 Tumor Imaging

Radiological assessment will be performed as per Table 11 with the first assessment performed at 42 days.

Efficacy endpoints in this study, including ORR, DCR, DOR, PFS will all be based on tumor assessment scan evaluation as per RECIST 1.1 (Eisenhauer et al., 2009).

Immune Response Evaluation in Solid Tumors (iRECIST) (optional) is to be used only when progression on RECIST 1.1 has been noted, the subject is clinically stable, and pseudo-progression is suspected (Seymour et al., 2017).

RECIST assessments will be performed using contrast-enhanced computerized tomography or magnetic resonance imaging (MRI) assessments of chest, abdomen, and pelvis. Additionally, x-ray and bone scans may be used if required. Additional anatomy should be imaged as appropriate, based on signs and symptoms of individual subjects at baseline and follow-up.

Baseline assessments should be performed during the 28-day screening period, and ideally should be performed as close as possible to the start of the study treatment. The screening imaging assessments must confirm the subject has measurable disease per RECIST 1.1 (see Section 5.1, Inclusion Criteria).

All participants will be evaluated with radiographic imaging to assess their response to treatment. Imaging will be performed at 6 weeks (± 7 days) and 12 weeks (± 7 days) and then every 9 weeks (63 days ± 7 days) for the first 48 weeks in the treatment period. Imaging will be performed every 12 weeks (84 days ± 7 days) subsequently.

For each subject, the same imaging modality used at Screening (CT or MR scan) must be used serially throughout the duration of study participation. All scan procedures will be performed according to standard local scan protocols to ensure consistency across study assessments.

All radiological and non-radiological (e.g. MRI) scans will be reviewed by the local site Investigator and, if possible, stored electronically at site.

A maximum of 5 target lesions, maximum of 2 per organ, must be selected at baseline. All target lesions should be measurable. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), and in addition, target lesions should lend themselves to reproducible repeated measurements. All remaining lesions present at baseline are considered non-target, irrespective of whether they are measurable or not.

A tumor response or disease progression should be confirmed no less than 28 days after the initial finding. If treatment administration is misaligned with weeks (e.g. because of treatment delay), the tumor imaging schedule should be maintained by week number from baseline.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in Table 11. Safety includes treatment emergent AE/treatment emergent SAE – their frequency, duration, and severity; lab parameters, vital signs, and ECG changes based on CTCAE v5.0 and will be assessed by the following parameters:

- Vital signs.
- ECG.
- Clinical laboratory tests (hematology, biochemistry, coagulation, pregnancy test, and urinalysis).
- AEs and SAEs.
- Immune mediated AEs.

8.3.1 Body Weight and Height

Body weight (kg with 1 decimal accuracy) will be measured at all visits. Height (cm) will be measured at Screening only.

Weight will be measured on a calibrated scale. Subjects should wear light clothing and no shoes. Stoma bags should be emptied prior to the measurement.

8.3.2 Vital Signs

The following vital signs will be collected: body temperature (ºC) (measured according to the site's usual procedure), pulse rate (beats/min), and seated diastolic and systolic blood pressure (mm Hg). During the treatment period visits, vital signs will be collected prior to administration of study treatment.

On pembrolizumab dosing days, vital signs will be taken both pre-dose and at the end of the infusion.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject, in a quiet setting without distractions. Blood pressure and pulse rate measurements will be performed with a completely automated device. Manual techniques must be used only if an automated device is not available.

8.3.3 Electrocardiogram

- For each ECG assessment, triplicate 12-lead ECGs must be taken less than 5 minutes apart, with the patient having rested for at least 10 minutes in the supine position prior to the assessment.
- ECGs will be recorded at 25 mm/sec. All efforts should be made to ensure that an identical ECG machine is used to collect traces for individual subjects throughout the duration of the clinical study participation. The Investigator or designated physician will review the ECG results.
- If any clinically significant findings are observed on the ECG, the Investigator will record it as part of the medical history prior to C1D1, and as an AE after C1D1, if the finding represents a change from baseline. Clinically significant findings identified prior to C1D1 must be checked against the study exclusion criteria, see Section 5.2.
- On C1D1, ECGs should be taken prior to the bemcentinib dose and 6 hours post-dose. All other timepoints are pre-dose only, unless clinically indicated. Note that the average value of the 3 assessments performed at each time point should be applied. Subjects may be excluded based on the initial triplicate assessment at Screening.
- Subjects who discontinue bemcentinib but continue with CIT will stop undergoing regular ECGs.
- If a subject has bemcentinib interrupted for 14 days for toxicity, an ECG will be conducted twice weekly for the following 2 weeks when the subject restarts daily dosing. This is to ensure cardiac safety monitoring while bemcentinib returns to steady state.
- If a subject permanently discontinues bemcentinib (but continues CIT), the last ECG will be performed at the next visit.
- 12-lead ECG will be obtained as outlined in Table 11, using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QTcF, and RR intervals.

8.3.4 Echocardiography or MUGA

An echocardiography or MUGA assessment will be performed at Screening. Clinically significant findings identified prior to start of dosing must be checked against the study exclusion criteria.

8.3.5 Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments, as defined in Appendix 2 must be conducted in accordance with the laboratory manual and Table 11.

Safety laboratory tests include hematology, biochemistry, urinalysis, and coagulation parameters assessed are listed in Appendix 2.

All samples should be taken prior to dosing, if dosing occurs on the same day as the study visit. The date and time of collection will be recorded in the source data and in the eCRF.

All testing will be performed at each site's local laboratory.

Copies of laboratory accreditation certificates and reference ranges will be obtained from each study site prior to the analysis of their first subject sample.

If any clinically significant findings are identified from the safety laboratory assessments at Screening, the Investigator will record it as part of the medical history prior to C1D1 and as an AE post-dose, where the finding represents a change from baseline or thereafter. Findings identified prior to C1D1 must be checked against the study inclusion and exclusion criteria.

8.3.6 Dose Limiting Toxicities

Dose Limiting Toxicities will be assessed over the first 21 days of treatment for each subject. If 2/6 subjects experience a DLT in the first 21 days of the first cycle, at any dose level, no further subjects will be enrolled at that dose and the rules for dose de-escalation described in Section 6.1.3 will be applied.

The safety and tolerability of the quadruplet combination will be assessed by the DSMB by reviewing the safety data from the DLT assessment period, i.e. the first 21 days from C1D1 for each subject.

The safety data will include the frequency and severity of occurrence of treatment-related AEs including AEs leading to treatment interruptions and discontinuation, dose reductions (during the first 21 days) and changes in safety parameters (vital signs, laboratory values, physical examinations, ECG) since baseline.

Subjects will take oral bemcentinib capsules within 4 hours of consuming food, according to the following schedules:

- Cohort 1: Bemcentinib 75 mg daily.
- Cohort 2: Bemcentinib 100 mg daily.
- Cohort 3: Bemcentinib 150 mg daily.
- Alternative dose level: Cohort 4: Bemcentinib 125 mg daily dose.

If Cohort 3 is tolerable, no further dose escalation will occur. If Cohort 3 is not tolerable, an alternative dose level, Cohort 4, at 125 mg will be implemented.

Based on overall safety and tolerability, the DSMB will recommend the bemcentinib dose for the phase 2a expansion cohort.

Dose Limiting Toxicities

A DLT is defined as an AE or SAE that occurs during Cycle 1 and cannot be attributed to disease progression, intercurrent illness, or concomitant medications.

The following toxicities occurring during Cycle 1 will be considered a DLT, only if assessed as related (possibly, probably, and definitely related) to bemcentinib:

- Grade 4 non-hematologic toxicity (non-laboratory).
- Grade 4 hematologic toxicity (except thrombocytopenia) lasting ≥7 days.
- Thrombocytopenia:
    - Grade 4 thrombocytopenia of any duration.
    - Grade 3 thrombocytopenia associated with clinically significant bleeding.
- Any non-hematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions:
    - Grade 3 fatigue lasting ≤3 days.

  - Grade 3 diarrhea, nausea, or vomiting if persistent <7 days with optimum prophylactic medication per standard of care.

- Any Grade 3 or Grade 4 non-hematologic laboratory value if:
  - Clinically significant medical intervention is required to treat the subject, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for >7 days.
  - The abnormality results in a Drug induced Liver Injury.
  - Grade 3 QTcF by CTCAE v5.0 on triplicate ECGs (mean QTc >= 501 ms; >60 ms change from baseline).
  - Exceptions: Clinically non-significant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc. Imaging will be performed at the investigator's discretion to rule out pancreatitis for asymptomatic Grade 3 or Grade 4 amylase or lipase increase.
- Febrile neutropenia (FN):
  - FN is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
- Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
- Grade 5 toxicity (death).

All toxicities will be graded using NCI CTCAE Version 5.0 based on the Investigator assessment.

None of the above toxicities when assessed as related to CIT will be included in the DLT assessment. Although all AEs will be recorded, only AEs reported as definitely, probably, or possibly related to bemcentinib will contribute toward the DLT assessment.
To be DLT evaluable, the subject must have received at least 80% of the bemcentinib dose (at least 17 of 21 days, with no more than 2 consecutive days of dosing missed) and completed evaluation for DLT in Cycle 1 or received a partial dose of bemcentinib and developed DLT during Cycle 1.

In phase 1b of the clinical study, subjects who are not DLT-evaluable will be replaced.

8.4 Adverse Events and Serious Adverse Events

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to any of the study medications, to study procedures, or that caused the subject to discontinue study medication or withdraw from the study. See further guidance in Section 10.3.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs, whether serious or non-serious, must be collected from the time a signed and dated informed consent form is obtained and until the End of Study visit is performed.

Progression of the cancer under study or death attributed to disease progression should not be considered an AE unless the Investigator considers it to be drug related.

All AEs that occur after the consent form is signed must be reported by the Investigator if they cause the subject to be excluded from the trial or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

The reporting timeframe for AEs meeting any serious criteria is in Section 10.3.4. The Investigator will make every attempt to follow all subjects with non-serious AEs for outcome.

The reporting timeframe for a new pregnancy is described in Section 8.4.5.

Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last seen?" at each contact with the study site. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All AEs, regardless of seriousness, severity, or presumed relationship to any study medication, must be recorded and evaluated by the Investigator. Whenever possible, diagnoses should be given when signs and symptoms are due to a common aetiologia. If no diagnosis can be made, the Investigator should record each sign and symptom as individual AEs. Investigators must record their opinion concerning the relationship of the AE to any of the study medications. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

- All AEs will be reported in the eCRF (SAEs will be reported in the SAE form).
- AE information should as a minimum include the following:
    - Date and time of onset
    - Date and time of Investigators first information about the AE
    - Seriousness
    - Severity
    - Causal relationship with study medication
    - Measures taken as a consequence of the AE
    - Interruption or discontinuation of study medication
    - Outcome or date of resolution and final outcome

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

All SAEs will be recorded and reported to Sponsor immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE information to Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation (i.e. after the safety follow-up visit). However, if the Investigator learns of any SAE, including death, at any time after a subject has been discontinued from the

study, and the Investigator considers the event to be reasonably related to the study medication or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.2.2). Like the initial AEs, follow-up information is reported in the eCRF; for SAEs, paper forms will be used. Follow-up questions regarding SAEs are queried directly by Sponsor to the Investigator. Further Information on follow-up procedures is provided in Appendix 3.

Follow-up information must be reported according to the following:

- **SAEs**: All SAEs must be followed until the outcome of the events is "recovered/resolved", "recovered/resolved with sequelae", or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer, or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the Investigator to recover.

The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the Investigator's first knowledge of the information. This is also the case for previous non-serious AEs which subsequently become SAEs.

- **Non-serious AEs**: Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved", or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer, or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome of "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when subject has completed the follow-up period and is expected by the Investigator to recover.

The Investigator must ensure that the worst severity and seriousness of an event is consistent throughout the trial, i.e. if the severity of an AE changes over time, it should be reported as a single AE with the worst severity recorded. A worsening of an unresolved AE must be reported as follow-up with re-assessment of severity and/or seriousness of the event.

If an AE is resolved and re-occurs later, it should be reported as a new AE.

Queries or follow-up requests must be responded within 14 calendar days from the date of receipt of the request, unless otherwise specified in the follow-up request.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities regarding the safety of subjects and the study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

For all studies, except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator receiving an Investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate, according to local requirements.

8.4.5 Pregnancy

WOCBP will have a pregnancy test carried out at Screening. This test must be carried out within 3 days prior to C1D1. A pregnancy test may be a urine or blood test as per local guidelines. A positive or equivocal urine test must be confirmed by a blood test. Subjects confirmed as pregnant will be excluded from participation in the clinical study. WOCBP will continue to have a pregnancy test before Day 1 of each cycle or at least monthly.

Female subjects who have a postmenopausal status, require documented confirmation of this by having their FSH levels assessed at Screening. Where postmenopausal status is not confirmed, subjects will be required to undergo pregnancy testing per protocol to confirm suitability to proceed to dosing as described above for WOCBP.

Pregnancy during the study should be avoided and the subjects must be instructed regarding highly effective contraception as per local guidelines (see contraception guidance in Appendix 4).

Details of all pregnancies in female subjects and female partners of male subjects who sign informed consent will be collected after C1D1 and through to the outcome of the pregnancy, or up to 30 days following discontinuation of bemcentinib or if a patient initiates a new anticancer therapy, whichever is earlier.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4. A study-specific pregnancy form will be provided for pregnancy reporting.

If a subject becomes pregnant during the study, the subject should be withdrawn from the clinical study (see Section 7.2).

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.5 Treatment of Overdose

Bemcentinib
Bemcentinib overdose is defined as any dose exceeding 150 mg of bemcentinib daily. In the event of an overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided, if clinically indicated.

Pembrolizumab
For this clinical study, a pembrolizumab overdose is defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available for the treatment of an overdose of pembrolizumab. In the event of an overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided, if clinically indicated.

Pemetrexed
Reported symptoms of overdose include neutropenia, anemia, thrombocytopenia, mucositis, sensory polyneuropathy and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia and anemia. In addition, infection with or without fever, diarrhea, and/or mucositis may be seen. In the event of suspected overdose, the subject should be monitored with regular blood counts and should receive supportive therapy as necessary. The use of calcium folinate/folinic acid in the management of pemetrexed overdose should be considered.

Carboplatin
There is no known antidote for carboplatin overdose. If necessary, however, the subject may need supportive treatment relating to myelosuppression, renal, hepatic and auditory function impairment. Reports of doses up to 1600 mg/m^2 indicate subjects become extremely ill and develop diarrhea and alopecia. Use of higher than recommended doses of carboplatin has been associated with loss of vision.

If the pharmacy discovers that an overdose has or may have been administered, they should contact the Investigator immediately. In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 5 days).
- Obtain a plasma sample for PK analysis within 5 days from the date of the last dose of study medication (only applicable for bemcentinib) if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.6 Pharmacokinetics

8.6.1 Analysis Population

Pharmacokinetic analysis will be determined from subjects who receive at least 1 dose of bemcentinib and have evaluable PK data available.

8.6.2 Determination of Bemcentinib Concentration in Plasma

- Blood samples of approximately 4.5 mL will be collected for measurement of plasma concentrations of bemcentinib as specified in the Flowchart.
- A maximum of 11 samples may be collected at additional time points during the study, if warranted and agreed upon between the Investigator and the Sponsor.
- Samples should be taken contemporaneously with the ECG assessments and be marked with actual times. In the event of site closures or holidays (or pandemic restrictions) PK samples can be missed with the prior approval of the Sponsor. All sample times are approximate, but every effort should be made to take PK samples at the specified times.
- The following PK samples will be taken during the study (all phases), Table 12.

Table 12 Bemcentinib PK Sampling Timepoints and Permitted Windows

Study Day	Time Point (hour)	Permitted Time Window
Cycle 1 Day 1	Pre-dose	within 1 hour prior to dosing
	2h	+/- 15 mins (from C1D1 dose)
	6h	+/- 45 mins (from C1D1 dose)
Cycle 1 Day 2	Pre-dose	within 1 hour prior to dosing
Cycle 1 Day 8	Pre-dose	within 1 hour prior to dosing
Cycle 1 Day 15	Pre-dose	within 1 hour prior to dosing

- Full details on pharmacokinetic (PK) sample collection, timepoints, processing, storage, and shipment are provided in the local laboratory manual.
- The actual date and time of each sample will be recorded.
- Samples will be used to evaluate the PK of bemcentinib. Each plasma sample will be divided into 2 aliquots. Samples collected for analyses of bemcentinib plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples [unless consent for this was included in the informed consent]. Subject confidentiality will be maintained.
- Plasma samples for determination of bemcentinib will be analyzed by a laboratory using a validated bioanalytical method. Details of the analytical method used will be described in a bioanalytical report.

8.6.3 Pharmacokinetic Analysis

PK parameters listed in Table 13 (but not limited to) will be derived from relevant bemcentinib plasma concentration data generated in each part of the study, utilizing a PK model. Full details of the PK methodology will be written in the PK analysis plan.

Table 13 Plasma PK Parameters

C_{max}	The observed maximum plasma concentration after single dose administration
T_{max}	The time to reach C_{max}
$AUC_{(0-t)}$	The area under the curve within a dosing interval, calculated by the linear up-log down trapezoidal method.
L_z	The apparent terminal rate constant estimated from individual linear regression of the terminal part of the log concentration vs. time curve
$T_{1/2}$	The apparent terminal half-life, calculated by 0.693/lz

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this clinical study.

8.8 Genomics

Blood for isolating circulating tumor DNA (CtDNA-liquid biopsies) will be collected at two timepoints (Screening and End of Treatment) as shown in Table 11. Blood samples will be processed at a specialty laboratory for isolation of DNA and subjected to sequencing to identify mutations in STK11 gene along with other genes on a panel. Approximately 20 mL of blood will be collected at each timepoint for the liquid biopsies.

Additionally, DNA and RNA will be isolated from the tumor tissue for sequencing.

Tumor tissue will be obtained from diagnostic blocks (archival tumor blocks used for the diagnosis of the patient at the hospital). If the diagnostic/archival block is not available or does not have adequate tumor for sequencing, then fresh tumor biopsy will be required.

An additional 5-6 mL K_2 EDTA blood tube will be collected at Screening to obtain normal genomic DNA to be used as control.

Details of sample collection, processing, storage and shipping are provided in the study specific laboratory flowchart.

8.9 Biomarkers

Blood and tumor DNA will be sequenced to obtain data on gene mutations. In phase 1b part of the clinical study, blood and solid tumor biopsies from all subjects will be sequenced for mutations retrospectively. In part 2a of the clinical study, liquid biopsies at Screening will be used to identify subjects who have mutations in the STK11 gene before enrollment in the clinical study. Subjects harboring STK11 mutations, as reported by the hospital will also be enrolled on the clinical study, but the mutational status will be validated by the assessment of liquid and solid tumor biopsies. Solid tumor material will be subjected to a dual isolation of both DNA and RNA (for transcriptomics).

Sections from tumor tissue (diagnostic block or fresh tumor biopsy) may be subjected to analysis of biomarkers such as AXL, PD-L1 and immune cell subtypes using immunohistochemistry (IHC) or other suitable techniques. A blood tube (4.5 mL) will be collected for isolation of serum for biobanking for analysis or validation of any biomarkers that may need assessment at a future timepoint.

Blood and tumor material will be collected as shown in Table 11.

Details of sample collection, processing, storage, and shipping are provided in the study-specific laboratory flowchart.

8.10 Estimate of Total Blood Volume Collected

Total blood volumes required during study participation will be provided in the Informed Consent Form provided to each patient. Blood samples will be drawn for hematology, clinical chemistry, coagulation, PK, liquid biopsies, biomarkers, and pregnancy test, if applicable, as per the Flowchart. The total volume of blood to be drawn is approximately 50 mL at Screening, 100 mL during Cycle 1 and 50 mL during subsequent cycles. If additional blood samples are required, the amount of blood drawn may be more than this stated value, however the total volume of blood drawn per cycle will be less than the volume taken during a blood donation (approximately 400 mL).

8.11 Storage of Biological Samples

- PK samples will be retained for as long as the quality of the material permits evaluation, but for no longer than 12 months after completion of the CSR.
- Samples for hematology, clinical chemistry, coagulation, and urinalysis will not be stored.
- All samples for biomarker and gene analysis will be stored by a central laboratory. When the study is completed, all samples collected for NGS (blood and tumor materials) will be stored in a regional ethical committee approved biobank for up to 5 years (unless longer is required to adequately address any queries from regulatory and governmental authorities) and may be used for analysis of biomarkers during this time. If the study subject authorizes the use of their biological samples for future research, their samples will be stored for up to 25 years after study completion. Samples may however be retained for longer to adequately address any ongoing queries from regulatory and governmental authorities.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal statistical hypotheses will be tested.

9.2 Sample Size Determination

The basis for the sample size is based on non-statistical considerations. The analysis will be primarily descriptive in nature and the study is not statistically powered.

9.3 Analysis Sets

The following populations are defined:

Table 14 Analysis Sets

Analysis set	Description
DLT-evaluable population set	The DLT evaluable population set includes all enrolled subjects in phase 1b who received at least 80% of the bemcentinib dose during cycle 1 (at least 17 of 21 days, with no more than 2 consecutive days of dosing missed) and completed evaluation for DLT in Cycle 1 or developed DLT during Cycle 1.
Per-protocol analysis set (efficacy analysis set)	The per-protocol analysis set comprises all subjects who received at least 1 dose of bemcentinib, without major protocol deviations with impact on efficacy and who have at least 1 post baseline efficacy assessment or have disease progression before the first post-baseline efficacy assessment (treatment failure). Criteria for exclusion from the per-protocol analysis set will be listed in the statistical analysis plan (SAP). Final decisions on exclusion from the per-protocol analysis set will be made prior to database lock.
Safety analysis set (intention-to-treat set)	All subjects who receive at least 1 dose of bemcentinib. Subjects are analyzed according to the treatment they actually received.
Pharmacokinetic analysis set	All subjects who received at least 1 dose of bemcentinib who have at least 1 evaluable PK assessment, without any major protocol deviations with relevant impact on PK analysis.

The subjects or observations to be excluded, and the reasons for their exclusion must be documented before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the CSR.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will include a more detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

An overview of the endpoints is provided in Table 1.

9.4.1 General Considerations

Baseline for this clinical study is defined as the last pre-dose assessment.

9.4.2 Primary Endpoints

Phase 1b
The primary endpoint of the phase 1b part of the study is the DLT during a 21-day DLT assessment period.

The primary endpoint for phase 1b, will be analyzed on the DLT-evaluable population set, using only phase 1b data. The incidence of subjects with DLTs occurring during Cycle 1 will be summarized by cohort, and decisions for dose escalation will be performed by the rules stated in the study design and methodology section.

Phase 2a
The primary endpoint for phase 2a of the study is the ORR calculated from start of treatment (C1D1) to confirmation of response per RECIST 1.1 at 6 and 12 months.

The primary endpoint of the phase 2a study will be analyzed on the per-protocol analysis set, using only phase 2a data. Analysis of ORR will occur in a Bayesian framework. The posterior distribution of both treatment groups will be obtained separately (and pooled if data are assumed to have equal performance), at each timepoint of interest; the posterior probability each dose level being greater than 33% will be estimated and the posterior probability of the high dose level being better than the low dose will also be estimated.

The endpoint distribution is Bernoulli that means independent observations of the form:

$Y_{ij} \sim Binomial(1, p_k)$

for treatment k=1,2 and for patient $j=1,..,n_k$.

In case of any missing data due to safety, death, or disease progression occurring after start of treatment, these patients will be considered as non-responders in the calculations above. Patients discontinuing due to lack of efficacy will also be considered as treatment failures. Early discontinuations for other reasons will not be imputed for the primary analysis, but imputation methods may be used for sensitivity analyses.

The phase 1b part of the study may include subjects that would be eligible for the phase 2a at dose levels tested in phase 2a. In such case a sensitivity analysis may occur pooling data from the 2 parts of the study.

9.4.3 Secondary Endpoints

9.4.3.1 Confirmatory Secondary Endpoints

Not applicable.

9.4.3.2 Supportive Secondary Endpoints

All data on secondary endpoints will be listed. Quantitative data will be described by summary statistics and frequency tables will be provided for qualitative data. Time-to-event endpoints will be analyzed using Kaplan-Meier methodology. The 2 parts of the clinical study will be described and analyzed separately, should data from phase 1b part of the clinical study include subjects that would be eligible for the phase 2a at dose levels tested in phase 2a, then pooled analyses may be performed in an exploratory manner.

For details on analyses of additional supportive secondary endpoints, please refer to the SAP.

9.4.4 Exploratory Endpoints

For details on analyses of exploratory endpoints, please refer to the SAP.

9.4.5 Other Safety Analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively, including any notable changes of clinical interest. For safety, each part of the study will be summarized separately, but pooled summaries for the selected doses may also be performed in case safety signals of such dose are identified.

Vital signs
All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities will be flagged. Summary statistics will be provided by study part, treatment and visit/time.

ECG evaluations
All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by study part, treatment, and visit/time.

As the ECG data are collected in triplicate, the intervals will be presented and summarized as the average of the replicate values at each timepoint instead of the individual values.

Clinical laboratory evaluations
All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by study part, treatment, and visit/time.

Adverse events
All information obtained on AEs will be displayed by study part, treatment, and subject.

The number and percentage of subjects with AEs will be tabulated by body system and preferred term with a breakdown by study part and treatment. A subject with multiple AEs within a body system is only counted once toward the total events within this body system.

9.4.6 Other Analyses

For other analyses, please refer to the SAP.

9.5 Interim Analyses

An interim analysis is planned when 20 subjects have completed 2 cycles of treatment in phase 2a and all 20 subjects have had their first response assessment performed (not earlier than Day 42). The Bayesian inferential analysis described above may be conducted to support decision making; based on this interim analysis, a dose level may be dropped due to futility, or the clinical study stopped, but no explicit efficacy or futility criteria are pre-specified, and evidence will be viewed in its totality due to the limited data expected to be available.

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the Sponsor’s clinical development program in general, or in case of safety concerns.

The SAP will describe the planned interim analyses in greater detail.

9.6 Independent Data Safety Monitoring Board

The independent DSMB reviews and evaluates accumulated safety data from the clinical study at pre-defined intervals to assure subject safety and to evaluate benefit-risk balance during the conduct of the clinical study. The members of the DSMB will have expertise within the therapeutic area and other relevant medical areas as appropriate and the DSMB will provide recommendations to the Sponsor regarding study continuation, modification, or termination after each meeting. The responsibilities, procedures, and workflow of the DSMB are specified in the DSMB charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide BGB with sufficient, accurate financial information as requested, to allow BGB to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests for the entire duration of the study and one year after completion of the study.

For US sites: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Liability and Insurance

Appropriate insurance for this clinical study will be arranged by the Sponsor in accordance with the regulatory requirements of the countries involved. A copy of the country-specific insurance certificate will be held in the Trial Master File and in the Investigator Site File.

The Sponsor will take out reasonable third-party liability insurance cover, in accordance with all legal requirements. The civil liability of the Investigator or designee and the hospital, practice, or institute in which they are employees and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of carrying out this clinical study are governed by the applicable law.

The Sponsor will arrange for liability insurance if study subjects should be injured due to the participation in the study provided that the Sponsor is legally liable for that. Excluded from the insurance cover are injuries to health and deteriorations of illnesses already in existence, which would have occurred or continued to exist even if the study subject had not taken part in the clinical study.

The insurance cover is jeopardized if the study subject fails to report immediately to the Investigator or responsible physician any injury to health, which might have resulted from participation in the clinical study, or if the subject undergoes any other medical treatment without their consent before the clinical study has been completely finished insofar as the individual study subject is concerned. Any injury to health, which might have occurred as a result of participation in the clinical study, must be reported by the subject to the Investigator without delay. The Investigator is obliged to make such a report in any case.

10.1.4 Informed Consent Process

- The Investigator or designee will explain the nature of the study to the subject and answer all questions regarding the study. This includes the use of an impartial witness where required, according to local requirements.
- The Investigator must provide the subject ample time to come to a decision regarding study participation.
- Subjects must be informed that their participation is voluntary.
- Subjects must be informed about their privacy rights.
- Subjects will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines, Declaration of Helsinki and the IRB/IEC or site.
- The medical record must include the date when the written informed consent was obtained and a statement that written informed consent was obtained before any study-related activity was performed. The authorized person obtaining the informed consent must also sign and date the informed consent form before any study-related activity is undertaken.
- The responsibility of seeking informed consent must remain with the Investigator, however the Investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Subjects must be re-consented to the most current version of the informed consent form during their participation in the study.
- A copy of the informed consent form must be provided to the subject.

Patient participation card

A study participation card will be provided to each subject in the clinical study. The card will indicate that the subject is participating in a clinical study and include the name and contact details of the Sponsor and the Investigator/study site. The subject will be asked to retain this card for the entire duration of the study participation and show it to any other medical practitioners consulted during this time. Subjects will be advised to contact the Investigator/study site if there are any questions.

10.1.5 Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

All data will be handled in accordance with the EU's current Data Protection Law Enforcement Directive (European Parliament and Council of the European Union, 2016a), The General Data Protection Regulation (GDPR) (European Parliament and Council of the European Union, 2016b) and the local data protection regulations.

For this study, the Sponsor and Investigational Site are the data controller of all data processed during the study and the clinical research organization (CRO) and other sub-contractors are data processors.

In case the data security has been breached for any of the participants, the Sponsor must promptly but no later than 24 hours after becoming aware of the breach be notified. Prompt action to investigate the cause of the data breach must be made, and assistance to the Sponsor in complying with Articles 32 to 36 of the GDPR

10.1.6 Committees Structure

An independent DSMB is established, and the roles and responsibilities defined in the DSMB charter. The DSMB will be responsible for reviewing the safety data from each cohort at the end of the DLT assessment period of that dose level, will provide recommendations to the Sponsor on the dose cohort management and will recommend the bemcentinib dose for the phase 2a expansion cohort.

10.1.7 Dissemination of Clinical Study Data

Information regarding the study will be disclosed at clinicaltrials.gov and other publicly accessible sites (e.g. European Clinical Trials Database [EudraCT]). It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE), the Food and Drug Administration Amendment Act (FDAAA), European Commission Requirements (Directive 2001/20/EC and Regulation (EC) No 726/2004) and other relevant recommendations or regulations. If a subject requests to be included in the study via a BGB e-mail contact at these web sites, BGB disclose the Investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of Investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint and for this study it is the last subject first treatment + 25 months. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data Quality Assurance

10.1.8.1 Data recording

BGB or designee is responsible for the data management of this study including quality checking of the data.

The Investigator will be responsible for the recording of all data in the CRFs provided, as certified by the Investigator's signature and date on the designated pages. All study data will be collected using an eCRF within a fully validated and CFR 21 Part 11-compliant electronic data capture system. All data will be entered into the eCRF by the site staff. These data will then be source data verified and reviewed by the CRA before data cleaning by Data Management is performed. All queries will be raised and resolved within the electronic data capture system. During entry, programmatic checking of the data will be performed and once saved into the database, more complex programmatic checks will also be performed. During the conduct of the study, all system users will have real-time access to the data. The level of access to the data and study privileges will be determined by their user role.

After all queries have been resolved, the SAP approved and signed, and any summary/analysis populations approved, the database will be locked, and the data released for summary and analysis. All summary and analysis of the data will be performed using SAS® version 9.3 and/or WinNonLin Pro (Version 6.3 PhoenixTM, Pharsight®), or later.

An explanation will be given for all missing, unused, and spurious data in the relevant sections of the CSR.

10.1.8.2 Monitoring

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents), data and records. Direct access includes permission to examine, analyze, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study. If the electronic medical record does not have a visible audit trail, the Investigator must provide the CRA with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

Study monitors/CRAs will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; to monitor drug accountability and collect completed paper CRF pages, if applicable, and verify that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a specified period required by local regulations,

ICH GCP, and/or Regulation (EU) No 536/2014 after study completion, unless local regulations or institutional policies require a longer retention period.

U.S Federal laws require that an Investigator maintain all study records for the indication under investigation for 2 years following the date a Product Licensing Application is approved or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

European law require that the Investigator maintain all study records (excluding the patients' medical files) for at least 25 years after completion or discontinuation of the study.

No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor assumes accountability for actions delegated to other individuals (e.g. CROs).

10.1.8.3 Protocol Compliance

The policy of BerGenBio is that no waivers will be issued.

Deviations from the protocol should be avoided. If deviations do occur, the Investigator must inform the CRA without delay and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by capturing a brief description of the deviation and stating the reason, date, and the action(s) taken.

Serious Breach of GCP

The Principal Investigator must promptly provide the Sponsor or Sponsor's representative, i.e., the CRA, with reports on any serious breaches of the protocol, GCP, EU Clinical Trial Directive, or any change that is likely to significantly affect the safety and rights of a subject, or the reliability and robustness of the data generated in the study.

10.1.8.4 Study Audit

The Sponsor, Sponsor representative, or external regulatory agency may at any time during or after completion of the study conduct a GCP audit at any trial site. Prior notice will be given to each site selected for audit in advance of a planned audit.

10.1.8.5 Clinical Study Report

The results of the study will be presented in an integrated CSR according to ICH guidelines.

10.1.9 Source Documents

- All data entered in the eCRF must be verifiable in source documentation other than the eCRF.
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper SAE CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the

discrepancies must be explained. The Investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

- It must be possible to verify subject's medical history in source documents, such as subject's medical record.
- The Investigator must document any attempt to obtain external medical information by noting the date when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Study and Site Start

Study start is defined by the first subject entering the screening period, however, the First Subject In (FPI) is when the first subject receives the first dose of study medication.

10.1.11 Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study intervention development

If the clinical study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization used in the clinical study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform all subjects, as appropriate, and should ensure appropriate subject therapy and/or follow-up.

A pre-planned interim analysis will be conducted to support decision making and based on this interim analysis, a dose level may be dropped due to futility, or the study stopped, see Section 9.5.

10.1.12 Responsibilities

The Investigator is accountable for the conduct of the clinical study at his/her site and must ensure adequate supervision of the conduct of the clinical study at the site. If any tasks are delegated, the Investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified study-related duties. The Investigator

must ensure that there is adequate and documented training for all staff participating in the conduct of the clinical study. It is the Investigator's responsibility to supervise the conduct of the clinical study and to protect the rights, safety, and wellbeing of the subjects.

A qualified physician, who is an Investigator or a sub-Investigator for the clinical study, must be responsible for all study-related medical decisions.

The Investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit the evaluation of the conduct of a clinical study and the quality of the data produced) in the Investigator trial master file. The documents, including the subject identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

The Investigator will take all necessary technical and organizational measures to prevent accidental or wrongful destruction, loss or deterioration of data. The Investigator will prevent any unauthorized access to data or any other processing of the data in accordance with applicable law. The Investigator must be able to provide the necessary information or otherwise demonstrate to the Sponsor that such technical and organizational measures have been taken.

During any period of unavailability, the Investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to ensure continued care of the study subjects during that time.

If the Investigator is no longer able to fulfill the role as Investigator (e.g. if he/she moves or retires), a new Investigator will be appointed in consultation with the Sponsor.

The Investigator and other site personnel must have sufficient English skills according to their assigned task.

10.1.13 Publication Policy

- The results of this clinical study may be published or presented at scientific meetings. If this is foreseen. The Sponsor will review all publications before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi center studies only in their entirety and not as individual site 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.
- No confidential information shall be disclosed to others without prior written consent from the Sponsor. Such information shall not be used except in the performance of this clinical study.

One Investigator (known as the Principal Investigator) will be appointed by BGB to review and sign the CSR (signatory Investigator) on behalf of all participating Investigators.

10.2 Appendix 2: Clinical Laboratory Tests

- The Investigator must review all laboratory results for concomitant illnesses and AEs.
- Laboratory samples will be destroyed no later than at finalization of the CSR.

Table 15 Protocol-Required Safety Laboratory Assessments

Clinical Chemistry	**Hematology, including Coagulation**
Calcium	Red cell count, mean corpuscular volume
Total protein	Hemoglobin
Albumin	Absolute reticulocyte count
Total bilirubin	Platelet count
Alanine transaminase (ALT, SGPT)	White blood cells
Aspartate transaminase (AST, SGOT)	Leucocyte differential count (% & absolute)
Lactate dehydrogenase (LDH)	International normalized ratio or prothrombin time
Alkaline phosphatase	Activated partial thromboplastin time
Glucose (random)	**Urinalysis**
Sodium	Glucose
Potassium	Protein
Bicarbonate	Bilirubin
Chloride	Ketones
Magnesium	Blood
Urea = Blood urea nitrogen	pH
Creatinine	Specific gravity
Phosphate	Microscopic examination when indicated
Amylase	FSH (female menopausal patients; at Screening)
TSH, Free thyroxine (T4), triiodothyronine (T3), Free T3	HCG (female premenopausal patients; at Screening)

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of Adverse Events

AE Definition

- An AE is any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

AEs include:

- A clinically significant worsening of a pre-existing condition recorded at baseline including either an increase in frequency and/or intensity of the condition.
- A clinical laboratory AE: a laboratory abnormality including those that worsen from baseline, which is clinically significant assessed by the Investigator, i.e., any abnormality that suggests a disease and/or organ toxicity and requires active management.
    - Active management includes active treatment or further investigations, e.g., change of dose, changing concomitant medication or more frequent follow-up due to the abnormality.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of any study medication or a concomitant medication.
    - Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

The following should not be considered as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first study-related activity after the subject has signed the informed consent (e.g. annual endoscopy or blood tests).
- Signs and symptoms of disease progression, unless the progression is unexpected assessed by the Investigator.
- Death is an outcome and not an AE. The cause of death should be reported as an AE with outcome fatal. If cause of death is not available, signs and symptoms leading to death should be captured as AEs.

10.3.2 Definition of Serious Adverse Events

An SAE is an AE that fulfil one or more of the following serious criteria.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.
- Hospitalizations for social or practical reasons are not considered an SAE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Results in a congenital anomaly/birth defect

f. Important Medical Event:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF; in addition, an SAE form will be sent to the Sponsor.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to Drug Safety CRO in lieu of completion of the AE/SAE CRF page. All SAEs will be reported to Sponsor immediately and under no circumstance should this exceed 24 hours.
- There may be instances when copies of medical records for certain cases are requested by Drug Safety CRO. In this case, all subject identifiers, with the exception of the subject number, will be redacted by site on the copies of the medical records before submission to Drug Safety CRO.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

- The following information should be captured for all AEs: date of onset and resolution, severity of the event (using the classifications of NCI CTCAE v5.0, see below; Assessment of Severity), Investigator's opinion of the relationship to any of the study medications (assessment of causality, see below) and assessment whether the event was serious or non-serious (see definitions in Section 10.3.2). In addition, treatment required for the AE, action taken with any of the study medications, information regarding resolution/outcome.

Assessment of Severity

All AEs (including SAEs) are to be accurately recorded on the AE page of the patient's eCRF. Each event will be graded for severity using the classifications of NCI CTCAE v5.0. For events not addressed in the NCI CTCAE v5.0, classifications the following grading will apply:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate Instrumental Activities of Daily Living, ADL
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care, ADL
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Assessment of Causality

- The Investigator is obligated to assess the relationship between each of the study medications and each occurrence of each AE/SAE.
  - A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The following causality terms are defined based on their respective assessment criteria:

Causality term	Assessment criteria
Almost certain	A clinical event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals.
Probable	A clinical event with a reasonable time sequence to drug administration and which is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Possible	A clinical event with a reasonable time sequence to drug administration but which could also be explained by concurrent disease or other drugs or chemicals.
Unlikely	A clinical event whose time relationship to drug administration makes a causal connection improbable, but which could be explained by an underlying disease or other drugs or chemicals.
Unrelated	A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals.

WHO assessment scale

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. Alternative etiology should be provided if a "reasonable possible" relationship to the AE exists.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in their assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of Outcome

The Investigator must judge outcome of the AE by the following terms:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving:** The condition is improving, and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae:** The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: The condition of the subject has not improved, and the symptoms are unchanged, or the outcome is not known.
- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", or "not recovered/not resolved".
- **Unknown**: This term is only applicable if the subject is lost to follow-up.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. For SAEs reported on a paper SAE form, the SAE follow-up information should only include new (e.g., corrections or additional) information. All SAE follow-up information must be reported to Sponsor **within 24 hours** of the Investigator's first knowledge of the information. This is also the case for previous non-serious AEs which subsequently become SAEs.
- If a subject dies during participation in the trial or during a recognized follow-up period, the Investigator will provide Sponsor with a copy of any post-mortem findings including histopathology, if possible.
- New or updated information will be recorded in the originally completed eCRF.

- The Investigator will submit any updated SAE data to the Drug Safety CRO within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Drug Safety CRO/Syneos Health via SAE paper form

- The primary mechanism for reporting an SAE will be the SAE paper form.
- The site will use the paper SAE form to report the event **within 24 hours**.
- The site will enter the SAE data into the AE eCRF page and complete the SAE paper form within 24 hours of becoming aware of the SAE.
- After the study is completed at a given site, the eCRF will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE, then the site should report this information on an updated paper SAE form (see next section).
- Contacts for SAE reporting can be found below.

AE Reporting via eCRF and SAE Reporting via SAE paper form

- All AEs must be reported via the AE eCRF page
- All SAEs must be reported within 24 hours of awareness in the SAE paper form and emailed to Syneos Health.
- Initial notification via e-mail does not replace the need for the Investigator to complete the AE eCRF page and SAE paper form within the designated reporting timelines:
  - AE eCRF and a signed SAE paper form within 24 hours after first knowledge by the Investigator
  - Follow up information to be included in the AE ECRF page and an updated SAE paper form to be completed and emailed to Syneos Health
- Contacts for e-mail of the SAE paper form:

Drug Safety CRO:	Syneos Health LLC 1030 Sync Street Morrisville, North Carolina 27560
SAE e-Mail contact and facsimile:	safetyreporting@syneoshealth.com Global safety fax: +1 877 464 7787

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study medication, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

1. Premenarchal
2. Pre-menopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Females with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining clinical study entry.

   Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as amenorrhea for 12 months without an alternative medical cause.
   - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Male Subjects

For this trial, male subjects will be considered to be of reproductive potential unless permanently sterile by bilateral orchidectomy.

Contraception Guidance:

To participate in the study, subjects (both male and female) of reproductive potential must be willing to practice highly effective methods of contraception throughout the study and for 4 months after the last dose of pembrolizumab, 6 months after the last dose of chemotherapeutic agents or 30 days after the last dose of bemcentinib whichever is the later by complying with one of the following highly effective methods‡:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Practice abstinence from heterosexual activity†

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRB/ IECs. Periodic abstinence e.g., calendar, ovulation, symptothermal, post-ovulation methods, etc. and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Male subjects should also refrain from donating sperm during this period. Men should be advised to seek advice on sperm preservation before starting therapy due to the possibility of irreversible infertility after treatment with carboplatin.

Female subjects should be advised that they may experience amenorrhea (absence of menstrual periods) during treatment with carboplatin, and this effect may be irreversible.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study.

If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

Collection of Pregnancy Information

If a partner of a subject enrolled in the clinical study become pregnant, he must discontinue treatment immediately.

The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor preferably within (24 hours) of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any

termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the CRO within (24-hours) of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study product by the Investigator will be reported to the Sponsor as described in Section 10.3.4. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue treatment immediately.

10.5 Appendix 5: Genomics

Analysis of DNA and RNA

- Liquid (blood) and solid tumor biopsy samples of consenting patients will be collected and processed for isolation of genomic material in a Sponsor designated laboratory. DNA isolated from liquid and/or solid tumor biopsies may be sequenced for mutations and additionally may be sequenced for gene expression (Li et al., 2022).
- In the phase 1b part of the study, samples will be collected from all subjects and may be sequenced retrospectively to further understand the clinical data.
- In the phase 2a part of the study, liquid and/or solid tumor biopsies will be subjected to DNA sequencing during screening to select patients positive for STK11 mutations for enrollment and treatment with the study drugs.
- DNA samples will be analyzed for presence of mutations in genes including STK11 and associated pathways in NSCLC. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- If patients consent to future research, DNA and RNA samples will be used for research related to AXL inhibitors such as bemcentinib or NSCLC and related diseases. They may also be used to develop tests/assays including diagnostic

tests related to AXL inhibitors and NSCLC and related diseases. Genetic research may consist of the analysis of one or more candidate genes or analysis of the entire genome or transcriptome.

- The results of genetic analyses may be reported in the CSR and/or in a separate study report.
- All DNA/RNA will be stored securely in a Sponsor designated laboratory with adequate measures to protect confidentiality.
- Following completion of the study, all leftover materials will be stored in a regional ethical committee approved biobank for the period approved by the regional ethical committee.

10.6 Appendix 6: Drugs that Prolong QT and Induce Torsades de Pointes

See table below for a list of drugs that may cause Torsades de Pointes.

Table 16 Overview of Drugs that Prolong QT and Induce Torsades de Pointes

Generic Name	Brand Names	Drug Class	Therapeutic Use
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil	Antidepressant, SSRI	Depression (major), anxiety disorders
Flucanazole	Diflucan, Trican	Antifungal	Fungal infection
Probucol *(Removed from US Market)*	Lorelco	Antilipemic	Hypercholesterolemia
Gatifloxacin *(Removed from US Market)*	Tequin	Antibiotic	Bacterial infection
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation
Sertindole *(Only on Non-US Market)*	Serdolect, Serlect	Antipsychotic, atypical	Schizophrenia, anxiety
Astemizole *(Removed from US Market)*	Hismanal	Antihistamine	Allergic rhinitis
Arsenic trioxide	Trisenox	Anti-cancer	Cancer (leukemia)
Sparfloxacin *(Removed from US Market)*	Zagam	Antibiotic	Bacterial infection
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Ibutilide	Corvert	Antiarrhythmic	Arrhythmia
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Psychosis, nausea, many others

Generic Name	Brand Names	Drug Class	Therapeutic Use
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection
Dronedarone	Multaq	Antiarrhythmic	Arrhythmia
Sevoflurane	Ultane, Sojourn	Anesthetic, general	Anesthesia
Chloroquine	Aralen	Antimalarial	Malaria
Domperidone *(Only on Non-US Market)*	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic	Nausea, vomiting
Mesoridazine *(Removed from US Market)*	Serentil	Antipsychotic	Schizophrenia
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Roxithromycin *(Only on Non-US Market)*	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic	Bacterial infection
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Sotalol	Betapace, Sotalex, Sotacor, Sotalol-AF	Antiarrhythmic	Arrhythmia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Arrhythmia
Procainamide	Pronestyl, Procan	Antiarrhythmic	Arrhythmia
Pimozide	Orap	Antipsychotic	Psychosis, Tourette's Disorder
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)
Halofantrine *(Only on Non-US Market)*	Halfan	Antimalarial	Malaria
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection
Vandetanib	Caprelsa	Anti-cancer	Cancer (thyroid)
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Arrhythmia

Generic Name	Brand Names	Drug Class	Therapeutic Use
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection
Cisapride *(Removed from US Market)*	Propulsid	GI stimulant	Increase GI motility
Disopyramide	Norpace	Antiarrhythmic	Arrhythmia
Dofetilide	Tikosyn	Antiarrhythmic	Arrhythmia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain
Levomethadyl acetate *(Removed from US Market)*	Orlaam	Opioid agonist	Narcotic dependence
Erythromycin	E.E.S., Robimycin, Emycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility
Bepridil	Vascor	Antianginal	Angina Pectoris (heart pain)
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Arrhythmia
Terfenadine *(Removed from US Market)*	Seldane	Antihistamine	Allergic rhinitis
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia
Sulpiride *(Only on Non-US Market)*	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia
Grepafloxacin *(Removed from US Market)*	Raxar	Antibiotic	Bacterial infection
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, Anti-inflammatory	Malaria, SLE, rheumatoid arthritis
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication

Generic Name	Brand Names	Drug Class	Therapeutic Use
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Papaverine HCl (Intra-coronary)		Vasodilator, Coronary	Diagnostic adjunct
Levomepromazine (Methotrimeprazine) *(Only on Non-US Market)*	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia
Oxaliplatin	Eloxatin	Anti-cancer	Cancer
Terodiline *(Only on Non-US Market)*	Micturin, Mictrol	Muscle relaxant	Bladder spasm
Levosulpiride *(Only on Non-US Market)*	Lesuride, Levazeo, Enliva	Antipsychotic	Schizophrenia
Sultopride *(Only on Non-US Market)*	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Terlipressin *(Only on Non-US Market)*	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss	Vasoconstrictor	Septic shock
Ibogaine *(Only on Non-US Market)*		Psychedelic	Narcotic dependence, unproven efficacy
Chlorprothixene *(Only on Non-US Market)*	Truxal	Antipsychotic	Schizophrenia
Aclarubicin *(Only on Non-US Market)*	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer	Cancer
Hydroquinidine (Dihydroquinidine) *(Only on Non-US Market)*	Serecor	Antiarrhythmic	Arrhythmia
Nifekalant *(Only on Non-US Market)*	Shinbit	Antiarrhythmic	Arrhythmia
Cesium Chloride	Energy Catalyst	toxin	Alternative therapy cancer
Meglumine antimoniate *(Only on Non-US Market)*	Glucantime	Antiparasitic	Leishmaniasis

Generic Name	Brand Names	Drug Class	Therapeutic Use
Mobocertinib	Exkivity	Tyrosine kinase inhibitor	Cancer (Lung)

Source: https://crediblemeds.org

10.7 Appendix 7: Prohibited Medications During the Study

See table below for a list of prohibited medications.

Table 17 Prohibited Medications During the Study

Live or live-attenuated vaccine
Yellow fever vaccine
Chelating agents – Deferasirox, Trientine, Deferiprone, Deferoxamine, EDTA derivatives and Succimer

10.8 Appendix 8: Eastern Cooperative Oncology Group Performance Status

Grade	ECOG Performance Status
0	Fully active. Able to carry on all pre-disease 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, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al., 1982

10.9 Appendix 9: Abbreviations and Definitions of Terms

1L	First line
2L	Second line
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
AUC5	Area under the concentration– time curve, 5 mg per milliliter per minute
BBB	Blood-brain barrier
Bem	Bemcentinib
BGB	BerGenBio ASA
BSA	body surface area
C1D1	Cycle 1 Day 1
C1D2	Cycle 1 Day 2
C1D8	Cycle 1 Day 8
C1D15	Cycle 1 Day 15
CIT	Chemo-immunotherapy
CPI	Checkpoint inhibitor
CRA	Clinical Research Associate
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DC	Doublet chemotherapy
DCR	Disease control rate
DLT(s)	Dose limiting toxicity(ies)
DOR	Duration of response
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMT	Epithelial-mesenchymal transition
EoT	End of Treatment
FDA	US Food and Drug Administration

FDAAA	FDA Amendments Act
FFPE	Formalin-fixed, paraffin embedded
FN	Febrile neutropenia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRT	Hormone replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of technical requirements for pharmaceuticals for human use
IEC	Independent ethics committee
IFN	Interferon
ILS	Investigator-led study
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IV	intravenous
LFT	Liver function test
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	Median progression free survival
mOS	Median overall survival
MiST	Mesothelioma stratified therapy
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MUGA	Multigated acquisition
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PCD	Primary completion date
PD-L1	Programmed death-ligand 1

PFS	Progression free survival
PK	Pharmacokinetics
PK-PD	Pharmacokinetic-pharmacodynamic
PT	Prothrombin time
Q3W	Every 3 weeks
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of care
STK11m	Serine/threonine kinase 11 mutation
STK11wt	Serine/threonine kinase 11 wild type
SUSAR	Suspected unexpected serious adverse reaction
T3	Triiodothyronine
T4	Thyroxine
TdP	Torsades de pointes
TME	Tumor microenvironment
TNBC	Triple negative breast cancer
TPS	Tumor proportion score
TSH	Thyroid stimulating hormone
US	United States
WOCBP	Woman of childbearing potential

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Signing Complete	Security Checked	7/7/2023 12:03:06 PM
Completed	Security Checked	7/7/2023 12:03:13 PM

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