NOVARTIS

Clinical Development

Buparlisib (BKM120)

Protocol CBKM120H2201 / NCT01852292

Phase II multicenter randomized, double blind, placebo controlled study assessing the efficacy of buparlisib (BKM120) plus paclitaxel *vs.* placebo plus paclitaxel in patients with platinum pre-treated recurrent or metastatic head and neck squamous cell carcinoma.

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Document type	Amended Protocol Version
EUDRACT number	2013-000744-26
Version number	V03 Clean
Development phase	II
Document status	Final
Release date	30-Aug-2016

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List of abbreviations

AE	Adverse Event
AKT	Protein Kinase B
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BAL	Bronchoalveolar lavage
BUN	Blood Urea Nitrogen
CBC	Cells Blood Count
CERT	Center for Education and Research on Therapeutics
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CR	Complete response
CrCl	Creatinine Clearance
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P
DCR	Disease Control Rate
DHEA	Dehydroepiandrosterone
DILI	Drug-induced liver injury
DLCO	Carbon monoxyde diffusing capacity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DS&E	Drug Safety and Epidemiology
DSM- IV	Diagnosic and Statistical Manual of Mental Disorders, 4th Edition

EBV	Epstein-Barr Virus
EC	Ethic Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG P.S.	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EGFR	Epidermal growth factor receptor
EIAED	Enzyme-inducing anti-epileptic drug
EORTC	The European Organization for Research and Treatment of Cancer
EOT	End of Treatment
ESMO	European society for medical oncology
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FGF	Fibroblast growth factor
FPG	Fasting plasma glucose
FU/F up	Follow-Up
GAD-7	General Anxiety Disorder Assessment
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	Gamma-glutamyltranspeptidase
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony-stimulating factor
HbA_{1c}	Glycosylated Hemoglobin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
hCG	human chorionic gonadotrophin
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HDPE	High Density Polyethylene
HIV	Human immunodeficiency virus
H&N	Head and Neck
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human papillomavirus

HR	Hazard Ratio
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor 1
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IUD	intrauterine device
IUS	intrauterine system
i.v./IV	intravenous(ly)
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Liver Function Tests
LLN	Lower Limit of Normal
LMWH	Low molecular weight heparin
LVEF	Left Ventricular Ejection Fraction
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MedDRA	Medical Dictionary for Regulatory Activities
mOS	Median overall survival
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian target of rapamycin
MUGA	Multiple Gated acquisition scan
NA	North America
NaF PET	Sodium Floride Positron Emission Tomography
NCI CTC	National Cancer Institute Common Terminology Criteria
NCCN	National Comprehensive Cancer Network
ORR	Overall Response Rate
OS	Overall Survival

PD	Progressive disease
PD	Pharmacodynamics
PFS	Progression Free Survival
PHQ-9	Patient Health Questionnaire
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Gene which encode the p110alpha catalytic subunit
PK	Pharmacokinetics
PLT	Platelets
p.o.	per os/by mouth/orally
PHI	Protected Health Information
PR	Partial response
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
aPTT	Activated Partial Prothrombin time
QLQ	Quality of Life Questionnaire
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
Rb	retinoblastoma
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	*Recommended phase two dose*
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable disease
TBL	Total bilirubin
TdP	Torsades de Pointes
TTP	Time to Progression
TTR	Time to Response
TSC1/TSC2	TSC1 and TSC2 are the tumor-suppressor genes mutated in the tumor syndrome TSC (tuberous sclerosis complex).
UDPGA	Uridine 5'-diphospho-glucuronic acid
UGT	uridine diphosphate glucuronyltransferase
UNK	Unknown
UNL	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body

Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol summary:

Protocol number	CBKM120H2201
Title	Double blind, placebo controlled study assessing the efficacy of buparlisib (BKM120) plus paclitaxel vs. placebo plus paclitaxel in patients with platinum pre-treated recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).
Brief title	Study of efficacy and safety of buparlisib (BKM120) plus paclitaxel vs. placebo plus paclitaxel in recurrent or metastatic Head and Neck cancer previously pre-treated with a platinum therapy.
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the treatment effect of buparlisib in combination with weekly paclitaxel vs. buparlisib-matching placebo plus weekly paclitaxel on median PFS in patients with recurrent or metastatic HNSCC cancer that has progressed after platinum based regimen. [redacted]
Primary Objective(s)	• To estimate the efficacy of buparlisib in combination with paclitaxel on PFS according to local radiological assessment and RECIST 1.1 in patients with recurrent or metastatic HNSCC cancer
Key Secondary Objective	• To assess the efficacy of the combination with paclitaxel in this patient population in terms of overall survival
Other Secondary Objectives	• To assess the safety and tolerability of buparlisib in combination with paclitaxel in this patient population as assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.03 • To evaluate additional efficacy parameters: Overall Response Rate (ORR); Time to Response (TTR); Disease Control Rate (DCR); Duration of Response (DoR) • To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel • To assess the effect of buparlisib in combination with paclitaxel on patient's symptoms and health-related quality of life (HRQoL)
[redacted]	[redacted]
Study design	A multi-center, randomized, double-blind, placebo-controlled phase II trial Patients will be randomized to receive either buparlisib 100 mg daily in combination with weekly paclitaxel or buparlisib-matching placebo daily in

	combination with weekly paclitaxel and will be stratified according to the number of prior lines of treatment (1 vs 2) and the region of the investigator site (North America versus Rest of the World).
Population	Approximately 150 randomized patients, both females & males with histologically/cytologically-confirmed HNSCC, recurrent or metastatic disease progressing after platinum based first line treatment.
Key Inclusion criteria	• Patient has histologically/cytologically-confirmed HNSCC. • Patient has archival or new tumor tissue for the analysis of PI3K-related biomarkers. One tumor block (preferred) or a minimum of 12 (15 recommended) unstained slides to be provided. Enrollment in the study is contingent on confirmation of an adequate amount of tumor tissue. • Patients with recurrent or metastatic disease after failure to platinum-based chemotherapy (defined as progression while on or after platinum-based chemotherapy given in the recurrent/metastatic setting). Pretreatment with cetuximab (as part of chemoradiation, included in first-line regimen or as maintenance, or used as single-agent as second-line therapy) is allowed • Measurable disease as determined by per RECIST criteria v1.1. If the only site of measurable disease is a previously irradiated lesion, documented progression of disease and a 4 week period since radiotherapy completion is required • Adequate bone marrow function and organ function • ECOG Performance Status ≤ 1

Key Exclusion criteria	• Patient has received previous treatment with any AKT, mTOR inhibitors or PI3K pathway inhibitors;
	• Patient treated with more than one prior chemotherapy regimen for recurrent/metastatic disease (i.e. chemotherapy, chemotherapy in association with a biologic/targeted agent,)
	• Patient has symptomatic CNS metastases. Patients with asymptomatic CNS metastases may participate in this trial. The patient must have completed any prior local treatment for CNS metastases ≥ 28 days prior to the start of study treatment (including radiotherapy and/or surgery) and must have stable low dose of corticosteroid therapy;
	• Patient has not recovered to ≤ grade 1 (except alopecia) from related side effects of any prior antineoplastic therapy
	• Patient has any of the following cardiac abnormalities:
	  • symptomatic congestive heart failure,
	  • history of documented congestive heart failure (New York Heart Association functional classification III-IV), documented cardiomyopathy,
	  • Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
	  • myocardial infarction ≤ 6 months prior to enrolment,
	  • unstable angina pectoris,
	  • serious uncontrolled cardiac arrhythmia,

	• symptomatic pericarditis, • QTcF > 480 msec on the screening ECG (using the QTcF formula) • currently receiving treatment with medication that has a known risk to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. A list of prohibited drugs will be provided in the final protocol
Investigational and reference therapy	• buparlisib (BKM120) plus paclitaxel • Placebo plus paclitaxel
Efficacy assessments	Tumor assessment done 4 weeks after study treatment start and every 6 weeks afterwards; • CT/MRI of primary tumor • Chest and abdomen CT scan • Pelvis CT scan if clinically indicated • Whole body bone scan if clinically indicated to be performed according to institutional guidelines (if already performed within 6 weeks prior to start of treatment, this scan can be considered as the screening scan). • Localized CT, MRI or X-rays of all skeletal lesions identified on the screening bone scan, which are not visible on the chest, abdomen or pelvis CT (or MRI) must be taken at screening and at each subsequent tumor assessment. • Brain CT or MRI if clinically indicated • From protocol amendment v03, tumor assessment done as per local clinical practices.
Safety assessments	• Monitored by • ECOG Performance status • Vital signs • Physical examination • Weight • Pulmonary function testing • Hematology • Biochemistry • Creatinine clearance determination • Coagulation • Lipid profile • Fasting plasma glucose, C-peptide • HbA1c • Adverse events • Prior/concomitant medications • PHQ-9 • GAD-7 • Serious and non-serious Adverse Events (AE) collection

Data analysis	• The primary analysis will be performed when approximately 120 PFS events have been observed. • For the key secondary analysis, the analysis of Overall Survival will be performed when approximately 112 deaths have been recorded. The primary and the key secondary analyses will be based on the point estimate and posterior distribution of the respective hazard ratios estimated via a stratified Cox Proportional hazards model. All secondary analyses will be reported for the adequate population (i.e. FAS, Safety Set) by treatment groups.
	Buparlisib, BKM120, paclitaxel, platinum pre-treated recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).

Amendment 3 (30-Aug-2016)

Amendment rationale

Enrolment in study CBKM120H2201 was completed on 7 April 2015, with a total of 158 patients randomized. At the time of this amendment, all protocol planned analyses (Final PFS and Final OS) have been completed. No further analyses are planned except for safety updates after the Last Patient Last Visit (LPLV). As of 18 August 2016, six patients are still on study treatment.

The main purposes of this protocol amendment are to:

- Provide a clarification on the measures to follow when a patient exhibits suicidal ideation regardless of the response to question 9 of the PHQ-9 questionnaire (as has been described in the BKM120 Investigator's Brochure Ed. 8.0).

Rationale: Patient Health Questionnaire-9 (PHQ-9) is used to increase the sensitivity of identifying potential depression and suicidal thoughts via positive response to " question 9" . However, it has not been consistently predictive for suicidal ideation or attempt in buparlisib trials, as some patients who exhibited suicidal ideation or attempt, reported as an adverse event, either had a negative response to question 9 or did not answer it. Hence, measures to be followed for any adverse event of suicidal ideation regardless of the response to question 9 or the total score of PHQ-9 have been specified in the Investigator's Brochure Ed. 9.0/dated 29 April 2016.

A prospective suicidality assessment in clinical trials with buparlisib is important and is facilitated using question 9 of the PHQ-9 questionnaire. A timely interview with the patient after the questionnaire completion is recommended. Patients with a positive responses to question 9 (as indicated by selecting "1", "2" or "3"), or otherwise exhibiting any suicidal ideation must immediately interrupt the buparlisib/placebo treatment and must be assessed by a Psychiatrist. This is regardless of the response or lack of to question 9 or total PHQ-9 score or CTCAE grading of the suicidal ideation.

- Unblind patients' treatment considering that all planned analyses have been completed. The study will be closed after LPLV
- Reduce assessment schedule for patients still on study treatment. Tumor assessment will be performed per local clinical practices and safety evaluation will be done per revised visit schedule.
- For patients who are still on study treatment and are considered benefiting from study drug (s), study treatment will continue to be provided on or off this study. Treatment for these patients can also be managed according to local clinical practices per investigator discretion. Where feasible and available, patients may be transitioned to commercial paclitaxel.

Additional changes

Update to the guidelines for buparlisib/placebo administration related to food intake.

Rationale: A clinical pharmacology study [CBKM120C2108] investigating the food effect of both a low fat low calorie meal (LFLC) or a high fat, high calorie meal (HFHC) on the pharmacokinetics of buparlisib in healthy volunteers showed that intake of food concomitantly with buparlisib led to a delayed and reduced Cmax without a meaningful impact on exposure (AUCinf) compared to fasting administration (BKM120 Investigator's Brochure Ed. 8.0). Based on these findings, buparlisib can be administered with or without food and accordingly the guidelines had been updated.

Changes to the protocol

Changes to the protocol summary section: Tumor assessments in the randomized treatment phase and post-treatment follow-up phase updated

Update to the section on buparlisib dosing, regardless of food intake:

Buparlisib/Placebo can be taken with or without food;

Changes in the section on management and follow-up of mood alteration:

Clarification on measures to be followed (interruption of buparlisib/placebo and psychiatric consultation) for any patient who presents with suicide ideation of any grade

Changes to the study assessments:

- The inclusion of a statement that regardless of grade or response to question number 9 in PHQ-9 questionnaire, any patient who presents with suicide ideation must be referred for a psychiatric consultation.
- Adding a statement to require the investigator to assess the patient for suicidal ideation regardless of the answer to question 9 of PHQ- 9 or if the patient did not respond to question 9 in PHQ-9 questionnaire.
- For patients still on study treatment, assessment frequency will be reduced. Tumor assessment will be performed per local clinical practices and safety evaluation will be done per revised visit schedule. New Table 7-1b and Table 7-1c have been added to describe the assessments. Table 7-1 has been renamed 7-1a.
- Collection of EORTC QLQ-C30 and EORTC QLQ-HN35 questionnaires to be discontinued for patients still on study treatment

The following sections have been changed in the amended protocol:

- Section 4.1.1 Treatment phase: updated to clarify patient monitoring after unblinding.
- Section 4.1.2 Follow-up phase: implementation of the reduced assessments schedule and Figure 4-1 updated;
- Section 4.4 Definition of the end of the study: updated.
- Section 6.1.1 Dosing regimen: removal of the requirement that buparlisib/placebo be taken with regard to food intake
- Section 6.1.4 Treatment duration: disease progression to be evaluated as per standard of care instead of RECIST 1.1
- Section 6.2.2 Table 6-3 Criteria for interruption and re-initiation of buparlisib/placebo treatment - Mood alteration (Depression, anxiety): for grade 1 and 2 the inclusion of a

statement that any patient who presents with suicide ideation must be referred for a psychiatric consultation

- Section 6.2.2.3.6 Guidelines for the treatment of study drug induced psychiatric disorders: Statement that any patient who presents with suicide ideation must interrupt buparlisib/placebo and be referred for a psychiatric consultation regardless of grade or response to question 9 in the PHQ-9 questionnaire
- Section 6.4.3 Treatment blinding: clarification on the study unblinding given the completion of final OS analysis
- Section 6.5.3 Drug supply and storage: clarification for patients on paclitaxel alone to switch to commercial stock if feasible
- Section 7.1 Visit schedule and assessments: renamed Table 7-1 as 7-1a and addition of Table 7-1b and Table 7-1c to describe the assessments performed after unblinding
- Section 7.1.3 Treatment period: clarification for patients on study treatment after unblinding
- Section 7.1.4 End of treatment visit: implementation of the reduced assessments when patients discontinue treatment.
- Section 7.1.5 Follow-up period: implementation of the reduced assessments for efficacy and survival follow-up
- Section 7.2.1 Efficacy assessment and Table 7-2: description of the updated assessments schedule
- Section 7.2.2.1 Physical examination: description of the updated assessments performed.
- Section 7.2.2.2 Vital signs: description of the updated assessments performed.
- Section 7.2.2.3 Height and weight: description of the updated assessments performed.
- Section 7.2.2.4 Performance status: description of the updated assessments performed.
- Section 7.2.2.5 Table 7-4: Local clinical laboratory parameters collection plan updated
- Section 7.2.2.5.1 Hematology: description of the updated assessments performed.
- Section 7.2.2.5.2 Biochemistry: description of the updated assessments performed.
- Section 7.2.2.5.3 Fasting clinical laboratory parameters: monitoring fasting plasma glucose, c-peptide, serum lipid profile, lipase and HbA_{1C}: description of the updated assessments performed.
- Section 7.2.2.5.4 Coagulation: description of the updated assessments performed
- Section 7.2.2.5.5 Urinalysis: description of the updated assessments performed.
- Section 7.2.2.5.7 Viral hepatitis serology and other tests for hepatotoxicity follow-up: description of the updated assessments performed.
- Section 7.2.2.6 Radiological examinations: description of the updated assessments performed.
- Section 7.2.2.7.2 Cardiac assessments: description of the updated assessments performed
- Section 7.2.2.8 GAD-7 and PHQ-9 Questionnaires:
  - Adding a statement that any patient who presents with suicide ideation must interrupt buparlisib/placebo and be referred for a psychiatric consultation regardless of grade or response to question 9 in the PHQ-9 questionnaire.

- Adding a statement requiring assessment of suicidal ideation for any patient who does not answer question 9 or the whole PHQ-9.

- Section 7.2.4.1 EORTC QLQ-C30 and QLQ-HN35: clarification on requirements.
- Section 8.2.2 Reporting: updated

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Summary of previous amendments

Amendment 2

In the current study CBKM120H2201 the enrolment was completed as of 7 April 2015, and overall 158 patients have been randomized in this trial. As of 26 June 2015, 28 patients are still on treatment.

Amendment Rationale

The main purpose of this protocol amendment is to provide additional guidance to investigators around management of liver toxicities in view of the Aggregated Safety Finding Report submitted by Novartis to Health Authorities in May 2015.

Alterations in liver function tests (LFTs) have been commonly observed in clinical trials with buparlisib as an investigational agent. These include mostly transient increases in transaminase enzymes (ALT and/or AST), which often occur during the first 6 to 8 weeks of BKM120 (buparlisib) treatment, and rarely are associated with signs/symptoms of impaired liver function. Current buparlisib protocols have conservative inclusion criteria for LFTs at study entry with close monitoring guidelines to be followed during the treatment and stringent dose modification/interruption criteria.

In March 2015, a search for potential drug-induced liver injury (DILI) cases in buparlisib Novartis-sponsored trials using conservative biochemical criteria (e.g. AST/ALT >3.0x ULN and total bilirubin (TBL) >2.0xULN at any time during the treatment period, regardless of causality) has been conducted. Upon medical review, most of these occurred in the context of disease progression in advanced cancer patients and/or were confounded by other causes. However, six of these DILI candidates were consistent with Hy's law criteria (e.g. AST/ALT >3.0x ULN and TBL >2.0xULN in the absence of cholestasis and other explanatory causes). Five of these cases were in combination with fulvestrant in study CBKM120F2302, and one in combination with the investigational drug LDE225 (sonidegib) in study CLDE225X2114. All patients have recovered upon treatment discontinuation except one patient for whom the outcome is not available because the patient refused to return for safety follow-up. Of note, with the exception of the first case reported as Investigator notification (IN) in April 2014, it is unknown at this stage whether the remaining patients received BKM120 or placebo as the trial remains blinded. Updated liver safety including the identified DILI/Hy's law candidates for the randomized, blinded studies CBKM120F2302 and CBKM120F2303 were further presented to the Data Monitoring Committee (DMC) in April 2015; the DMC noted no change or additional liver safety concerns and recommended continuing the respective studies as planned.

An Aggregated Safety Finding Report was submitted to Health Authorities and all investigators participating in buparlisib studies in May 2015 informing them about the liver findings including a brief summary of six Hy's law cases identified. In addition, Novartis decided to update the current liver-related safety measures in ongoing protocols to enhance patient safety. Therefore, the purpose of this protocol amendment is to provide additional guidance to investigators around management of liver toxicities as outlined below.

On 11 May 2015, the DMC reviewed the safety data from 135 randomized patients, and have been presented a summary of the aggregated safety report of liver toxicity. The

recommendation was to continue with the trial as planned. The DMC also recommended that sites vigilantly monitor ongoing patients, in particular for AEs of special interest as thoroughly stated in the protocol.

Additional changes to the protocol

Changes to the protocol summary section:

- Clarification provided in the data analysis to reflect the change in wording for number of events needed for final Progression Free Survival and final Overall Survival analyses;

Changes to the background section:

- Update of the clinical background section on liver toxicity to align with the protocol amendment rationale.

Changes in the section on management and follow-up for selected toxicities:

- Addition of hepatotoxicity management guidelines

Changes to the visit schedule and assessments:

- Clarification of laboratory parameters collection plan and viral hepatitis testing.

Changes to the statistical section:

- Clarification of the wording for the number of Progression-free survival events required for the PFS analysis and for the number of deaths to be observed for the planned final Overall Survival analyses.

Changes to the protocol

The following sections have been changed in the amended protocol:

Section 1.2.1.2 Clinical experience: addition of the outcome from a recent medical review for the liver toxicity.

Section 4.3 Primary Statistical Analysis, wording change for the number of events to be obtained for the primary PFS Analysis

Section 4.4 Definition in the end of study, new wording added for a potential transition to another protocol for patients still on treatment at the time of the final OS analysis

Section 6.2 - Table 6-3 (Criteria for interruption and re-initiation of BKM120/placebo treatment): Clarification of the management of AST or ALT side effects.

Section 6.2.2.3.7 (Additional management and follow-up for selected toxicities): New section added “Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120/placebo” including detailed liver event follow-up assessments and close monitoring measures.

Section 7.1 Study flow and visit schedule - Table 7-1 (Visit evaluation schedule): addition of hepatotoxicity follow-up testing/procedures.

Section 7.1.4.1 Criteria for premature patient withdrawal updated with new wording for withdrawal of consent

Section 7.2.2.5 (Laboratory evaluations) and Table 7-4 (Clinical laboratory parameters collection plan): addition of hepatotoxicity follow-up testing and procedures (Note: testing not mandatory).

Section 7.2.2.5.7: New section added "Viral hepatitis serology and other tests for hepatotoxicity follow-up".

Section 10 Statistical methods and data analysis, wording change for the number of events to be obtained for the primary PFS Analysis

Sesction 10.4.2 Statistical hypothesis, model, and method of analysis, wording change for the number of events to be obtained for the primary PFS Analysis

Section 10.5.2 Other secondary efficacy objectives, wording change for the number of events to be obtained for the final Overall Survival Analysis

Section 10.5.3.2 Post-treatment period: starting at day 31 after last dose of study medication.Adverse events (AEs), updated with summary of deaths will include on-treatment and post-treatment deaths.

Other changes have been done for editorial purpose throughout the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (Dec 2013)

The main rationale of the amendment 1 was:

- To include PK sampling collection in a subset of patients in order to characterize the pharmacokinetics of buparlisib given in combination with paclitaxel. The aim is to assess if patients treated with buparlisib are exposed to the drug within the targeted range. The inclusion of this assessment is based on findings that emerged from study [CBEZ235A2118] which investigated the use of the same combination (buparlisib and paclitaxel). In this combination study, it was observed that the administration of 100 mg buparlisib led to a 35% lower exposure compared to the administration as single agent in study [CBKM120X2101]. The collection of additional PK data will provide more information in support of this study indication (dose exposure/effect relationship in the targeted population) and also to obtain a more robust population PK model based on several indications currently in clinical development using the same regimen. Objectives and statistical plan are updated accordingly

- To reduce the amount of tumor tissue required at baseline for HPV and PI3K pathway determination (inclusion criterion # 4). Novartis has adopted the use of a more sensitive platform (Next Generation sequencing) requiring smaller amount of DNA compared to the one previously used (Sanger sequencing). The list of biomarkers being assessed will not change.
- To allow confirmation of an adequate amount of tumor tissue for enrollment by central or local pathologist (following Novartis defined procedure) in order to accelerate the turn-around time for eligibility decision making process and eventually to start the study treatment earlier.
- To modify inclusion criteria #7 as follows:
  - Mild and asymptomatic transaminase elevations at baseline are a common finding in this patient population even in the absence of liver metastasis (e.g. related to concomitant medications, prior treatment/surgery, underlying disease, fatty liver, etc.). Therefore, the upper limit for AST/ALT in patients without liver metastasis will be slightly increased to allow 1.5x ULN for study inclusion. The ULN for bilirubin remains unchanged. Furthermore, the requirement to be above the lower limit of normal has been removed for AST/ALT and bilirubin since values below the normal range are considered not clinically relevant for the purpose of entry into this study.
  - Grade 1 and asymptomatic electrolyte alterations at baseline are a common finding in this patient population therefore if judge not clinically relevant by the investigator; patient may enter into the study.
- To update safety management guidelines for skin toxicity (section 6.2.2.3.4): rash being a frequent and expected AE observed with buparlisib, more detailed guidelines for dose reduction/interruption and therapeutic approach are provided for an optimal management of skin toxicities.
- To provide an update on clinical experience with buparlisib (section 1.2.1.2) and permitted concomitant therapy (section 6.3.1) according to information included in the latest Investigator's Brochure
- To provide additional clarification of study procedures during screening, baseline tumor evaluation requirements, and schedule of DMC meetings are included in the amendment

Changes to the protocol

The following sections were changed in the Amendment 1 of the protocol:

1. Section 1.2.1.2 Clinical experience with buparlisib has been updated according to the latest Investigator's Brochure
2. Section 1.2.2. Paclitaxel and potential for interaction has been updated to introduce the PK sampling added to this protocol
3. Section 2.3 Rationale for dose and regimen selections has been updated
4. Section 3 Objectives and endpoints has been updated to include an additional secondary endpoint based on PK

5. Section 5.1 Inclusion Criteria / criterion #4 has been revised to reduce the number of tumor tissue to be collected at screening and allow confirmation by both central and local pathologists
6. Section 5.1 Inclusion Criteria / criterion #7 has been revised to allow upper limit for AST/ALT in patients without liver metastasis to be slightly increased to 1.5x ULN and to allow patients to enter the study with grade 1 and asymptomatic electrolytes alterations if judge not clinically relevant by the investigator
7. Section 5.2 Exclusion Criteria/ criterion #8 and criterion #9 have been updated to reflect data from the last Investigator's Brochure
8. Section 6.1.1.1 has been updated to provide the definition of a light breakfast, and additional dosing guidelines for PK sampling
9. Section 6.2.2.1 Criteria for buparlisib /placebo dose modifications has been updated for skin toxicities
10. Section 6.3.1 Concomitant Medication, this section has been updated according to the latest Investigator's Brochure
11. Section 6.5.1 Study Drug Preparation and dispensation, this section has been updated to clarify the use of IRT for paclitaxel dispensation
12. Section 7.1 Study Flow and Visit Schedule has been updated to reflect PK sampling
13. Section 7.2.1 Efficacy assessments has been revised for imaging requirement at screening
14. Section 7.2.2 Safety and Tolerability / Laboratory Evaluation has been clarified for the situation when lab assessment has been done 7 days prior to study treatment start and PTT was corrected to aPTT
15. Section 7.2.3 Biomarkers has been updated based on the reduction on tumor tissue and blood requirement;
16. Section 7.2.5 has been amended and refers now to the PK section
17. Section 8.6 Data Monitoring Committee, has been amended to clarify schedule of the safety review by the DMC
18. Section 9.3 Data Collection has been updated to include PK data
19. Section 10.1 Analysis Sets has been amended to include PK analysis sets
20. Section 10.5 Secondary Objectives has been amended to add a section for Pharmacokinetics

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Epidemiology and current treatment options

Cancer of the head and neck includes all cancers arising from the upper aerodigestive tract, and typically refers to squamous cell carcinomas originating from mucosal surfaces which represent more than 90% of cases. The incidence of head and neck squamous cell carcinoma (HNSCC) has been gradually increasing over the last three decades. It is the fifth leading cause of cancer by incidence and the sixth leading cause of cancer mortality in the world (Parkin 2006). The most important risk factors so far identified are tobacco and alcohol which have a synergistic effect on the mucosal surfaces. Diet is another factor implicated in the etiology, especially a low consumption of fibers and vitamins (Majewski 2009). Oral hygiene and the state of dentition have also been linked to an increased risk of developing oro-pharyngeal cancer.

There has been increasing awareness of a subset of HNSCC, i.e. Human papillomavirus (HPV)-positive HNSCC. HPV infection contributes to the etiology of around 60% of oropharyngeal cancers, and HPV16 is the most frequently detected strain. HPV leads to tumorigenesis through the production of two oncoproteins, E6 and E7, which degrade the tumor suppressor proteins, p53 and retinoblastoma (Rb), respectively. These events lead to uncontrolled cell cycle progression and potential malignant transformation. HPV infection is currently the only biomarker capable of predicting response to chemotherapy in this tumor type, whereby HPV-positive tumors present a better response to chemotherapy, leading to improved locoregional control and longer overall survival (Braemer 2010). Patients with HPV-positive HNSCC tend to be younger and have a lower intake of tobacco and alcohol.

Treatment modalities for HNSCC include surgery, radiation therapy, and chemotherapy. Most patients with HNSCC present with advanced locoregional disease. With advanced HNSCC, only 35% to 55% of patients survive and remain disease-free for three years, despite aggressive therapy. Locoregional recurrence develops in 30% to 40% of patients and distant metastases develop in 12% to 22% of patients (Forastiere 1998). Palliative treatment of recurrent/metastatic HNSCC remains largely ineffective and little progress has been made. More effective, targeted treatments are needed.

Although HNSCC can be considered a chemosensitive disease as shown by high response rates with aggressive induction therapies (eg. combination of 5-FU, cisplatin and docetaxel), the results are poor at relapse (Posner 2007; Vermorken 2007). Despite the progress in the primary treatment by combining chemotherapy, surgery, radiation therapy, and supportive care, the recurrence rate ranges from 30 to 50%. Patients usually relapse locally and develop symptoms such as difficulties in swallowing, eating, and speaking. The median survival for patients with recurrent disease is six months and can reach 10 months in patients with good general status (Vermorken 2008). Thus, improving the clinical benefit in this population is important to improve patients' quality of life.

Platinum-based chemotherapy has been the cornerstone of first-line treatment for metastatic HNSCC since the 1980s. Two randomized Phase III studies conducted as first-line treatment in the metastatic setting showed that platinum-based doublets produced higher response rates than those of single-agent therapy, even though median overall survival (mOS) was not extended (Forastiere 1992; Jacobs 1992). In a phase III trial in patients with metastatic/recurrent HNSCC, there was no significant difference in survival between cisplatin plus 5-FU and cisplatin plus paclitaxel, but the safety profiles of the two regimens were different (Gibson 2005). Therefore, the combination cisplatin/5-FU still represents the most commonly used chemotherapy regimen in 1st line setting.

More recently, the addition of cetuximab to the combination of cisplatin and 5-FU for first - line treatment has shown not only a higher response rate when compared to chemotherapy alone and has also resulted in a remarkable increase in OS since the introduction of cisplatin (Vermorken 2008) (Table 1-1).

Table 1-1 Key randomized phase III trials as first-line treatment in recurrent or metastatic HNSCC

Reference	No. of patients and characteristics	Treatment	RR (%)	mPFS (months)	mOS (months)
Jacobs (1992)	N=245 PS 0–1 in 62%; mostly recurrent	A. Cisplatin/5-FU B. Cisplatin C. 5-FU	A. 32 (21–42) B. 17 (9–25) C. 13 (6–21) A vs B: p= .035 A vs C: p= .005	A. 2.4 B. 2.0 C. 1.7 p= .023	A. 5.5 (4.0–8.8) B. 5.0 (4.1–7.2) C. 6.1 (4.6–7.2) p= .49
Forastiere (1992)	N=261 PS 0–1 in 72%; recurrent (93%)	A. Cisplatin/5-FU B. Carboplatin/5-FU C. Methotrexate	A. 32 B. 21 C. 10 A vs B: p< .001 B vs C: p= .05	NR	6.6 5.0 5.6 p=NS
Vermorken (2008) (EXTREME trial)	N=442 KPS ≥70 (88%); recurrent only (53%); metastatic with or without recurrence (47%)	A.Platinum/5-FU /cetuximab B.Platinum/5-FU	36 (29–42) 20 (15–25) p= .001	5.6 (5.0–6.0) 3.3 (2.9–4.3) p= .001	10.1 (8.6–11.2) 7.4 (6.4–8.3) p= .04

Therefore, the combination of cetuximab with cisplatin/5-FU has become the standard first-line treatment for patients with recurrent or metastatic HNSCC, in fit patients with a good general status and in patients with more aggressive or symptomatic disease (NNCN guidelines; Price 2012). Platinum doublets with 5-FU or taxanes are still considered as an

alternative first-line treatment when it is not feasible to use cetuximab in association with platinum (Price 2012). In case of lack of tolerance, contraindication to platinum-based regimens or frail patients, the use of single agents (such as paclitaxel, docetaxel, capecitabine, methotrexate), is still considered an alternative option in first-line treatment.

For patients who progress after platinum-based therapy there is no standard second-line chemotherapy regimen. The most commonly used compounds after platinum failure are single agent methotrexate and taxanes (De Andrade 2012). For this group of patients, even if another treatment is initiated, median OS remains low (between three and seven months), thus highlighting the aggressiveness of this malignancy and the need for more effective therapies (Stewart 2009; Leon 2005). Other chemotherapeutic agents including bleomycin, oxaliplatin, cyclophosphamide, pemetrexed, gemcitabine and doxorubicin have been tested in the palliative setting, either in combination or as monotherapy.

Among targeted therapies, single-agent cetuximab is the only one currently approved (only by FDA) after platinum-failure based on the results of a single arm phase II study with 103 patients. The observed median TTP and OS were 2.3 and 5.9 months, respectively (see Table 1-2) (Vermorken 2007).

Only small studies have assessed the combination of cetuximab and cytotoxic agents, but none of these regimens is currently approved or recommended by international guidelines.

Table 1-2 Overview of key studies in recurrent HNSCC after platinum based treatment

Study and Reference	No. of patients and Characteristics	Treatment	RR (%)	mTTP/mPFS (months)	mOS (months)
Cetuximab					
Ph II (Vermorken 2007)	N=103 All pts platinum failure	Cetuximab	13%	2.3	5.9
Taxanes					
Ph II (Tahara 2011)	N=74 - 23% of patients 2nd line (after platinum) - 77% of patients 1st line (no platinum-compounds in rec/met phase)	Paclitaxel 100 mg/m^2 weekly for 6 out 8 weeks	37%	3.4	14.0
Ph II (Koussis 2007)	N=24 All pts platinum-failure	Docetaxel 35 mg/m^2 weekly	25%	3.2	Not assessed

1.1.2 The PI3K Pathway

The phosphatidylinositol 3-kinase (PI3K) signaling pathway regulates diverse cellular functions, including cell proliferation, survival translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis (Katso 2001). PI3K signaling also serves a central role in the pathogenesis of numerous forms of neoplasia. At the structural level, the enzyme PI3K is composed of a 110-kDa catalytic subunit and an 85-kDa adaptor

subunit. PI3K signaling is modulated by multiple regulators, including growth factors (such as EGF, IGF-1, and FGF), hormones (such as estrogen and thyroid hormone), integrins, intracellular calcium levels, and RAS signaling. PI3K signaling is negatively regulated at the level of PIP3 clearance by phospholipid phosphatases, such as the phosphatase and tensin homologue (PTEN) protein and the inositol 5-phosphatase-2 (SHIP2) protein.

Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors in many tumor types (Liu 2009). Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal therapy and anti-HER2 therapies, can also be linked to constitutive activation of the PI3K pathway (McCubrey 2006). Moreover, preliminary data suggest that activation of the PI3K pathway might be a predictor of poor prognostic outcome in many cancers.

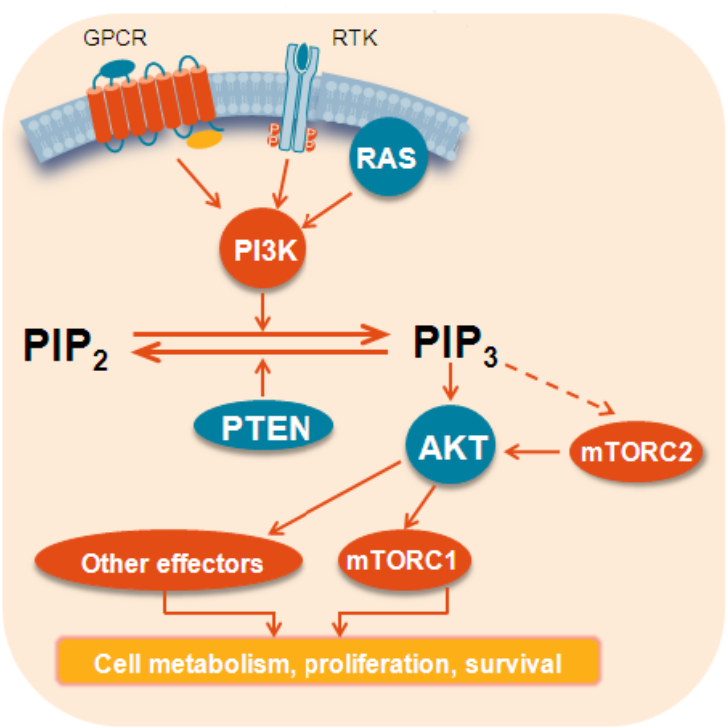
Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but are not limited to:

a. Gain-of-function mutations of PI3K subunits (*PIK3CA* encoding the PI3K catalytic subunit p110α; genes encoding the p85 regulatory subunit) or oncogenes encoding positive regulators of PI3K (e.g., HER2, EGFR, RAS, Src-family proteins)

b. Loss-of-function mutations or epigenetic alterations affecting negative regulators of PI3K signaling (e.g., loss of PTEN expression or function) (Chow 2006; Cully 2006)

Together these observations suggest that the PI3K pathway could be a critical therapeutic target for the treatment of patients with advanced solid malignancies who often have limited therapeutic options beyond the regional standard of care. Hence, pan-PI3K inhibitor treatment with buparlisib potentially addresses an unmet medical need in such patients. A schematic representation of these PI3K components is shown in Figure 1-1.

Figure 1-1 Schematic representation of the PI3K pathway



1.1.3 PI3K pathway in squamous head and neck cancer

The PI3K (phosphatidylinositol 3-kinase) pathway is a signal transduction cascade that is central to a variety of important physiological functions, including cell cycle, cell survival, protein synthesis, growth, metabolism, motility and angiogenesis. Constitutive PI3K-Akt-mTOR pathway activation, which occurs approximately in 30% of human cancers, has been associated with poor prognosis. In patients presenting with HNSCC, molecular alterations affecting both the level of expression and function of PI3K pathway constituents have been identified. These include gain-of-function mutations and amplifications in PIK3CA, loss of heterozygosity and inactivating mutations in PTEN (negative regulator of the PI3K pathway), as well as overexpression/activation of AKT and mTOR signaling (molecular components downstream of p110a but critical to overall PI3K pathway activation) (Leemans 2010; Molinolo 2009).

Multiple genetic and epigenetic events may converge to promote the activation of the PI3K-Akt-mTOR pathway in HNSCC. Copy number gain and amplification at 3q26, where the PI3Ka gene is located, represents a frequent (approximately 40% of cases) and early genomic aberration in HNSCC (Woenckhaus 2002), which may contribute, along with epigenetic events, to PI3K overexpression and Akt activation (Fenic 2007; Pedrero 2005). Interestingly, activating mutations in the PIK3CA gene can be observed in a small fraction (< 10%) of HNSCC tumors (Stransky 2011; Kozaki 2006; Murugan 2008) but have been seen with a higher frequency (20%) in HNSCC arising from a pharyngeal site (Qiu 2006; Qiu 2008). PTEN can display genetic alterations in 5–10% of HNSCC lesions. Remarkably, loss of PTEN expression can be observed in approximately 30% of HNSCCs, and may constitute an independent indicator of poor clinical outcome (Lee 2001; Squarize 2002).

Akt, another component of the PI3K pathway has been shown to be persistently activated in the vast majority of HNSCC cases. The activation status of Akt showed correlation with disease progression, with a different expression in dysplasia, carcinoma in situ and HNSCC (Amornphimoltham 2004). Activation of Akt represents an independent prognostic marker of poor clinical outcome in both tongue and oropharyngeal HNSCCs (Massarelli 2005; Yu 2007). Akt can be activated in HNSCC due to excessive activity of EGFR, RAS mutations, PI3Ka gene amplification, overexpression, or activating mutations, or defective PTEN activity resulting from genetic alterations and/or decreased expression. These multiple convergent pathways, all of which can result in enhanced Akt function, may explain why activation of this pathway represents one of the most frequent events in HNSCC (Molinolo 2007).

The PI3K pathway has also been shown to be activated in response to HNSCC-specific alterations, either as a mechanism of resistance to EGFR inhibition (Rebucci 2011) or associated with HPV infection (Yarbrough 2007). However, specifically with regards to HPV induced HNSCC, still preliminary is the role of PI3K pathway activation as predictive or prognostic factor.

In HPV negative oropharyngeal SCC, a retrospective analysis has been conducted on 73 patients primarily treated with surgery followed by postoperative radiation to assess the association between expression of EGFR, IGF1R, PI3KCA, TP53 and disease-free survival (DFS). Interestingly, in 40% of patients was observed an increased PI3KCA gene copy number and the results from the analysis have shown that PI3KCA amplification and polisomy were associated with better prognosis (HR: 3.20, p=0.003) (Perrone 2010).

Recently, a Phase I/II clinical trial evaluated the combination of everolimus with paclitaxel and carboplatin as induction treatment for advanced unresectable HNSCC stage III-IV patients. Preliminary results have shown promising antitumor activity, supporting the role of mTOR pathway inhibition in head and neck cancer treatment. Among 13 evaluable patients: 11 objective responses were observed, including one complete response (CR), 10 partial responses (PR) and one stable disease (SD) (Faivre Oral presentation ESMO 2012).

This evidence supports the need for further investigation of the PI3K pathway inhibition in the clinical setting in an attempt to improve quality of life, symptoms, disease control and outcome in patients with recurrent and/or metastatic head neck cancer in whom available treatments have shown a limited benefit.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of Buparlisib/BKM120

NVP-Buparlisib (BKM120) is a potent and highly specific oral pan-class I PI3K inhibitor that is a 2,6-dimorpholino pyrimidine derivative. This compound has been studied extensively in non-clinical models and is currently being evaluated in clinical trials. Class I PI3Ks are key components of the PI3K/AKT/mTOR signaling pathway, which regulates cell proliferation, growth, and apoptosis. In many tumors the PI3K signaling pathway is constitutively activated. This is thought to be a critical step in mediating the transforming potential and growth stimulating activity of various activated proto-oncogenes (ErbB2, EGFR, Ras, Src, etc) contributing to the onset and progression of solid tumors as well as of hematological

malignancies. This compound has been studied extensively in non-clinical models and is currently being evaluated in clinical setting.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacodynamics

Buparlisib inhibits all four PI3K catalytic subunits, including the PI3Kα mutant (H1047R-, E542K-, and E545K-p110α) with at least 50-fold selectivity towards this target compared to other protein and lipid kinases. Through this inhibition, it indirectly reduces activation of the direct downstream effector AKT. Buparlisib does not inhibit the related kinases mTor or Vps34, nor does it inhibit receptors and ion channels profiled (IC50 >10 μM).

Buparlisib demonstrates significant tumor growth inhibition in relevant tumor xenografts in mice and rats when administered orally, including models of renal cell cancer (RENCA, 786-0, Caki-1), glioblastoma multiforme (U87MG), prostate cancer (PC3M), lung cancer (A549, NCI-H1975), ovarian cancer (A2780), colorectal cancer (HCT116, HCT-15) and melanoma (A2058, A375). In vivo PK/PD analyses of tumor tissues shows a good correlation between exposure, PI3K pathway blockade (S473P-Akt levels), and anti-tumor activity.

1.2.1.1.2 Safety pharmacology and toxicology

Safety pharmacology studies in rats revealed no effects on neuronal (behavior) or respiratory functions. Cardiac safety studies, conducted in vitro and in vivo did not indicate a prominent electrophysiological risk. No relevant electrophysiological effect was seen in dogs. The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure, which was observed in two dog telemetry studies. In rats and dogs, clinical pathology and histopathology findings showed quantitative reductions of lymphoid and erythroid counts and lymphoid tissue hypoplasia.

The pancreas was seen to be affected by treatment with buparlisib, particularly in dogs, where acinar cell toxicity was seen in the exocrine part of this organ. At higher doses in the 2-week dose-range-finding study in rats, there were histopathological findings in both the endocrine as well as the exocrine pancreas.

Male sexual organs and associated tissues were found to be targets of toxicity in both rats and dogs. Changes included minimal to slight germ cell depletion, formation of spermatic giant cells and abnormal spermatids, and cellular debris in epididymal tubules. Testicular toxicity did not fully reverse after the 4-week treatment-free period in rats (highest dose), although a clear trend towards recovery was seen. In individual female rats, minimal to slight cyst formation occurred in the Graafian follicles. In dogs, there was no effect on female sexual organs.

Glucose homeostasis was affected in various species (mice, rats, dogs), as expected from the mode of action of buparlisib. However, these effects were minimal in both rats and dogs at the doses used in the 4-week studies.

Other safety considerations include:

- After up to 2 weeks of treatment with up to 2.5 mg/kg/day of buparlisib, alterations in the levels of multiple brain neurotransmitters were seen in rats.

- No evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests in vitro with buparlisib. However, evidence of a genotoxic potential with buparlisib has been seen in vitro and in vivo and is likely due to an aneugenic effect.
- No phototoxic potential or any effect on wound healing has been identified with buparlisib in pre-clinical studies.

In conclusion, the majority of the observed effects were related to the pharmacological activity of buparlisib as an inhibitor of PI3K, such as a potential influence on glucose homeostasis and the risk of increased blood pressure.

Please refer to the Investigator's Brochure for additional information on the preclinical testing of buparlisib.

1.2.1.1.3 Pharmacodynamic biomarkers

Preclinical in vivo studies with in mouse xenograft models indicate that detectable inhibition of AKT phosphorylation, which is an accurate readout of PI3K activity, as well as further suppression of downstream signaling (e.g., decrease of phosphorylation of S6) was obtained soon after buparlisib administration. PI3K is known to serve a pivotal role in the regulation of glucose homeostasis, and preclinical studies in which oral glucose and intraperitoneal insulin tolerance tests were performed have suggested post-treatment induction of insulin insensitivity/resistance. Therefore, throughout the trial the circulating levels of several markers for glucose metabolism (e.g., glucose, C-peptide) will be assessed as an additional measure of PI3K signaling modulation.

1.2.1.1.4 Non-Clinical experience of BKM120 in HNSCC

In preclinical setting it was already shown that the mTOR inhibitor rapamycin, either as single agent or in combination with carboplatin and paclitaxel exerts an antiproliferative effect on head and neck cancer cell lines. Indeed it was observed that mTOR inhibitors potentiate the proapoptotic effects of cytotoxic agents in HNSCC cells; this synergistic effect may counteract the resistance to chemotherapy (Aissat 2008).

Treatment of a series of HNSCC cell lines using BKM120 showed response in the majority of the lines (Figure 1-2). Furthermore in vivo treatment of a xenograft model (FaDu) showed down regulation of pAKT in tumor treatment as well as significant reduction of tumor hypoxia in the animals treated with doses equivalent to patient's MTD. Results from a study conducted in FaDu xenograft models with BKM120 have shown that inhibition of the PI3K-Akt-mTOR pathway can elicit tumor regression, normalizes the tumor vasculature and induces radiosensitization (Fokas 2012).

Figure 1-2 Effect of BKM120 on a variety of HNSCC cell lines

IC50s are under 1micromolar (equivalent to dose expected in patients) in the majority of the cell lines indicating a potential for benefit from a pan PI3K inhibitor.

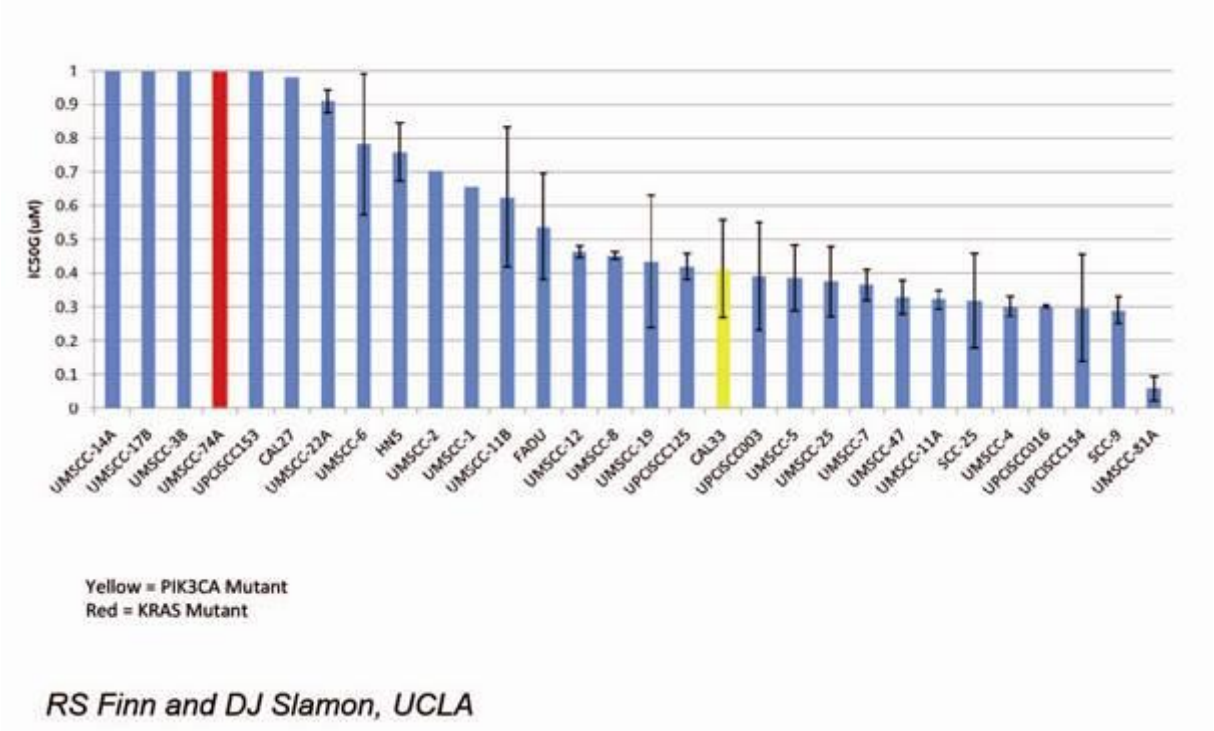
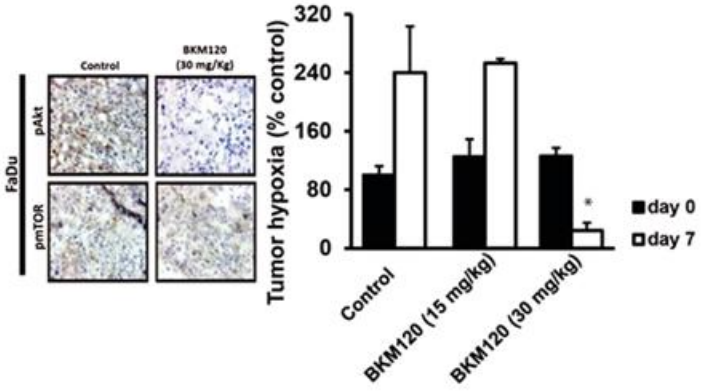


Figure 1-3 Treatment of a xenograft model of HNSCC (Fadu) with BKM120

Treatment with BKM120 elicits downregulation of pAKT in tumor tissue (left panel) while significantly decreasing hypoxia in the tumor (right panel) (Fokas 2012)



1.2.1.1.5 Non-clinical pharmacokinetics

Buparlisib showed favorable pharmacokinetic properties in all animal species tested. The absorption of [^{14}C]-BKM120- related radioactivity was > 84% in the rat. Oral bioavailability was moderate to high in rats, dogs and monkeys (42-100%). The estimated steady state plasma volume of distribution (Vss) was moderate in all species (3.0–3.5 L/kg). Buparlisib penetrated the blood brain barrier in rats with a tissue-to-plasma ratio about 2. Buparlisib was moderately bound to plasma protein across all species examined (free fraction ~15% and independent of concentration in humans).

Oxidative metabolism of buparlisib is predominantly mediated by cytochrome P450 (CYP) isoenzyme 3A4, the estimated fraction of the oxydative metabolism is above 0.9. Recombinant human CYP1A1 also has the capacity to metabolize buparlisib, however, its endogenous expression in the human liver is negligible, and therefore it is not expected to have any impact on hepatic buparlisib metabolism. Direct phase II metabolism (glucuronidation) via UGT1A4 is also observed in human liver microsomes supplemented with uridine diphosphate glucuronic acid (UDPGA). All phase I metabolites identified in human hepatocytes and microsomes are not unique to humans and were also detected in animals. Buparlisib and identified metabolites have a low potential for covalent binding to protein.

Buparlisib is a weak reversible inhibitor of CYP3A4 (Ki= 13.6 µM,) and it also weakly inhibits the CYP2C family (2C8, 2C9 and 2C19) with IC50 values ranging from 35–65 µM. Buparlisib did not show time-dependent inhibition of CYP450 enzymes. With respect to transporter-based drug-drug interactions, buparlisib is not an inhibitor or substrate of P-glycoprotein (P-gp), multi-drug resistance associated protein (MRP)-2, breast cancer resistance protein (BCRP), and organic cation transporter (OCT)2. Buparlisib can inhibit hMATE1 and hMATE2K *in vitro* at concentrations above 10 µM. Based on the observed free concentrations of buparlisib in plasma the impact *in vivo* of such inhibition is expected to be

very limited. It is possible that buparlisib activates the pregnane X receptor (PXR) *in vivo* and induces CYP3A4 at concentrations ≥50 µM, however, the absence of any time dependent changes in the pharmacokinetics of buparlisib in the relevant therapeutic dose range in humans, suggests that this may not be relevant *in vivo*. Finally, experiments showed a potential for buparlisib to induce UGT1A1 at concentrations between 0.5 and 100 µM. The mean maximum free concentration calculated at steady state to date in the study [CBKM120X2101] was 0.671 µM (Cmax,tot=4.20 µM). Therefore a potential induction of UGT1A1 cannot be formally excluded, however the clinical relevance of observed activation of UGT1A1 activity is unclear.

In GLP toxicology studies, buparlisib exposure in terms of AUC0-24h and Cmax increased in a dose proportional manner in rat and dog. There was no noticeable drug accumulation in dog or male rats after 13 weeks of daily dosing. There was a slight accumulation in female rats (< 2 fold). This gender based difference in the plasma concentrations has not been seen in the human Phase I study.

1.2.1.2 Clinical experience

- As of 15-September-2013, a total of 1469 patients and healthy volunteers have been enrolled into twenty two Novartis sponsored clinical studies of buparlisib: Phase I single agent studies [CBKM120X2101], [CBKM120X1101], [CBKM120Z2102], [CBKM120C2110], [CBKM120C2104], [CBKM120C2106], [CBKM120C2111] and [CBKM120C2102].
- Phase II single agent studies [CBKM120C2201] and [CBKM120D2201]
- Phase I combination studies [CBKM120B2101], [CBKM120X2107], [CBKM120E2101], [CBEZ235A2118], [CLDE225X2114], [CSTI571X2101], [CMEK162X2101], [CINC424A2104] and [CBEZ235D2101].
- Phase II combination study [CBKM120F2202]
- Phase III combination study [CBKM120F2302] and [CBKM120F2303]

1.2.1.2.1 Human safety, tolerability data, single agent buparlisib

Study [CBKM120X2101] was a Phase I first-in-man dose escalation study of single-agent oral buparlisib in patients with advanced solid tumors. This study has been completed, 83 patients were enrolled and treated with at least one buparlisib dose. The MTD/RP2D of single-agent oral buparlisib was determined to be 100 mg/day. The most frequent AEs (≥10%), regardless of grade, causality and buparlisib dose, were nausea (45.8%); decreased appetite (42.2%); asthenia (37.3%); diarrhea (36.1%); hyperglycemia (33.7%), rash (31.3%); constipation (30.1%); fatigue (28.9%); vomiting (26.5%); stomatitis (25.3%); abdominal pain (22.9%); pruritus (20.5%); anxiety (19.3%); depression or pyrexia (16.9% each); dry skin, dyspepsia, or somnolence (15.7% each); mood altered (14.5%); AST increased, dizziness, dyspnea, or transaminases increased (13.3% each); back pain, insomnia, or performance status decreased (12.0% each); and ALT increased, arthralgia, cough, or edema peripheral (10.8% each). The most common CTCAE grade 3 or 4 AEs (>2%), regardless of causality and buparlisib dose, were asthenia (12.0%); performance status decreased (9.6%); transaminases increased or hyperglycemia (8.4% each); rash (7.2%); hyperbilirubinaemia or AST increased (4.8% each); ALT increased, abdominal pain, fatigue, pneumonia, or diarrhea (3.6% each);

and affective disorder, anxiety, mood altered, glucose tolerance test abnormal, arthralgia, dyspnea, pruritus, or intestinal obstruction (2.4% each).

Another single agent trial, [CBKM120X1101], was a phase I dose escalation study in Japanese patients with advanced solid tumors; dose levels ranged from 25 to 100 mg/day (Doi 2011). Enrollment of 15 patients has been completed, including 9 patients at 100 mg/day. One DLT (G4 hepatic function abnormal) was observed in the 100 mg/day group. The most common G3 or G4 adverse events occurring in at least 2 patients were hepatic function abnormal in 6 patients, including transaminase increase in 2 patients, transaminase elevations typically occur during the first 6 to 8 weeks of treatment start, G3 anemia in 2 patients, and hypokalemia in 2 patients. The recommended Phase 2 dose (RP2D) in this population of Japanese patients has been determined to be 100 mg/day, which is identical to that in the western population.

[CBKM120D2201] is a Phase II open label two-stage study of orally administered buparlisib in patients with NSCLC with an activated PI3K pathway (defined by *PIK3CA* mutation, *PTEN* mutation, and/or PTEN loss of protein expression). As of 15 Sep 13, 62 patients have been enrolled and treated with at least one buparlisib dose of 100 mg/day. The median age was 64.5 (39-78) years, the male/female ratio was 40/22 patients, and the distribution of ECOG performance status of 0/1/2 at baseline was 18/41/3 patients, respectively. The most frequent AEs (≥10%), regardless of grade, causality and buparlisib dose, were decreased appetite and diarrhea (35.5% each); asthenia and nausea (32.3% each); hyperglycemia (30.6%); fatigue (25.8%); rash (24.2%); depression and pruritus (21% each); alanine aminotransferase increased, cough, anxiety or weight decreased (17.7% each); aspartate aminotransferase increased and vomiting (16.1% each); dry skin (14.5%); anaemia, constipation or dysgeusia (12.9% each). The most common CTCAE grade 3 or 4 AEs (seen in more than 2 patients) regardless of causality and buparlisib dose, were hyperglycemia (16.1%); asthenia (11.3%) and dyspnea, asparate aminotransferase increased, alanine aminotransferase increased or fatigue (8.1%). See [Investigator's Brochure] for more details.

1.2.1.2.2 Human safety and tolerability data, buparlisib combination therapy

Study [CBEZ235A2118] is a Phase Ib multi-center, open-label, four-arm dose-escalation study of oral BEZ235 or buparlisib in combination with weekly paclitaxel in patients with advanced solid tumors and weekly paclitaxel/trastuzumab in patients with HER2+ metastatic breast cancer. As of 02-Apr 13, 53 patients had been enrolled into buparlisib + paclitaxel arm and treated with at least one buparlisib dose. The MTD was determined to be buparlisib 100 mg/day in combination with weekly paclitaxel 80 mg/m^2 for cycles of 28 days. The most frequent AEs (≥10%), regardless of grade, causality, and buparlisib dose, were diarrhea (62.3%); nausea (58.5%); asthenia (54.7%); decreased appetite (49.1%); fatigue (41.5%), anemia (39.6%), alopecia (37.7%); hyperglycemia, constipation (34% each); vomiting (30.2%); stomatitis (28.3%); cough (24.5%); dry skin, dyspnea or epitaxis (22.6% each); depression, dysgeusia, neurotoxicity or pyrexia (20.8% each); peripheral edema (18.9%), abdominal pain, back pain or pruritus (17% each); hypomagnesaemia, neutropenia, peripheral sensory neuropathy, maculo-papular rash or decreased weight (15.1% each); dyspepsia, nasopharyngitis, or rash (13.2% each); abdominal pain upper, aspartate aminotransferase increased, acneiform dermatitis, hypophosphatemia, or pain in extremity (11.3% each). The most common CTCAE grade 3 or 4 AEs (seen in more than 2 patients), regardless of causality

and buparlisib dose, were neutropenia (15.1%), hyperglycemia (11.3%), fatigue (9.4%), dyspnea or hypokalemia (7.5% each); diarrhea, decreased appetite, peripheral sensory neuropathy, or hypomagnesaemia (5.7% each); asthenia, anemia, hypophosphatemia, blood bilirubin increased, lymphopenia, neutrophil count decreased, presyncope, performance status decreased or abdominal pain (3.8% each). An ongoing trial [CBKM120XUS01T] is evaluating the safety and efficacy of daily buparlisib administered with every-three-week carboplatin dosed at an AUC=5 and paclitaxel at 175 mg/m^2 in patients with solid tumors ([redacted] personal communication). Among 12 patients enrolled as of the data cut-off date, a preliminary evaluation indicates 1/6 DLT at 50 mg buparlisib, 0/3 DLT at 80 mg buparlisib, and 0/3 DLT at 100 mg buparlisib. In addition, one patient treated at 100 mg buparlisib was removed from the study during cycle 1 due to a hypersensitivity reaction associated with buparlisib administration.

A Phase Ib trial of buparlisib with docetaxel is ongoing [CBKM120XUS16T], and 8 patients have been enrolled as of 20 December 2012. The MTD of the treatment combination will be determined also in this study.

A recent liver safety review across Novartis-sponsored trials with BKM120 identified several potentially drug-induced liver toxicity (DILI) cases (e.g. AST/ALT >3.0 x ULN and TBL >2.0 x ULN at any time during the treatment, regardless of causality. Upon medical review, most of these cases occurred in the context of disease progression in terminally ill, advanced cancer patients and/or were confounded by other causes. However, six of these DILI candidates were consistent with Hy's law criteria (e.g. AST/ALT >3.0x ULN and TBL >2.0xULN in the absence of cholestasis and other explanatory causes) with probable causal relationship to study treatment. Five of these cases were enrolled in study CBKM120F2302 in combination with fulvestrant, and one in combination with the investigational drug LDE225 (sonidegib). All patients have recovered upon treatment discontinuation except one patient for whom no data is available since the patient refused to return for safety follow-up.

1.2.1.2.3 Clinical pharmacokinetics

Buparlisib has been administered from 25 mg to 150 mg daily, and the single agent RP2D is 100 mg. When orally administered, buparlisib is rapidly and well absorbed, and the extent of absorption is estimated to be between 57 and 85%, with a median Tmax between 0.5 and 3 hours after administration. Cmax and AUC appeared to be linear in the tested range, with an estimated slope close to 1, but the 90% CI for both AUC0-24, [0.75, 1.21], and Cmax, [0.72, 1.16], was fairly wide, most likely due to low sample size at extreme doses. In plasma, buparlisib concentrations follow a bi-exponential decay, with a long terminal half-life that could not be well estimated given the initial sampling schedule used after daily dosing. It was however well estimated from the terminal half-life cohort and was found to be 48 hours. After repeated dosing the effective half-life (T1/2, acc), was obtained from the observed drug accumulation (Racc). The median T1/2, acc (T1/2 accumulation) calculated from exposure data on Day 28 ranged between 36 and 58 hours across all dose levels. After repeated single dose, steady state is reached in almost 8 days with an accumulation ratio around 3. Buparlisib is eliminated mainly through metabolism in a plethora of entities. After administration of a single dose of [^{14}C]-buparlisib, 51% of the radioactivity was recovered in urine even though buparlisib only contributed to less than 2%. The rest of the radioactivity was recovered in feces with buparlisib represented 15% all other metabolites being below 5%. CYP3A4 was

found *in vitro* to be a major contributor to buparlisib metabolism together with direct glucuronidation which would contribute for less than 10%.

For further details please refer to the [Investigator's Brochure].

1.2.1.2.4 Clinical activity of buparlisib in squamous cell carcinoma

Although tumors of squamous histology from different tissue beds are biologically distinct, clinical data in other squamous tumor settings provides evidence to support the investigation of buparlisib in squamous head and neck cancer.

These collective data summarized in Table 1-3, suggest that tumors of squamous histology may be sensitive to buparlisib-containing therapy.

Furthermore, patients with tumors of squamous histology pretreated with chemotherapy (including taxanes) obtained confirmed tumor responses with paclitaxel-BKM120 treatment. (Dirix ESMO 2012).

The ongoing [CBKM120D2201] trial of buparlisib in PI3K pathway activated NSCLC, is enrolling patients with squamous or non-squamous histology who have received 1 or 2 prior lines of therapy for metastatic disease. The analysis of efficacy is being conducted separately for patients with NSCLC of squamous and patients with non-squamous histology.

Table 1-3 Disease control in individual patients with tumors of squamous histology treated with buparlisib

Clinical Trial*	Tumor histology	Study treatment	Best response
[CBEZ235A2118]	Cervical SCC	buparlisib/paclitaxel	PR
[CBEZ235A2118]	Vulvar SCC	buparlisib/paclitaxel	PR
[CBEZ235A2118]	Penile SCC	buparlisib/paclitaxel	CR
[CBKM120X1101]	HNSCC	buparlisib	PR
[CBKM120D2201]	NSCLC squamous	buparlisib	PR
[CBKM120D2201]	NSCLC squamous	buparlisib	PR
[CBKM120D2201]	NSCLC squamous	buparlisib	PR (not confirmed due to drug interruption in setting of AE and subsequent death)

Data for patients included on clinical trial CBEZ235A2118 were those only in the BKM arm of the study.

* Results of individual patients from indicated clinical trial

1.2.2 Paclitaxel and potential for interaction

- Paclitaxel

Paclitaxel is administered as an intravenous infusion at different doses with different infusion times and administration intervals. In the current trial, paclitaxel will be administered at a dose of 80 mg/m^2 every week as a 1-hour infusion with a cremophor EL formulation. This paclitaxel formulation exhibits strong linearities related partly to the high level of protein binding of paclitaxel and as well to the vehicle (Henningson 2003). Paclitaxel is mainly eliminated via metabolism, with only 5% of the administered dose recovered unchanged in the

feces; the urinary route only contributes to a small extent, with 14% of the administered dose present in the urine. The main metabolite is 6α-hydroxypaclitaxel, which appears to be mainly formed via CYP2C8. Another metabolism route of paclitaxel is via CYP3A4, forming 3'-p-hydroxypaclitaxel. Both metabolites lead to 6α-3'-p-hydroxypaclitaxel.

- Potential for interaction

No major risk for pharmacokinetic interaction is anticipated between the two drugs. In addition, the interaction between buparlisib and paclitaxel has already been investigated in the trial [CBKM120A2118], where buparlisib was administered at doses between 40 and 120 mg and where paclitaxel was administered weekly at the dose of 80 mg/m^2 as a 1-hour infusion every week. No impact of buparlisib has been observed on the pharmacokinetics of paclitaxel. However at the dose of 100 mg, buparlisib exposure could decrease up to 36%. This decrease is not observed at other doses of buparlisib or when combined with paclitaxel and trastuzumab. Therefore, the relation between paclitaxel and buparlisib exposure remains unclear.

A pharmacokinetic assessment will be conducted in a group of patients to further evaluate buparlisib exposure in this specific patient population.

2 Rationale

2.1 Study rationale and purpose

The purpose of this randomized, placebo controlled study is to assess the treatment effect of buparlisib in combination with weekly paclitaxel vs. buparlisib-matching placebo plus weekly paclitaxel on PFS in patients with recurrent or metastatic HNSCC cancer that has progressed after prior platinum based regimen. [redacted]

The rationale behind assessing the effectiveness of buparlisib plus weekly paclitaxel is based on:

- The unmet medical need in this indication and poor outcome with rapid clinical deterioration observed in patients progressing after platinum based regimen in metastatic setting

[redacted]

- Treatment of a series of HNSCC cell lines using buparlisib showed response in the majority of the lines. The preclinical data in Fadu xenograft models of HNSCC treated with buparlisib have shown that inhibition of the PI3K-Akt-mTOR pathway can elicit tumor regression (see Figure 1-3).

2.2 Rationale for the study design

This is a multicenter, randomized, double-blind placebo controlled phase II study. Patients with histologically/cytologically-confirmed HNSCC, recurrent or metastatic disease progressing after prior platinum-based first-line treatment will be randomized in a 1:1 ratio to receive in a blinded manner one of the two treatment arms: buparlisib in combination with paclitaxel or placebo in combination with paclitaxel.

It is anticipated that approximately 150 subjects will be enrolled in this trial.

For patients who progressed after platinum-based therapy, there is no standard second-line chemotherapy. The standard treatment of patients with incurable or metastatic head and neck cancer is in large part dictated by the patient's performance status. In this setting, there is only one targeted therapy only approved in the US, which is cetuximab as single-agent.

Patients will be stratified according to prior lines of systemic treatments received, (1 line *vs*. 2 lines; i.e. patients that received single agent cetuximab as 2nd line) and by region (North America *vs*. Rest of the world).

Patients will continue to receive study treatment according to randomization until disease progression (assessed by RECIST 1.1), unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new neoplastic therapy or at the discretion of the investigator).

[redacted]

The study will be conducted under DMC supervision and regular safety data reviews are planned.

2.3 Rationale for dose and regimen selection

As described in Section 1.2.1.2, buparlisib 100 mg once daily has been established as the MTD/RP2D in two single agent trials ([CBKM120X2101] and [CBKM120X1101]) and in one combination trial ([CBKM120X2107] with trastuzumab), and single agent dosing with 100 mg daily buparlisib in patients with solid tumors is generally well tolerated.

In study [CBEZ235A2118], one treatment arm evaluated buparlisib in combination with weekly paclitaxel in patients with advanced solid tumors, and the drug combination was well tolerated. As of 02-Apr-13, 53 patients had been enrolled into the buparlisib + paclitaxel arm and treated with at least one buparlisib dose. The MTD/RP2D was defined as being buparlisib 100 mg/day of buparlisib in combination with weekly paclitaxel 80 mg/m² with each treatment cycle being of 28 days (Section 1.2.1.2).

Based on preliminary efficacy results in squamous cell tumors and the favorable safety profile of this combination, the same dose regimen is proposed in this study (Section 1.2.1.2 where the study is described). Moreover PK assessment will be conducted to ensure appropriate patient's exposure to the combination buparlisib –paclitaxel (Section 7.2.5)

A randomized, double-blind, placebo controlled, phase II study [CBKM120F2202] assessing buparlisib in combination with weekly paclitaxel in patients with HER2 negative inoperable locally advanced or metastatic breast cancer is currently ongoing. A safety review was performed by the DMC on June 1, 2013. The DMC confirmed that no action was needed and recommended that the study should proceed as planned.

2.4 Rationale for choice of combination drugs

Paclitaxel is one of the agents widely used in the treatment of HNSCC (Table 1-2); either as single agent or in combination with other agents as recommended by international guidelines (NCCN 2012, Section 2.4).

It is recognized that paclitaxel treatment failure may be related either to inherited resistance against the drug or/and the acquired resistance during the therapy. While the exact mechanism(s) underlying the development of treatment resistance towards paclitaxel remain largely unknown, it has been demonstrated that activation of the PI3K-Akt-mTOR pathway confers resistance to paclitaxel (Hu 2002), and that increase in Akt activity may be an early compensatory mechanism of resistance to chemotherapy (Clark 2002). It is thus believed that activation of the PI3K pathway plays an important role in either primary or secondary paclitaxel resistance (Clark 2002). Additionally, in preclinical models, concomitant inhibition of the PI3K pathway enhances the efficacy of paclitaxel as compared to each agent given separately by reducing tumor burden by 80% as opposed to 38% and 51% for agents given individually (Hu 2002).

Paclitaxel has been evaluated in association with LY294002, a PI3K inhibitor, in NSCLC and breast cancer cell lines. It was observed that the PI3K inhibitor greatly enhanced the apoptotic effects of paclitaxel used at the lowest clinically relevant concentration (10 nM) that blocks normal cell cycle progression and induces Raf-1 and ERK1/2 activation. Increasing concentrations of LY294002 from suboptimal (4 μM) to complete inhibition (50 μM) of PI3K inhibitor combined with low-dose paclitaxel resulted in a dose-dependent enhancement of tumor apoptosis (apoptosis enhanced 6-fold over paclitaxel alone) (MacKeigan 2002).

Therefore, considering the established activity of paclitaxel in recurrent/metastatic HNSCC, the relevance of PI3K pathway inhibition in this tumor type as a potential therapeutic target and for overcoming resistance to paclitaxel and also due to the preliminary encouraging clinical activity observed with buparlisib as single agent and in combination with paclitaxel in patients with squamous cell carcinomas, the regimen buparlisib/paclitaxel deserves to be investigated in the setting of recurrent/metastatic HNSCC.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To estimate the efficacy of buparlisib in combination with paclitaxel	PFS according to local radiological assessment and RECIST 1.1	Refer to Section 10.4
Key Secondary		
To assess the efficacy of the combination with paclitaxel in this patient population in terms of overall survival	Overall Survival	Refer to Section 10.5.1
Secondary		
To assess the safety and tolerability of buparlisib in combination with paclitaxel in this patient population	Frequency and severity of adverse events Other safety data as considered appropriate	Refer to Section 10.5.3
To evaluate additional efficacy parameters	Overall Response Rate (ORR) Time to Response (TTR) Disease Control Rate (DCR) Duration of Response (DoR)	Refer to Section 10.5.2
To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel	PK parameters including Cmax, AUCtau	Refer to Section 10.5.4
To assess the effect of buparlisib in combination with paclitaxel on patient's symptoms and health-related quality of life (HRQoL)	Change from baseline in the global health status/QOL and pain scale scores of the EORTC QLQ-C30 and QLQ-HN35, respectively Time to definitive 10% deterioration in the global health status/QOL and pain scale scores of the	Refer to Section 10.5.6

4 Study design

4.1 Description of study design

This is a multi-center, randomized, double-blind, placebo-controlled phase II trial to evaluate the efficacy and safety of 100 mg daily of buparlisib in combination with weekly paclitaxel compared to buparlisib-matching placebo in combination with weekly paclitaxel in patients with histologically/ cytologically confirmed HNSCC, recurrent or metastatic disease progressing after prior platinum based treatment.

Approximately 150 patients will be randomized in a 1:1 ratio.

Patients will be stratified according to number of prior lines of treatment (1 *vs.* 2) and the region of investigator's site (North America *vs.* Rest of the World). [redacted]

4.1.1 Treatment Phase

Patients will continue to receive study treatment according to randomization until disease progression (assessed by RECIST 1.1), unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator). Efficacy and safety monitoring will continue as per visit schedule (Table 7-1a). Tumor assessments will be performed 4 weeks after study treatment start and afterwards every 6 weeks until radiological progression.

After unblinding, patients who are still benefiting from study drug (s) will continue to be provided study treatment as long they benefit if considered in their best interest. Safety monitoring will continue as per updated visit schedule (Table 7-1b or Table 7-1c).

Tumor assessments will be performed as per local clinical practices. Imaging assessments will no longer be sent to central vendor.

4.1.2 Follow – up Phase

After discontinuation of treatment, patients will be followed according to Section 7.1.5

All patients, regardless of reason for treatment discontinuation will be followed for safety for 30 days after the last dose of study treatment.

All patients who discontinue from study treatment due to disease progression must have their progression clearly documented according to the criteria specified in RECIST v1.1. If a patient did not discontinue study treatment due to disease progression, death, start of new anti-neoplastic therapies, lost to follow-up, or withdrawal of consent to efficacy follow-up, then tumor assessments should continue to be performed every 6 weeks until the start of new anti-cancer therapy, disease progression, death, lost to follow-up or withdrawn consent to efficacy follow-up.

In addition, all new anticancer therapies given after the last dose of the study treatment, until disease progression, death, lost to follow-up, or withdrawal of consent will be recorded in the electronic Case Report Forms (eCRFs).

All patients will be followed for survival status every 3 months or earlier if needed, regardless of treatment discontinuation reason (except if consent is withdrawn or patient is lost to follow-up). Additional survival assessments may be performed outside the 3 months follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

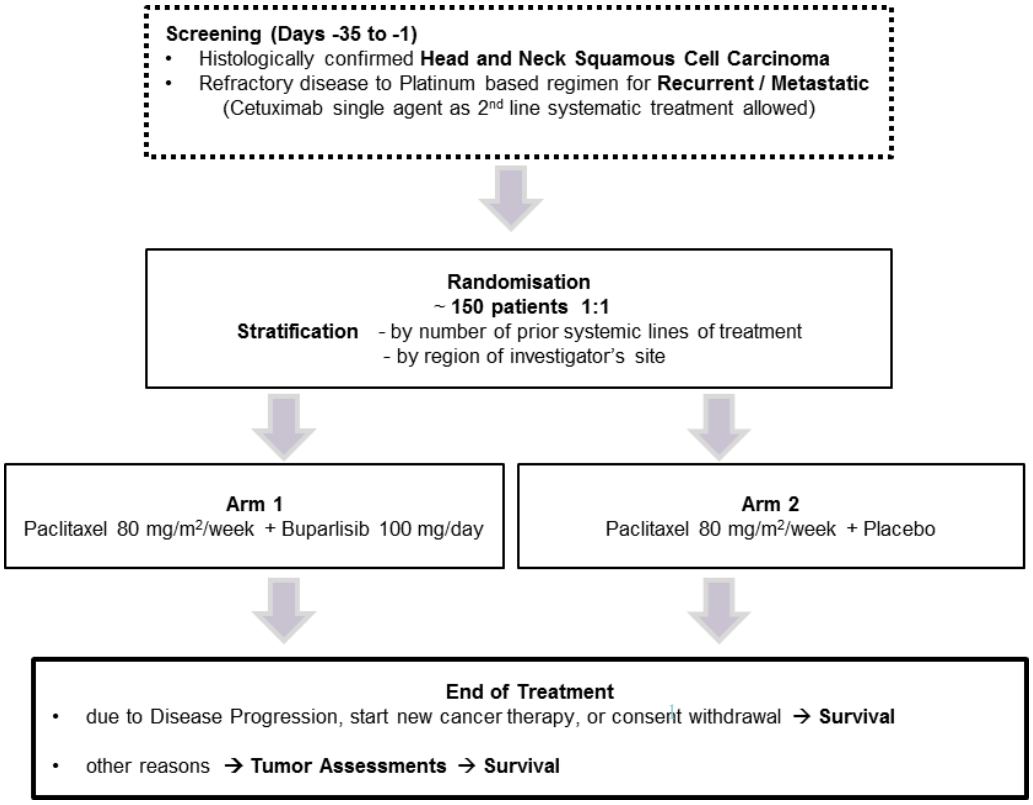
From protocol amendment v.03, regardless of reason for study treatment discontinuation, tumor assessments will be performed as per local practices in the follow-up phase and scans will neither be collected nor sent to BIRC for review.

Patients continuing to receive study treatment, will be followed up for safety up to 30 days after last dose of study treatment.

Patients in efficacy and survival follow up at the time of this protocol amendment, will come off study and be followed-up per local clinical practices.

For details on required assessments, please refer to Table 7-1b and Table 7-1c.

Figure 4-1 Study design



[1] From protocol amendment v.03, regardless of EOT reason, patients will only be followedup for 30 days after last dose of study treatment. These patients will not continue in Efficacy and Survival follow-up phases.

4.2 Timing of interim analyses and design adaptations

There is no planned efficacy interim analysis. Safety data will be reviewed every 6 months or more frequently if needed by a Data Monitoring Committee (DMC).

4.3 Primary statistical analysis

The primary statistical analysis will be based on data from all patients up to the time at which approximately **120** PFS events have been observed. The first CSR will be based on the primary analysis of the data and the final CSR will be based on additional data (e.g. survival and safety data) that were not summarized in the first CSR for patients who were still receiving treatment, patients in follow-up phase or patients in survival follow-up phase after the last patient last visit has occurred. The duration of OS follow-up should be up until approximately 112 patient deaths have occurred.

4.4 Definition of the end of the study

The End of Study is defined as the time point when data collection will stop and the final analysis of the study will occur.

- End of Study will be declared when the study is terminated early or at the latest occurrence of: All patients have completed the safety follow-up period (30 days after treatment discontinuation) or
- Approximately 112 deaths have been observed.

4.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible for an End of Treatment (EOT) visit and the assessments for EOT should be performed similar to that for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Patient population

The targeted patient population is patients with histologically/cytologically-confirmed HNSCC, recurrent or metastatic disease progressing after platinum based first-line treatment.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient is ≥ 18 years old;
2. Written informed consent obtained before any trial related activities and according to local guidelines.

3. Patient has histologically/cytologically-confirmed HNSCC.
4. Patient has archival or new tumor tissue for the analysis of PI3K-related biomarkers. One tumor block (preferred) or a minimum of 12 (15 recommended) unstained slides to be provided. Enrollment in the study is contingent on confirmation of an adequate amount of tumor tissue.
5. Patients with recurrent or metastatic disease after failure to platinum-based chemotherapy (defined as progression while on or after platinum-based chemotherapy given in the recurrent/metastatic setting). Pretreatment with cetuximab (as part of chemoradiation, first-line therapy or maintenance, or as single agent second line regimen) is allowed
6. Measurable disease as determined by per RECIST criteria v1.1. If the only site of measurable disease is a previously irradiated lesion, documented progression of disease and a 4 week period since radiotherapy completion is required
7. Adequate bone marrow function and organ function as shown by:
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    - Hemoglobin ≥ 9 g/dl (which may be reached by transfusion)
    - Platelets $\geq 100 \times 10^9$/L (which may be reached by transfusion)
    - INR ≤ 1.5
    - Potassium, calcium (corrected for serum albumin) and magnesium within normal limits (WNL) or $\leq$ grade 1 severity according to NCI-CTCAE version 4.03 if judged clinically not significant by the investigator
    - Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) $\leq$ 1.5xULN (or < 3.0 x ULN if liver metastases are present)
    - Total serum bilirubin below or equal upper limit of normal range (or ≤ 1.5 x ULN if liver metastases are present; or total bilirubin ≤ 3.0 x ULN with direct bilirubin below or within normal range in patients with well documented Gilbert's Syndrome, which is defined as presence of episodes of unconjugated hyperbilirubinemia with normal results from CBC count (including normal reticulocyte count and blood smear), normal liver function test results, and absence of other contributing disease processes at the time of diagnosis (see Appendix in the final protocol)
    - Serum creatinine ≤ 1.5 x ULN or calculated or directly measured CrCl $\geq$ 50% LLN (Lower Limit of Normal)
    - Fasting plasma glucose (FPG) $\leq$ 120mg/dL or ≤ 6.7 mmol/L
    - HbA1c $\leq$ 8%
8. ECOG Performance Status ≤ 1
9. Patient is able to swallow and retain oral medication

Note: patients able to swallow oral medication but mostly self-nourished through gastric or jejunal feeding tube are eligible

5.2 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient has received previous treatment with any AKT, mTOR inhibitors or PI3K pathway inhibitors;
2. Patient received treatment with a taxane as part prior treatment for metastatic disease
3. Patient treated with more than one prior chemotherapy regimen for recurrent/metastatic disease (i.e. chemotherapy, chemotherapy in association with a biologic/targeted agent,)

   Notes:
   - Patients treated with adjuvant/neoadjuvant chemotherapy and/or concomitant chemoradiotherapy regimen that may have included biologic/targeted agent are eligible.
   - Cetuximab single agent used in metastatic setting is allowed.
4. Patient has symptomatic CNS metastases. Patients with asymptomatic CNS metastases may participate in this trial. The patient must have completed any prior local treatment for CNS metastases ≥ 28 days prior to the start of study treatment (including radiotherapy and/or surgery) and must have stable low dose of corticosteroid therapy;
5. Patient who has received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered to grade 1 or better from related side effects of such therapy (except alopecia)
6. Patient has not recovered to grade 1 or better (except alopecia) from related side effects of any prior antineoplastic therapy
7. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects
8. Patient is currently receiving increasing or chronic treatment (> 5 days) with corticosteroids or another immunosuppressive agent
   - The following uses of corticosteroids are permitted: single doses; standard premedication for paclitaxel; topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
9. Patient is being treated at start of study treatment with any of the following drugs:
   - Drugs known to be strong inhibitors or inducers of isoenzyme CYP3A4 including herbal medications (list of prohibited CYP3A4 inhibitors and inducers are provided in Appendix 2 and Appendix 3)
   - Drugs with a known risk to induce Torsades de Pointes (list of prohibited QT prolonging drugs provided in Appendix 5)

   Note: The patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the treatment is initiated. Switching to a different medication prior to starting study treatment is allowed.
10. Patient is currently receiving warfarin or other coumarin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed;
11. Patient has a known hypersensitivity and/or contra indication to paclitaxel, standard pre-treatment for paclitaxel or other products containing Cremophor;

12. Patients who have other concurrent severe and/or uncontrolled medical conditions that would, in the investigator's judgment, contraindicate patient participation in the clinical study (eg. active or uncontrolled severe infection, chronic active hepatitis, immunocompromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.)
13. Patient has a known history of HIV infection (testing not mandatory) infection
14. Patient has any of the following cardiac abnormalities:
    - symptomatic congestive heart failure,
      - history of documented congestive heart failure (New York Heart Association functional classification III-IV), documented cardiomyopathy,
      - Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - myocardial infarction ≤ 6 months prior to enrolment,
    - unstable angina pectoris,
    - serious uncontrolled cardiac arrhythmia,
    - symptomatic pericarditis,
    - QTcF > 480 msec on the screening ECG (using the QTcF formula)
    - currently receiving treatment with medication that has a known risk to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. A list of prohibited drugs will be provided in the final protocol;
15. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection);
16. Patient has a score ≥ 12 on the PHQ-9 questionnaire;
17. Patient selects a response of "1, 2 or 3" to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9);
18. Patient has a GAD-7 mood scale score ≥ 15;
19. Patient has a medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (e.g. risk of doing harm to self or others);), or patients with active severe personality disorders (defined according to DSM- IV) are not eligible. Note: for patients with psychotropic treatments ongoing at baseline, the dose and the schedule should not be modified within the previous 6 weeks prior to start of study drug.
20. Patient has ≥ CTCAE grade 3 anxiety;
21. Patient has other prior or concurrent malignancy (except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, early gastric or GI cancer resected completely by endoscopy procedures or any other cancer from which the patient has been disease free for ≥ 3 years);

22. Patient has a history of non-compliance to medical regimen or inability to grant consent;
23. Patient is concurrently using other approved or investigational antineoplastic agent.
24. Pregnant or nursing (lactating) women Patients with elevated hCG at baseline that is judged to be related to the tumor are eligible if hCG levels do not show the expected doubling when repeated 5-7 days later, or pregnancy has been ruled out by vaginal ultrasound;
25. Patient who does not apply highly effective contraception during the study and through the duration as defined below after the final dose of study treatment:
    - Men should use an effective method of contraception and not father a child during the trial and up to six months after treatment and are recommended to seek advice on conservation of sperm prior to treatment with paclitaxel as per product label.
    - Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and through at least 4 weeks after the final dose of study treatment or as specified in the local prescription guidelines for paclitaxel (e.g. for 6 months after final dose of paclitaxel according to the PI/SmPC from France and United Kingdom).
    - Highly effective contraception is defined as either:
        1. Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
        2. Female sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
        3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female study subjects, the vasectomized male partner should be the sole partner for that patient]
        4. Use a combination of the following (both a+b):
            - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
            - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

              Note: Hormonal contraception methods (e.g. oral, injected, implanted) are not allowed as buparlisib decreases the effectiveness of hormonal contraceptives.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6 Treatment

6.1 Study treatment

The study drugs to be used in the course of this trial are the following: buparlisib or placebo and paclitaxel. As this is a double blind study, the investigator and patient, as well as the clinical team, will be blinded (i.e. will not know if the patient is receiving buparlisib or buparlisib-matching placebo).

Study treatment is defined as buparlisib once daily plus weekly paclitaxel or buparlisib-matching placebo plus weekly paclitaxel depending on the randomization arm (described in Section 6.1.1 Dosing regimen and Section 6.2 Dose modifications).

Study treatment consists of either a combination regimen (paclitaxel and buparlisib/placebo) or a monotherapy regimen if one of the study drugs (paclitaxel or buparlisib/placebo) is permanently discontinued.

Novartis Drug Supply Management or its designee will provide buparlisib and buparlisib-matching placebo as 10-mg, and 50-mg hard gelatin capsules as individual patient supply, packaged in bottles. Buparlisib will be dosed on a flat scale of mg/day and not be adjusted to body weight or body surface area.

Paclitaxel is a commercially available product. If available, generic paclitaxel may be used as part of study treatment, when possible. Paclitaxel will be prescribed by the investigator and obtained as outlined in the investigator Clinical Trial Agreement. Medication labels will comply with the legal requirements of each country and be printed in the local language. The labels will supply no information about the patient.

6.1.1 Dosing regimen

Patients will be randomized to receive either:

- Buparlisib plus weekly paclitaxel
- Buparlisib-matching placebo plus weekly paclitaxel

Buparlisib or buparlisib-matching placebo will be administered orally once daily on a continuous dosing schedule starting on day 1 in combination with once weekly paclitaxel at a dose of 80 mg/m^2 i.v. (days 1, 8, 15 and 22) in a 28-day cycle. Buparlisib/placebo will be given before paclitaxel and any associated premedication, as described in Section 6.1.1.1.

Weekly paclitaxel at 80 mg/m^2 plus buparlisib-matching placebo at a continuous dosing schedule will be used for the control arm. Patients will be treated until disease progression, unacceptable toxicity, death or discontinuation from study treatment due to any other reason. Permitted dose modifications are presented in Section 6.2.2.2.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose[2]	Frequency and/or Regimen
Buparlisib	Oral gelatin capsules	100 mg (2x 50mg capsules[1])	Once daily

Study treatments	Pharmaceutical form and route of administration	Dose[2]	Frequency and/or Regimen
Paclitaxel	Intravenous infusion	80 mg/m^2	Once every week
Buparlisib-matching Placebo	Oral gelatin capsules	Matching placebo 100 mg (2x placebo to 50 mg capsules[1])	Once daily

1. In case of patient supply difficulties, any combination of buparlisib/placebo (according to patient assignment) 50 mg or 10 mg capsules may be taken to consume a dose of 100 mg/day (or dose reduction level).
2. Dose reduction levels for buparlisib/placebo will be administered according to Table 6-2. For example, buparlisib/placebo 80 mg should preferentially be administered as 1x 50mg capsule, and 3x10 mg capsules or the equivalent in placebo capsules.

A complete treatment cycle is defined as 28 days of once daily continuous treatment with buparlisib/placebo with once weekly paclitaxel.

6.1.1.1 Buparlisib/placebo dosing

Buparlisib/placebo will be administered on a continuous once daily dosing schedule. There will be no breaks between dosing cycles.

The following general guidelines should be followed for buparlisib/placebo administration:

- Patients should be instructed to take the dose of buparlisib/placebo once daily in the morning, at approximately the same time each day
- Buparlisib/placebo can be taken with or without food.
- Buparlisib/placebo should be taken with a glass of water. Patients should swallow the capsules as a whole and not chew them.
- During the study, the patient should record if the dose was taken or not in the buparlisib/placebo patient diary.
- Premedication for paclitaxel (e.g. H2 antagonists) or other stomach acid reduction treatments (e.g. proton pump inhibitors, antacids) should be taken at least 1 hour after buparlisib/placebo administration, if indicated.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.
- If the patient forgets to take his/her dose until 18:00 (6:00 PM), then the dose should be withheld that day and buparlisib/placebo should be restarted the following day.
- Patients must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos, starfruits and cranberry juice from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A interaction. Regular orange (Citrus X sinensis) juice is allowed.
- Patients must avoid concomitant intake of strong CYP3A inhibitors and inducers. Detailed information on potential drug interactions and a list of prohibited concomitant CYP3A interfering medications is provided in Table 14-1 in Appendix 2.

6.1.1.1.1 Additional dosing guidelines for pharmacokinetic sampling

On days with pharmacokinetic sampling (e.g., Cycle 1 Day 15 and Day 22), the following additional guidelines should be followed:

- The patient should take his/her dose in the clinic. The patient does not have to fast overnight, unless they are also having a fasting plasma glucose and c-peptide sample taken (See Section 6.1.1.1.2).
- The pre-dose sample should be drawn just before buparlisib/placebo dosing. The sampling time of the pre-dose PK sample and the dosing time of buparlisib/placebo must be precisely recorded in the eCRF. Furthermore, the dosing time of buparlisib/placebo on the previous day must be precisely recorded in the eCRF and in the buparlisib/placebo patient diary. If vomiting occurs, the exact time of the first vomiting episode within the first 4 hours post-dosing on that day must be noted.

6.1.1.1.2 Additional dosing guidelines for fasting glucose and/or c-peptide sampling

- On days with a pre-dose fasting (overnight) glucose and/or c-peptide sample (e.g. Day 1 of each cycle for both, Day 15 of cycle 1 and 2 for fasting plasma glucose), the patient must be fasting overnight for at least 10 hours prior to the blood collection for fasting glucose and C-peptide, but can freely drink water. After this blood sample, the patient should take his/her dose of buparlisib/placebo in the clinic (Section 6.1.1.1). If a pharmacokinetic sample is also being drawn, then the additional guidelines described in Section 6.1.1.1.1 must be followed as well.

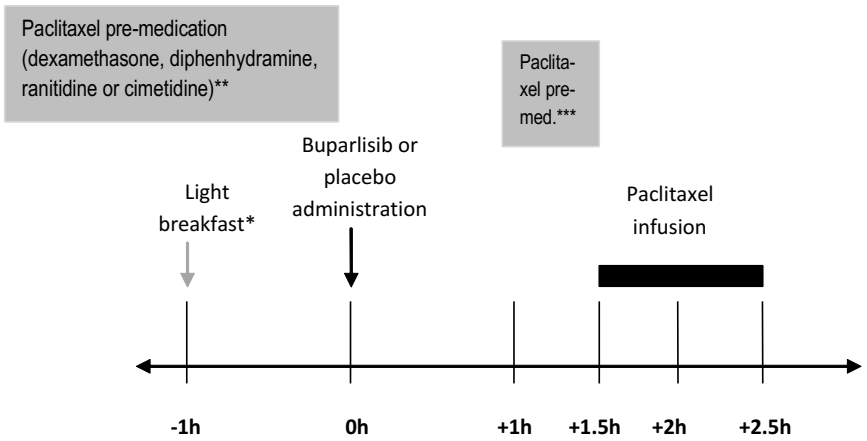
6.1.1.2 Paclitaxel preparation and dosing

Paclitaxel is supplied as multi-dose vials for injection. Paclitaxel must be diluted using 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP, or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL.

Paclitaxel will be administered every week as a 1-hour (± 15 minutes) IV infusion after standard premedication on Day 1 of every cycle.

Following the initial administration of therapy, patients should be observed for any hypersensitivity reaction for at least 1 additional hour.

Figure 6-1 Combined paclitaxel and buparlisib/placebo dosing scheme



*On days with fasting plasma glucose and/or c-peptide monitoring, breakfast should not be eaten until after the blood sampling has been completed (Section 6.1.1.1)

**in accordance to local clinical practice

***premedication for paclitaxel (stomach acid reduction treatments such as H2 antagonists, proton pump inhibitors, antacids) should be taken at least 1 hour after buparlisib/placebo administration, if indicated.

Patients should be observed for any hypersensitivity reaction for at least one hour after the end of the first paclitaxel infusion.

6.1.2 Supportive treatment

6.1.2.1 Paclitaxel pre-medication

Prior to administration of paclitaxel, patients should be pre-medicated according to the standard institutional practice or the product label in order to prevent severe hypersensitivity reactions. Anti-hypersensitivity therapy may be administered prior to the ECG of each cycle.

The following is a suggested anti-hypersensitivity therapy guideline. Any one or more of the following may be used to prevent hypersensitivity reactions and can be modified in accordance to local practice:

- Dexamethasone: 20 mg PO to be administered approximately 12 and 6 hours prior to the start of paclitaxel administration.
- Diphenhydramine (or equivalent): 50 mg IV to be administered approximately 30-60 minutes prior to the start of paclitaxel administration.

AND:

- Ranitidine: 50 mg IV to be administered approximately 30-60 minutes prior to the start of paclitaxel administration. Of note, there are no clinically significant interactions foreseeable at the level of the isozymes CYP1A2, and CYP3A4 in the therapeutic use of ranitidine. (Martinez 1999)

OR:

- Cimetidine: 300 mg IV to be administered approximately 30-60 minutes prior to the start of paclitaxel administration. **Note:** Cimetidine is a CYP3A4 and CYP1A2 inhibitor, and therefore administration of cimetidine as a single dose should only be considered if no alternative can be found.

If hypersensitivity occurs during the administration of paclitaxel, the following treatment guidelines may be followed:

- For mild symptoms (e.g., mile flushing, rash, pruritus) it is possible to complete the infusion under close supervision
- For moderate symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension),
  1. Stop the paclitaxel infusion and give diphenhydramine 25-50 mg IV and methylprednisolone 125 mg IV.
  2. Once symptoms have resolved, resume paclitaxel infusion at a rate of 10% of original rate for 15 minutes, then at 25% of original rate for 15 minutes. If no further symptoms develop, continue at original rate until infusion is complete.
- For severe symptoms (e.g., one or more of: respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy),
  1. Stop the paclitaxel infusion and give diphenhydramine and methylprednisone as above. Use epinephrine or bronchodilators, if indicated.
  2. Do not rechallenge the patient with paclitaxel.

6.1.3 Guidelines for continuation of treatment

For guidelines for continuation of treatment, refer to Section 6.2 Dosing modifications.

Patients who discontinue one of the study drugs for any reason other than disease progression may continue the other study drug as part of the trial therapy at the investigators discretion and should follow the protocol safety and efficacy assessments as scheduled. After discontinuing study treatment, further treatment is left to the physician's discretion. No cross over to the buparlisib arm will be allowed.

6.1.4 Treatment duration

Treatment will be continued until disease progression (radiologically confirmed according to RECIST v1.1) or until discontinuation due to any other reason (see Section 6.2.1).

After unblinding, treatment will be continued until disease progression (radiologically confirmed according to local clinical practices) or until discontinuation due to any other reason.

6.1.5 Definition of treatment cycle

A complete treatment cycle is defined as 28 calendar days during which buparlisib/placebo is given once daily and paclitaxel is given once weekly.

The last day of a complete treatment cycle is day 28. Day 1 of the next cycle starts on day 29.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Any changes in buparlisib/placebo or paclitaxel administration must be recorded on the eCRF. In addition, for paclitaxel infusion, site personnel must record the infusion start and stop date and times, the volume of drug infused, the actual dose given and the intended dose in the patient's medical records.

Buparlisib/placebo dose modification guidelines are described in Section 6.2.2.1 and the paclitaxel recommendations for dose modification are described in Section 6.2.2.2. Any planned variance from these guidelines in the view of the patient safety must be previously discussed with the Sponsor unless there is an urgent need for action.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.03). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycle.

If the administration of buparlisib/placebo or paclitaxel is interrupted for reasons other than toxicity, then treatment with the respective study drug may be resumed at the same dose. The same provision applies if the patient experienced an unacceptable toxicity not specifically described in Table 6-3 and Table 6-4 provided that this toxicity resolved to ≤ CTCAE grade 1, unless otherwise specified.

6.2.2 Treatment interruption and treatment discontinuation

During the treatment phase following cytotoxic therapy administration, patients requiring a buparlisib/placebo dose delay of > 28 days must be permanently discontinued from study drug. Grade 4 adverse events will lead to permanent discontinuation, irrespective of recovery time, unless otherwise specified. In addition, in most instances, patients that experience a treatment interruption because of an adverse event will decrease the dose of study drug after their recovery (see specific tables for dose adjustment guidelines). Furthermore, patients requiring > 3 dose reductions for buparlisib/placebo will be permanently discontinued from study drug. Any need for dose reduction of buparlisib/placebo below 80 mg/day will require discontinuation from this study drug.

If one or more study drugs are held due to toxicity, scheduled visits and all assessments should continue to be performed (with the exception of the dosing of the held study drug), as described in Table 7-1a, Table 7-1b and Table 7-1c.

If treatment with buparlisib or matching placebo is permanently discontinued the patient may continue to receive paclitaxel on the study at the discretion of the investigator until disease progression, unacceptable toxicity, death or discontinuation from study treatment due to any other reason (see the criteria for patient withdrawal in Section 7.1.4.1).

Patients who discontinue paclitaxel may continue to receive buparlisib or matching placebo at the discretion of the investigator until disease progression, unacceptable toxicity, death or discontinuation from study treatment due to any other reason (see the criteria for patient

withdrawal in Section 7.1.4.1). The patients will not need to return to the investigational site for days 8 and days 22 of all cycles following paclitaxel discontinuation.

Patients who permanently discontinue all study drugs should have weekly follow-up for 30 days after discontinuation of all study treatment or resolution of the AE to ≤ grade 1, whichever occurs first, that includes all study assessments appropriate to monitor the event.

6.2.2.1 Criteria for buparlisib/placebo dose modifications

A maximum of 3 dose reductions of buparlisib/placebo will be allowed according to the dose levels described in Table 6-2. For patients already receiving buparlisib/placebo at the Dose level – 3 (80 mg/day 5 days out of 7) no further dose reductions are allowed; in that case the patient will be discontinued from treatment with buparlisib/placebo. Dose reduction should be based on the worst preceding toxicity. A change from continuous schedule to intermittent (5 days out of 7) must be preceded by 2 days without buparlisib/placebo treatment.

Table 6-2 Dose reduction steps for Buparlisib/placebo

Buparlisib/placebo dose levels and dose reductions*	
Starting dose level	100 mg/day continuously
Dose level – 1	80 mg/day continuously
Dose level – 2	100 mg/day 5 days out of 7
Dose level – 3	80 mg/day 5 days out of 7**

*Dose reduction should be based on the worst preceding toxicity

**Dose reduction below 80 mg/day 5 days out of 7 is not allowed. If a dose reduction below dose level –3 is required, the patient should be permanently discontinued from buparlisib/placebo.

Guidelines for dose modification and dose interruption of buparlisib/placebo are described in Table 6-3.

When toxicities requiring study treatment dose adjustment are potentially attributable to either buparlisib or paclitaxel, the first dose adjustment should be made for buparlisib according to Table 6-3. At this time, the paclitaxel dose also may be adjusted consistent with Section 6.2.2.2 according to the investigator's clinical judgment. If there is a second occurrence of the same adverse event after dose adjustment of buparlisib, or there is persistence of the adverse event beyond 7 days, then an adjustment of the paclitaxel dose should be made where relevant according to Section 6.2.2.2.

For hematologic toxicities, the first dose adjustment should be made with paclitaxel according to Section 6.2.2.2. At this time, the buparlisib dose also may be adjusted consistent with Table 6-3 and according to the investigator's clinical judgment. If there is a second occurrence of the same adverse event after dose adjustment of paclitaxel, or there is persistence of the adverse event beyond 7 days, then an adjustment of the buparlisib dose should be made where relevant according to Table 6-3.

After treatment is resumed at a lower dose:

- If the same toxicity recurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration.
- If the same toxicity recurs with a worse severity, then the patient must discontinue treatment with buparlisib/placebo.

- These stipulations do not apply to hyperglycemia, as specific rules are stated in Table 6-3.

Table 6-3 Criteria for interruption and re-initiation of buparlisib/placebo

These changes must be recorded on the Dosage Administration Record CRF

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for buparlisib/placebo
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1.0 – 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
RENAL	
Serum creatinine	
Grade 1 (< 2 x ULN)	Maintain dose level
Grade 2 (2 – 3 x ULN)	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue patient from buparlisib/placebo
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from buparlisib/placebo
HEPATIC	
Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only) will be fractionated if elevated	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from buparlisib/placebo
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from buparlisib/placebo
AST or ALT	

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for buparlisib/placebo
AST or ALT without bilirubin elevation > 2ULN Note: confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorder, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction	
Same grade as baseline (i.e. Grade 0 or Grade 1 (> ULN – 3.0 x ULN) if presence of liver metastasis)	Maintain dose level with LFTs* monitored per protocol
Increase from baseline Grade 0 to > 1.5 ULN or from baseline Grade 1 to Grade 2	Can continue treatment at ↓ 1 dose level
Increase of two grades from baseline (from baseline Grade 0 to Grade 2 or from baseline Grade 1 to Grade 3)	Omit dose until resolved to Grade 1 or less, then ↓ 1 dose level** If no recovery in ≤ 28 days, discontinue permanently BKM120/placebo
Grade 3 (> 5.0 - 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level** If no recovery in ≤ 28 days, discontinue permanently BKM120/placebo
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Permanently discontinue patient from BKM120/placebo
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Permanently discontinue buparlisib/placebo***
*(LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT) ** In case of recurring Grade 3 or higher toxicity after re-challenge, patients should be permanently discontinued *** All patients with ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN in the absence of cholestasis must immediately be withdrawn from BKM120/placebo and every attempt should be made to carry out the liver event follow-up assessments as described below in Section 6.2.2.3.7 Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120/placebo and Section 7.2.2.5.7 Viral hepatitis serology and other tests for hepatotoxicity follow-up Hepatic toxicity monitoring (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT): Cycle 1 and 2: every other week (if visit schedule allows a more frequent monitoring this should be considered) or more frequently if clinically indicated especially for patients with borderline acceptable AST/ ALT or bilirubin* values Cycle 3 and onward: monthly or more frequently if clinically indicated In case of any occurrence of ALT/AST or bilirubin* increase ≥ grade 2 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1 In case of any occurrence of ALT/ AST or bilirubin* increase ≥ grade 3 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1; hereafter the monitoring should be continued every other week or more frequently if clinically indicated until the end of treatment with study medication Patients who discontinued study treatment should be monitored weekly, including LFTs* or more frequently if clinically indicated until resolved to ≤ grade 1 or stabilization (no CTCAE grade change over 4 weeks).	
ENDOCRINE/METABOLIC	
Fasting Plasma Glucose (FPG)	

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for buparlisib/placebo
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L]	Maintain dose level, check FPG every week initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study consider use of oral anti-hyperglycemic therapy such as metformin (or intensify existing medications) check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks
Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	If asymptomatic, maintain dose and re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 2: maintain dose level and monitor FPG at least weekly until FPG resolves to ≤ Grade 1 initiate or intensify medication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if no improvement after several days instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study If FPG does not resolve to ≤ Grade 1 within 14 days after institution of appropriate anti-diabetic treatment reduce buparlisib/placebo by 1 dose level Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks
Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	Omit buparlisib/placebo, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 3: administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate continue to omit buparlisib/placebo monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1 If FPG resolves to ≤ Grade 1 in 7 days or less, then re-start buparlisib/placebo and ↓ 1 dose level If FPG remains greater than Grade 1 severity for more than 7 days, then discontinue patient from buparlisib/placebo initiate or continue anti-diabetic treatment as appropriate instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study consider use of oral anti-hyperglycemic therapy such as metformin check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks For non-fasting plasma glucose >250-500 mg/dL (> 13.9 - 27.8 mmol/L) accompanied by signs/symptoms of

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for buparlisib/placebo
	hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, omit BKM120/placebo and following guidance for management of Grade 3 fasting plasma glucose (FPG)
Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]	Immediately omit BKM120/placebo, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours. If grade improves then follow specific grade recommendations. If FPG is confirmed at Grade 4: administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate discontinue patient from BKM120/placebo instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study consider use of oral anti-hyperglycemic therapy such as metformin check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks if clinically indicated For non-fasting plasma glucose >500 mg/dL (> 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, discontinue BKM120 and following guidance for management of Grade 4 fasting plasma glucose (FPG).
CARDIAC	
Cardiac - Left Ventricular systolic dysfunction	
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain dose level, and continue buparlisib with caution Repeat LVEF within 4 weeks or as clinically appropriate
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	Omit buparlisib/placebo until resolved* (as defined below), then ↓ 1 dose level LVEF measurement to be repeated, if not resolved* within 3 weeks, permanently discontinue patient from buparlisib treatment *the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline
Refractory or poorly controlled, ejection fraction < 20%	Permanently discontinue patient from buparlisib/placebo
Cardiac – QTc prolongation	
QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	First Occurrence: omit buparlisib/placebo Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. Perform a repeat ECG within one hour of the first QTcF of > 500 ms or >60ms from baseline If QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input. Once QTcF prolongation has resolved, buparlisib/placebo

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for buparlisib/placebo
	may be restarted at a one lower dose level Second Occurrence: Permanently discontinue patient from buparlisib/placebo
Other Cardiac Events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue patient from buparlisib/placebo
OTHER	
Mood alteration	
Grade 1*	Maintain dose level Consider psychiatric consultation at the investigator's discretion and introduce optimal management except in presence of suicidal ideation where dose must be interrupted and psychiatric consultation is required to provide optimal management
Grade 2*	Omit dose until resolved to ≤ Grade 1, or baseline status Consider psychiatric consultation at the investigator's discretion and introduce optimal management except in presence of suicidal ideation where dose must be interrupted and psychiatric consultation is required to provide optimal management First event: if the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then maintain dose level Second and further events: if the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then ↓ 1 dose level
Grade 3*	Omit dose until resolved to ≤ Grade 1, or baseline status Psychiatric consultation is required and introduce optimal management If the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then then ↓ 1 dose level
Grade 4*	Permanently discontinue patient from buparlisib/placebo Psychiatric consultation is required and introduce optimal management
* Note: A timely interview with the patient after the questionnaire completion is recommended. For all grades, if question 9 on the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), and/or the patient presents with suicidal ideation, interrupt study drug and refer patient for psychiatric consultation regardless of the total questionnaire score or CTCAE grading for optimal management and to confirm if study drug should be interrupted or permanently discontinued. . If the patient does not respond to question 9 on the PHQ-9 or to the whole questionnaire, then the investigator must assess if the patient has suicidal ideation. If the investigator identifies suicidal ideation, then study drug must be interrupted and the patient referred for psychiatric consultation for assessment.	
Skin Toxicity	
Maculopapular rash	
Grade 1 (macules or papules covering <10% BSA with or without symptoms)	Maintain dose level. Consider to initiate recommended treatment* with topical steroid bid and oral antihistamines.
Grade 2 (macules or papules covering 10-30% BSA with or without symptoms)	Tolerable: same management as G1 Intolerable: Start recommended treatment* with topical steroids bid, oral antihistamines and oral steroids.

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for buparlisib/placebo
	First occurrence: Omit dose until resolved to Grade ≤ 1 then: If resolved in ≤ 2 weeks, maintain dose level. If resolved in more than 2 weeks, ↓ 1 dose level. Second occurrence: ↓ 1 dose level Treatment can be continued up to 2 weeks after rechallenge with buparlisib; consider prompt implementation in case of flare after interruption of recommended treatment.
Grade 3 (macules or papules covering >30%BSA with or without symptoms)	Omit dose until resolved to CTCAE Grade ≤ 1; then ↓ 1 dose level. Start recommended treatment* with topical steroids bid, oral antihistamines and oral steroids. Treatment can be continued up to 2 weeks after rechallenge with buparlisib; consider prompt implementation in case of flare after interruption of recommended treatment
Grade 4 (Papules and/or pustules covering any % BSA, associated with symptoms or not but associated with extensive superinfection)	Permanently discontinue patient from buparlisib/placebo
*Recommended treatment: please refer to Section 6.2.2.3.4	
Acneiform Rash	
Grade 1 (<10% body surface area BSA; no associated erythema or pruritus)	Maintain dose level. Consider to initiate recommended treatment** with topical steroid moderate potency and topical antibiotic bid
Grade 2 (10 to 30% BSA and associated with erythema or pruritus; limited instrumental activities of daily living (ADL)	Tolerable: same management as G1 Intolerable: First occurrence: Omit dose until resolved to Grade ≤ 1 then: If resolved in ≤ 2 weeks, maintain dose level. If resolved in more than 2 weeks, ↓ 1 dose level. Start recommended treatment** oral antibiotic for 6 weeks; stop topical antibiotics if being used and start with topical steroids of moderate potency Second occurrence: ↓ 1 dose level Initiate or intensify recommended treatment as described above
Grade 3 (>30% BSA And associated with pruritus; limiting self ADL)	Omit dose until resolved to CTCAE Grade ≤ 1; then ↓ 1 dose level. Start recommended treatment** with oral antibiotic for 6 weeks. If infection suspected (yellow crusts, purulent discharge, painful skin / nares) then switch to broad spectrum/gram negative antibiotics; consider skin swab for bacterial culture. Add topical steroid of moderate potency.
Grade 4 Papules and/or pustules covering any % BSA, associated with symptoms or not but associated with extensive superinfection	Permanently discontinue patient from buparlisib/placebo
**Recommended treatment: please refer to Section 6.2.2.3.4	

Pruritus	Clinical Management and placebo/buparlisib dose adjustment
Grade 1 (Mild or localized pruritus)	Maintain dose level. Consider to start recommended treatment with topical steroid moderate strength or topical antipruritics applied twice daily
Grade 2 (Intense or widespread; intermittent; skin changes from scratching; limiting instrumental ADL)	• Tolerable: same management as G1 • Intolerable: - First occurrence: Omit dose until resolved to Grade ≤ 1 then: • If resolved in ≤ 2 weeks, maintain dose level. • If resolved in more than 2 weeks, ↓ 1 dose level. Start recommended treatment with topical steroids moderate potency or topical antipruritics twice daily and add oral antihistamines - Second occurrence: ↓ 1 dose level Initiate or intensify recommended treatment as described above
Grade 3 (Intense or widespread; constant; limiting self-care ADL or sleep)	Omit dose until resolved to CTCAE Grade ≤ 1; then ↓ 1 dose level. Start recommended treatment with: oral corticosteroids or oral antihistamines in association with GABA agonists
Grade 4	Discontinue placebo / buparlisib
Recommended treatment : please refer to Section 6.2.2.3.4	
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓ 1 dose level
Pneumonitis	Please see Section 6.2.2.3.1
Stomatitis/Oral mucositis	
Grade 1 /Tolerable Grade 2 Intolerable Grade 2 or Grade 3 Grade 4	Maintain dose level. Non alcoholic or salt water mouth wash see also Section 6.2.2.3.2 • First occurrence: hold until ≤ G1 and ↓ 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). Second occurrence: hold until ≤ G1 and ↓ 1 dose level. • Permanently discontinue patient from buparlisib/placebo.

Other non- hematological adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue patient from buparlisib/placebo ***Note:*** Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic

6.2.2.2 Criteria for paclitaxel dose modifications

The following guidelines should be considered for dose modifications for AEs that are suspected to be caused by paclitaxel.

- Paclitaxel should be administered only if ANC > 1.500/mm3 (1.5 x 10^9/L) and platelets > 100.000/mm3 (100 x 10^9/L) (Seidman 2008).
- In case of a life-threatening event, consider discontinuing paclitaxel
- In case of grade 3 or 4 AEs despite medical management:
  - Hold paclitaxel until the event has resolved to grade 1 or better, then re-introduce at the reduced dose.
  - In case of a second episode of the same event at grade 3 or 4, consider discontinuing paclitaxel
- In cases of grade 2 non-hematologic AE (except alopecia) that are persistent despite medical management, consider holding paclitaxel until event resolves to grade 1 or better, then re-introduce at a reduced dose.
- The minimum paclitaxel dose allowed on study and the first dose reduction level is 65 mg/m^2 (i.e. only one dose reduction of paclitaxel is permitted to 65 mg/m^2).

Additionally, paclitaxel should be dose adjusted as needed, in accordance with local prescribing information and practice.

Patients who permanently discontinue paclitaxel but continue buparlisib/placebo can reduce the frequency of hematology visits as described in Section 7.1.

6.2.2.3 Additional follow-up for selected toxicities

6.2.2.3.1 Management of Pneumonitis in patients receiving buparlisib/placebo

All patients participating in clinical trials with buparlisib will be routinely asked about and observed for the occurrence of adverse events which could include new or changed pulmonary symptoms (consistent with lung abnormalities). CT scans and pulmonary function tests should be done, as clinically indicated, or if there are symptoms that indicate that the patient has developed Pneumonitis. In case of a documented Pneumonitis, the guidelines (including dose modifications) in Table 6-4 should be followed. Consultation with a pulmonologist is highly recommended for any Pneumonitis case during the study treatment.

Table 6-4 should be followed. Consultation with a pulmonologist is highly recommended for any Pneumonitis case during the study treatment.

Table 6-4 Management of Pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	buparlisib/placebo Dose Adjustment
Grade 1	CT scans with lung windows. Repeat at least every 8 weeks until return to within normal limits.	No specific therapy is required	Administer 100% of buparlisib/placebo dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce buparlisib/placebo dose by 1 dose level (see Table 6-2) until recovery to < Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to < Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment with buparlisib/placebo until recovery to < Grade 1. May restart study treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment with buparlisib/placebo.

6.2.2.3.2 Guidelines for the treatment of buparlisib/placebo induced stomatitis/oral mucositis

General guidance and management include patient awareness and early intervention.

Evaluation for herpes virus or fungal infection should be considered.

Patients should be informed about the possibility of developing mouth ulcers/oral mucositis and instructed to report promptly any signs or symptoms to their physician, Patients should be educated about good oral hygiene, instructed to avoid spicy/acidic/salty foods, and should follow the following guidelines:

- For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.

- For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
- Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with buparlisib metabolism.

6.2.2.3.3 Guidelines for the treatment of buparlisib/placebo induced diarrhea

The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Concomitant medication for the treatment of diarrhea should be considered, as per local practice and best investigator's judgment and may consist for example, as per "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson 2004), of loperamide given at a standard dose (e.g. initial administration of 4mg, then 2mg every 4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures could be considered for Grade 1-2 diarrhea. More severe diarrhea should be treated appropriately according to investigator discretion, including for example IV fluids.

Dose adaptations of buparlisib/placebo in case of treatment related diarrhea should follow the guidelines presented above for other non-hematological adverse events.

6.2.2.3.4 Guidelines for the treatment of buparlisib/placebo induced skin toxicity

Skin toxicity is a class-effect observed with PI3Ki/mTORi agents. Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as adverse event. The most frequent skin adverse events reported are: maculopapular rash (only a minority present acneiform rash) (refer to Table 6-3 for clinical management); pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate concomitant medication and treatment interruption if needed. Photographs of skin rashes events as well as skin biopsy if possible are recommended. According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) to further assess rash if clinical appropriate.

Recommended therapies for skin toxicity events (refer to table 6.3 for specific guidance according to the type of skin toxicity):

- Topical steroids of Moderate Potency (face and folds): triamcinolone 0.025%; aclometasone 0.05% (<8 weeks continuously)

- Topical steroids of High Potency (trunk/extremities): fluocinonide 0.05%; clobetasol 0.05% cream or spray (<8 weeks continuously)
- Oral antihistamines (sedating, evening): diphenhydramine 25-50mg tid; hydroxizine 25mg tid or q.i.d;
- Oral antihistamines (non-sedating, day time): fexofenadine 180mg QD or 60mg tid (monitor the use of this class of drugs since skin toxicity has also been reported)
- Oral corticosteroids: prednisone 0.5mg/kg or equivalent up to 5 days of treatment
- Topical antibiotics: clindamycin 1 - 2%; erythromycin 1% -2% (gel or solution formulation can be used, ointments cannot be used) ; metronidazole 1%; silver sulphadiazine.
- Oral antibiotics: doxycycline 100mg bd; minocycline 100mg bd; oxytetracycline 500mg bd
- Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
- GABA Agonists: Gabapentin 300mg every 8 hours Pregabalin 50-75 mg every 8 hours (to adjust of renal impairment). Depending on patient's clinical condition be of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others AEs.

Dry skin has been reported, it is recommended that patients with dry skin use mild and fragrance free soaps and detergents. According to the severity and BSA extension patients may apply mild moisturizers, ammonium lactate cream 12% or salicylic acid cream 6% bid.

Photosensitivity has been described in patients although preclinical experiments demonstrated that buparlisib has no potential phototoxic effect. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including regular use of sunscreen (factor 20 at least), wearing of sunglasses, using of hats, and protective clothes when outdoors.

Paronychia and nail changes should also be followed up especially in association with taxanes. The following guidelines are proposed:

Worst Grading	**Clinical Management and Taxane dose reduction**
Grade 1: (Nail fold edema or erythema; disruption of the cuticle)	Maintain taxane dose. Consider start recommended treatment: cooling during infusions with ice packs on hands/feet (start 15 min before, during, and 15 min after infusion)
Grade 2: (nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL)	Maintain taxane dose. Recommended treatment: localized intervention (cooling measures) + oral antibiotics intervention during 15 days (cephalosporines 1stG, ciprofloxacin, trimethroprim/sulfamethoxazole; antifungal, cultures if indicated)
G3 or higher (limiting self-care ADL)	Interrupt taxane and monitor (resume treatment decreasing one dose level when G1 or less) Start recommended treatment with oral antibiotics plus local cooling measures (see above)

6.2.2.3.5 Guidelines for the treatment of buparlisib/placebo induced hyperglycemia

Buparlisib may affect glucose homeostasis which could result in increases of plasma glucose and insulin levels. Optimal glucose control should be achieved before starting a patient on study treatment and patients requiring insulin should be treated with caution. Patients with hyperglycemia should be instructed to follow dietary guidelines provided by the American Diabetes Association. They may also need to initiate, continue or intensify medication with appropriate anti-diabetic treatment including insulin or oral agents. (Note: some oral anti-diabetic drugs are CYP2C9 substrate and should be used with caution; others are CYP3A inducers or inhibitors and are prohibited; See Appendix 2 and Appendix 3, respectively, for more details). Patients who develop Grade 3 or 4 hyperglycemia should be managed urgently as per standard clinical practice, with the goal of stabilizing glycemic control within 24 hours.

6.2.2.3.6 Guidelines for the treatment of buparlisib/placebo induced psychiatric disorders

Psychiatric adverse events will be closely monitored and evaluated at each planned visit until recovery to Grade ≤ 1 or baseline status. The grading of psychiatric adverse events/mood alterations must be based on the clinical interpretation of severity according to the NCI-CTCAE (v 4.03) guidelines.

For patients who experience new or worsening of existing psychiatric AEs of Grade ≥1, psychiatric consultation should be considered as described in Table 6-3.

Patient self-reported mood questionnaires (GAD-7 and PHQ-9) will be used for screening and during the study treatment phase to aid the investigator in identifying new or worsening of events. For additional information regarding safety assessments based on patient self-reported mood questionnaires, please refer to Section 7.2.2.8.

If question 9 in the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), and/or patient presents with suicide ideation,interrupt treatment with study drug and refer the patient for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading and confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient's PHQ-9 self-assessment.

During the study, subjects will be monitored at regular scheduled visits (eg, Day 1 and Day 15 of Cycles 1, 2 and 3, Day 1 of each subsequent cycle, and at the End of Treatment visit) by the investigator/site staff through personal interaction and the two self-reported questionnaires. Additional assessments may be done according to the clinical judgment of the investigator if desired.

6.2.2.3.7 Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120/placebo

Criteria for interruption and re-initiation of BKM120/placebo treatment in case of the occurrence of AST, ALT or bilirubin increase are detailed in Section 6.2, Dose Modification (Table 6-3).

Patients with clinically significant liver test abnormalities should perform liver-directed medical history, physical examination and other tests as medically indicated to assess

potential relationship with study treatment and rule out other underlying causes (e.g. disease progression/obstruction, infection/hepatitis or other liver diseases, sepsis, metabolic diseases including diabetes, concomitant medications including herbals, alcohol, drug-drug interaction, cardiovascular disease/ischemia, other organ injuries, etc.). Any pre-existing liver conditions or risk factors should be reported in the respective medical history and concomitant medication CRF pages (if not done already).

All patients with ALT or AST >3.0 x ULN and total bilirubin > 2.0 x ULN in the absence of cholestasis (elevation of ALP in patients without bone metastasis or if bone metastasis are present elevation of 5'-nucleotidase and ALP liver fraction) must be immediately withdrawn from buparlisib/placebo, and every attempt should be made to carry out locally the **liver event follow-up assessments** as described below:

- Inform the sponsor about the event immediately after its occurrence by reporting the event immediately in the clinical database if it meets the criteria for an AE or SAE.
- Evaluate if associated with the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia, or other organ involvement.
- Obtain fractionated bilirubin, serum Alkaline Phosphatase (ALP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and blood count with differential to assess eosinophilia.
- Perform liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease including metastasis or new lesions, obstruction/compression, etc.
- Perform viral hepatitis and other serology tests:
  - Hepatitis C (HCV) serology and viral RNA, Hepatitis B (HBV) serology and viral DNA, Hepatitis A (HAV) Immunoglobulin M (IgM) and HAV total
  - Hepatitis E (HEV) serology: IgM and IgG, viral RNA
  - Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Epstein-Barr viral (EBV) serology
- Obtain PK sample, as close as possible to last dose of study drug if the patient has consented for PK Record the date and time of the PK blood sample draw and the date and time of the last dose of BKM120/placebo prior to blood sample draw on the eCRF
- Verify and record the use of concomitant medications, acetaminophen, herbal remedies, and other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Consultation with a specialist(s) or a hepatologist(s) is recommended.
- Liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury
- LFTs should be followed-up weekly until resolve to ≤ grade 1, baseline or stabilization (no CTCAE grade change over 4 weeks) and outcome documented on the respective AE and lab chemistry pages.

6.3 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted (see Section 6.3.1), except as specifically prohibited (see Section 6.3.2).

All medications (excluding study treatment and prior antineoplastic treatments), procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered within 28 days prior to the administration of buparlisib/placebo through 30 days after the last dose of study treatment (either buparlisib/placebo or paclitaxel, whichever is later) will be recorded in the Concomitant medications or Surgical and medical procedures eCRF. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications (prohibited, see Section 6.3.2.8) and food or vitamin supplements.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF, respectively.

6.3.1 Permitted concomitant therapy

6.3.1.1 Corticosteroids

High dose of corticosteroids administered chronically are known to induce CYP3A enzymes, thereby increasing the risk of reducing buparlisib drug exposure to sub-therapeutic levels. A clinical pharmacology study evaluated the impact of chronic administration of 4 mg dexamethasone on the exposure of buparlisib ([CBKM120C2106]). No impact of dexamethasone on the exposure to buparlisib was observed. Based on these new findings the administration of corticosteroids to doses equivalent to 4 mg dexamethasone are allowed. However to avoid any potential under exposure, the treatment should remain as short as possible and should be avoided whenever possible.. In addition, corticosteroids are allowed as well in the following situations:

- topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);
- systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease, or as an antiemetic);
- as premedication for paclitaxel, as described in Section 6.1.2.1.

6.3.1.2 Drugs that are metabolized by CYP450 enzymes

In vitro metabolism studies performed to examine the reversible and metabolism-dependent inhibition of CYPP450 enzymes showed that buparlisib is a weak, reversible inhibitor of CYP3A4/5, CYP2C8, CYP2C9 and CPY2C19. Note that with the data available, it is not possible to confirm whether such interactions will occur in patients. Therefore, investigators, at their discretion, may administer concomitant medications known to be metabolized by CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19. Patients receiving such medications must be

monitored for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate.

Refer to Table 14-2 in Appendix 3: List of CYP450 substrates to be used with caution. Particularly, caution is advised when buparlisib is co-administered with drugs that are sensitive substrates and/or have a narrow therapeutic index (e.g., SSRI).

Concomitant treatment of buparlisib/placebo with weak inducers of CYP3A4 is permitted, however, duration of concomitant treatment should be kept as short as possible (e.g., less than 1 week), or fully avoided whenever possible. Note that coadministration of buparlisib/placebo with strong inducers is prohibited (refer to Section 6.3.2.7).

6.3.1.3 Non-enzyme Inducing Anti-epileptic drugs

Non-enzyme inducing anti-epileptic medication (Non-EIAED) is allowed, except for those listed in Table 14-1 in Appendix 2.

6.3.1.4 Bisphosphonates

The use of bisphosphonates for bone metastatic disease is allowed. If bisphosphonate therapy is initiated after start of study medication, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.

6.3.1.5 Drugs with a conditional or possible risk to induce Torsades de Pointes

If a patient, after enrollment in the study, requires the concomitant use of any QT prolonging medication with a possible or conditional risk for Torsades de Pointes included in Table 14-4 of Appendix 5, then investigators, at their discretion, may co-administer such medications. Patients receiving such medications must however be closely monitored.

6.3.1.6 Gastric protection agents

Buparlisib is characterized by a pH-dependent solubility. Medicinal products that alter the pH of the upper Gastro-Intestinal (GI) tract may alter the solubility of buparlisib and hence its bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. buparlisib/placebo should be dosed in a staggered manner at least 1 hour before or 10 hours after dosing with medicinal products that may alter the pH of the upper GI tract.

6.3.2 Prohibited concomitant therapy

6.3.2.1 Other anticancer therapy

Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is enrolled in the treatment portion of the trial. If such agents are required for a patient then the patient must be permanently discontinued from the treatment portion of the study.

6.3.2.2 Other investigational therapies

Other investigational therapies must not be used while the patient is on the study.

6.3.2.3 Hematopoietic growth factors

Prophylactic use of hematopoietic growth factors (e.g. erythropoietins, granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF)) are not permitted. However, in the event of an emergency (e.g. acute myelosuppression with infection), a patient may be given hematopoietic growth factors according to the investigator's judgment, and the sponsor should be notified as soon as possible. Subsequent secondary prevention use is permitted at investigator's discretion.

Patients who begin erythropoietin or darbepoetin therapy before randomization, may continue this treatment at the discretion of the investigator.

6.3.2.4 Warfarin and coumarin derivatives

Therapeutic doses of warfarin sodium or any other coumarin-derivative anticoagulants are not permitted.

Buparlisib is a weak inhibitor of CYP2C8 and 2C9, the major metabolizing enzyme of warfarin. Despite the fact that the inhibitory signal was weak, an increase of 40-50% of warfarin exposure is possible and for a drug like warfarin, this might be clinically relevant.

6.3.2.5 Enzyme-inducing anti-epileptic drug (EIAED)

Use of enzyme-inducing anti-epileptic drug (EIAED) is not permitted. Refer to for a list of prohibited EIAED.

If a patient is currently taking EIAED, they must have discontinued the EIAED therapy for at least two weeks prior to starting study drug.

If a patient is previously on a non-EIAED and needs to permanently change the anticonvulsant agent, but cannot change to another non-EIAED, the patient will be taken off buparlisib/placebo.

6.3.2.6 Drugs with a known risk for Torsades de Pointes

If a patient requires the concomitant use of any medication included in Table 14-3 in Appendix 4 entitled "List of Prohibited QT prolonging drugs" (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a risk of causing Torsade de Pointes), study treatment must be delayed. Note that Table 14-3 lists drugs with a known risk for Torsades de Pointes (TdP) as well as sensitive CYP3A substrates (with narrow TI) with a possible or conditional risk for TdP. Study treatment administration must be interrupted as long as the patient requires therapy with the QT prolonging agent.

6.3.2.7 Strong CYP3A inhibitors and inducers

In vitro metabolism studies suggest that oxidative metabolism of buparlisib is predominantly mediated by CYP3A4 and UGT1A4. Based on these in-vitro finding, a clinical trial was conducted in healthy volunteers. The study investigated then impact of a strong CYP3A4

inhibitor, ritonavir, on the pharmacokinetics of buparlisib [CBKM120C2111]. The results showed that the contribution of CYP3A4 in-vivo was not as important as initially thought in-vitro. Exposure of buparlisib increased by 1.73 fold upon concomitant administration of ritonavir which suggested that CYP3A4 only contributed to around 40%.

Based on these findings, strong CYP3A4 inhibitors and inducers are prohibited as they might substantially impact buparlisib exposure.

Please refer to Table 14-1 in Appendix 2 for a list of prohibited drugs. Please note that this list may not be comprehensive.

6.3.2.8 Herbal medications

Herbal preparations/medications are not allowed throughout the study, as a potential drug-drug interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

Patients should stop using these herbal medications at least 7 days prior to first dose of study treatment.

6.3.2.9 Hormonal contraception

Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study, since induction of CYP3A4 may not be excluded in patients receiving buparlisib.

6.4 Patient numbering, treatment assignment and randomization

6.4.1 Patient numbering

Each patient is identified in the study by a 7-digit Patient Number (Patient No.) that is assigned when the patient is first enrolled for screening, and is retained as the primary identifier for the patient throughout her entire participation in the trial.

- The Patient No. consists of the 4-digit Center Number (assigned by Novartis to the investigative site) and a sequential 3-digit patient number suffixed to it, so that each subject is numbered uniquely across the entire study
- The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information for the patient to register them into the IRT system
- Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed, even if the patient is re-screened
- If the patient fails to be started on treatment for any reason, the reason will be entered into the Screening Phase Disposition eCRF
- IRT should be notified within 2 days if the patient on screening was not started on treatment (Section 7.1.2.1)

6.4.2 Treatment assignment and randomization

Approximately 150 patients will be randomized in a 1:1 ratio to one of the two treatment arms (Section 4.1 and Section 6.1).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments. The randomization number will not be communicated to the person contacting the IRT.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify unique medication number(s) for the first packages of study treatment to be dispensed to the patient.

6.4.3 Treatment blinding

- This is a double blind study. In particular, patients, investigators, local radiologists, , or anyone involved in the study conduct will remain blinded to the identity of the treatment from the time of randomization until the final OS analysis
- The Novartis study team remained blinded until the primary analysis.
- Given the final OS analysis has been completed, unblinding will occur and the Investigator will decide whether to continue the patient on study treatment based on clinical benefit.
- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible to anyone involved in the conduct of the study. The identity of the treatments will be concealed by the use of investigational drugs (buparlisib or buparlisib-matching placebo) that are identical in packaging, labeling, schedule of administration and in appearance. Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of patients
- Unblinding of study drug assignment will only occur in the case of patient emergencies, for regulatory reporting purposes and at the conclusion of the study, using the IRT system
- In rare cases when unblinding occurs because of emergency patient management, the actual treatment arm will not be communicated to any of the Novartis employees involved in running the trial in order to remain blinded
- An independent statistician, not involved in the trial conduct, will prepare data reports for the DMC. Details will be presented in the DMC charter

6.5 Study drug supply

6.5.1 Study drug preparation and dispensation

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms. Study medication will be dispensed by an authorized person at the investigator's site. Investigator staff will identify the study drug package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Investigator staff will add the patient number on the label. Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Patients will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive buparlisib/placebo on an outpatient basis. The investigator shall provide the patient with instructions for buparlisib/placebo administration according to the protocol.

Paclitaxel should be prepared and dispensed according to the local prescribing information and practice. Investigator staff will register paclitaxel dispensation to the patient by using the IRT.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.5.2 Study drug packaging and labeling

Buparlisib/placebo will be supplied as 10-mg and 50-mg hard gelatin capsules, packaged in bottles, and will be given orally on a flat scale of mg/day. The capsules are packaged in HDPE bottles with a plastic child resistant closure.

Each bottle received will have a 2-part label. A unique medication number is printed on each part of the label which corresponds to one of the treatment arms.

Medication labels comply with the legal requirements and are printed in the local language. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

Table 6-5 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Buparlisib or Buparlisib-matching placebo	Capsules in bottle 10 mg 50 mg	Labeled as "BKM120/Placebo" Once daily dosing
Paclitaxel	Refer to local product information	Refer to local product information

Paclitaxel packaging and labeling will be according to locally available supplies of Paclitaxel and according to local regulations.

6.5.3 Drug supply and storage

Each site will be globally supplied by Novartis with oral buparlisib/placebo bottles. Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access.

Upon receipt, buparlisib/placebo should be stored according to the instructions specified on the drug labels. These instructions should also be made clear to the patient for storage and self-administration of buparlisib at home.

If available, generic paclitaxel should be used for study treatment, when possible. Paclitaxel should be prepared and stored according to the local prescribing information and practice. If feasible and available per local practices, patients who are receiving paclitaxel alone may be transitioned to commercial drug.

Site staff will be responsible for managing adequate re-supplies for paclitaxel. For buparlisib/placebo, re-supplies are managed with the IRT system, using local depots or regional hubs where possible. It is therefore required that the site staff enters any receipt of drug supplies and any dispensed drug into the IRT system immediately to not run the risk that the IRT cannot provide drug re-supplies on time.

6.5.4 Study drug compliance and accountability

6.5.4.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit using pills counts and information provided by the patient and/or caregiver. Records of study medication used, dosages administered, and intervals between visits and the completion of the study will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

A buparlisib/placebo patient medication diary will be provided for each patient. Patients or caregivers are required to complete this diary during the study.

6.5.4.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all used and unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.5 Disposal and destruction

The drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1a lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

Written informed consent must be obtained before any study specific assessments are performed, including screening. Baseline radiographic tumor assessments should be performed within 28 days prior to treatment start. Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol.

During the study (post- screening):

- All assessments have a ± 3 day window unless otherwise indicated
- Tumor assessments have a window of ± 3 days at cycle 2 Day 1 and ± 4 days for subsequent cycles starting from cycle 3 Day 15
- Paclitaxel will be administered once weekly (± 1 day). Missed doses will not be made up.
- Buparlisib/placebo will be administered once daily, continuously. Missed doses will not be made up.
- Additional assessments may be performed as clinically indicated.
- There is no visit or treatment window for Cycle 1 Day 1.

A complete cycle is defined as 28 days (± 3 days).

If one or both study drugs are being held due to toxicity, scheduled visits and assessments should still be performed (with the exception of the dosing of the held study drug) as described in Table 7-1a, unless otherwise specified.

Patients who permanently discontinue paclitaxel, but continue buparlisib/placebo will have assessments only on days 1 and 15 of each subsequent cycle (the patients will not be required to come to the investigational site on day 8 and 22 of subsequent cycles except for PK sampling on Cycle 1 Day 22). In this case, IRT will be contacted only on days 1 and 15 of each cycle.

Please refer to Table 7-14, Table 7-15 and Table 7-16 for PK sampling windows and to Table 7-8 for biomarker sampling windows. Similar adherence to the outlined schedule should be applied for all biomarker analyses. In general, where possible, every effort must be made to follow the schedule outlined in Table 7-1a.

Table 7-1b lists the assessments for patients receiving paclitaxel alone after unblinding. Those patients will be assessed as per local clinical practices and at investigator discretion.

Table 7-1c lists all the assessments for patients receiving buparlisib +/- paclitaxel after unblinding.

Table 7-1a Visit evaluation schedule

	Category	Protocol Section	Screening	Cycle 1				Cycle 2				Subsequent cycles				EOT	Post treatment F up	Survival phase
Cycle Days			-35 to -1	1	8	15	22	1	8	15	22	1	8	15	22	Last Dose +≤ 7d	Safety & efficacy F up	Survival F up every 3 months
Study Informed consent	D	11.3	X															
Inclusion/Exclusion criteria	D	5.1 5.2	X															
Relevant medical history/ Current medical conditions	D	7.1.2.3	X															
Smoking History	D	7.1.2.3	X															
Alcohol Consumption History	D	7.1.2.3	X															
Diagnosis and extent of cancer	D	7.1.2.3	X															
HPV historical status (if available)	D	7.1.2.3	X															
Prior antineoplastic therapy (surgery/medication /radiotherapy)	D	7.1.2.3	X															
IRT Registration/ Buparlisib/placebo/ paclitaxel management	S	6.4.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Category	Protocol Section	Screening	Cycle 1				Cycle 2				Subsequent cycles				EOT	Post treatment F up	Survival phase
Cycle Days			-35 to -1	1	8	15	22	1	8	15	22	1	8	15	22	Last Dose +≤ 7d	Safety & efficacy F up	Survival F up every 3 months
Eligibility checklist via IRT	S	7.1.2.1	X															
IRT Randomization	D	6.4.2		X														
End of Phase Disposition	D	7.1.4	X													X	X	
Demography	D	7.1.2.3	X															
Weight	D	7.2.2.3	X	X				X				X				X		
Height	D	7.2.2.3	X															
Vital Signs	D	7.2.2.2	X	X				X				X				X		
Physical examination	S	7.2.2.1	X	X				X				X				X		
ECOG P.S.	D	7.2.2.4	X	X				X				X				X		
PHQ-9 Patient self-rating mood scale	D	7.2.2.8	X	X		X		X		X		X		X (Cycle 3 only)		X		
GAD7 Patient self-rating mood scale	D	7.2.2.8	X	X		X		X		X		X		X (Cycle 3 only)		X		

	Category	Protocol Section	Screening	Cycle 1				Cycle 2				Subsequent cycles				EOT	Post treatment F up	Survival phase
Cycle Days			-35 to -1	1	8	15	22	1	8	15	22	1	8	15	22	Last Dose +≤ 7d	Safety & efficacy F up	Survival F up every 3 months
EORTC QLQ-C30 + QLQ-HN35	D	7.2.4.1	X					X Every 6 weeks starting from cycle 2 day 15								X		
Laboratory Assessment																		
Hematology	D	7.2.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Biochemistry (full panel)	D	7.2.2.5.2	X	X				X				X				X		
Biochemistry (partial panel) (AST, ALT, Alkaline phosphatase, total bilirubin, creatinine)	D	7.2.2.5.2			X	X	X		X	X	X							
Hepatotoxicity follow-up testing/procedures	D	7.2.2.5.7	As clinically indicated															
Coagulation	D	7.2.2.5.4	X	X				X				X				X		
Creatinine clearance	D	7.2.2.5.2	X	X				X				X				X		
Lipid profile	D	7.2.2.5.2	X													X		
Fasting plasma glucose	D	7.2.2.5.3	X			X		X		X		X		X		X		
Fasting C-peptide	D	7.2.2.5.3	X			X		X				X				X		
HbA1c	D	7.2.2.5.3	X									X (every 3 cycles starting cycle3 day 1)				X		
Urine dipstick	D	7.2.2.5.5	X	As clinically indicated												X		

	Category	Protocol Section	Screening	Cycle 1				Cycle 2				Subsequent cycles				EOT	Post treatment F up	Survival phase
Cycle Days			-35 to -1	1	8	15	22	1	8	15	22	1	8	15	22	Last Dose +≤ 7d	Safety & efficacy F up	Survival F up every 3 months
Pregnancy test, if applicable	D	7.2.2.5.6	X	X				X				X				X		
Blood sample for BKM120 full PK sampling		7.2.5				X[1]	X[1]	X[1]										
Blood sample for BKM120 sparse PK sampling		7.2.5		X[2]		X[2]	X[2]	X[2]				X[2] (every second cycle until cycle 6)						
Trough Blood sample for BKM120 PK sampling		7.2.5				X[3,4]	X[3,4]	X[3,4]				X[3,4] (every second cycle until Cycle 6)						
Imaging / Other assessments																		
Tumor response assessment (MRI/CT)	D	7.2.1	X (window -28 to -1)					X				X (every 6 weeks starting from cycle 3 day 15)				X	X (every 6 weeks)	
Pulmonary function tests	D	6.2.2.3.1	As clinically indicated for pneumonitis management (refer to Table 6-4)															
12 Lead ECG	D	7.2.2.7.1	X	X				X				X				X		

	Category	Protocol Section	Screening	Cycle 1				Cycle 2				Subsequent cycles				EOT	Post treatment F up	Survival phase
Cycle Days			-35 to -1	1	8	15	22	1	8	15	22	1	8	15	22	Last Dose +≤ 7d	Safety & efficacy F up	Survival F up every 3 months
Cardiac assessment by MUGA/ECHO	D	7.2.2.7.2	X									Cycle 4 day 1 and every 4th cycle thereafter				X		
Biomarkers																		
Tumor biopsy (archival or new tumor blocks/slides)	D	5.1	X															
Plasma for Circulating DNA	D	7.2.3	X													X		
[redacted]																		
Safety																		
Adverse events	D	8.1	X	Continuous, up to 30 days after last dose of study treatment														
Prior/concomitant medications	D	6.3	X	Continuous, up to 30 days after last dose of study treatment														
Prior/concomitant medical and surgical procedures	D	6.3																

	Category	Protocol Section	Screening	Cycle 1				Cycle 2				Subsequent cycles				EOT	Post treatment F up	Survival phase
Cycle Days			-35 to -1	1	8	15	22	1	8	15	22	1	8	15	22	Last Dose +≤ 7d	Safety & efficacy F up	Survival F up every 3 months
New antineoplastic therapy since EoT	D	7.1.4 7.1.5															X	
Survival FU [1] (every 3 months from EoT)	D	7.1.5.3																X[1]
Drug Administration																		
buparlisib/ placebo administration	D	6.1.1.1		Daily														
Paclitaxel administration	D	6.1.1.2		Once a week starting cycle 1 day 1 (days 1, 8, 15, 22 of each cycle)														

1. In patients with full PK sampling, pharmacokinetic assessments will be performed on Cycle 1 Day 15 (at pre-dose, at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 24h [before Cycle 1 Day 16 dose] post-dose). Only pre-dose samples will be collected on Cycle 1 Day 22 and Cycle 2 Day 1.
2. Pharmacokinetic assessments in patients with sparse PK sampling will be performed on Cycle 1 Day 1 at 1, 2, and 6h, and a recommended 9 hours post dose sample. Only pre-dose sample will be collected on Cycle 1 Day 15 and 22 and Cycle 2 Day 1.
3. Buparlisib trough concentrations - a PK sample will be collected before drug administration (pre-dose) on Cycle 1 Day 15 and Day 22, Cycle 2 Day 1, Cycle 4 Day 1 and Cycle 6 Day 1 unless buparlisib/placebo is permanently terminated.
4. For all remaining patients who did not participate for Full PK and Sparse PK sampling

Table 7-1b Visit evaluation schedule for patients receiving paclitaxel alone after unblinding

	Category	Reference to Section 7.2	Subsequent cycles – Day 1	End of treatment
End of phase disposition	D	7.1.4		X
Paclitaxel administration	D	6.1.1.2	Once a week (days 1, 8, 15, 22 of each cycle)	
Adverse events	D	8.1	Continuous up to 30 days after last dose of treatment	
Prior/concomitant medications	D	6.3	Continuous up to 30 days after last dose of treatment	
Prior/concomitant medical and surgical procedures	D	6.3	Continuous up to 30 days after last dose of treatment	
Tumor response assessment	D	7.2.1	As per local practices	
Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion. Survival F-up will no longer be collected after 30 day safety Follow-up..				

Table 7-1c Visit evaluation schedule for patients receiving buparlisib +/- paclitaxel after unblinding

	Category	Reference to Section 7.2	Subsequent cycles – Day 1	End of treatment
IRT registration	S	6.4.2	X	X
End of phase disposition	D	7.1.4		X
Performance status (ECOG)	D	7.2.2.4	X	X
Weight	D/S	7.2.2.3	As clinically indicated	X
Vital signs	D/S	7.2.2.2	X	X
Patient self-reported Mood scales for depression (PHQ-9) and anxiety (GAD 7)	D	7.2.2.8	X	X
Pulmonary function tests	D	6.2.2.3.1	As clinically indicated	
12-lead ECG	D	7.2.2.7.1	As clinically indicated	X
Cardiac imaging (MUGA/ECHO)	D	7.2.2.7.2	As clinically indicated and at least every 4 months	X (if not done within the last 4 months)
Hematology	D	7.2.2.5.1	X	X
Biochemistry	D	7.2.2.5.2	X	X
Hepatotoxicity follow-up testing/procedures	D	7.2.2.5.7	As clinically indicated	
Fasting plasma glucose, lipase	D	7.2.2.5.3	X	X
Buparlisib administration	D	6.1.1.1	Daily	
Paclitaxel administration	D	6.1.1.2	Once a week (days 1, 8, 15, 22 of each cycle)	
Adverse events	D	8.1	Continuous up to 30 days after last dose of treatment	
Prior/concomitant medications	D	6.3	Continuous up to 30 days after last dose of treatment	
Prior/concomitant medical and surgical procedures	D	6.3	Continuous up to 30 days after last dose of treatment	
Tumor response assessment	D	7.2.1	As per standard of care	

Survival F-up will no longer be collected after 30 day safety Follow-up.

7.1.1 Molecular pre-screening

Not applicable

7.1.2 Screening

After signing the main study ICF (S-ICF), the screening assessments will be done within 1 to 35 days prior to treatment start (except for radiological tumor assessments which need to be done within 1 to 28 days prior to treatment start).

Re-screening of patients is only allowed once per patient if the patient was not registered as entering the treatment phase before (i.e. IRT randomization). In this case the Subject No assigned to the patient initially will be used and the patient will be identified with this number throughout their entire participation to the study.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria.

For details of assessments, refer to Table 7-1a.

7.1.2.1 Eligibility screening

In order to determine and confirm the eligibility of the patient, once all screening procedures are completed, an eligibility checklist must be completed via IRT by the investigator or designee prior to receiving the first dose of study drug.

After the eligibility has been checked and confirmed that the patient is eligible for the trial, then the patient can be enrolled into the study.

The IRT system will randomize patients to treatment in a 1:1 ratio to receive, paclitaxel + buparlisib or paclitaxel + buparlisib-matching placebo.

To evaluate a patient for enrollment into the study:

- Obtain written consent and complete all the screening evaluations
- Call the Interactive Response Technology (IRT) as close as possible to the day study treatment is due to start. Verification of eligibility criteria must be known **prior** to contacting IRT. Randomization to one of the 2 treatment arms (paclitaxel + buparlisib or paclitaxel + buparlisib-matching placebo) will be provided by the IRT. The specific information and instructions will be provided separately to each study site.

7.1.2.2 Information to be collected on screening failures

Patients who sign ICF, but are not randomized via IRT for any reason will be considered a screening failure. A patient who is randomized via IRT but does not start treatment is not considered a screening failure. The reason for not proceeding with the treatment will be documented on the End of treatment page. Limited data will be collected for these patients.

For screening failure patients, the reason for not proceeding with randomization will be entered on the End of Phase Disposition Page. No waivers will be granted.

The following eCRFs must be completed for screening failure patients:

- End of phase disposition eCRF page (including reason for not being started on treatment)
- Informed Consent, including additional biomarker ICF if relevant.
- Inclusion/Exclusion Criteria
- Demography
- Adverse Events (only if the patient experienced a Serious Adverse Event during the Screening Period after signing the ICF - see Section 8 for SAE reporting details)

If a screening failure patient experiences an AE which does not meet the SAE criteria, details about the AE will be recorded only in the investigator's source documents. In case of an SAE, data must be recorded on both the AE and SAE forms.

No other data will be entered into the clinical database for patients who are screen failures.

If on screening, the patient fails to start on treatment, then IRT must be notified within 2 days of the screen failure.

7.1.2.3 Patient demographics and other baseline characteristics

Patient information to be collected at screening will include:

- Historical HPV status
- Demography
- Diagnosis and Extent of Cancer
- Relevant Medical History (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / Current Medical Conditions (e.g., all relevant current medical conditions which are present before the first dose of study drug is administered)
    - Cancer-related conditions and symptoms which are recorded on the Medical History eCRF should include the grade
- Prior Anti-neoplastic Medications
- Prior Anti-neoplastic Radiotherapy
- Prior Anti-neoplastic Surgery
- All other medications and non-drug therapies (including physical therapy, oxygen and blood transfusions) administered to the patient within 28 days prior to the first dose of study drug) must be reported on the appropriate eCRFs

Furthermore the following assessments will be performed to assess the eligibility of the patient:

- Physical Examination (See Section 7.2.2.1)
- Vital signs (See Section 7.2.2.2)
- Height, weight (See Section 7.2.2.3)
- ECOG performance status (See Section 7.2.2.4)

- Patient self-rating mood questionnaires (PHQ-9 and GAD7) (See Section 7.2.2.8)
- Patient self-rating EORTC QLQ-C30 and QLQ-HN35 (See Section 7.2.4.1)
- ECG (See Section 7.2.2.7.1)
- Cardiac imaging (See Section 7.2.2.7.2)
- Radiological assessments (e.g., CT scan) (See Section 7.2.1)
- Laboratory evaluations (e.g., hematology, coagulation, chemistry, urinalysis) (See Section 7.2.2.5)
- Serum pregnancy (See Section 7.2.2.5.6)

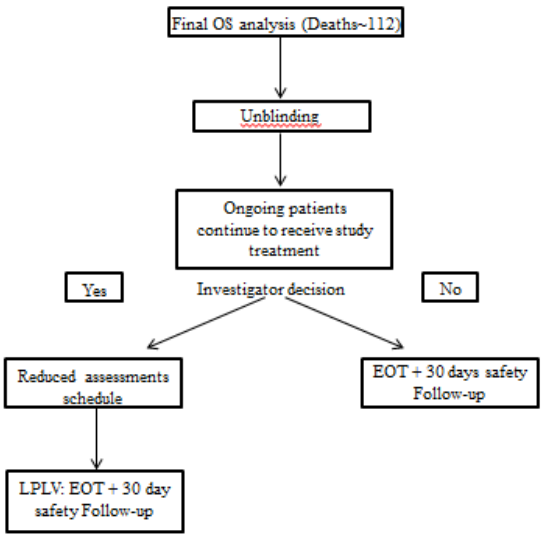
7.1.3 Treatment period

Patients will be treated with paclitaxel + buparlisib or paclitaxel + buparlisib-matching placebo until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason.

As the Final OS analysis has been performed, unblinding will occur. Patients still on treatment may continue to receive study treatment if the investigator considers they are clinically benefiting from continuing it. The patient will continue receiving study treatment on or off study until physician decision. If feasible and available per local standard of care, patients who are receiving paclitaxel alone may be transitioned to commercial drug.

Patients will continue with a reduced schedule of study evaluations as described in Table 7-1b and Table 7-1c. Table 7-1b describes the assessments required for patients receiving paclitaxel alone and Table 7-1c describes the assessments required for the patients receiving buparlisib alone or in combination with paclitaxel.

Figure 7-1 On-treatment patients Follow-up after unblinding (from protocol amendment v.03)



For details of assessments, refer to Table 7-1a, Table 7-1b and Table 7-1c.

- Visits and associated assessments that occur +/- 3 days from the scheduled date (except for cycle 1 Day1 where no visit window is allowed) will not constitute protocol deviations.
- MRI/CT scans must be performed at Cycle 2 Day 1 (+/- 3 days) and every 6 weeks (+/-4 days) until disease progression, withdrawal consent, lost to follow-up, start of another anti-neoplastic therapy, or death, whichever occurs first.
- Laboratory assessments performed as part of the screening evaluations and within 7 days of the first dose of study treatment, are not required to be repeated on the first dosing day.

7.1.4 End of treatment visit

Patients who completely discontinue study treatment should be scheduled for an End of Treatment (EOT) visit within 7 days following the date study treatment is permanently discontinued, at which time all of the assessments listed for the EOT visit will be performed. For details of assessments, refer to Table 7-1a, Table 7-1b and Table 7-1c. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

The investigator (or designee) must contact IRT to register the patient's treatment discontinuation.

7.1.4.1 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue the study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Adverse Event
- Lost to follow-up
- Non-compliance with study treatment
- Physician decision
- Pregnancy
- Progressive Disease
- Protocol deviation

- Study terminated by sponsor
- Technical problems
- Subject/guardian decision
- Death

In addition, the following study specific criteria will also require study treatment discontinuation:

- Adjustments to study treatment that result in discontinuation. Please refer to Section 6.2
- Use of prohibited medication. Please refer to Section 6.3.2
- Interruption of study treatment for > 28 days, regardless of reason, from the intended day of the next scheduled dose

The appropriate personnel from the site and Novartis will assess whether the investigational treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.5.4.

Patients who discontinue study treatment should undergo an end of study visit and then enter the follow-up epoch.

From protocol amendment v.03, regardless of EOT reason, tumor assessments for efficacy follow-up will not be assessed and Study Phase Completion eCRF is not applicable; for patients still under efficacy follow up at the time of protocol amendment v.03, Study Phase Completion eCRF will continue to be completed as per eCRF completion guidelines (eCCG).

The investigator must also contact the IRT to register the patient's discontinuation from investigational treatment.

7.1.4.2 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.5 Follow up period

7.1.5.1 Safety follow up

All patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations (i.e., assessment of AEs and/or SAEs, concomitant medications) for 30 days after the last dose of study treatment. Patients whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed at least once a week for 4 weeks and subsequently at 4-weeks intervals until resolution or stabilization of the event, whichever comes first.

If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.) and a Study Phase Completion Disposition eCRF page should be completed.

All new anti-cancer therapies given after the last dose of the study drug will be recorded on eCRFs designed to capture anti-neoplastic therapies administered after discontinuation of study treatment.

7.1.5.2 Efficacy follow-up

If a patient did not discontinue study treatment due to disease progression, death, start of new anti-neoplastic therapies, lost to follow-up, or withdrawal of consent to efficacy follow-up, then tumor assessments should continue to be performed every 6 weeks until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, or withdrawn consent to efficacy follow-up. At that time, the reason for study completion should be recorded on the Study Phase Completion Disposition eCRF page. In addition, all new anticancer therapies given after the last dose of the study drug, until disease progression, death, lost to follow-up, or withdrawal of consent to efficacy follow-up will be recorded in the eCRFs. From protocol amendment v.03, regardless of EOT reason, efficacy follow up will be done as per local practices.

7.1.5.3 Survival follow-up

All patients will be followed for survival status every 3 months regardless of treatment discontinuation reason until death, lost to follow-up, or withdrawal of consent to survival follow-up. Additional survival assessments may be performed outside the 3 months follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

From protocol amendment v.03, survival follow-up will not be performed.

7.1.5.4 Lost to follow-up

Patients lost to follow up should be recorded as such in the eCRFs. 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. A patient should not be considered lost to follow-up until due diligence has been completed.

7.1.5.5 End of post-treatment follow-up (Study phase completion)

Prior to collecting survival follow-up information, end of post-treatment eCRF (study phase completion) will be completed once a patient has discontinued study treatment, completed safety follow-up, and can no longer perform efficacy assessment.

Study phase completion may occur for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

From protocol amendment v.03, End of post-treatment follow-up (Study phase completion) is not applicable; for patients still under efficacy follow up Study Phase Completion eCRF will continue to be completed as per eCCG.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be determined locally according to the Novartis guideline (Appendix 6) on the Response Evaluation Criteria in Solid Tumors (RECIST), based on RECIST Version 1.1. The local investigator's assessment will be used for the primary endpoint analysis and for treatment decision making. Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. Central review of the imaging data may be performed if deemed necessary.

The following radiologic and clinical assessments will be performed:

- All potential sites of tumor lesions will be assessed at screening by radiologic techniques (e.g. CT or MRI imaging). At screening, in addition to CT or MRI scan of the primary tumor, all patients must have chest CT (or MRI) and an abdominal/ CT (or

MRI) with IV contrast. CT/MRI of the primary tumor, chest and abdomen must be performed at every tumor assessment. If no pelvic lesions are suspected at baseline then pelvic CT (or MRI) scan does not need to be performed. The preferred radiologic technique is CT with intravenous (i.v.). If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of abdomen should be performed.

- If clinically indicated, a full body bone scan at screening for bone lesions should be performed at screening according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, sodium fluoride positron emission tomography (NaF PET), or Fluorodeoxyglucose PET (FDG PET)).
  - If such a scan was already done during the regular work-up of the patient within 6 weeks prior to start of treatment, this scan can be considered as the screening scan for this study. After screening, scans need not be repeated, unless clinically indicated. If indicated, the same methodology as at screening should be used.
- Localized CT, MRI or X-rays of all skeletal lesions identified on the screening bone scan, which are not visible on the chest and abdomen CT (or MRI) must be taken at screening and at each subsequent tumor assessment.
- If brain metastases are suspected at screening, brain CT or MRI scan should be performed. Brain CT or MRI will be continued at subsequent tumor assessments if brain metastases were identified at screening.
- If skin lesions are present at screening, color photography should be acquired using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.
- CT or MRI of any other lesion not captured by any of the above listed images (e.g., neck, pelvis) at screening and at each subsequent tumor assessment.

Ultrasound and chest x-ray should not be used to measure tumor lesions.

Tumor assessment according to Appendix 6 (RECIST 1.1) will be assessed at the following time points:

- Screening Visit
  - All known lesions (measurable, and non-measurable) should be documented during screening to serve as baseline tumor evaluation within 28 days before the start of treatment (except for the full body bone scan as described above, within 6 weeks). Therefore the first dose of the study drug should be administered within 28 days considering the date in which the CT scan/ MRI has been performed and all screening procedures should be completed accordingly within this timeframe. For subsequent scans in the same patient, the radiologist must account for all lesions that were present at screening and must use the same technique as used at screening. If possible, a single radiologist should perform all tumor response evaluations for an individual patient.
- During treatment: At Cycle 2 Day 1 (± 3 days) and every 6 weeks (± 4 days) after Cycle 2 Day 1

  - Complete tumor assessment is mandatory week 4, 10, 16 and every 6 weeks, as defined in Table 7-1a, until disease progression, death, start of new anti-cancer therapy, withdrawal of consent to efficacy follow-up or lost to follow up whichever occurs earlier, or as clinically indicated. After screening, other imaging studies are required at the same interval if lesions were identified at screening (e.g. brain, bone lesions) or if there is clinical evidence of a potential new lesion during the study. Tumor lesions assessed by physical examination must also be assessed at the same schedule.
- From protocol amendment v3.0, CT/MRI scanning of the head and neck, chest, abdomen and pelvis will be performed for all ongoing patients as per local clinical practices. Tumor response data will be collected to facilitate investigator assessment of continuing clinical benefit.
- End of Treatment visit: Tumor assessments at EOT are required for patients who discontinue study treatment before the first scheduled post-screening tumor assessment and for patients whose previous tumor assessment did not demonstrate PD and was done at least 6 weeks (+/- 4 days) prior to end of treatment visit.
- From protocol amendment v3.0, Tumor assessments at EOT are not required unless the previous assessment was done more than 6 weeks prior to EoT
- After the End of Treatment visit, continued every 6 weeks (± 4 days) from the randomization date,
  - if a patient did not discontinue study treatment due to disease progression, death, start of new anti-neoplastic therapies, lost to follow-up, or withdrawal of consent to efficacy follow-up, then tumor assessments should continue being performed every 6 weeks (± 7 days) until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, or withdrawn consent to efficacy follow-up. From protocol amendment v.03, regardless of EOT reason, tumor assessments for efficacy follow up are no longer required.

All patients who discontinue from study treatment due to disease progression must have their progression clearly documented according to the criteria specified in Appendix 6 (RECIST v1.1). No additional tumor assessment is required to confirm response (CR or PR) outside the protocol specified 6-week tumor assessments.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media. FDG-PET may be utilized to document progressive disease per RECIST 1.1.

Any lesion that has been previously treated with radiotherapy should be considered as a non-target lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a target lesion.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Definitions for measurable and non-measurable lesions, and criteria for response, should be based on RECIST v1.1 (Appendix 6).

Additional CT/MRI safety based assessments are described in Section 7.2.2.6.

Table 7-2 Imaging collection plan

Procedure	Screening	During Treatment[1]	During Follow-up[1]
CT/MRI of primary tumor	Mandatory	Mandatory, after completion of 4, 10, 16 weeks of treatment, and every 6 weeks thereafter and at the end of study treatment	Mandatory for patients who have not progressed at the time of treatment discontinuation: every 6 weeks
CT/MRI Chest	Mandatory	Mandatory, after completion of 4, 10, 16 weeks of treatment, and every 6 weeks thereafter and at the end of study treatment	Mandatory for patients who have not progressed at the time of treatment discontinuation: every 6 weeks
CT/MRI Abdomen	Mandatory	Mandatory, after completion of 4, 10, 16 weeks of treatment, and every 6 weeks thereafter and at the end of study treatment	Mandatory for patients who have not progressed at the time of treatment discontinuation: every 6 weeks
CT/MRI Pelvis	If clinically indicated	If abnormal at screening, after completion of 4, 10, 16 weeks of treatment, and every 6 weeks thereafter and at the end of study treatment	If abnormal at screening, for patients who have not progressed at the time of treatment discontinuation: every 6 weeks
Whole body bone scan	If clinically indicated	Only if clinically indicated	Not applicable
Bone x-ray, CT or MRI (bone lesions only)	Mandatory only if skeletal abnormalities identified by bone scan at screening, which are not visible on the chest and abdomen CT/MRI	If bone lesions at screening, after completion of 4, 10, 16 weeks of treatment, and every 6 weeks thereafter and at the end of study treatment	If bone lesions at screening, for patients who have not progressed at the time of treatment discontinuation: every 6 weeks
Brain CT/MRI	If clinically indicated	For patients that met the eligibility criteria and had brain metastases at baseline, after completion of 4, 10, 16 weeks of treatment, and every 6 weeks thereafter and at the end of study treatment	For patients that met the eligibility criteria and had brain metastases at baseline, who have not progressed at the time of treatment discontinuation: every 6 weeks

Procedure	Screening	During Treatment[1]	During Follow-up[1]
Skin color photography	Mandatory only if skin lesions at screening	If skin lesions at screening, after completion of 4, 10, 16 weeks of treatment, and every 6 weeks thereafter and at the end of study treatment	If skin lesions at screening, for patients who have not progressed at the time of treatment discontinuation: every 6 weeks
Any of the imaging methods listed above may be acquired at any time during treatment if clinically indicated. 1. From protocol amendment v.03, all procedures during Treatment are performed as per local clinical practices to assess continuing treatment benefit and efficacy Follow-up assessment are not required to be performed.			

7.2.2 Safety and tolerability assessments

Safety will be monitored by physical examination, vital signs, weight, performance status evaluation, ECG, cardiac imaging, laboratory evaluations including glucose monitoring and assessment of patient rated mood scales as shown in Table 7-6 and Table 7-7 below as well as collecting all serious and non-serious Adverse Events (AE). For details on AE collection and reporting, please refer to Section 8.1.

If one or both study drugs are being held due to toxicity, scheduled visits and assessments should still be performed (with the exception of the dosing of the held study drug) as described in Table 7-1a, unless otherwise specified.

7.2.2.1 Physical examination

A complete physical examination will be performed at screening at Day 1 of each cycle and at the EOT visit. The physical examination comprises a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph-nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site.

From protocol amendment v.03, the physical exam will be performed for all patients as per investigator discretion.

7.2.2.2 Vital signs

Clinically significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's CRF. Significant new findings that begin or worsen after informed consent and meet the definition of an AE must be recorded on the Adverse Event page of the patient's CRF.

Vital signs (body temperature, pulse rate, blood pressure) will be monitored once daily before administration of buparlisib/placebo at screening, at Day 1 of each cycle and at the EOT visit. Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for five minutes.

From protocol amendment v.03, patients receiving buparlisib alone or in combination with paclitaxel will be followed on day 1 of each cycle and at EOT visit. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

7.2.2.3 Height and weight

Height and body weight will be measured. Weight will be measured at the screening visit, at Day 1 of each cycle, and at EOT. Height will be collected at screening only.

From protocol amendment v.03, weight will be measured as clinically indicated and at EOT visit for patients receiving buparlisib alone or in combination with paclitaxel. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

7.2.2.4 Performance status

The performance status will be assessed according to the ECOG performance status scale (Oken 1982). ECOG performance status will be assessed at screening, at Day 1 of each cycle and at the EOT visit.

From protocol amendment v.03, performance status will be assessed on day 1 of each cycle and at EOT visit for patients receiving buparlisib alone or in combination with paclitaxel. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

Table 7-3 ECOG performance status

Grade	ECOG 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 house work, 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

7.2.2.5 Laboratory evaluations

Table 7-4 Local Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) From protocol amendment v.03 assessments will be performed as described in Section 7.2.2.5.1 Hematology
Chemistry (full panel)	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Calcium, Chloride, Creatinine, Potassium, Sodium, Magnesium, Phosphate Direct Bilirubin, Total Bilirubin, , Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Total Protein, Amylase, Gamma-glutamyl-transferase (GGT), Lactate

	dehydrogenase (LDH), Lipase, Creatinine Clearance From protocol amendment v.03 assessments will be performed as described in Section 7.2.2.5.2 Clinical chemistry
Chemistry (partial panel)	AST, ALT, Alkaline phosphatase, total bilirubin, creatinine From protocol amendment v.03 assessments will be performed as described in Section 7.2.2.5.2 Clinical chemistry
Lipid Profile	Total Cholesterol, LDL, HDL, Triglycerides
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, WBC, pH, Protein, Specific Gravity) From protocol amendment v.03 the urinalysis assessment will not be performed
Coagulation	Prothrombin time (PT) or International normalized ratio [INR], Activated Partial thromboplastin time (aPTT) From protocol amendment v.03 the coagulation assessment will not be performed
Additional tests	Fasting Plasma Glucose (FPG), HbA1C, C-Peptide From protocol amendment v.03 assessments will be performed as described in Section 7.2.2.5.3 Monitoring FPG, c-peptide and HbA1c
Pregnancy Test	Serum hCG at screening, EOT or unscheduled; other time points test serum hCG or urine From protocol amendment v.03 assessments will be performed as described in Section 7.2.2.5.6 Pregnancy and assessments of fertility
Viral hepatitis serologic tests and other tests for hepatotoxicity follow-up *	HAAb, HBsAg, HBsAb HBcAb, HCV RNA or HDV RNA (where needed), HEAb, CMVAb, EBcAb, ALP, CPK, LDH, WBC (eosinophilia), and others. From protocol amendment v.03 assessments will be performed as described in Section 7.2.2.5.7 Viral hepatitis serology and other tests for hepatotoxicity follow-up
* Hepatotoxicity follow-up testing/procedures will be performed locally (refer to Section 6.2.2.3.7) Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120/placebo and Section 7.2.2.5.7 Viral hepatitis serology and other tests for hepatotoxicity follow-up).	

Clinical laboratory analyses (Hematology, Biochemistry, coagulation, Fasting Plasma Glucose (FPG), HbA1C, C-Peptide and pregnancy test) are to be performed by the local laboratory according to the Visit Schedule outlined in Table 7-1a. Visit windows of +/- 3 days are allowed (except at cycle 1 Day 1). Screening laboratory assessments performed seven days of first dosing do not need to be repeated at Cycle 1 Day 1.

Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or

interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 4.0.3. Additional analyses are left to the discretion of the investigator.

Hepatotoxicity follow-up testing will be performed when needed (refer to Section 6.2.2.1. Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN in patients receiving BKM120/placebo.

7.2.2.5.1 Hematology

Hematology tests are to be performed according to the Visit Schedules outlined in Table 7-1a, Table 7-1b and Table 7-1c. For details of the Hematology panel refer to Table 7-4.

From protocol amendment v.03 and as detailed in Table 7-1c, the following parameters will be assessed on day 1 of each cycle and at EOT visit: hemoglobin, platelet count, total white blood cells (WBC) count, and a WBC differential (absolute values) including neutrophils, lymphocytes, monocytes, eosinophils and basophils for patients receiving buparlisib alone or in combination with paclitaxel. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

7.2.2.5.2 Clinical chemistry

Clinical chemistry tests are to be performed according to the Visit Schedules outlined in Table 7-1a, Table 7-1b and Table 7-1c are given in Table 7-4.

Refer to the dose modification table for buparlisib and paclitaxel Section 6.2.2.1 and Section 6.2.2.2 (respectively) regarding what tests are mandatory for patients requiring LFT follow up due to toxicity.

From protocol amendment v.03 and as detailed in the Table 7-1c, the following parameters will be assessed on day 1 of each cycle and at EOT visit: creatinine, sodium, magnesium, potassium, total bilirubin, alkaline phosphatase, AST/SGOT and ALT/SGPT for patients receiving buparlisib alone or in combination with paclitaxel. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

7.2.2.5.3 Monitoring FPG, C-peptide, and HbA1C

Fasting plasma glucose (FPG), C-peptide, and HbA1C will be assessed according to the visit schedules in Table 7-1a, Table 7-1b and Table 7-1c. Patients must be fasting overnight for at least 10 hours prior to the blood draw. The study personnel will ask the patient whether he/she has been fasting, which will be captured in the eCRF as well.

From protocol amendment v.03 and as detailed in the Table 7-1c, fasting plasma glucose and lipase will be assessed on day 1 of each cycle and at EOT visit for patients receiving buparlisib alone or in combination with paclitaxel. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

7.2.2.5.4 Coagulation

INR or pro-thrombin time (PT), and partial thromboplastin time will be measured according the visit schedules (see Table 7-1a, Table 7-1b and Table 7-1c).

From protocol amendment v.03 the coagulation assessment will not be performed.

7.2.2.5.5 Urinalysis

Urinalysis includes dipstick analysis will be performed as outline in Table 7-1a, Table 7-1b and Table 7-1c.

From protocol amendment v.03 the coagulation assessment will not be performed.

7.2.2.5.6 Pregnancy and assessments of fertility

All female patients of childbearing potential must undergo a serum pregnancy test at screening to confirm eligibility in the trial (≤ 7 days before first dose of either study drug), on day 1 of each cycle and at EOT. Women who are not of child-bearing potential do not require a pregnancy test, but must fulfill the conditions for the non-childbearing status given in Section 5.2.

In case an additional pregnancy test is indicated during the trial, a serum test should be performed. In case of pregnancy, the patient must permanently stop study treatment immediately, withdraw from the trial, and the pregnancy must be reported on the Clinical Trial Pregnancy Form.

7.2.2.5.7 Viral hepatitis serology and other tests for hepatotoxicity follow-up

During study treatment, viral hepatitis serologic and other tests will be performed as per the guidelines of management of hepatotoxicity (ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN) in patients receiving BKM120/placebo, refer to Section 6.2.2.3.7_Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120/placebo for details.

Viral hepatitis serology includes the following:

- Hepatitis A IgM antibody and hepatitis A serology total
- Hepatitis B surface antigen, Hepatitis B Core Antibody (IgM) and viral RNA
- Hepatitis C serology and viral RNA
- Hepatitis D RNA (where needed)
- Hepatitis E IgM and IgG antibody and viral RNA

Obtain fractionated bilirubin, serum Alkaline Phosphatase (ALP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and blood count with differential to assess eosinophilia.

Additional viral serology tests may include:

- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
- Herpes Simplex Virus

- From protocol amendment v03, patients receiving buparlisib alone or in combination with paclitaxel will be followed as clinically indicated. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

7.2.2.6 Radiological examinations

An unscheduled CT scan should be performed if any of following criteria is met:

- For any ≥ CTCAE grade 1 pneumonitis, CT scans with lung windows must be performed and repeated at least every 6 weeks until it returns to within normal limits
- For any CTCAE grade 3 or 4 hepatic toxicity that does not resolve within 7 days to ≤ grade 1 (or ≤ grade 2 if liver infiltration with tumor present), an abdominal CT scan must be performed to assess any relationship to disease progression.
- Within 1 week of the first occurrence of any ≥ CTCAE grade 3 of amylase or lipase, a CT scan must be performed to assess the pancreas, liver, and gallbladder.
- Any other additional examination may be performed as deemed necessary by the investigator based on clinical assessment of the patient status.

Efficacy based CT/MRI requirements are described in Section 7.2.1.

From protocol amendment v03, patients receiving buparlisib alone or in combination with paclitaxel will be followed as clinically indicated. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed

- at screening and/or baseline
- at pre-does on day 1 of every cycle
- at the end of study

Table 7-5 Local ECG collection plan

Visit or Cycle	Day	Time	ECG Type
1	-35 to -1	Pre-dose	12 Lead
All Cycles	1	Pre-dose	12 Lead
End of Treatment			12 Lead
Unscheduled visit		Anytime	12 Lead

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened

clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

From protocol amendment v.03, ECG will be done as clinically indicated and at EOT for patients receiving buparlisib alone or in combination with paclitaxel. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

7.2.2.7.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

Cardiac imaging will be performed by Multiple Gated acquisition (MUGA) scan or Echocardiogram (ECHO) in order to assess the left ventricular ejection fraction (LVEF). This assessment will be performed at screening for confirmation of eligibility and subsequently every 4 cycles beginning with Cycle 4 Day 1 visit.

The same technique (MUGA or ECHO) must be used during the course of the trial, and the method used will be recorded in the eCRF. Only clinically significant abnormalities should be reported in the Adverse Events eCRF.

In case a patient develops left ventricular systolic dysfunction while on study treatment dose adjustment guidelines described in Table 6-3 must be followed.

From protocol amendment v.03, cardiac imaging will be done as clinically indicated and at least every 4 months. The exam will be performed at EOT if not performed within the last 4 months for patients receiving buparlisib alone or in combination with paclitaxel. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

7.2.2.8 Patient self-rating mood questionnaire

The Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) will be collected to screen patients for the study and to aid in the identification and severity assessment of potential mood alterations. The PHQ-9 and GAD-7 are validated (Kroenke 2001, Spitzer 2006, Spitzer 1999) patient self-administered questionnaires developed for use in clinical practices.

The PHQ-9 (Appendix 7, Table 14-5) consists of 9 questions that assess anhedonia, depressed mood, sleep, energy, appetite, guilt and worthlessness, concentration, feeling slowed down or restlessness, and suicidal thoughts. For each of these questions, patients are asked to rate how much over the past 2 weeks they have been bothered by the symptom. Scoring of the PHQ-9 is based on a Likert-type scale from 0 to 3 (0 indicates not at all; 1, several days; 2, more than half the days; 3, nearly every day). The sum of all nine questions is used to determine a total PHQ-9 score ranging from 0 to 27.

The GAD-7 (Appendix 7, Table 14-6) is a one-dimensional questionnaire consisting of 7 questions. Similarly to the PHQ-9, in the GAD-7, patients are asked to indicate how often, over the past 2 weeks, they have been bothered by each of the seven core symptoms of generalized anxiety disorder as referenced in the DSM IV. Response options are ‘‘not at all,’’ ‘‘several days,’’ ‘‘more than half the days,’’ and ‘‘nearly every day,’’ scored as 0, 1, 2, and 3,

respectively. The sum of all seven questions calculates the total GAD-7 score. Therefore, GAD-7 scores range from 0 to 21.

The patient must complete two different mood questionnaires, (PHQ-9 and GAD-7) according to the visit schedule in Table 7-1a,Table 7-1b,Table 7-1c and Table 7-6. Additional assessments may be done according to the clinical judgment of the investigator.

All questionnaires should be given by the site to the patient in the patient's local language and reviewed for completeness and possible adverse events. Additional guidance regarding the general administration of patient questionnaires is described in Section 7.2.4 regarding Patient-reported Outcomes.

On visits when additional patient questionnaires (as specified in Section 7.2.4) are also to be completed, sites should instruct patients to complete the mood questionnaires after all other patient questionnaires and prior to administration of any study-related treatment or clinical assessments or procedures.

From protocol amendment v.03, patients receiving buparlisib alone or in combination with paclitaxel will complete PHQ-9 and GAD-7 questionnaires on day 1 of each cycle and at EOT visit. Patients receiving paclitaxel alone will be assessed as per standard of care and at investigator discretion.

Table 7-6 Patient self-reported mood questionnaire collection plan

Patient Questionnaires	Visit/ Cycle	Day	Time
PHQ-9 GAD-7	Screening	Day -35 to -1	Prior to any clinical assessments, study drug dosing or diagnostic testing. After EORTC QLQ-C30 and QLQ-HN35 assessment if scheduled for same day.*
	Cycle 1	Day 1, Day 15	
	Cycle 2	Day 1, Day 15	
	Cycle 3	Day 1, Day 15	
	Every Cycle	Day 1	
	End of treatment	Day of end of treatment assessment	

- *From protocol amendment v.03, EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires are not administered for patients still on study treatment

The severity classification table described in Table 7-7 for the PHQ-9 and GAD-7 will be used in this study to increase the sensitivity of identifying potential anxiety and/or depression disorders. During the study, questionnaire scores and corresponding severity classification can be used to aid the investigator in identifying new or worsening of events. However, grading must be based on the clinical interpretation of severity according to the NCI- CTCAE (v 4.03).

Table 7-7 Classification of severity based on depression and/or anxiety questionnaire scores

PHQ-9 (depression)		GAD-7 (anxiety)	
Score	**Severity**	**Score**	**Severity**
0-4	None	0-4	None
5-9	Mild	5-9	Mild
10-19	Moderate	10-14	Moderate
20-27	Severe	≥ 15	Severe

At Screening, a patient may be judged by the investigator or a psychiatrist to be ineligible based on medical mental health history as listed in the exclusion criteria. Alternatively, patients who score ≥ 12 on the PHQ-9 or ≥ 15 on the GAD-7 mood scale, respectively, or select a positive response of '1, 2, or 3' to question number 9 regarding suicidal thoughts or ideation will be excluded from the study.

A timely interview with the patient after the questionnaire completion is recommended. During the treatment phase, patients who indicate a positive response by selecting '1, 2, or 3' to question number 9 in the PHQ-9 and/or present with suicidal ideation must interrupt treatment with study drug (buparlisib or placebo) and must be referred for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading and to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient PHQ-9 self-assessment. If question 9 on the PHQ-9 was not answered, or the whole questionnaire was not answered, the investigator must assess the patient for suicidal ideation. If the investigator identifies suicidal ideation, then study drug must be interrupted and the patient referred for psychiatric consultation for assessment.

Investigators must not encourage the patients to change responses reported in questionnaires. Guidelines on how to instruct the patient to complete the questionnaires as well as how to determine the scores will be provided with each instrument. Guidance on scoring questionnaires is also provided in Appendix 8. Dosing modification guidelines for buparlisib/placebo are provided in Table 6-3. For additional information on AE reporting, please refer to Section 8.1.

7.2.3 Biomarkers

Genetic aberrations that lead to a gain in PI3K signaling are observed in squamous cell head and neck cancer. Investigating aberrations of the PI3K pathway in all patients enrolled in this study will therefore allow for the assessment of the potential predictive value of pathway activation for benefit from buparlisib in metastatic, squamous cell, head and neck cancer. [redacted]

Tumor and blood samples will be collected before and during treatment with buparlisib for biomarker assessments.

All assessments will be performed by a Novartis designated laboratory. Instructions for collection, preparation and shipment can be found in the laboratory manual. Required sample collection information must be entered on the appropriate eCRF pages and requisition forms

Table 7-8 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Tumor samples			
Mandatory Representative baseline tumor biopsy or archival paraffin embedded tissue To be evaluated for adequate amount of tumor tissue	N/A	Screening	Day -35 to -1
[redacted]			
Sample Type	**Volume**	**Visit**	**Time point**
Blood samples			
Mandatory Blood for circulating DNA	6 mL	Screening	Day -35 to -1
	6mL	End of Treatment	Not pre-specified
[redacted]			

7.2.3.1 Biomarker assessments in tumor samples

Tumor tissue samples will be collected in this trial for identifying biomarkers that may be predictive of benefit from buparlisib. Tumor tissue samples may be archival, however when available, new tumor biopsies should be collected.

In addition, these samples are planned to be used for assessment of HPV status and other molecules (e.g., gene expression, mutations, amplifications and/or protein expression/activation etc.) in the PI3K signaling pathway, such as but not limited to PIK3CA mutation, PTEN mutation, PTEN protein expression, AKT, TSC1 and TSC2, KRAS mutation, other pathways that may interact with the PI3K pathway, or are thought to be important in cancer.

If a biopsy is collected at screening, during treatment, or upon progression the PI3K signaling inhibition status will be evaluated by assessing changes in activation of relevant downstream markers such as S6, AKT and 4EBP1 (e.g. by immunohistochemistry). If a biopsy is collected upon progression through treatment other markers potentially relevant to resistance to PI3K inhibitors may also be analyzed, depending on sample and assay availability.

[redacted]

Table 7-9 Summary of tissue biomarkers

Marker	Tumor sample	Purpose	Comments
Molecular markers relevant to the PI3K pathway such as- but not limited to-PIK3CA mutation, PTEN mutation, and PTEN protein expression	New pre-treatment tumor biopsy or archival sample	Potential predictor of efficacy	All patients
p-Akt, p-S6, p-4EBP1	New tumor biopsy collected at screening, on treatment or upon progression	Drug effect on PI3K signaling	When new tumor is available at screening, during treatment or upon progression
Other markers relevant to PI3K activation pathway such as PIK3CA amplification (FISH), Ki67 and others	New formalin-fixed pre-treatment tumor biopsy or archival sample	Potential predictor of efficacy Potential markers of de novo resistance	All patients
[redacted]	[redacted]	[redacted]	[redacted]

7.2.3.1.1 Mandatory tumor tissue required for study participation

All patients must provide a representative tumor sample (archival or new tumor material) during the study. A FFPE tumor block is preferred. If not available, 15 slides are requested (minimum of 12 slides must be provided) at 4 to 5µm on superfrost positively charged slides. The number of slides required is indicated based on surgical resection samples. In case samples from small biopsies are provided, the number of slides provided should be increased according to the sample size. A pathology report should also be provided.

The samples will be assessed for tissue quantity and tumor content by a pathologist. If local pathologist assessment is preferred, a Novartis defined procedure (See laboratory Manual) can be followed allowing faster turnaround time. If tissue does not pass this assessment, additional tissue must be provided, otherwise, patient is not eligible for the study (see Section 5.1 inclusion criteria). Guidelines for optimal sample identification can be found in the CBKM120H2201 laboratory manual.

Molecular analysis of tumor, in particular- but not limited to - PIK3CA and PTEN molecular alterations (PIK3CA and PTEN gene mutation and PTEN expression by IHC) will be performed in all samples received. [redacted]

7.2.3.1.2 Optional new tumor tissue collection

Collection of optional new tumor samples while on treatment or at progression is critical for assessing drug effect and understanding mechanisms of resistance. Therefore new tumor sampling is encouraged at baseline, anytime during the study and at progression/the end of treatment visit, after signature on the appropriate ICF. If a new biopsy sample is collected for screening (no archival tissue was available), an additional baseline sample does not need to be collected. Patient may have up to three optional biopsies (at screening and/or on treatment and/or at the end of treatment in case of disease progression). Please refer to the lab manual for sample collection requirements.

The sample collection date, the exact time of collection, and the time of exposure to fixative (formalin) must be entered on the appropriate tumor tissue collection eCRF pages and requisition forms.

[redacted]

Table 7-10 New biopsies collection: division, priority, disposition

Tumor Pass number	Disposition	Priority	Purpose
1	Formalin-fixed (immediately after fixation to be shipped in ethanol to designated lab)	First	Primary Biomarker Studies (e.g. IHC)
[redacted]			

[redacted]

7.2.3.2 Biomarker assessments in blood

Before and during treatment with buparlisib, at time points detailed in the visit Table 7-1a and Table 7-8, blood samples will be collected in order to investigate drug induced changes in markers relevant to PI3K signaling and anti-cellular effect.

Table 7-11 Summary of biomarkers in blood

Marker	Purpose
Circulating DNA	mutational analysis
[redacted]	[redacted]

7.2.3.2.1 Plasma for circulating DNA

This will allow additional testing for mutations of genes that are relevant for PI3K signaling and cancer, (e.g. PIK3CA mutation, KRAS mutation) and ideally provide a more updated description of the tumor molecular profile as compared with a tumor sample from the same patient.

[redacted]

[redacted]

7.2.4 Patient reported outcomes

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ-C30, version 3.0) and head and neck cancer specific questionnaire (QLQ-HN35) will be used to explore patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms and treatment-related side effects in the current study. The EORTC QLQ-C30 and QLQ-HN35 are recognized reliable and valid measures (Aaronson 1993, Bjordal 1999) frequently used in clinical trials of patients with non-small cell lung cancer.

Health-related quality of life questionnaires, EORTC QLQ-C30 and QLQ-HN35, will be administered before any study drug administrations at the visits indicated in Table 7-6. Collections of the EORTC QLQ-C30 and QLQ-HN35 have a ±7 day window unless otherwise indicated. All questionnaires should be administered in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests. This is to avoid potentially biasing patients or their responses to study questionnaires. Attempts should be made to collect all questionnaires for all patients, including those who discontinue prior to the study evaluation completion visit.

Patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all patients, including from those who discontinue prior to the study evaluation completion visit, however, if patients refuse to complete questionnaires, this should be documented in study source records. Patient's refusal to complete study questionnaires are not protocol deviations unless otherwise specified in this protocol.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, must be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. This review for potential AEs or SAEs should be documented in study source records.

If an AE or SAE is confirmed then the physician should record the event as instructed in Section 8 of this protocol. Investigators should not encourage the patients to change responses reported in questionnaires.

7.2.4.1 EORTC QLQ-C30 and QLQ-HN35

The EORTC QLQ-C30 contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale (Aaronson 1993). The QLQ-HN35 is used in conjunction with the QLQ-C30 and provides additional information on 7 multi-item symptom scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality and 11 single-item scales assessing symptoms of problems with teeth, problems with opening one's mouth, having dry mouth, having sticky saliva, coughing, feeling ill, use of pain killers, use of nutritional supplements, use of feeding tube, weight loss, and weight gain.

All the multi-item scales and single-item measures range in score from 0 to 100 in both the QLQ-C30 and QLQ-HN35. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale item represents a high level of symptomatology / problems. All scoring will follow the scoring procedures defined by the EORTC Scoring Manual (Fayers 2001).

The EORTC QLQ-C30 and QLQ-HN35 should be administered as per Table 7-12. From protocol amendment v.03, EORTC QLQ-C30 and EORTC QLQ-HN35 questionnaires are not administered to patients still on study treatment.

Table 7-12 Patient health-related QOL questionnaire collection plan

Patient Questionnaires	Visit/ Cycle	Day	Time
EORTC QLQ-C30 EORTC QLQ-HN35	Screening	Day of screening visit from Day -35 to Day -1	Prior to any clinical assessments, study drug dosing or diagnostic testing. Before PHQ-9 and GAD-7 assessments if scheduled for same day.
	Every 6 weeks after randomization until progression starting from Cycle 2 Day 15	Day 1 or Day 15	
	End of treatment	Day of end of treatment assessment	

7.2.5 Pharmacokinetics

Blood samples for PK assessment of buparlisib will be collected in randomized patients, irrespective of treatment assignment. Full PK sampling will be conducted in approximately 16 patients, and sparse PK sampling will be conducted in approximately 40 patients. In addition, trough samples will be collected from all remaining randomized patients, if applicable. Measurement of buparlisib will be performed only in patients randomized to the buparlisib arm. An independent bioanalyst not involved in study conduct will be unblinded to treatment assignment for analysis purposes.

An evaluation of PK will be done with the final analysis in approximately 16 patients undergoing the Full PK sampling in order to evaluate the exposure of buparlisib in the targeted population. For these patients, blood samples will be collected for a full PK profiles on D15 according to the following schedule: at pre-dose, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h and 24h post-dose. The 24h time point should be collected before the dose administration on D16. Additional trough samples (pre-dose samples) will be collected on Cycle 1 Day 22 and Cycle 2 Day 1 (pre-dose), as indicated in Table 7-14. PK sampling needs to be re-scheduled if buparlisib/placebo has been interrupted for 7 days or more. PK sampling needs to be done when the patient has a minimum of 7 consecutive doses.

In addition to the full PK profile collection, PK will be assessed via a sparse PK sampling strategy. For these approximately 40 patients, blood for buparlisib pharmacokinetics will be collected on Cycle 1 Day 1 (at 1h, 2h, and 6h post dose; a recommended 9h post dose sample may be drawn if the patient is still in the clinical center at time of sampling), Cycle 1 Day 15 and Day 22, Cycle 2 Day 1 Cycle 4 Day1 and Cycle 6 Day 1(pre dose).

The rationale to collect sparse samples on Cycle 1 Day 1 is to assess absorption and distribution phases of the PK and the rationale to collect three other trough samples on separate days later in the trial, once PK steady state has been attained, is to capture information on buparlisib clearance. The Cycle 1 Day 1 9 hour sample is recommended: this

sample is to be collected whenever possible, as it would provide valuable pharmacokinetic information on buparlisib in this population. This information will be used to update the current population pharmacokinetic model with this new data to better characterize the pharmacokinetic of buparlisib with paclitaxel in the targeted population. This updated model will be reported independently of this trial.

Trough PK (pre-dose) samples will be collected on Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2 Day 1, Cycle 4 Day 1 and Cycle 6 Day 1 for all the remaining randomized patients unless buparlisib/placebo is permanently discontinued (Refer to Table 7-16). The trough concentration will be used to explore exposure response relationship in the treated population.

Results from any unscheduled samples will not be a part of the PK analysis and will not be made available until the end of the trial.

To ensure compliance with sampling procedures, on the days of PK collection, patients will take their buparlisib/placebo doses at the clinic under the supervision of the investigator or his/her designee. Patients who forget to postpone their dose until they arrive at the site on Day 15 or Day 22 of Cycle 1 or Day 1 of Cycle 2 and instead take their medication at home will not participate in pharmacokinetic analysis for that day; they should not have blood samples collected. Pharmacokinetic assessment for these patients should be postponed to the next day (i.e. Day 16 or Day 23 of Cycle 1 or Day 2 of Cycle 2, respectively). Patients do not need to fast specifically for PK sampling (see Section 6.1.1.1.2 for details).

The collection time of all samples must be documented in the Pharmacokinetic Blood Collection eCRF pages. On days of PK collection and on the previous day the exact time of oral buparlisib/placebo dosing, date sample taken, and actual time of sampling must be entered on the eCRF. Any sampling problems (e.g., patient took study drug before a pre-dose sample) must be noted in the comments section of the eCRF.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed, and medication should resume on the next day. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF. In addition, on days of PK collection, the exact time of the first vomiting episode within the first 4 hours post-dosing on that day must be noted. If a vomiting episode occurs within the first 4 hours post-dosing during the day of the last dose prior to trough PK samples the exact time (whenever possible) must be noted on the eCRF.

The plasma samples from all patients will be assayed for buparlisib concentrations by Novartis or its designee using methods described in the Laboratory manual. Values below the assay LLOQ will be reported as 0.00 ng/mL. Missing values will be labeled accordingly. All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings. Concentrations below the limit of quantitation will not be imputed and will be treated as zero in summary statistics.

Non compartmental analysis for patients with full PK sampling

Pharmacokinetic parameters will be determined for patients with full PK sampling using non-compartmental method(s) using Phoenix WinNonlin. PK parameters listed in Table 7-13 will be estimated and reported, when feasible. Calculation of PK parameters will include up to last measurable concentration Tlast, as outlined in the Novartis Internal Guidance Standardization of pharmacokinetic parameters. Exploratory analysis will be conducted to determine PK parameters using compartmental modeling when necessary.

Table 7-13 Non-compartmental PK parameters

Term	Definition
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCtau	The area under the plasma concentration-time curve from time zero to the end of the dosing interval, tau (mass x time x volume^{-1})
Cmax	The maximum (peak) observed plasma drug concentration after single dose administration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma drug concentration after single dose administration (time)
CL/F	Apparent total body clearance of drug from the plasma after oral administration (volume x time^{-1}) at steady-state (based on AUC value from C1D15)
Rsqadj[1]	Square of the correlation coefficient associated with λz

[1] Rsqadj will be used in the interpretation of the primary PK parameters and therefore will be included in the listings only.

Population PK analysis

A population PK model characterizing the concentration-time profile of buparlisib has been developed based on the following trials: [CBKM120X2101], [CBKM120X1101], and [CBEZ235A2118]. Further details regarding the model are provided in Section 10.1.4.

Separate report to document the population PK model will be released before the study results are reported.

7.2.5.1 Pharmacokinetic blood sample collection and handling

7.2.5.1.1 Blood collection plan

Table 7-14 Pharmacokinetic log table for patients with full PK sampling (16 patients)

Cycle	Day	Time	Dose Reference ID[3]		PK Sample No
1	15	Pre-dose	1	101	101
1	15	0.5 hour post dose ± 10 min	1		102
1	15	1 hour post dose ± 15 min	1		103
1	15	1.5 hour post dose ± 15 min	1		104
1	15	2 hour post dose ± 15 min	11		105
1	15	3 hour post dose ± 30 min	11		106

Cycle	Day	Time	Dose Reference ID[3]		PK Sample No
1	15	4 hour post dose ± 30 min	1		107
1	15	6 hour post dose ± 60 min	1		108
1	15	9 hour post dose ± 60 min	1		109
1	16	Pre-dose (24 hour post dose ± 120 min)	1	102	110
1	22	Pre-dose[1]	2	201	111
2	1	Pre-dose[1]	3	301	112
		Unscheduled[2]			1001+

[1] Take sample immediately before the buparlisib/placebo administration of the current day.
[2] Unscheduled blood samples will be uniquely, sequentially numbered 1001, 1002, etc.
[3] Left column refers to the dose reference ID following the pre-dose sample and right column refers to the dose reference ID prior to sampling.
Sample volume will be 2 mL per collection for all samples

Table 7-15 Pharmacokinetic log table for patients with sparse PK sampling (40 patients)

Cycle	Day	Time	Dose Reference ID[4]		PK sample No
1	1	1 hour post dose ± 15 min	10		201
1	1	2 hour post dose ± 15 min	10		202
1	1	6 hour post dose ± 30 min	10		203
1	1	9 hour post dose ± 60 min (recommended)[1]	10		204
1	15	Pre-dose[2]	11	111	205
1	22	Pre-dose[2]	12	121	206
2	1	Pre-dose[2]	13	131	207
4	1	Pre-dose [2]	14	141	208
6	1	Pre-dose [2]	15	151	209
		Unscheduled[3]			2001+

[1] Optional sample: may be drawn if the patient is in the clinical site at the sampling time.
[2] Take sample immediately before the buparlisib/placebo administration of the current day.
[3] Unscheduled blood samples will be uniquely, sequentially numbered 2001, 2002, etc.
[4] Left column refers to the dose reference ID following the pre-dose sample and right column refers to the dose reference ID prior to sampling.
Sample volume will be 2 mL per collection for all samples

Table 7-16 Pharmacokinetic log table for patients with trough samples collection (all remaining randomized patients)

Cycle	Day	Time	Dose Reference ID[3]		PK sample No
1	15	Pre-dose[1]	40	401	301
1	22	Pre-dose[1]	41	411	302
2	1	Pre-dose[1]	42	421	303
4	1	Pre-dose[1,2]	43	431	304
6	1	Pre-dose[1,2]	44	441	305
		Unscheduled[2]			3001+

[1] Take sample immediately before the buparlisib/placebo administration of the current day.
[2] Unscheduled blood samples will be uniquely, sequentially numbered 3001, 3002, etc.

Cycle	Day	Time	Dose Reference ID[3]	PK sample No

[3] Left column refers to the dose reference ID following the pre-dose sample and right column refers to the dose reference ID prior to sampling.
Sample volume will be 2 mL per collection for all samples

For detailed instructions for the collection, handling, and shipping of samples refer to the [CBKM120H2201 Lab Manual].

7.2.6 Other assessments

No additional tests will be performed on patients entered into this study.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

For patients who sign the ICF, all AEs will be captured in the AE eCRF from time of signature through 30 days after permanent study treatment discontinuation. For patients who fail the screening, only SAEs will be captured in the AE eCRF page.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)

3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
   or
   Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (as per RECIST 1.1 criteria for solid tumors), should not be reported as a serious adverse event or adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be

required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study treatment name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

Study treatment must be discontinued once emergency unblinding has taken place.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established prior to the randomization of the first patient to monitor and review the safety of the study treatment. It is expected that the DMC will consist of members who are not involved in patient recruitment or trial conduct. There will be a meeting with the DMC to have agreement on their roles and responsibilities and the potential data format and procedures that will be reviewed during the course of the study. Meetings may be held by sponsor's requests at the time of some safety issues occurrence, especially when serious events (e.g., death) occur on the study or safety notifications regarding the study treatment come out and as further described below.

The DMC will conduct the first safety review 3 to 6 months after the first patient has been randomized to determine if the proposed dosing schedule of the combination is safe and tolerable for this patient population. Thereafter the DMC will conduct the safety review every 6 months (+/- 30 days for scheduling purposes). The DMC will also review biomarkers data regarding PI3K activation status when approximately 70 patients have been randomized and been on the study for at least a month. If the timing of this additional review falls within 1 month of any of the periodic safety reviews, then this shall be combined with the scheduled safety review and will not be done separately. Should the ratio of PI3K activated versus non activated population not be as expected, the current protocol may be amended to proceed with pre-screening for additional patients.

It is envisioned that the DMC may make the following type of recommendations, namely:

1. No safety issues, ethical to continue the study as planned

2. Serious safety concerns precluding further study treatment, regardless of efficacy
3. Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments)

If the DMC recommends continuing the study, no details about the results of the current safety review will be revealed prior to the next scheduled analysis.

Details regarding the constitution of the DMC and its specific roles will be provided in the DMC charter prior to the randomization of the first patient.

8.7 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating/enrolling patients in the trial, i.e., not being members of the DMC, and Novartis representatives from the Clinical Trial Team.

The SC will ensure management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a Steering Committee charter. The SC will not have access to un-blinded trial data.

9 Data Collection and Management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

PK and Biomarker (blood and tissue) samples drawn during the course of the study will be collected from the investigator sites and analyzed by Novartis or a central laboratory contracted by Novartis. The site staff designated by the investigator will enter the information required by the protocol onto the Biomarker Sample Collection eCRFs, as well as onto the designated CRO's requisition form. One copy of the requisition form will be information (including study number, subject ID, etc.) and one copy will be retained by the site.

Imaging Data used for tumor assessments will be centrally collected and subjected to quality control. It will be prospectively reviewed by a BIRC.

From protocol amendment v03, CT-scans/MRI will no longer be sent to central imaging vendor.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data for biomarkers, imaging and IRT will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

The primary statistical analysis will be based on data from all patients up to the time at which approximately **120** PFS events have been observed. The final analysis will be performed at the end of the study (see Section 4.3 and Section 4.4.for further details).

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who were randomized to study treatment. According to the intent to treat principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

10.1.2 Safety Set

The Safety Set includes all patients who received study treatment (either paclitaxel or buparlisib) and had at least one post-baseline safety assessment. Patients will be analyzed according to the study treatment they actually received. Treatment actually received is defined as the study treatment the patient received on Study Day 1.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) comprises all patients in the FAS who do not have any protocol deviations that could confound the interpretation of the primary analyses conducted on the FAS.

10.1.4 Pharmacokinetic analysis sets

The Pharmacokinetic Analysis Set (PAS) will include all patients who received at least one dose of study medication buparlisib and had at least one evaluable post-treatment concentration measurement.

The Full Sampling Pharmacokinetic Analysis Set (FPAS) will include all patients who received buparlisib every day from Cycle 1 Day 1 to the day at which full PK profile is collected and have at least one dose of paclitaxel prior to the collection of the PK sample for the full PK profile (without any vomiting within 4 hours of any dosing) and had an evaluable full PK profile.

Patients in the FPAS will also be included in the PAS.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for all patients in the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The actual cumulative dose and duration of exposure in days of buparlisib and paclitaxel as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the

safety set. Dose reductions and interruptions (including the reasons for dose modifications) will be summarized for each study drug.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized (by treatment group) for the Safety set.

10.4 Primary objective

The primary objective is to estimate the treatment effect of once daily buparlisib in combination with paclitaxel on PFS (based on local radiological assessment) in patients with platinum pre-treated recurrent or metastatic head and neck squamous cell carcinoma.

10.4.1 Variable

The primary efficacy variable is PFS as assessed by local radiological reviewed as per RECIST v1.1 (see guidelines in Appendix 6). PFS is defined as the time from the randomization date until objective tumor progression or death from any cause The date of progression is the earliest time when any RECIST progression event (i.e. radiological progression or death) is observed with no more than one prior missing assessment.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be a comparison of PFS between the two treatment groups. The hazard ratio (HR) for buparlisib + paclitaxel versus placebo + paclitaxel will be estimated by a stratified Cox proportional hazard model, using the randomization strata (prior lines of treatment: 1 vs 2) and region of investigator's site (North America vs Rest of World)).

The efficacy criteria are:

- The estimated hazard ratio is equal or less than 0.67 (i.e. 33% reduction in risk of PFS event with buparlisib compared to the placebo arm)

and

- Posterior probability (HR < 1) > 97.5% (PFS treatment benefit of buparlisib compared to the placebo).

The posterior probability in the second criterion will be derived from the Bayesian posterior distribution of the HR. Assuming an uninformative prior distribution, the distribution of the HR will be updated with all available data from the patients included in the FAS. (See the Statistical Appendix 9 for the details).

The primary analysis will be performed when approximately 120 PFS events have been observed in the FAS. The operating characteristics based on this number of events are presented in Section 10.8.

HR will be presented together with the 95% confidence interval. Numbers and types of PFS events (i.e. objective tumor progression, death) will be displayed by treatment group.

10.4.3 Handling of missing values/censoring/discontinuations

For the final analysis, PFS will be censored if no PFS event is observed before the cut-off date or on the date a new anti-neoplastic therapy is started. If the patient is alive and progression free at the date of the analysis (i.e. cut-off date), the censoring date is the date of the last

adequate tumor assessment prior to the cut-off. If the patient starts a new anti-neoplastic therapy (including new chemotherapy regimen or radiotherapy), the censoring date is the date of the last adequate tumor assessment before the initiation of the therapy, or before the cut-off date, whichever comes first. The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case, the last tumor evaluation date at that assessment is used. If disease progression is documented after two or more missing or non-adequate tumor assessments, then the date of PFS will be censored at the date of the last tumor assessment with overall lesion response of CR, PR, or SD. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used, as per the RECIST 1.1 (Appendix 6).

10.5 Secondary objectives

All secondary analyses will be reported by treatment groups. Analyses will be based on the FAS unless otherwise specified.

10.5.1 Key secondary objective

Overall Survival

OS is defined as the time from randomization to the date of death due to any cause. If a patient is not known to have died by the date of analysis cut-off, OS will be censored at the date of last contact.

OS will be described by treatment arm using Kaplan-Meier curves with appropriate summary statistics based on FAS. OS will be compared between the two treatment groups. The HR for buparlisib + paclitaxel versus placebo + paclitaxel will be estimated by a stratified Cox proportional hazard model, using the randomization strata (i.e. prior lines of therapy and region (North America vs Rest of the world)). HR will be presented together with the 95% confidence interval. OS will also be described using Kaplan-Meier curves with appropriate summary statistics.

In order to guide the Phase III design for this indication, Proof of Concept (PoC) for Overall Survival is defined based on the following criteria:

- The estimated hazard ratio is equal or less than 0.77 (i.e. 23% reduction in risk of OS event with buparlisib compared to the comparator arm)

and

- Posterior probability (HR < 1) > 90% (OS treatment benefit of buparlisib compared to the control).

The posterior probability of HR < 1 will be derived from the Bayesian posterior distribution of the HR for Overall Survival. Assuming an uninformative prior distribution, the distribution of the HR will be updated with all available data from the patients included in the FAS. (See the Statistical Appendix 9 for the details).

The PoC analysis of OS will be performed at the time approximately 112 deaths have been recorded.

10.5.2 Other secondary efficacy objectives

All secondary analyses will be reported for the full population and by treatment groups. Analyses will be based on the FAS unless otherwise specified.

Overall response rate

Overall response rate (ORR) is defined as the proportion of patients with a best overall response of complete response (CR) or PR, based on the investigator assessment (see RECIST Version 1.1 guidelines, Appendix 6). In this study, the objective responses must be confirmed as per RECIST criteria.

The ORR and corresponding exact 95% confidence intervals (Clopper 1934) will be presented by treatment group.

Disease control rate

Disease control rate (DCR) is defined as the proportion of patients with a best overall response of CR, PR or stable disease (SD), based on the investigator assessment (see RECIST Version 1.1 guidelines, Appendix 6).

The DCR and corresponding exact 95% confidence intervals (Clopper 1934) will be presented by treatment group.

Duration of response

Duration of overall response (DR) is defined only for the responder subset, i.e. patients with confirmed CR or PR based on the investigator assessment. It is the elapsed time between the date of first documented response and the following date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, DoR is censored at the date of last adequate tumor assessment.

DR will primarily be listed. It may be described using Kaplan-Meier curves and any related statistics if relevant and will be presented by treatment group.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

All safety analyses for both stages will be carried out on the Safety set. The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., ECG, vital signs) will be considered as appropriate.

The safety data will be summarized and listed by study treatment. The overall observation period for all safety analyses will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication.
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication.

3. post-treatment period: starting at day 31 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables for AEs will include AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. Summary of deaths will include on-treatment and post-treatment deaths. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades version 4.03), type of AE, relation to study treatment.

Deaths reportable as SAEs and non-fatal serious AEs will be listed by patient and tabulated by type of AE.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). SEC will be defined at project level and may be regularly updated. The grouping of AEs in SEC according to project standards will be specified in the project level master statistical analysis and/or the study RAP. For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

10.5.3.3 Laboratory abnormalities

Laboratory data will be graded according to CTCAE version 4.03, if applicable. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For some cases, (e.g. white blood cell differentials), the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinical meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Number and percentage of patients with laboratory abnormalities, by parameter and worst post-baseline CTC grade. Each patient will be counted only for the worst grade observed post-baseline, regardless of the baseline status.
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the project level master statistical analysis and/or the study RAP.

10.5.3.4 Other safety data

Other safety data collected will be listed and summarized using descriptive statistics as appropriate. Notable values may be flagged. Notable/Abnormal values for safety data will be further specified in the statistical analysis plan and will be used for shift tables.

ECG and cardiac imaging

- shift table of ECG parameters from baseline to worst on-treatment result
- listing of ECG evaluations for all patients with at least one abnormality
- a summary of baseline, worst post-baseline and change from baseline for LVEF values
- listing of cardiac imaging evaluations, LVEF values and overall interpretation for all patients, by visit

Vital signs / WHO performance status

Definitions of notably abnormal results will be included in the RAP.

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.5.3.5 Supportive analyses for secondary objectives

There is no supportive analysis planned.

10.5.3.6 Tolerability

Tolerability will be studied in terms of dose reductions or drug interruption due to an AE.

10.5.4 Pharmacokinetics

FPAS will be used in the non-compartmental analysis and PAS will be used in the population PK analysis.

Non compartmental analysis

The aim of this PK analysis is to have a preliminary PK assessment of buparlisib exposure when administered in combination with paclitaxel in this specific population. Descriptive graphical plots of geometric mean and arithmetic mean (SD) buparlisib plasma concentration – time profiles at cycle 1 Day 15 will be generated. Additionally graphical plots of individual buparlisib plasma concentration – time profiles may be generated. Further graphical exploratory analyses may be carried out if deemed appropriate.

PK parameters of buparlisib will be summarized using descriptive statistics presenting number of observations, arithmetic mean, SD, coefficient of variation CV (%), geometric mean, geometric CV%, median, minimum and maximum. For Tmax only median, minimum

and maximum will be provided. Similarly summary statistics will be provided for concentration by scheduled time point including both n(number of values to be reported) and m(number of non-zero values to be reported) in addition to the summary statistics listed above.

The derived PK parameters will be compared with PK data collected in other trials with [CBEZ235A2118] or without paclitaxel [CBKM120A2101]. This analysis aims to further characterize buparlisib exposure in this specific population but no formal analysis will be conducted.

Population pharmacokinetic analysis

A population PK model has been developed for buparlisib: The pharmacokinetics of buparlisib could be described with a linear two-compartment model with a lag-time and first order absorption. The model appears to provide an overall good fit to the data. Further details regarding the model can be found in the population PK report. All the parameters of this model, fixed and random effects will be fixed to their estimated values. (Hong Y, 2013)These parameters will be used to provide Empirical Bayes Estimates of individual PK parameters from concentrations available in this trial, if deemed appropriate. Depending on the quality of the data available, additional exploratory analyses may be performed.

Once generated the model derived PK parameters will be compared to the theoretical distribution of the parameters obtained from the model and derived parameters collected in other trials with [CBEZ235A2118] or without paclitaxel [CBKM120A2101]. No formal statistics will be conducted.

[redacted]

[redacted]

10.5.5.1 Outline of the data analysis

No adjustment for multiple comparisons is planned. The following structured approach is proposed. The first core step involves producing tables, listings and preferably visual displays to describe the data, detect trends and draw preliminary conclusions. [redacted]

[redacted]

There may be circumstances when a decision is made to stop a sample collection, or not perform or discontinue the analysis of blood/archival tumor due to either practical or strategic reasons (e.g. issues related to the quality and or quantity of samples). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

10.5.5.2 Data handling principles

Biomarker analyses will be done on the subset of the FAS population for whom the relevant biomarker data is available.

Biomarker values below the lower limit of quantification (LLOQ) will be considered as 0.5*LLOQ.

For IHC variables the H-score will be calculated using the following standard algorithm

H-score = Low level stain *1+ medium level stain *2+ high level stain *3.

Data handling will be further addressed in the statistical analysis plan.

10.5.5.3 Data analysis principles

10.5.5.3.1 Analysis sets

The FAS set will be used for all biomarker analysis depending on the study phase to be analyzed. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

10.5.5.3.2 Basic tables, figures and listings

The biomarker data analysis will include the following:

Description of distribution of baseline level by using mean, standard deviation, median, minimum and maximum of raw data for quantitative biomarker data collected only at baseline.

Categorical markers, such as mutation or amplification status, will be summarized using frequency and percentages for all baseline and post baseline time points.

Mean, standard deviation, median, minimum, and maximum of raw data, absolute change from baseline and relative change or fold increase from baseline for IHC measured at baseline and at different time points.

Mean, standard deviation, median, minimum, and maximum, geometric mean and CV% geometric-mean of raw data and fold increase from baseline for ELISA data measured at baseline and at different on treatment timepoints.

If any trends appear from these graphical more advance analysis might be performed in order to better quantify the potential concentration effect relationship between the buparlisib plasma concentration and the different pathways inhibition.

[redacted]

All these analyses will be outlined in full in the statistical analysis plan.

[redacted]

10.5.6 Patient-reported outcomes

The EORTC QLQ-C30 questionnaire along with the head and neck cancer module (QLQ-HN35) will be used to collect data on patient's QoL. Scoring and handling of missing QoL data will be in accordance to the EORTC scoring manual (Fayers 2001). No imputation will be applied if the total or subscale scores are missing at a visit.

The global health status/QoL scale and pain score of the QLQ-C30 and QLQ-HN35 are identified as the primary patient-reported outcome of interest. Physical functioning, emotional functioning and social functioning scale scores of the QLQ-C30 and the head and neck cancer symptom scales for swallowing, sense and speech of the QLQ-HN35 are identified as secondary patient-reported QoL variables of interest. No formal statistical test will be performed and hence no multiplicity adjustment will be applied.

Descriptive statistics will be primarily used to summarize the scored scales at each scheduled assessment time point. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

Mixed effect model for repeated measures (MMRM) will be used to compare the two treatment arms in terms of change from baseline in the global health status / QoL, physical functioning, emotional functioning, social functioning, and HN35 subscales for pain, swallowing, senses and speech over time. All available data during the study will be used in the MMRM analyses which assume that the missing scores at any time point are missing-at-random. Additional sensitivity analysis may be performed to assess the possible violation of missing-at-random assumption for the missing data mechanism if deemed appropriate. Details will be specified in the RAP.

The number of patients completing the EORTC QLQ-C30 and QLQ-HN35 questionnaires and the number of missing or incomplete assessments might also be summarized by each treatment group for each scheduled assessment time points. Appropriate methods to handle missing data will be described in the RAP.

Time to definitive 10% deterioration in the global health status / QoL, physical functioning, emotional functioning, social functioning, and head and neck cancer symptoms scales for pain, swallowing, senses, and speech will be assessed in the two treatment arms in the FAS. The time to definitive 10% deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% relative to baseline worsening of the corresponding scale score or death due to any cause. If a patient has not had an event, time to deterioration will be censored at the date of the last adequate QoL evaluation. The distribution will be presented descriptively using Kaplan-Meier curves. Summary statistics from Kaplan-Meier distributions will be determined, including the median time to definitive 10% deterioration along with two-sided 95% confidence interval. Additionally, time to definitive deterioration with different cutoff definitions (e.g. 5%, 15%) may be specified in the RAP as deemed appropriate. A stratified Cox regression will be used to estimate the hazard ratio (HR), along with two-sided 95% confidence interval.

10.7 Interim analysis

No formal interim analysis is planned.

10.8 Sample size calculation

Most of the studies that evaluated chemotherapy agents for the treatment of recurrent/metastatic HNSCC were small, not randomized or even retrospective, with a heterogeneous patient population. More specifically, 2 studies evaluating single-agent taxanes in platinum-pretreated patients have been reported and considered for the purpose of the current study: 1. A single-agent paclitaxel study reported a mTTP of 3.4 months (Tahara 2011); 2. A single-agent docetaxel study reporting a mTTP of 3.2 months (Koussis 2007). It must be noted that the paclitaxel study used a definition of mTTP that considers death as a progression event, and included a mixed patient population with paclitaxel administered as 1st line treatment for metastatic disease in 77% and 2nd line treatment for metastatic disease in 23% of patients, respectively (Tahara 2011). Based on these observations, also considering that in the current study all the patients enrolled will be pretreated with platinum-based regimens as 1st line treatment for metastatic disease and also might have received cetuximab as 2nd line, it is expected a median PFS in the paclitaxel arm (control arm) would be approximately 3 months. A 50% increase in median PFS from 3.0 to 4.5 months can be considered clinically meaningful in this setting (e.g. a HR of 0.67).

Proof of concept (PoC) will be declared if there is sufficient clinical and statistical evidence based on the criteria listed below that the buparlisib-containing regimen is superior to matching placebo in the full population

- The estimated hazard ratio is equal or less than 0.67 (i.e. 33% reduction in risk of PFS event with buparlisib compared to the comparator arm)

and

- Posterior probability (HR < 1) > 97.5% (PFS treatment benefit of buparlisib compared to the control).

Approximately 150 patients (75 per arm) have to be randomized in the study in order to observe 120 PFS events, assuming a true median PFS of 3 months in the control arm, a HR of 0.67, a recruitment rate of 10 patients/month and a drop-out rate of 15%. Given the above assumptions, the primary analysis is expected to occur after approximately 19 months if the true HR is 0.67.

A minimum number of 114 PFS events is required so that the operating characteristics of the design (obtained by simulation) provide adequate properties (i.e. if the true HR is 1, the probability to obtain a positive conclusion is less than 0.05; if the true HR is 0.67, the probability to obtain a positive conclusion is approx. 0.50). However with consideration given to OS objectives and other exploratory objectives the required number of events is raised to 120. Table 10-1 presents the Operating Characteristics of the design for the Primary Objective of study with 120 PFS events and the expected duration till the primary analysis under different scenarios of True Hazard Ratio of PFS.

Table 10-1 Study Operating Characteristics

True HR(buparlisib / Control)	True Median PFS (buparlisib+paclitaxel)	Probability of PFS PoC(Power)	Expected Duration for PFS events (months)
1	3.0	0.012	17.12
0.86	3.5	0.09	17.67
0.75	4.0	0.246	18.27
0.67	4.5	0.512	18.92
0.6	5.0	0.730	19.57
0.55	5.5	0.877	20.14
0.5	6.0	0.943	20.92

10.9 Operating characteristics of key secondary variables

OS will likely be considered as a primary endpoint for a confirmatory registration study in this indication.

Based on literature review in this indication, also considering that in the current study all the patients enrolled will be pretreated with platinum-based regimens as 1st line treatment for metastatic disease and also might have received cetuximab as 2nd line, it is expected a median OS in the paclitaxel arm (control arm) would be approximately 7 months. A 2 month increase in median OS from 7 to 9 months can be considered clinically meaningful in this setting (e.g. a HR of 0.77). A Phase III combination study of Cetuximab in association with Platinum based chemotherapy as a 1st line therapy reported a median OS of 7.4 months for the patients in the platinum arm and 10.1 months for the patients in the Cetuximab + Platinum arm.

In order to guide the Ph III design for this indication, Proof of Concept (PoC) is defined based on the following criteria:

- The estimated hazard ratio is equal or less than 0.77 (i.e. 23% reduction in risk of OS event with buparlisib compared to the comparator arm)

and

- Posterior probability (HR < 1) > 90% (OS treatment benefit of buparlisib compared to the control).

With a total of 150 randomized patients (75 per arm) with a recruitment rate of 10 patients/month and a drop-out rate for OS of 5%, the OS analysis is expected to occur approximately 25 months after FPFV.

A minimum of 112 OS events is required so that the operating characteristics for OS PoC based on the current design have adequate properties (obtained by simulation) (i.e. if the true HR is 1, the probability to obtain a positive conclusion is less than 0.10; if the true HR is 0.70, the probability to obtain a positive conclusion is approximately 0.70).

Table 10-2 Study Operating Characteristics to meet Proof of Concepts for OS

True Median OS	True HR	Expected	Probability of OS
buparlisib + paclitaxel	buparlisib/control	Duration for OS Events	Proof of Concept(Power)
7	1.00	23	0.093
7.5	0.93	23	0.162
8	0.88	24	0.246
8.5	0.82	24	0.356
9	0.78	25	0.477
9.5	0.74	25	0.587
10	0.70	26	0.695

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors,

Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1: Gilbert syndrome

Gilbert syndrome is an autosomal recessive medical condition characterized by deficiency of the enzyme uridine diphosphate glucuronyl transferase (UGT), which causes unconjugated hyperbilirubinemia and intermittent jaundice, abdominal pain, weakness and fatigue. Gilbert syndrome may also be asymptomatic.

Hyperbilirubinemia is mild (total bilirubin < 6 mg/dL) and most patients exhibit total bilirubin levels of <3 mg/dL. Daily and seasonal variations are observed, and bilirubin levels occasionally can be normal in 33% of patients.

Gilbert syndrome may be precipitated by dehydration, fasting, menstruction, or stress, such as an intercurrent illness or vigorous exercise. These episodes resolve spontaneously, and no treatment is required, except for supportive care.

Pathophysiology

Unconjugated hyperbilirubinemia in Gilbert syndrome is due to underactivity of the conjugating enzyme system bilirubin uridine diphosphate glucuronyltransferase (bilirubin-UGT) (Lee P 2007). Bilirubin-UGT is one of several UGT enzyme isoforms responsible for the conjugation of a wide array of substrates that include carcinogens, drugs, hormones, and neurotransmitters.

Knowledge of these enzymes has been enhanced greatly by characterization of the *UGT1* gene locus in humans. The gene that encodes bilirubin-UGT has a complex structure and is located on chromosome 2 (Ferraris 2006, Hsieh 2007; Ostanek 2007; Petit 2007; Rigato 2007; Ehmer 2008).

There are 5 exons, of which exons 2-5 at the 3' end are constant components of all isoforms of UGT, and these encode the UDP-glucuronic acid-binding site.

Exon 1 encodes a unique region within each UGT that confers substrate specificity. However, multiple exon 1 variants (at least 13) exist. Exons 1a and 1d encode the variable region for bilirubin UGT1*1 (also known as UGT1A1) and UGT1*2, respectively. UGT1*1 is responsible for virtually all bilirubin conjugation, and UGT1*2 has little, if any, known physiological role. Expression of UGT1*1 expression is regulated by a promoter region 5' of exon 1 that contains a TATAA box. Impaired bilirubin glucuronidation can result from mutations in exon 1a, its promoter, or exons common to UGT alleles. The genetic basis of Gilbert syndrome has been shown in some instances to comprise abnormalities in the TATAA region of the promoter. The addition of 2 extra bases (TA) to the TATAA region interferes with binding of the transcription factor IID (TF-IID) and results in reduced expression of bilirubin-UGT1 (30% of normal). In the homozygous state, diminished bilirubin glucuronidation is observed, with bile containing an excess of bilirubin monoglucuronide over diglucuronide. Moreover, additional mutations have been identified.

Some healthy Asian patients with Gilbert syndrome do not have promoter mutations but are heterozygous for missense mutations (Gly71Arg, Tyr486Asp, Pro364Leu) in the coding

region. These individuals also have significantly higher unconjugated bilirubin levels than do those with the wild-type allele.

Whether reduced bilirubin-UGT activity results from a reduced number of enzyme molecules or from a qualitative enzyme defect is not known in every instance. Moreover, other factors such as occult hemolysis or hepatic transport abnormalities can modify the clinical expression of Gilbert syndrome. Many individuals homozygous for the TATAA defect do not demonstrate unconjugated hyperbilirubinemia, and patients with reduced levels of bilirubin-UGT, as observed in some granulomatous liver diseases, do not develop hyperbilirubinemia.

Because of the high frequency of mutations in the Gilbert promoter, heterozygous carriers of Crigler –Najjar syndrome types 1 and 2 can also carry the elongated Gilbert TATAA sequence on their normal allele. Such combined defects can lead to severe hyperbilirubinemia and also help explain the finding of intermediate levels of hyperbilirubinemia in family members of patients with Crigler-Najjar syndrome. Gilbert syndrome can also frequently coexist with the conditions associated with unconjugated hyperbilirubinemia, such as thalasemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency (Seo 2007; Udomuksorn 2007).

Epidemiology

The worldwide prevalence of Gilbert syndrome varies considerably depending on which diagnostic criteria are used, such as number of bilirubin determinations, method of analysis, bilirubin levels used for diagnosis, and whether the patient was fasting. This may be complicated further by polymorphisms in the TATAA promoter region, which are present in as many as 36% of Africans but only 3% of Asians. The clinical phenotype may not be as apparent as the determined genotype because of environmental influences, such as alcohol-induced bilirubin glucuronidation, which can reduce bilirubin levels. The prevalence of Gilbert syndrome in the United States is 3-7% of the population. Population studies show that Gilbert syndrome occurs predominately in men, with a male-to-female ratio ranging from 2-7:1.

Gilbert syndrome is usually diagnosed around puberty, possibly because of the inhibition of bilirubin glucuronidation by endogenous steroid hormones.

In older persons, the diagnosis is usually made when unconjugated hyperbilirubinemia is noted on routine blood test results or is unmasked by an intercurrent illness or stress.

Clinical Features

Gilbert syndrome is a benign condition with no associated significant morbidity or mortality.

At least 30% of patients are asymptomatic, although nonspecific symptoms, such as abdominal cramping, fatigue, and malaise, are common. Abdominal symptoms in these patients are a poorly defined entity and may be secondary to underlying anxiety. However, not all patients with Gilbert syndrome and abdominal symptoms are anxious; nevertheless, they appear to have organic-type discomfort that is hard to characterize and frequently eludes diagnosis. No relationship exists between these abdominal symptoms and plasma bilirubin levels. Abdominal symptoms apparently may be multifactorial, with underlying anxiety probably playing an important role.

Mild jaundice is present intermittently in some individuals, but no other abnormal physical examination findings are evident. Infants homozygous for Gilbert syndrome may have a greater increase in neonatal jaundice when breastfed or when other disorders of heme metabolism are co-inherited (Papez MJ 2009; Tapan S 2009)

Exacerbating conditions: Dehydration, fasting, (which causes an increase in the plasma unconjugated bilirubin level), intercurrent illness, menstruation, and stress (such as trauma and strenuous exercise).

Diagnosis

Diagnosis of Gilbert syndrome can be made in the presence of (1) unconjugated hyperbilirubinemia noted on several occasions; (2) normal results from a CBC count, reticulocyte count, and blood smear; (3) normal liver function test results; and (4) an absence of other disease processes

Laboratory data

- CBC count (including reticulocyte count and blood smear): This is a useful screening test to exclude hemolysis as a cause of hyperbilirubinemia. Rarely, red blood cell abnormalities resembling variegate porphyria have been described in persons with Gilbert syndrome, possibly due to the increased hepatocellular bilirubin concentration.
- Lactate dehydrogenase: Levels are elevated in persons with hemolysis but are normal in those with Gilbert syndrome.
- Liver function tests: With the exception of unconjugated hyperbilirubinemia, standard liver function test results are normal. However, a familial increase in serum alkaline phosphatase levels has been reported in some persons with Gilbert syndrome.

Imaging Studies

- Imaging studies are not routinely required to confirm a diagnosis of Gilbert syndrome.

Other Tests

Additional tests are rarely required, but the following investigations are occasionally performed to confirm a diagnosis of Gilbert syndrome.

- Fasting: This usually results in a 2- to 3-fold rise in the plasma unconjugated bilirubin level within 48 hours of a fast that returns to normal levels within 24 hours of resuming a normal diet. Although unconjugated bilirubin levels also rise with fasting in patients with hemolysis or liver disease, the magnitude of the rise is less than that observed with Gilbert syndrome. A similar rise in plasma bilirubin is also observed with normocaloric diets deficient in lipids and reverses promptly with lipid replacement. The fasting test remains of historic interest and has limited usefulness in the diagnosis of Gilbert syndrome.
- Nicotinic acid: Intravenous administration of 50 mg of nicotinic acid results in a 2- to 3-fold rise in plasma unconjugated hyperbilirubinemia within 3 hours. The mechanisms are multifactorial and probably related to (1) elevated osmotic fragility of red blood cells, (2) increase in splenic production of bilirubin, (3) transient inhibition of hepatic bilirubin-UGT activity, and (4) increased splenic heme oxygenase activity. Similar but less

impressive increase is observed in healthy individuals. The nicotinic test, does not clearly distinguish patients with Gilbert syndrome from those who are healthy or who have other disease processes.

- Phenobarbital: Phenobarbital and other enzyme inducers of the bilirubin-UGT system will normalize plasma bilirubin in patients with Gilbert syndrome. Steroids can also reduce plasma bilirubin levels in Gilbert syndrome by increasing hepatic uptake and storage of bilirubin.
- Radioactive-labeled chromium: This is used to measure red blood cell survival. As many as 60% of patients with Gilbert syndrome have a mild and fully compensated state of hemolysis together with increased hepatic heme production. As a result, hyperbilirubinemia may be due to reduced bilirubin clearance and increased production, the latter from increased erythroid or hepatic heme turnover.
- Thin-layer chromatography: This test is diagnostic for Gilbert syndrome when it shows a significantly higher proportion of unconjugated bilirubin compared with individuals with chronic hemolysis or liver disease or those who are healthy. If confirmation of the diagnosis is truly essential, chromatographic determination is of potential use. This shows an increased ratio of bilirubin monoglucuronide to diglucuronide, reflecting reduced bilirubin-UGT activity.
- Drug clearance: Approximately 30% of patients have impaired clearance of bromosulfophthalein, indocyanine green, and free fatty acid, suggesting an abnormality in hepatic uptake, transport, or both. The metabolic clearance of tolbutamide is also reduced in persons with Gilbert syndrome, but, because it does not undergo glucuronidation, hepatic uptake appears to be defective. Plasma clearance of most drugs that undergo glucuronidation (eg, benzodiazepines) is unaffected. However, with regard to acetaminophen, patients with Gilbert syndrome are a heterogeneous group, with some demonstrating normal metabolism and others exhibiting marked reduction in glucuronidation and an increase in oxidation.
- Polymerase chain reaction: Polymerase chain reaction is a novel and rapid method of identifying genetic polymorphisms in the TATA box of the *UGT1*1* gene using fluorescence resonance energy transfer.

Liver Biopsy

- Liver biopsies are not performed routinely and are rarely necessary. The liver is normal histologically, except for occasional accumulation of a lipofuscinlike pigment around the terminal hepatic venules.

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14.2 Appendix 2: List of prohibited CYP3A inhibitors and inducers

Table 14-1 List of prohibited CYP3A inhibitors and inducers

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers	Moderate CYP3A inducers
clarithromycin	amprenavir	carbamazepine *	felbamate *
conivaptan	aprepitant	phenobarbital *	topiramate * (>200 mg/day)
indinavir	atazanavir	phenytoin *	oxcarbazepin *
itraconazole	cimetidine	fosphenytoin *	eslicarbazepin *
ketoconazole	ciprofloxacin	primidone *	rufinamide *
lopinavir	darunavir	avasimibe	bosentan
mibefradil	diltiazem	rifabutin	efavirenz
nefazodone	elvitegravir	rifampin	etravirine
nelfinavir	erythromycin	St. John's Wort	modafenil
posaconazole	fluconazole		nafcillin
ritonavir	grapefruit juice		ritonavir
saquinavir	schisandra sphenanthera		talviraline
telithromycin	tipranavir		tipranavir
troleandomycin	tofisopam		
voriconazole	verapamil		

* These drugs are Enzyme Inducing Anti-Epileptic drugs

This database of CYP inhibitors and inducers was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, from the University of Washington's Drug Interaction Database based on in vitro studies and from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche 2008).

14.3 Appendix 3: List of CYP450 substrates to be used with caution

Table 14-2 List of CYP450 substrates to be used with caution*

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
amodiaquine	celecoxib	amitriptyline	adinazolam	felodipine[1]
cerivastatin	diclofenac	citalopram	alfentanil[1,2]	fentanyl[2]
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine[1]	flunitrazepam
repaglinide	fluvastatin	clomipramine	alprazolam	fluticasone[1]
rosiglitazone	glibenclamide (glyburide)	clopidogrel	amlodipine	lovastatin[1]
torasemide	gliclazide	diazepam	aripiprazole	maraviroc[1]
troglitazone	glimepiride	fluoxetine	atorvastatin	midazolam[1]
	glipizide	imipramine	brecanavir	nifedipine
	indomethacin	lansoprazole	brotizolam[1]	nisoldipine
	irbesartan	mephobarbital	budesonide[1]	nitrendipine
	ketobemidone	moclobemide	buspirone[1]	perospirone[1]
	lornoxicam	omeprazole	capravirine	quinine
	losartan	pantoprazole	cerivastatin	sildenafil[1]
	meloxicam	progesterone	chlorpheniramine	simvastatin[1]
	naproxen	quazepam	cyclosporine[2]	sirolimus[1,2]
	nateglinide	rabeprazole	darifenacin[1]	tolvaptan
	piroxicam	sertraline	diazepam	trazodone
	rosiglitazone	S-mephenytoin	diergotamine[2]	triazolam[1]
	S-ibuprofen		ebastine[1]	
	sulfamethoxazole		eletriptan[1]	
	tenoxicam		eplerenone[1]	
	tolbutamide		ergotamine[2]	
	torasemide		estazolam	
	valdecoxib		everolimus[1]	

* This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, and from (Zhou 2009)

** CYP3A substrates were compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; and supplemented by the FDA's "Guidance for Industry, Drug Interaction Studies" and the University of Washington's Drug Interaction Database.

(1) Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

(2) Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

14.4 Appendix 4: Prohibited QT prolonging drugs with risk of Torsades de Pointes

All QT-prolonging drugs listed in Table 14-3 are prohibited for all patients from screening through permanent discontinuation of study treatment. Table 13-2 lists drugs with a known risk for Torsades de Pointes (TdP) as well as sensitive CYP3A substrates (with narrow TI) with a possible or conditional risk for TdP.

Table 14-3 List of prohibited QT prolonging drugs

Drug	QT risk(*)	Comment
Amiodarone	Known risk for TdP	Females>Males, TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females>Males.
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
Droperidol	Known risk for TdP	
Halofantrine	Known risk for TdP	Females>Males
Haloperidol	Known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females>Males
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate

(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT

Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

Note: drugs with a known risk for TdP that are also moderate or strong inhibitors of CYP3A are not repeated here and only mentioned in Table 14-1.

14.5 Appendix 5: List of QT prolonging drugs to be used with caution

Patients receiving any study treatment may use the following medications but should be monitored closely.

Table 14-4 List of QT prolonging drugs to be used with caution

Drug	QT risk (*)
Alfuzosin	Possible risk for TdP
Amantadine	Possible risk for TdP
Amitriptyline	Conditional risk for TdP
Azithromycin	Possible risk for TdP
Chloral hydrate	Possible risk for TdP
Citalopram	Conditional risk for TdP
Clomipramine	Conditional risk for TdP
Clozapine	Possible risk for TdP
Desipramine	Conditional risk for TdP
Diphenhydramine	Conditional risk for TdP
Dolasetron	Possible risk for TdP
Doxepin	Conditional risk for TdP
Dronedarone	Possible risk for TdP
Escitalopram	Possible risk for TdP
Flecainide	Possible risk for TdP
Fluoxetine	Conditional risk for TdP
Foscarnet	Possible risk for TdP
Galantamine	Conditional risk for TdP
Gatifloxacin	Possible risk for TdP
Gemifloxacin	Possible risk for TdP
Granisetron	Possible risk for TdP
Imipramine	Conditional risk for TdP
Indapamide	Possible risk for TdP
Isradipine	Possible risk for TdP
Levofloxacin	Possible risk for TdP
Lithium	Possible risk for TdP
Mexiletine	Conditional risk for TdP
Moexipril/HCTZ	Possible risk for TdP
Moxifloxacin	Possible risk for TdP
Nicardipine	Possible risk for TdP
Nortriptyline	Conditional risk for TdP
Octreotide	Possible risk for TdP
Ofloxacin	Possible risk for TdP
Ondansetron	Possible risk for TdP
Oxytocin	Possible risk for TdP

Drug	**QT risk (*)**
Paliperidone	Possible risk for TdP
Paroxetine	Conditional risk for TdP
Perflutren lipid microspheres	Possible risk for TdP
Protriptyline	Conditional risk for TdP
Ranolazine	Possible risk for TdP
Risperidone	Possible risk for TdP
Roxithromycin*	Possible risk for TdP
Sertindole	Possible risk for TdP
Sertraline	Conditional risk for TdP
Solifenacin	Conditional risk for TdP
Tizanidine	Possible risk for TdP
Trazodone	Conditional risk for TdP
Trimethoprim-Sulfa	Conditional risk for TdP
Trimipramine	Conditional risk for TdP
Venlafaxine	Possible risk for TdP
Ziprasidone	Possible risk for TdP

14.6 Appendix 6: Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse, et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer, et al 2009).

The efficacy assessments described in Section 2 and the definition of best response in Section 3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 4 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse, et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer, et al 2009) European Journal of Cancer; 45:228-247.

2.1 Definitions

2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 3.2.8

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at

baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

2.2.1 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 3.2.8.

2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
  - For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have

a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

  - A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must

normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- Target lesions: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 2.1.1.
- **Nodal target**: See Section 2.1.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 2-5) and non-target lesions (Table 2-6) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 2-7) as well as the presence or absence of new lesions.

2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

2.4.1.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

2.4.1.2 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a “non-zero size” will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

2.4.2 Determination of target lesion response

Table 2-5 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm^2.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

SOD for CR may not be zero when nodal lesions are part of target lesions

Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR

Methodology change See Section 2.2.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 2-5 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.

- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

2.4.3 Determination of non-target lesion response

Table 2-6 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 2.2.

2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 2-7.

Table 2-7 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

This overall lesion response also applies when there are no non-target lesions identified at baseline.
Once confirmed PR was achieved, all these assessments are considered PR.
As defined in Section 2.4.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status

other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

3.2 Time to event variables

The protocol should state which of the following variables is used in that study.

3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

3.2.4 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

3.2.5 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates... If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis, et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

3.2.6 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

3.2.7 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the

assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 3.2.8).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

3.2.8 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires

special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 3-1.

Table 3-1 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 2.4.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

3.2.9 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP

specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 3-2 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

=Definitions can be found in Section 3.2.7.

=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 3.2.7.

=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.

- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 3-2 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee 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.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems

- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

4.4 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

4.5 Programming rules

The following should be used for programming of efficacy results:

4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 3-2)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

5 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

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Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

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Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

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14.7 Appendix 7: Patient Self-Reported Mood Questionnaires

Table 14-5 PHQ-9 Depression Scale

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✔" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless.	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy.	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television.	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
For Office Coding	__*0*__ + _____ + _____ + _____ = Total Score: _____			

If you checked off **any** problems, how **difficult** have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult

Note: The questionnaire provided here is a sample for information purposes only. Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents.

Table 14-6 GAD-7 Anxiety Scale

Over the last 2 weeks, how often have you been bothered by the following problems? (Use "✔" to indicate your answer")	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
(For office coding: Total Score T	_____	= _____	+ _____	+ _____)

Note: The questionnaire provided here is a sample for information purposes only. Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents.

14.7.1 Scoring the PHQ-9 and GAD-7

14.7.1.1 Calculating the Total Score for the PHQ-9

Total scores from the PHQ-9 will be calculated to assess depression severity according to the developer's guidelines [Instruction Manual: Instructions for Patient Health Questionnaire (PHQ) and GAD-7 Measures. Accessed on 2010 Sept 9 from:.phqscreeners.com]. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. PHQ-9 total score for the nine items ranges from 0 to 27.

PHQ-9 Scoring Example:

In the example below, the Total Score for the PHQ-9 depression severity is 8, where the score is the sum of four items scored "0" (questions: #3, 7, 8, 9), three items scored "1" (questions: #1, 4, 6), one item scored "2" (question: #2), and one item scored "3" (question: #5).

PATIENT HEALTH QUESTIONNAIRE - 9 (PHQ - 9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

(Use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	☐ 0	☒ 1	☐ 2	☐ 3
2. Feeling down, depressed, or hopeless	☐ 0	☐ 1	☒ 2	☐ 3
3. Trouble falling or staying asleep, or sleeping too much	☒ 0	☐ 1	☐ 2	☐ 3
4. Feeling tired or having little energy	☐ 0	☒ 1	☐ 2	☐ 3
5. Poor appetite or overeating	☐ 0	☐ 1	☐ 2	☒ 3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	☐ 0	☒ 1	☐ 2	☐ 3
7. Trouble concentrating on things, such as reading the newspaper or watching television	☒ 0	☐ 1	☐ 2	☐ 3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	☒ 0	☐ 1	☐ 2	☐ 3
9. Thoughts that you would be better off dead or of hurting yourself in some way	☒ 0	☐ 1	☐ 2	☐ 3
Column totals:	*0*	+ *3*	+ *2*	+ *3*
PHQ-9 TOTAL SCORE:		*8*		

14.7.1.2 Calculating the Total Score for the GAD-7

Similar to the PHQ-9, scores for the GAD-7 will calculated to assess anxiety severity according to the developer's guidelines [1]. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. A total score for the GAD-7 can range from 0 to 21.

GAD-7 Scoring Example:

In the example below, the Total Score for the GAD-7 anxiety severity is 9, where the score is the sum of two items scored "0" (questions: #6, 7), two items scored "1" (questions: #2, 3), two items scored "2" (questions: #1, 5), and one item scored "3" (question: #4).

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?

(Use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	☐ 0	☐ 1	☒ 2	☐ 3
2. Not being able to stop or control worrying	☐ 0	☒ 1	☐ 2	☐ 3
3. Worrying too much about different things	☐ 0	☒ 1	☐ 2	☐ 3
4. Trouble relaxing	☐ 0	☐ 1	☐ 2	☒ 3
5. Being so restless that it is hard to sit still	☐ 0	☐ 1	☒ 2	☐ 3
6. Becoming easily annoyed or irritable	☒ 0	☐ 1	☐ 2	☐ 3
7. Feeling afraid as if something awful might happen	☒ 0	☐ 1	☐ 2	☐ 3
Column totals:	***0***	+ ***2***	+ ***4***	+ ***3***
GAD-7 TOTAL SCORE:	***9***			

14.8 Appendix 8: Health Related Quality of Life Questionnaires

Figure 14-1 EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Note: The questionnaire provided here is a sample for information purposes only. Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Note: The questionnaire provided here is a sample for information purposes only. Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents

Figure 14-2 EORTC QLQ-HN35 (version 1.0)

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

Note: The questionnaire provided here is a sample for information purposes only. Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

Note: The questionnaire provided here is a sample for information purposes only. Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents

14.9 Appendix 9

The study is designed based on a double criteria for Proof of Concept that is defined for Primary endpoint (PFS) and Key Secondary endpoint (OS).

14.9.1.1 Primary Endpoint – Progression Free Survival

The Proof of Concept criteria are:

1. Estimate of HR is ≤ 0.67.
2. The posterior probability that HR is < 1 is at least 97.5%.

14.9.1.2 Key Secondary Endpoint – Overall Survival

The Proof of Concept criteria are:

1. Estimate of HR is ≤ 0.77.
2. The posterior probability that HR is < 1 is at least 90%.

It must be noted here that the threshold for HR in the double criteria setup is not the same as the classical alternative as would be used in a hypothesis testing with a given Type 1 Error (2.5%) and power (90%) in a standard design. For example if 90% power were needed for the alternative log-HR = log(0.67), the critical value for the estimated log(HR) would be approximately log(0.80), which for our study is not of clinical interest. The threshold denoted in the Criteria 1 for each of the endpoints represents the indifference point for the improvement in the endpoint above which there would be reasonable clinical interest in the treatment.

For a standard design with effect size δ the critical value for statistical significance is defined as where α and β are the Type 1 and Type 2 Error respectively.

14.9.1.3 Posterior Distribution of HR

Let θ_2 denote the natural logarithm of the hazard ratio (HR). Assume θ_2 follows a normal prior distribution:

$$[\theta_2] \sim N(m_0, 4/n_0)$$

where m_0 is the assumed prior mean and n_0 is the number of events worth of prior information.

Let y_2 denote the log(HR) observed in the current study based on n_2 observed events, with likelihood function

$$[Y_2 \mid \theta_2] \sim N(\theta_2, 4/n_2).$$

The posterior distribution is therefore given by

$[\theta_2 \mid y_2] \sim N(\phi y_2 + (1-\phi)m_0, 4/(n_0+n_2))$, where $\phi = n_2/(n_0+n_2)$.

For no prior information (uninformative prior distribution for θ_2), this simplifies to

$$[\theta_2 \mid y_2] \sim N(y_2, 4/n_2) \qquad (1).$$

Due to the computational complexity arising out of multiple criteria, the variation in the enrollment rate and censoring, no analytic formula is used to derive the sample size. Simulations, described in detail in Section 14.9.1.5, were used to determine sample size, number of events and operating characteristics.

14.9.1.4 Joint distribution of PFS and OS

Even though there is uncertainty on how good is PFS is a surrogate of OS, one cannot necessarily assume them to be independent because any death event of a subject is counted both as a PFS and OS event. Time to PFS event is defined as the minimum of the time to progression (TTP) and time to death(OS). If TTP and OS are assumed to be independent, then

$$P(PFS \geq x) = P(TTP \geq x).\ P(OS \geq x) \qquad (2)$$

In this study we assume that both TTP and OS are exponentially distributed with hazard rates λ_{TTP} and λ_{OS}. Therefore based on Equation (2) PFS should follow an exponential distribution with hazard rate as $\lambda_{TTP} + \lambda_{OS}$.

The clinical assumptions for PoC are given in terms of improvement in terms of median PFS and median OS. However in order to do the simulation for evaluating the operating characteristics of the design one needs to generate the PFS data based on the OS and TTP data. In order to the following transformations are used

$$\lambda_{OS} = \log(2)/\text{mOS}\ ;\ \lambda_{PFS} = \log(2)/\text{mPFS} \qquad (3.1)$$

$$\lambda_{TTP} = \lambda_{PFS} - \lambda_{OS} \qquad (3.2)$$

For each scenario described in the simulations in section the trial data is generated using a given mTTP and mOS such that the mPFS and mOS are what the clinical assumptions require.

14.9.1.5 Scenarios

Following scenarios were considered for the evaluation of the design in terms of the probability of meeting the Proof of Concept criteria

Median PFS (months)							
placebo+paclitaxel	**buparlisib + paclitaxel**						
3	**3**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6**

Median OS (months)							
placebo+paclitaxel	**buparlisib + paclitaxel**						
7	**7**	**7.5**	**8**	**8.5**	**9**	**9.5**	**10**

14.9.1.6 Data Simulation

1. For each patient, we randomly assigned treatment group based on randomization ratio
2. Without loss of generality, we assumed the order of patients was their enrollment order. For example, if the enrollment rate was 10 patients per month, then we assumed the first

10 simulated patients were enrolled in the 1st month, and the next 10 patients were enrolled in the 2nd month. The date of enrollment within that month was randomly determined using a uniform distribution U(0,30), assuming each month has 30 days.

3. Study cutoff date was assumed to be the date when a pre-specified number of events had occurred. For example, if it were pre-specified that 125 events were needed and the 125th event happened on Study Day 200, then the study would end after 200 days. In this study we have two cutoff dates - one for PFS analysis and second for OS analysis.
4. Each patient's TTP and OS event time was simulated from one of the two different exponential distributions: control group, treatment group, depending on the patient's randomization. The PFS event time was derived as the minimum of the TTP and OS event times.
5. In addition the patient drop out event was simulated based on hazard for dropout ($\lambda_{Dropout}$) . Different dropout rates were considered for OS and PFS. Any patient whose dropout event occurred before the event time was considered to be censored due to dropout. Of those patients who were not censored due to dropouts a study cutoff date was derived as described in Step 3. If the event time plus enrollment date was longer than study cutoff date, then the event time was censored; otherwise, it was observed. In other words, if a patient did not have event before the study end date, then the event time of this patient was censored; otherwise, the event time was observed.

14.9.1.7 Data Analysis

1) An R function coxph() from the package survival was applied to each simulated trial dataset, first using all the observations to estimate the point estimate and standard error of the HR for PFS and OS.
2) Number of trials were counted that met the PoC criteria for PFS and the PoC criteria for OS.
3) A non-informative prior (n_0=0) was used to derive the posterior distribution of θ

14.9.1.8 Results Summary

The simulation results were summarized in terms of the probabilities of PoC for PFS in Table 10-1 and PoC for OS in Table 10-2 in Section 10.