Clinical Development

LGX818, MEK162, BKM120, BGJ398, INC280, LEE011

Protocol CLGX818X2109

The LOGIC 2 trial
A phase II, multi-center, open-label study of sequential LGX818/MEK162 combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma

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List of abbreviations

ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AKT/PKB	See PKB
ALT/SGPT	Alanine aminotransferase/glutamic pyruvic transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST/SGOT	Aspartate aminotransferase/glutamic oxaloacetic transaminase
ATP	Adenosine triphosphate
AUC	Area under the curve
AUC0-12h,ss	Area under the curve from 0-12 hours at steady state
BCRP	Breast cancer resistance protein
BID	Bis in diem/twice daily
BLRM	Bayesian logistic regression model
BOR	Best overall response
BRAF	V-raf murine sarcoma viral oncogene homolog B1
BRAFi	BRAF inhibitor
BSEP	Bile salt export pump
CHF	Congestive heart failure
CK/CPK	Creatine kinase / Creatine phosphokinase
CL	Clearance
Cmax	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
CRC / mCRC	Colorectal cancer / metastatic CRC
CrCl	Creatinine clearance
CRO	Contract research organization
CSF	Colony Stimulating Factor
CSR	Central serous retinopathy / 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
CV	Coefficient of variation
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-Drug Interaction
DDS	Dose determining set
DHEA	Dehydroepiandrosterone
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid

DOR	Duration of response
DS&E	Drug safety and epidemiology
DTIC	Dacarbazine
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report/record form
EDC	Electronic data capture
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EOT	End of study treatment
ErbB	Erythroblastic leukemia viral oncogene
ERG	Electroretinogram
ERK	Extracellular signal regulated kinase
EWOC	Escalation with overdose control
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
FU	Follow up
GCP	Good clinical practice
Gen. Ass.	Genetic Assessment
GI	Gastrointestinal
GLP	Good laboratory practice
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GTPase	Guanosine-5'-triphosphatase
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HDPE	High-density polyethylene
hERG	Human ether-à-go-go related gene
HFSR	Hand foot skin reaction
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hr(s)	Hour(s)
i.v.	Intravenous
IB	Investigator brochure
IC50	Inhibition concentration 50%
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Institutional ethics committee
IHC	Immunohistochemistry
IIT	Investigator Initiated Trial
IN	Investigator notification

INR	International normalized ratio
IOP	Intra ocular pressure
IRB	Institutional review board
IUD	Intra-uterine device
IUS	Intra-uterine system
KA	Keratoacanthomas
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LC/MS/MS	Liquid chromatography tandem mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LIMS	Laboratory information management system
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
LPLT	Last patient last treatment
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MATE	Multidrug and toxin extrusion protein
MedDRA	Medical dictionary for regulatory activities
MEK	Mitogen-activated protein kinase kinase
MIA	Melanoma inhibitory activity
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
MXR	Mitoxantrone-resistant protein
NaF PET	Sodium fluoride positron emission tomography
NCI	National Cancer Institute
NRAS	Neuroblastoma RAS viral oncogene homolog
NSCLC	Non-small cell lung cancer
NTI	Narrow therapeutic index
NYHA	New York Heart Association
OAT	Organic anion transporter
OCT	Optical coherence tomography / organic cation transporter
ORR	Overall response rate
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamic / Progression of disease
PFS	Progression free survival
P-gp	Permeability glycoprotein
PHI	Protected health information
Pi	Inorganic phosphorus/phosphate
PI3K	Phosphatidylinositol 3' kinase
PIK3CA	Phosphatidylinositol 3' kinase catalytic alphapolypeptide

PK	Pharmacokinetic
PKB	Protein kinase B (also known as AKT)
PLT	Platelets
po	Per os/by mouth/orally
PPS	Per protocol set
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTC	Papillary thyroid carcinomas
PTEN	Phosphatase and tensin homolog
QD	Quaque die/once daily
QHS	Every bed time
QOD	Every other day
QTcB	QT interval adjusted according to Bazett
QTcF	QT interval adjusted according to Fridericia
RAF	V-raf murine sarcoma viral oncogene
RAP	Report and Analysis Plan (RAP) (i.e. regulatory document which provides evidence of preplanned analyses)
RAS	Rat sarcoma viral oncogene homologue
RBC	Red blood cells
REB	Research ethics board
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase II dose
RTK	receptor tyrosine kinase
RT-PCR	Reverse-transcriptase polymerase chain reaction
RVO	Retinal vein occlusion
s.a.	Single agent
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Stable disease
SEC	Study evaluation completion
SUSAR	Suspected unexpected serious adverse reactions
TBIL	Total bilirubin
T/C	Tumor volume over control volume
T1/2	Terminal elimination half-life
tCa	Total calcium
TdP	Torsades de Pointes
TGI	Tumor growth inhibition
TID	Three times per day
TKIs	Tyrosine kinase inhibitors
TLC	Therapeutic lifestyle change
tmax	Time to reach maximum plasma concentration
TSH	Thyroid-stimulating hormone

TTR	Time to response
ULN	Upper limit of normal
US	United States
Vss	Volume of distribution at steady state
WBC	White blood cells
WHO	World Health Organization

Amendment 7

Amendment rationale

In June 2018, encorafenib (LGX818) 450 mg orally QD, in combination with binimetinib (MEK162) 45 mg orally BID, received marketing approval in the United States and several jurisdictions for the treatment of patients with unresectable or metastatic *BRAF* V600-mutant melanoma with subsequent regulatory approvals in the European Union and Japan. This approval was based on the randomized Phase 3 COLUMBUS Study (CMEK162B2301).

At this stage of development, the toxicity profile of encorafenib in combination with binimetinib has been well established. As all patients who continue to receive encorafenib and binimetinib under this study protocol have been treated for a minimum of 3 years, this protocol has been amended to reduce the frequency of safety assessments to align with study centers' institutional standards for patients with *BRAF* V600-mutant locally advanced unresectable or metastatic melanoma.

As of the release date of this amendment, 13 patients in the Part I of Study CLGX818X2109 were receiving study treatment with encorafenib and binimetinib. There are no patients receiving treatment in the Part II triple combination arm with LEE011.

The protocol has also been amended to discontinue enrollment to the triple combination arm containing LEE011 due to the limited efficacy and minimal interest in further clinical development of this combination. The BKM120 combination was closed on 10 July 2015 due to a significant drug-drug interaction (DDI) between LGX818 and BKM120 (Amendment 03) and the INC280 and BGJ398 arms were closed in Amendment 06 due to the lack of responses observed in the 13 patients treated in the INC280 arm or in the single patient treated in the BGJ398 arm.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

Section 1

- Section 1.2.1.1.1 Overview of combination treatments, Non-clinical experience, LGX818/MEK162.
- Section 1.2.2.2.1 Overview of single agent LGX818, Clinical experience, Clinical safety and efficacy.
- Section 1.2.3.2. Overview of single agent MEK162, Clinical Experience
- Section 1.2.3.2.1. Clinical Safety and Efficacy

The above sections were updated with recent marketing authorization information and number of patients treated with LGX818 and MEK162.

Section 4

- Section 4.1, Study Design; Figure 4-1, Study Design; and Table 4-1, Assignment of triple combination treatment [Assignment of triple combination treatment based on molecular alteration(s) detected at progression under LGX818/MEK162 combination].

  Figure 4-1 and Table 4-1 were modified to close Part II of the study including the discontinuation of the triple combination with LEE011. The study design was also clarified to state patients will be followed per local standard-of-care practice and that all SAE's should be reported to the Sponsor.

Section 5

- Section 5.3 Exclusion criteria enrollment in Part II, triple combination LGX181/MEK162 + LEE011.

Section was amended under Part II to clarify that the enrollment of the triple combination arm containing LEE011 has been discontinued.

Section 6

- Section 6.1, Study treatment and 6.1.1 Dosing regimen, Table 6-1 Dose and treatment schedule.
- Section 6.2.1, Part II LGX818/MEK162 + LEE011.
- Section 6.2.2, Provisional dose levels, Table 6-2 Provisional dose levels for LGX818 and MEK162 [Part 1 and Part II], and Table 6-3 Provisional dose levels for third agents [Part II].
- Section 6.2.3.2, Implementation of dose escalation decisions.
- Section 6.2.3.3, Intra-patient dose escalation.
- Section 6.2.4, Definitions of dose limiting toxicities [DLTs].
- Section 6.5.4, Part II Treatment assignment or randomization.
- Section 6.6, Study drug preparation and dispensation

The above sections were amended to discontinue the enrollment of the triple combination arm containing LEE011.

- Section 6.1.5 Treatment Duration

Section was modified to provide guidance that safety evaluations should occur in accordance with local standard-of-care clinical practice for patients who have been on LGX818 + MEK162 for ≥ 36 months until treatment discontinuation.

- **Section 7:** Section 7.1 Study Flow and Visit Schedule

- Table 7-5, Part 1- LGX818 + MEK162 Visit Evaluation Schedule for patient on treatment ≥ 36 months (Amendment 07)

New Table 7-5 added to detail the reduction in the frequency of safety assessments in the visit evalution schedule for patitents that have received LGX818 + MEK162 treatment for ≥ 36 months. Due to the addition of this new Table 7-5, subsequent table numbers were adjusted accordingly in Section 7.

- Sections 7.1.4. Treatment Period
- Section 7.1.5. End of Study Treatment visit including study completion and premature withdrawal
- Section 7.1.6.2. Disease progresson follow-up period.
- Section 7.2.2.4. Vital Signs
- Section 7.2.2.5. Laboratory evaluations
- Section 7.2.2.5.1. Hematology
- Section 7.2.2.5.2. Clinical Chemistry
- Section 7.2.2.5.6. Ophthalmologic evaluation
- Section 7.2.2.6. Cardiac Assessments

A reference link to new Table 7-5, Part 1- LGX818 + MEK162 Visit Evaluation Schedule for patient on treatment ≥ 36 months (Amendment 07), was added to the sections listing above.

- Section 7.1.6.1. 30-day Follow-up period

Section was amended to reduce the safety assessments at the 30-day follow-up visit to a review of concomitant medications, assessment of compliance with study drug administration, and a review of AEs with recording of all Grade 3 or 4 AEs and all SAEs (Other safety evaluations may be conducted if clinically indicated).

- Section 7.2.1. Efficacy Assessments

Section was amended to reduce the timing of the tumor lesion assessments for patients in Part I and the Run-in phase.

- Section 7.2.2.1 Physical Exams

Section was amended to add a bullet for Part I and Run-in patients on treatment ≥ 36 months to reduce the frequency of physical exams to per local standard of care with a Sponsor recommendation to occur every 4 weeks (Table 7-5).

- Section 7.2.2.6.1 Electrocardiogram (ECG)

A reference link to Table 7-5 was added to the sections listing above.

- Section 7.2.3. Pharmacokinetics

The above sections were amended to discontinue the enrollment of the triple combination arm containing LEE011.

- Section 7.2.4. Biomarkers

Section have been amended, to remove the requirement to provide a new tumor biopsy at disease progression for patients in Part I who have been on the combination treatment with LGX818/MEK162 for ≥ 36 months.

Section 8

- Safety monitoring and reporting

Section was clarified for Part I patients who have been on LGX818 + MEK162 for ≥ 36 months that only Grade 3 or 4 AEs and all SAEs will be recorded on the AE eCRF. Any AEs that meet these criteria until 30 days after the last dose of study drug must be recorded. All SAEs are to be reported to the Sponsor or designee using the SAE form.

Amendment 6

Amendment rationale

As of the release date of this amendment, 17 patients in the CLGX818X2109 study (16 in Part I and 1 in Part II [LGX818/MEK162/LEE011]) were receiving study treatment. There are no patients ongoing in the Part II triple combination arms with INC280, BGJ398, or BKM120.

The protocol is being amended to discontinue enrollment to the triple combination arms containing INC280 and BGJ398 due to the lack of efficacy in these arms and because there is no interest in further clinical development of these combinations. The BKM120 combination was closed on 10 July 2015 due to a significant drug-drug interaction (DDI) between LGX818 and BKM120 (Amendment 3). There have been no responses observed in the 13 patients treated in the INC280 arm or in the single patient treated in the BGJ398 arm.

Additional revisions include the following:

- Change in the frequency and type of ophthalmologic examinations.

  Rationale: In a Phase 3 study (CMEK162B2301; ClinicalTrials.gov identifier NCT01909453) in patients with *BRAF* V600-mutant melanoma treated with the combination of LGX818 (450 mg once daily [QD]) plus MEK162 (45 mg twice daily [BID]), the median time to onset of retinopathy (all grades) was 1.2 months, and there were no patients with a new-onset event after 24 months. No patients treated with the combination LGX818 (450 mg QD) plus MEK162 (45 mg BID) experienced a retinal vein occlusion event. Based on these findings, and in order to minimize the burden on both dual- and triple-combination patients who continue to derive benefit from study treatment, this amendment allows patients who have been receiving LGX818/MEK162 ≥ 24 months (Cycle 25 Day 1 onward) who have not had a retinal adverse event (AE) within the past 12 months to be evaluated for visual acuity at each scheduled patient visit and at the End of Treatment. Patients with changes in visual acuity or other ocular complaints at any time on study should be referred to an ophthalmologist for full ophthalmic examination.

- Change in the frequency of ECGs.

  Rationale: In the safety analysis of pooled studies of encorafenib 450 mg once daily in combination with 45 mg binimetinib twice daily (Combo 450), the incidence of new QTc prolongation > 500 ms was 0.7% (2/268 patients) and QTc prolongation > 60 ms compared to pre-treatment values was observed in 4.9% of patients (13/268 patients). Based on these findings, and to further minimize the burden on both dual- and triple-combination patients who continue to derive benefit from study treatment, patients who have been receiving study treatment ≥ 24 months (Cycle 25 Day 1 onward) can undergo an ECG every 3 cycles (12 weeks).

- Removal of the collection of an unscheduled PK sample taken in the event of a QTcF change from baseline > 60 ms or a new absolute QTcF interval ≥ 501 ms.

  Rationale: This is being done to reduce the burden on the patients and the sites. Collection and analysis of unscheduled PK samples would not significantly contribute to the PK data already accumulated on this study. Additionally, collection of PK data in the event of QTcF

changes provides minimal actionable information to the investigator due to the processing time required for PK samples.

- Removal of the fasting requirement for the dual- and triple-combination treatments.

  Rationale: Based on results of two dedicated clinical pharmacology studies, exposures of binimetinib (clinical trial CMEK162A2103) and encorafenib (clinical trial ARRAY-818-102) were unaffected by food, indicating patients can take the dual-combination treatment with or without food. Since the package insert for LEE011 indicates patients can take LEE011 with or without food, the fasting restriction was removed for the triple combination.

- Removal of the restriction of agents that elevate gastric pH, including antacids, proton pump inhibitors, and H2 antagonists.

  Rationale: Based on available data from the results of a dedicated clinical pharmacology study (ARRAY-162-105), exposures of binimetinib and encorafenib were unaffected by rabeprazole, a proton pump inhibitor, indicating patients can take the dual-combination treatment with agents that elevate gastric pH. Since the package insert for LEE011 (ribociblib) indicates patients can take LEE011 with gastric pH–elevating agents, the restriction was removed for the triple combination..

In Appendix 7 of the protocol, language was added to the appendix header regarding Table 14-16 through Table 14-28 stating that the substrates in the tables do not represent an exhaustive list of substrates, inducers or inhibitors.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

Section 4

- Section 4.1 Description of study design and Table 4-1 (Assignment of triple combination treatment based on molecular alteration(s) detected at progression under LGX818/MEK162 combination).

  Section 4.1 and Table 4.1 were modified to discontinue enrollment to the triple combination arms containing INC280, BGJ398, and BKM120.

- Section 4.3 Definition of end of study

  The above section was amended to clearly define the end of study.

Section 5

- Section 5.3 Exclusion criteria enrollment in Part II, additional exclusion criteria for Part II for selected triple combination LGX181/MEK162 + INC280 and LGX818/MEK162 + BGJ398.

  Section was amended under Part II to clarify that the enrollment of the triple combination arms containing INC280 and BGJ398 has been discontinued. Patients who are eligible may only enroll in the LGX818/MEK162 + LEE011 arm.

Under LGX818/MEK162 + LEE011, added exclusion criteria to maintain consistency with the LEE011 program standards.

Section 6

- Section 6.1 Study treatment and 6.1.1 Dosing regimen, Table 6.1 Dose and treatment schedule.

  Amended to clarify that the enrollment of the triple combination arms containing INC280 and BGJ398 has been discontinued. Patients who are eligible may only enroll in the LGX818/MEK162 + LEE011 arm.
- Section 6.1.1.1 Instructions for administration of LGX818, MEK162, INC280, BKM120, LEE011 and BGJ398.

  The above section was modified to allow patients to take either the dual combination (LGX818 and MEK162) or the triple combination (LGX818, MEK162 and LEE011) with or without food.
- Section 6.2.1 Part II LGX818/MEK162 + BGJ398 and LGX818/MEK162 + INC280;
  Section 6.2.2 Provisional dose levels
  Table 6-2 Provisional dose levels for LGX818 and MEK162 [Part 1 and Part II],
  Table 6-3 Provisional dose levels for third agents [Part II],
  Section 6.2.2.1 INC280 Dose Escalation: Capsule and Tablet Formulations,
  Section 6.2.3.2 Implementation of dose escalation decisions,
  Section 6.2.3.3 Intra-patient dose escalation,
  Section 6.2.4 Definitions of dose limiting toxicities [DLTs],
  Section 6.3.3.1 Anticipated risks and safety considerations of the study drug combinations,
  Section 6.5.4 Part II Treatment assignment or randomization,
  Section 6.6 Study drug preparation and dispensation

  The above sections were amended to discontinue the enrollment of the triple combination arms containing INC280, BKM120 and BGJ398. Patients who are eligible may only enroll in the Part II LGX818/MEK162 + LEE011 arm.
- Section 6.3.1, Table 6-7 and Table 6-11

  To maintain consistency with the LEE011 program standards, Table 6-7 was updated for ECG QTcF interval prolongation, Table 6-7 was modified to include dose modification for a Grade ≥ 2 renal impairment, and Table 6-11 was removed, as the same recommended dose modifications for LGX818 + MEK612 + LEE011 for QTc-interval prolongation are contained in Table 6-7. Table numbers were updated as appropriate.
- Section 6.4.2.1 Permitted concomitant therapy requiring caution and/or action throughout the study based on LGX818 and MEK162 DDI potential (Part I and Part II)

  The above section was amended to remove the restriction of agents that elevate gastric pH.

Section 7

- Table 7-1, Part I - Visit evaluation schedule for patients enrolled in Group A,
  Table 7-2, Run-in Visit evaluation schedule for patients enrolled in Group B, and

Table 7-4, Part II - Visit evaluation schedule for Part II (28 day cycles for LEE011 and BGJ398)

The above visit evaluation schedule tables were amended in the row for ophthalmologic examination to allow patients who have received LGX818/MEK162 for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE in the past 12 months to be evaluated only for visual acuity at each scheduled patient visit and at the End of Treatment visit. These patients are also required to have a full ophthalmic examination if clinically indicated and at the End of Treatment visit.

The above tables were amended to add the recommendation, following the 30-day follow-up period and when clinically appropriate, for patients to be monitored with physical examinations, dermatological examinations and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last LGX818 dose or until initiation of another antineoplastic therapy.

The above visit evaluation schedule tables were also amended to discontinue the enrollment of the triple combination arms containing INC280 and BGJ398. Patients who are eligible may only enroll in the Part II LGX818/MEK162 + LEE011 arm.

The above visit evaluation schedule tables were also amended to clarify that, in subsequent cycles, ECGs are to be obtained every 3 cycles after ≥ 24 months (Cycle 25 Day 1 onward) of treatment.

- Table 7-3, Part II - Visit evaluation schedule for Part II (21 day cycles for triple combinations with INC280 and BKM120)

  The above visit evaluation schedule table was amended to discontinue the enrollment of the triple combination arms containing INC280 and BKM120.

- Section 7.2.2.5.7 Ophthalmologic examination

  The above section was amended to allow patients who have received LGX818/MEK162 treatment for ≥ 24 months without a retinal AE in the past 12 months to be evaluated only for visual acuity at each scheduled patient visit and at the End of Treatment visit. These patients are required to have a full ophthalmic examination if clinically indicated and at the End of Treatment visit. Also, additional testing for BGJ398 will no longer be required due to the discontinuation of enrollment to the LGX818/MEK162 + BGJ398 treatment arm.

- Section 7.2.2.6.1 Electrocardiogram (ECG)

  The above section was amended to remove text around unscheduled PK sample collection when an ECG with a QTcF change from baseline > 60 ms or a new absolute QTcF ≥ 501 ms result is observed. Also, patients who have been on study treatment for ≥ 24 months (Cycle 25 Day 1 onward) will have ECGs every 3 cycles.

- Section 7.2.3. Pharmacokinetics

  Clarification was added that the enrollment was discontinued for the triple combination arms containing BKM120, INC280, and BGJ398. Patients who are eligible may only enroll in the Part II LGX818/MEK162 + LEE011 arm.

  The following section was modified as described below.

- Section 7.2.3.1.1 Blood collection plan

  The above section was amended to stop collection of unscheduled PK samples, and text was removed where this practice was discussed. This includes addition of footnotes in Table 7-11 Pharmacokinetic blood collection log for LGX818 and MEK162 during Part I Run-In (LGX818/MEK162 combination), Table 7-12 Pharmacokinetic blood collection log for LGX818 and MEK162 during Part II (triple combination, 28 days cycle with LEE011 and BGJ398), and Table 7-17 Pharmacokinetic blood collection log for LEE011 during Part II (triple combination) (28 days cycle) denoting collection should be stopped upon the effective date of Amendment 06.

Section 10

- Section 10.8 Sample size calculation, Part II other arms

  Section amended to discontinue enrollment to the BKM120-, BGJ398-, and INC280-containing arms. Patients who are eligible may only enroll in the LGX818/MEK162 + LEE011 arm.

Amendment 5

Amendment rationale

As of 12 September 2017, 27 patients in the CLGX818X2109 study (25 in Part I and 2 in Part II [both on LGX818/MEK162/LEE011 combination]), were continuing to derive benefit from study treatment. In order to minimize the burden on the patients and to reduce their radiation exposure, this amendment allows the frequency of tumor assessments in all Part I continuing patients to be reduced to every 6-12 weeks based on Investigator discretion. Patients may be transitioned to this less frequent imaging schedule once they have completed ≥ 24 months of study treatment in Part I and the Run-in phase.

In addition, this protocol is also being amended to change the freaquency and type of ophthalmologic examinations. In a separate Phase 3 study (CMEK162B2301; ClinicalTrials.gov identifier NCT01909453) in patients with *BRAF* V600-mutant melanoma treated with the combination of LGX818 (450 mg once daily [QD]) plus MEK162 (45 mg twice daily [BID]), the median time to onset of retinopathy excluding retinal vein occlusion (in patients with at least one event) was 0.2 months (95% confidence interval [CI] 0.1, 0.9) and there were no patients with a new onset event after 24 months. Based on these findings, and in order to minimize the burden on patients who continue to derive benefit from study treatment, this amendment allows patients who have been receiving study treatment ≥ 24 months in Part I and the Run-in phase and who have not had a retinal adverse event (AE) to be evaluated only for visual acuity at each scheduled patient visit (Day 15 of all cycles) with a full ophthalmic examination required every 12 weeks (i.e., every 4 cycles) or more frequently if clinically indicated, and at End of Study Treatment visit.

Additional revisions have been to sections of the protocol that are specific to the Part II triple combination arm with LEE011 in order to reflect recent clinical development changes pertaining to patient selection and dose modification.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

- Synopsis and Section 5.3 – Exclusion criteria for the LGX818/MEK162/LEE011 combination

The above sections were amended to add additional cardiac restrictions for the eligibility of patients for treatment with the LGX818/MEK162/LEE011 combination.

- Section 4.1 Description of study design

The above section was amended to remove the requirement for an analysis when all patients have potentially completed at least 6 cycles of treatment in Part II or discontinued treatment.

- Table 6-5 LEE001 Dose modification guidelines; Section 6.3.1 Dose modification and dose delay

The above table was added to provide LEE001 dose modification guidelines for patients undergoing treatment with the LGX818/MEK162/LEE011 combination.

- Table 6-7 Criteria for interruption and re-initiation of LGX818 and MEK162 in combination with third agent (BGJ398, INC280, BKM120 or LEE011); Section 6.3.1 Dose modification and dose delay

The above table was updated to provide dose modification details for patients undergoing treatment with the LGX818/MEK162/LEE011 combination for the following: Blood and Lymphatic System Disorders, Investigations-blood, Investigations-hepatic and Electrocardiogram QTcF interval prolonged.

- Table 6-11 Specific criteria for interruption and re-initiation of LEE011 treatment in LGX818/MEK162/ LEE011 triple combination; Section 6.3.1 Dose modification and dose delay

The above table was updated to provide dose modification details for patients undergoing treatment with the LGX818/MEK162/LEE011 combination who experience cardiac arrhythmia with QTcF interval prolonged.

- Section 6.3.2.6 – Additional follow-up for hepatic toxicities in patients receiving LEE011

The above section was amended to add additional guidance for patients in case of AST, ALT, and/or bilirubin increase requiring dose interruption during treatment with the LGX818/MEK162/LEE011 combination.

- Section 6.4.1 – Permitted concomitant therapy

The above section was revised for bisphosphonates to add that prophylactic treatment is not allowed for bisphosphonates with the LGX818/MEK162/LEE011 combination treatment. A subsection was also added with guidance on the use of corticosteroids while on study.

- Section 6.4.2.6 – Permitted concomitant therapy requiring caution and/or action during triple combination with LEE011

The above section was amended to add additional guidance on the use of concomitant therapy requiring caution for patients during treatment with the LGX818/MEK162/LEE011 combination.

- Section 6.4.3 – Prohibited concomitant therapy

The above section was amended to add additional guidance on prohibited concomintant therapy for patients during treatment with the LGX818/MEK162/LEE011 combination.

- Table 7-1 Part I – Visit evaluation schedule for patients enrolled in Group A; Table 7-2 Run-in Visit evaluation schedule for patients enrolled in Group B; Section 7.1 Study flow and visit schedule.

The above tables were amended in the row for ophthalmologic examination to allow patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months (25 cycles) in Part I and the Run-in phase without a retinal AE to be evaluated only for visual acuity at each scheduled patient visit (Day 15 of all cycles) and at End of Study Treatment visit. These patients are also required to have a full ophthalmic examination every 12 weeks (i.e., every 4 cycles) or more frequently if clinically indicated, and at End of Study Treatment visit instead of Day 15 of all cycles.

The above tables were also amended in the row for tumor evaluation per the Response Criteria in Solid Tumors (RECIST) by computed tomography (CT) / magnetic resonance imaging (MRI) to allow patients enrolled in Part I and the Run-in phase, who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months to have CT/MRI scans every 6-12 weeks (+/- 7 days) instead of every 6 weeks. Also, this row was amended to allow patients enrolled in Part I and the Run-in phase who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression to have CT/MRI scans every 9-12 weeks (+/- 7 days) instead of every 9 weeks.

- Section 7.1.6.2 Disease progression follow-up period

The above section was amended for tumor evaluation per RECIST by CT/MRI to allow patients enrolled in Part I and the Run-in phase, who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression to have CT/MRI scans every 9-12 weeks (+/- 7 days) instead of every 9 weeks.

- Section 7.2.1 Efficacy assessments

The above section was amended for tumor evaluation per RECIST by CT/MRI to allow patients enrolled in Part I and the Run-in phase, who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months to have CT/MRI scans every 6-12 weeks (+/- 7 days) instead of every 6 weeks. Also, this section was amended to allow patients in Group B who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months to be evaluated for all potential sites of tumor lesions every 6-12 weeks (+/- 7 days) until disease progression instead of every 6 weeks. The above section was also amended for tumor evaluation per RECIST by CT/MRI to allow patients enrolled in Part I and the Run-in phase, who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression to have CT/MRI scans every 9-12 weeks (+/- 7 days) instead of every 9 weeks.

- Table 7-5 Disease assessment collection plan; Section 7.2.1 Efficacy assessments

The above table was amended for tumor evaluation per RECIST by CT/MRI to allow patients enrolled in Part I and the Run-in phase, who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months to have CT/MRI scans every 6-12 weeks (+/- 7 days) instead of every 6 weeks. Also, this table was amended to allow patients enrolled in Part I and the Run-in phase, who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression to have CT/MRI scans every 9-12 weeks (+/- 7 days) instead of every 9 weeks.

- Section 7.2.2.5.7 Ophthalmologic evaluation

The above section was amended to allow patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months in Part I and the Run-in phase without a retinal AE to be evaluated only for visual acuity at each scheduled patient visit (Day 15 of all cycles) and at End of Study Treatment visit. These patients are also required to have a full ophthalmic examination every 12 weeks (i.e., every 4 cycles) or more frequently if clinically indicated, and at End of Study Treatment visit instead of Day 15 of all cycles after Cycle 2.

- Section 10 Statistical methods and data analysis

The above section was amended to remove the requirement for an analysis when all patients have potentially completed at least 6 cycles of treatment in Part II or discontinued treatment, died or withdrew consent prior to this time. The text was revised to clarify that study data will be analyzed and reported at the end of the study.

- Table 14-18 Additional prohibited concomitant therapy for the LGX818/MEK162/LEE011 combination; Table 14-21 Narrow therapeutic index substrates and substrates of CYP3A4, CYP2B6, CYP2C8 and CYP2C9, CYPC19 and CYP1A2; Table 14-23 List of CYP inhibitors; Appendix 7 – List of prohibited and concomitant medications to be used with caution

The above tables were revised to update and expand the list of prohibited concomitant therapy for patients during treatment with the LGX818/MEK162/LEE011 combination, and to match changes made in Section 6.4 on concomitant medications.

- Table 14-21 Narrow therapeutic index substrates and substrates of CYP3A4, CYP2B6, CYP2C8 and CYP2C9, CYPC19 and CYP1A2; Table 14-23 List of CYP inhibitors; Appendix 7 – List of prohibited and concomitant medications to be used with caution

The above tables were revised to update and expand the list of compounds with CYP interactions, and to match changes made in Section 6.4 on concomitant medications.

- Table 14-25 List of BSEP inhibitors, P-gp inhibitors/inducers and P-gp, BCRP, MATE1, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 substrates; Appendix 7 – List of prohibited and concomitant medications to be used with caution

The above table was revised to update and expand the list of compounds with inhibitory, induction, or substrate activity, and to match changes made in Section 6.4 on concomitant medications.

- Table 14-26 List of QT prolonging drugs; Appendix 7 – List of prohibited and concomitant medications to be used with caution

The above table was revised to update and expand the list of QT prolonging drugs, and to match changes made in Section 6.4 on concomitant medications.

Other minor clarification changes and corrections to typographical errors have been made.

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 4

Amendment rationale

One of the main purposes of this protocol amendment is to provide additional information and guidance to investigators for the management of liver toxicities for the INC280 combination.

Clarifications in the dose modification guidelines in case of liver toxicity, updated rules with regards to study treatment discontinuation for events that meet the Hy's Law criteria and specific work-up guidelines for potential drug-induced liver injury (DILI) cases are added in the protocol. Patients with increased AST/ALT and total bilirubin (TBIL) values that may be indicative of potential DILI, should be considered as clinically important events; therefore, specific guidance for actions to be taken on study treatment (e.g. discontinuation) and for monitoring of liver function tests (LFTs) have been implemented and clarified. In addition, this protocol is amended to include the following serious adverse event (SAE): a female patient experienced a serious, unexpected, possibly related adverse event (AE) of abnormal LFTs during treatment with a combination of INC280 and gefitinib while enrolled in the [CINC280X2202] study (Initial Investigator Notification Letter issued 12 March 2015). The investigator assessed the AE as suspected to be related to the combination of INC280 and gefitinib. This AE met the criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination.

Secondly, this protocol amendment introduces the use of INC280 tablets with different dosage strengths (100 mg and 200 mg, instead of 50 mg and 200 mg) in order to improve the convenience of study drug administration for patients. Related to this, the protocol also allows for intra-patient crossover from the capsule formulation to the tablet formulation once the capsule formulation is no longer available.

Thirdly, the eligibility criteria for amylase and lipase have been updated to be consistent across the different INC280 studies.

Lastly, the list of prohibited and concomitant medications to be used with caution has been updated.

Changes to the protocol

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

- Table 4.1; Section 6.1.1.1 Instructions for Administration of LGX818, MEK162, INC280, BKM120, LEE011 and BGH398.

The above sections were amended to include further clarification that the MEK162 + LGX818 + BKM120 Arm closed on 10 July 2015 (per Amendment 03) due to drug-drug interaction (DDI) between LGX818 and BKM120.

- Table 6-4; Table 6-6; Section 6.3.2.7 Additional follow-up for hepatic toxicities in patients receiving INC280; Section 6.3.2.8 Follow up on potential drug-induced liver injury cases (new sections)

The above sections were amended to reflect the changes for INC280 safety updates.

- Table 6-3; Section 6.2.2.1 INC280 Dose Escalation: Capsule and Tablet Formulations (new section); Section 6.6 Study drug preparation and dispensation

The above sections were amended to reflect the changes for the use of INC280 tablets.

- Section 5.3

The above section was amended to reflect the changes to amylase and lipase exclusion criteria to be consistent with the updates for INC280 dosing.

- Table 14-17; Table 14-18; Table 14-19; Table 14-20; Table 14-21; Table 14-22; Table 14-23; Table 14-24; Table 14-25; Table 14-26

The above sections were amended to reflect updates to the lists of prohibited medications and concomitant medications to be used with caution.

Other minor clarification changes and corrections to typographical errors have been made.

Study update: Study recruitment was completed on 09 November 2015. As of November 2015, 157 patients have been treated (151 patients with LGX818 and MEK162 combination in Part I/ Part II Run-in). Thirty-four patients have been treated with a triple combination in Part II (20 patients with LGX818, MEK162 and LEE011 combination; 6 patients with LGX818, MEK162 and BKM120 combination; 1 patient with LGX818, MEK162 and BGJ398 combination; and 7 patients with LGX818, MEK162 and INC280 combination).

- Section 10.5.4

The version of software used in either analysis (non-compartmental or compartmental approach) will be documented in the final clinical study report (CSR). Due to the sponsor change, the software used may be incompatible with the language in the protocol. The language proposed would allow for the sponsor or sponsor-designated contract research organization (CRO) to use any software version that would be reported in the final CSR.

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 3

Amendment rationale

The main purpose of this protocol amendment is to provide additional guidance to investigators around management of toxicities for three of the compounds used in the study; BKM120 (buparlisib), INC280 and LEE011, and to document a change in study sponsorship from Novartis to Array BioPharma.

Alterations in LFTs have been commonly observed in clinical trials with BKM120 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 treatment, and rarely are associated with signs/symptoms of impaired liver function. Current BKM120 protocols have conservative inclusion criteria for baseline LFTs 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 BKM120 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) back 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 BKM120 studies in May 2015 informing them about the liver findings including a brief summary of the six Hy's law cases. 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.

A decision was taken on 10 July 2015 to halt further recruitment to the BKM120 arm, which was communicated to Health Authorities and sites. Pharmacokinetic analysis of the patients already treated with triple combination LGX818 (encorafenib), MEK162 (binimetinib) and BKM120 has shown a significant drug-drug interaction (DDI) between LGX818 and BKM120. The BKM120 exposure in triple combination was found to be substantially reduced, by up to 80% compared to single agent BKM120 based on the preliminary PK analysis. Based on this

observed DDI between LGX818 and BKM120, reaching efficacious exposures of BKM120 is unlikely with the current doses of LGX818 and MEK162. At the time that this protocol was amended, one patient was still receiving treatment with triple combination LGX818, MEK162 and BKM120; therefore, the safety updates related to BKM120 have still been implemented.

This protocol amendment also provides additional information and guidance to investigators for the management of liver toxicities when taking INC280. After the cut-off date of the current INC280 Investigator's Brochure (28-Sep-2014), a female patient experienced a serious, unexpected, possibly related adverse event of abnormal liver function tests during treatment with a combination of INC280 and gefitinib while enrolled in the CINC280X2202 study. This adverse event met the lab criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination. Therefore, clarifications in the dose modification guidelines in case of liver toxicity and updated rules with regards to study treatment discontinuation for events that meet the Hy's Law criteria are added.

Based on the preclinical data which suggest photosensitization potential for INC280, precautionary measures against ultraviolet exposure are being included in this amendment, in addition to the information provided in the current Investigator's Brochure.

This amendment also updates the dose modification guidelines for QTcF prolongation by adding specificity for monitoring and dose adjustment in order to better manage patient safety in patients taking LEE011. The guidelines for QTcF prolongation have been revised following an event of sudden death (IN PHHO2015AR001238). This fatal case was reported from the MONALEESA-2 trial (NCT 01958021; LEE011 in combination with letrozole). As a result, new guidelines for management of QTcF prolongation were instituted throughout the LEE011 program in order to improve safety. Life threatening hepatic toxicity has also been reported in patients treated with ceritinib as well as patients treated with LEE011. Due to these findings, the protocol has been amended to update the guidelines for the management of hepatic toxicity.

A second purpose of this amendment is to allow patients who do not tolerate triple therapy to be rechallenged with dual therapy after discussion with Sponsor Medical Monitor. Furthermore, this amendment provides clarification regarding antineoplastic therapy, which is permitted for patients between Part I and Part II upon discussion with Sponsor Medical Monitor.

The sections on concomitant medications to be used with caution have been updated to reflect changes to the most recent MEK162 Investigator Brochure. Non-clinical and clinical pharmacokinetic data have been updated to reflect recent changes to the MEK162 and LGX818 Investigator Brochures.

Changes to 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 underline for insertions.

- Sections 1.2.4 Overview of single agent BKM120; 6.3.2.5 Management of hepatotoxicity (ALT and/or AST >5.0x ULN and total bilirubin >1.5x ULN) in patients receiving BKM120; Table 7-3 Part II - Visit evaluation schedule for Part II (21 day cycles for triple combinations with INC280 and BKM120); Table 7-7 Local Clinical laboratory parameters collection plan

The above sections were amended to reflect the changes for BKM120 safety updates.

- Sections 1.2.6 Overview of single agent INC280; 6.1.1.1 Instructions for administration of LGX818, MEK162, INC280, BKM120, LEE011 and BGJ398; Table 6-4 Criteria for defining dose-limiting toxicities; Table 6-6 Criteria for interruption and re-initiation of LGX818 and MEK162 in combination with third agent (BGJ398, INC280, BKM120 or LEE011)

The above sections were amended to reflect the changes for INC280 safety updates.

- Sections 6.3.2.6 Additional follow-up for hepatic toxicities in patients receiving LEE011l; Section 6.4.3 Prohibited concomitant therapy; Table 6-6 Criteria for interruption and re-initiation of LGX818 and MEK162 in combination with third agent (BGJ398, INC280, BKM120 or LEE011); Table 7-4 Part II - Visit evaluation schedule for Part II (28 day cycles for LEE011 and BGJ398); Table 7-7 Local Clinical laboratory parameters collection plan

The above sections were amended to reflect the changes for LEE011 safety updates.

- Section 6.1.5 Treatment duration

The above section was amended to allow patients who do not tolerate triple therapy to be re-challenged with dual therapy

- Section 6.4.3 Prohibited concomitant therapy

The above section was amended to clarify that antineoplastic therapy between Parts I and II is permitted upon discussion with Sponsor Medical Monitor.

- Table 1-1 Summary of Drug-Drug Interaction assessment between combination partners; Section 1.2.2 Overview of single agent LGX818; Section 1.2.3 Overview of single agent MEK162; Section 6.4.2 Permitted concomitant therapy requiring caution and/or action throughout the study; Table 14-22 List of inhibitors and inducers of UGT1A1 to be used with caution; Table 14-24 List of P-gp inhibitors and BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 substrates

The above sections were amended to reflect the changes in pharmacokinetic data.

Other minor changes/corrections in the protocol text, tables and footnotes were made for consistency and/or clarifications.

IRB/IEC/HA

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. In addition, if 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 amended protocol.

Amendment 2

Amendment rationale

The main purpose of this amendment is to allow patients who have already received treatment with any BRAF and/or MEK inhibitor to begin treatment in the trial with the dual therapy, LGX818 and MEK162 prior to disease progression and upon consultation between the Investigator and the Sponsor Medical Monitor. The current protocol requires that only patients who have progressed on either single-agents or double combinations of BRAF and MEK inhibitors may begin treatment with the LGX818/MEK162 combination in this study. Specifically, this amendment will allow patients who received LGX818 and/or MEK162 in other trials to enter LOGIC 2 prior to progression. In addition, the amendment will allow patients who have received other BRAF and/or MEK inhibitors, and have not progressed, but are not tolerating their treatment, to receive LGX818/MEK162 combination in this trial. The combination of a BRAF and a MEK inhibitor appears to improve efficacy and also seems to ameliorate some of the known BRAF-inhibitor related adverse events, such as skin and musculoskeletal (Flaherty, NEJM 2012). Approvals have been recently granted for the combination of the MEK inhibitor trametinib (Mekinist) and the BRAF inhibitor dabrafenib (Tafinlar) by the Therapeutic Goods Administration (TGA) in Australia (i.e. March 2014) and by the Food and Drug Administration (FDA) in the United States (i.e. Accelerated Approval in January 2014) for melanoma patients.

A second purpose of this protocol amendment is to allow patients who develop brain metastasis during Part I of the study to continue treatment on Part II of the study, at the discretion of the Investigator and the Sponsor Medical Monitor. This is because preliminary activity has been reported in brain tumors with INC280 and BGJ398. Moreover, BKM120 is known to cross the blood brain barrier, thereby ensuring brain metastasis are reached.

Moreover, DDI risk assessments as well as the list of concomitant medications for some study treatments have been updated due to emerging data. Preliminary PK data for LEE011X2105 study was based on very few patients and will be updated in the LEE011 IB when more definitive data are available. Please refer to the PK data provided in the most recent LEE011 IB. Lastly, changes and clarifications have been made following health authority requests, namely:

- Clarification that patient minimum age must be 18 years at time of informed consent signature
- The end of study definition has been expanded to clarify that the End of study (Last Patient Last Visit [LPLV]) will be upon completion of the safety follow-up, disease progression follow-up and survival follow-up (only for Part II), whichever comes later, or if the study is terminated early.
- Clarification has been provided to the exclusion criterion for Enrollment in Part 2 as the word “all” has been replaced by “any” in the following sentence: “if they meet any exclusion criteria listed above, and any of the applicable additional exclusion criteria listed below”.

- Clarification has been provided indicating that patients who become pregnant must discontinue the study (Section 7.1.5). Wording has been added to the exclusion criterion 10 to explain that total abstinence (one of the highly effective contraception methods) should be considered only "when this is in line with the preferred and usual lifestyle of the subject".
- The word "non-malignant" was deleted because it is incorrectly associated to SCC/KA skin (Squamous cell carcinoma/keratoacanthoma) lesions in Section 6.3.1, Treatment discontinuation.
- Molecular pre-screening was modified to clarify that for patients in the US, for whom BRAF status is assessed during molecular pre-screening, an FDA-approved BRAF assay must be used.

Other changes/corrections in the protocol text, tables and footnotes were made for consistency and/or clarifications:

- Additional text has been provided to allow MRI to be used
- Collection of blood for PK CCI assessments has been increased to 3ml and 10ml respectively due to requirements of the study for analysis.
- The instructions for fasting before and after drug administrations were clarified.

Other minor changes/corrections in the protocol text, tables and footnotes were made for consistency and/or clarifications.

Changes to 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 underline for insertions.

- Protocol Summary
- All changes made in the body of the protocol are reflected in the Protocol Summary. Sections 2.2; 4.1, Description of Study Design; 5.2, Inclusion Criteria; 7.1, Study flow and visit schedule; 5.3, Exclusion Criteria; 7.2.4 Biomarkers ; 7.1.3 Run-in period (only for Group B)

The above sections were updated to allow patients who had previously been treated with any BRAF and/or MEK inhibitors (included LGX818/MEK162 combination).

- Table 1-1 Summary of Drug-Drug Interaction assessments between combination partners.

LEE011X2105 PK data were deleted from this section.

- Section 4.3, Definition of the End of Study and Section 10, Statistical methods and data analysis

These sections were updated to clarify the end of study definition

- Section 5.2 Inclusion Criteria

This section has been updated to reflect the change in Inclusion Criterion #2. Inclusion criterion #10 was added to include also patients who did not progress on their prior BRAF and/or MEK inhibitor regimen.

- Section 5.3 Exclusion Criteria

This section was updated to reflect changes in requirements for patients regarding abstinence and for patients who develop brain metastases during Part I of the study.

- Clarification in the exclusion criteria for Enrollment in Part II section has also been provided. Moreover, additional exclusion criteria for LGX818/MEK162 + INC280 combination arm have been provided due to new data available in the latest IB. Section 6.3.1, Treatment discontinuation.

The word “non-malignant” was deleted.

- Section 6.1.1.1 Instructions for administration of LGX818, MEK162, INC280, BKM120, LEE011 and BGJ398.

This section was modified to clarify the fasting condition before or after drug administration. In addition, one sentence was deleted because not appropriate.

- Section 6.3.3.1.5, LGX818/MEK162 + LEE011- Main anticipated adverse events

This section was modified to add thrombocytopenia and rash.

- Section 6.2.1 Starting Dose Rationale (LGX818/MEK162 + LEE011)

LEE011X2105 PK data were deleted from this section.

- Section 6.3.3.1.5, LGX818/MEK162 + LEE011

This section was updated with additional anticipated AEs for LEE011.

- Section 6.4.2.6 Permitted concomitant therapy requiring caution and/or action during triple combination with LEE011.

This section was modified to include recent findings from other ongoing studies.

- Section 6.4.3 Prohibited concomitant therapy

This section was updated with additional prohibited concomitant therapy for LGX818+MEK162+INC280 combination.

- Appendix 7 List of prohibited and concomitant medications to be used with caution

Tables in the Appendix 7 were updated to be consistent with the new information provided in the related protocol Sections 6.4.2.6 and 6.4.3

- Section 7.1.1 Molecular pre-screening

It was modified to implement the use of FDA-approved BRAF test for US patients without documented BRAF mutation. Moreover, this section was modified to allow patients previously treated with any BRAF and/or MEK inhibitors to have their tumor samples fully characterized through a comprehensive genomic analysis at pre-screening.

- Section 7.1.2.2 Information to be collected on screening failures

This Section was modified to allow collection of LGX818/MEK162 in the eCRF for patients in group C during the genetic assessments in the screening, if they become screen failure during that time.

- Section 7.1.5 Criteria for Premature Patient Withdrawal
- This section was updated to clarify requirements for end of treatment in the event of patient pregnancy.
- Section 7.2.1 Efficacy Assessments

This section was updated to allow MRI for patients where CT imaging is more restrictive

- Sections 7.2.3 Pharmacokinetics, 7.2.4 Biomarkers

These sections were updated to reflect changes in the amount of blood collected for PK CCI CCI samples in Part I/Run-in and Part II. In addition, some minor consistency edits were also implemented in the above sections.

- Table 7-1, Visit evaluation schedule (Group A), Table 7-2, Visit evaluation schedule (Group B); Table 7-3, Part II - Visit evaluation schedule for Part II (21 day cycles), Table 7-4, Part II - Visit evaluation schedule for Part II (28 day cycles) and Table 7-5, Disease Assessment collection plan

These sections have been modified to clarify the brain CT/MRI scans requirements and that color photography is required if skin lesions are present. These were already described in Section 7.2.1, Efficacy assessments; therefore, no additional assessments were implemented with these changes. In addition, Tables 7-3 and 7-4 have been updated to delete Cycle 2 Day 8 visit because no assessments were scheduled in that visit.

- Section 7.2.2.5.2, Clinical chemistry

It was clarified that the cardiac enzyme (CK) must be analyzed at the same timepoint s as the other clinical chemistry parameters.

- Table 7-7, Local Clinical laboratory parameters collection plan.

Fasting plasma glucose and Hemoglobin HbA1c were added to Table 7-7. Moreover, amylase and LDH were added to the list of parameters to be analyzed, while LDL and BUN were removed because not informative.

- Section 8.1.1, Definitions and reporting

This section was updated to indicate that an AE is defined as “Ongoing” when not resolved by the end of the 30 day Safety Follow-up period.

- Section 10.5.4, Pharmacokinetics

Pharmacokinetic parameters will be determined for all PK-evaluable patients using either non-compartmental method(s), using Phoenix WinNonlin® Pro 6.2 (Pharsight, Mountain View, CA), **and/or** compartmental method(s).

- Section 13, References, was updated

- Appendix 5 - Phosphate-lowering therapy, was modified to be consistent with Section 6.1.2.1 Phosphate-lowering therapy for LGX818/MEK162 + BGJ398 combination

Other minor changes/corrections in the protocol text, tables and footnotes were made for consistency and/or clarifications.

IRB/IEC/HA

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. In addition, if 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 amended protocol.

Amendment 1

Amendment rationale

The reason for the current amendment is to comply with health authority request to better define some DLT criteria by excluding only Grade ≥3 cutaneous squamous cell carcinoma, rather than SCC (squamous cell carcinoma), from the DLT definition. Moreover, Grade ≥3 laboratory abnormalities, which are clearly drug related, will also be considered DLT.

In addition, minor changes for consistency and clarification were implemented.

Changes to the protocol

1. In Table 6-4, Criteria for defining dose-limiting toxicities, "Other Adverse Events" was moved from a subcategory under "General Disorders" to the first column of a new row in the table to define "any other Grade ≥3 toxicity" as a DLT.
2. In Table 6-4, Criteria for defining dose-limiting toxicities, the exclusion of cutaneous squamous cell carcinoma rather than SCC (squamous cell carcinoma) from the "Other Adverse Events" category was specified in the footnote c.
3. In Table 6-4, Criteria for defining dose-limiting toxicities, in "Other Adverse Events" exclusion of grade 3 laboratory abnormalities was removed from DLT definition. Any grade 3 laboratory abnormalities which are clearly drug related will be considered a DLT.
4. In the footnote c of the Table 6-5, Criteria for interruption and re-initiation of LGX818/MEK162 combination treatment, and Table 6-6, Criteria for interruption and re-initiation of LGX818 and MEK162 in combination with third agent (BGJ398, INC280, BKM120 or LEE011), reference to electrolyte abnormalities and study-drug related fever are removed.
5. In the footnote c of Table 6-5, Criteria for interruption and re-initiation of LGX818/MEK162 combination treatment, and Table 6-6, Criteria for interruption and re-initiation of LGX818 and MEK162 in combination with third agent (BGJ398, INC280, BKM120 or LEE011), it was specified that cutaneous squamous cell carcinoma, rather than SCC, may not require dose modification.
6. The Appendix 14.1.1, Statistical model and prior distributions, was modified to specify that the doses related to INC280 in Table 14-3 are the total daily doses (INC280 is administered BID).

IRB/IEC/HA

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. In addition, if 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 amended protocol.

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: 21 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
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	A unique identifying number assigned to each patient who enrolls in the study
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
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
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoint s

Protocol Summary

Protocol number	CLGX818X2109
Title	A phase II, multi-center, open-label study of sequential LGX818/MEK162 combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma
Brief title	Study with selected triple combinations to overcome resistance after treatment with LGX818/MEK162 in melanoma patients.
Sponsor and Clinical Phase	Array BioPharma Interventional
Investigation type	Drug
Study type	Interventional LGX818, MEK162, BKM120, BGJ398, INC280, LEE011
Purpose and rationale	The combination to be evaluated in an individual patient will be based on the molecular alteration(s) detected at progression after LGX818/MEK162 combination treatment
Primary Objective(s)	The primary objective for this study is to assess the anti-tumor activity of LGX818/MEK162 in combination with third targeted agents after progression on LGX818/MEK162 combination therapy.
Secondary Objectives	To estimate the MTD/RP2D of triple combinations after progression on LGX818/MEK162 therapy To characterize the safety and tolerability of LGX818/MEK162 in combination with targeted agents To further assess anti-tumor activity of LGX818/MEK162 combination, and in combination with targeted agents after progression on LGX818/MEK162 combination To characterize genomic alterations in tumor tissue at baseline and at tumor progression. To determine the PK profiles of LGX818,MEK162 and the third agents when given in combination and to assess drug-drug interaction
Study design	This study consists of two parts: in Part I, naïve patients to selective BRAF and MEK inhibitors will be treated with the LGX818/MEK162 combination until disease progression (as defined per RECIST v1.1). Based on the genetic analysis of a tumor biopsy obtained at that time, patients will enter Part II of the study for tailored combination treatment in one of four arms of LGX818/MEK162 + either BKM120, BGJ398, INC280 or LEE011. **Note: As of Protocol Amendment 06, enrollment to the BKM120-, BGJ398- and INC280-containing arms in Part II is closed. As of Amendment 07, enrollment to the LEE011-containing arm in Part II is closed.**
Population	This study will enroll approximately 140 patients with BRAF mutant locally advanced unresectable or metastatic melanoma

Inclusion criteria	• Patients (males and females) age ≥ 18 years • Histologically confirmed diagnosis of unresectable stage III or metastatic melanoma (stage IIIC to IV per American Joint Committee on Cancer [AJCC]) • Documented evidence of BRAF V600 mutation. • Newly obtained tumor biopsy at baseline, and patient agrees to a mandatory biopsy at the time of progression, if not medically contraindicated. • Evidence of measurable disease, as determined by RECIST v1.1.
Inclusion criteria (for triple combinations)	Progressive disease following prior treatment with LGX818/MEK162 combination. A pre-LGX818/MEK162 combination archival tumor sample must be available

Exclusion criteria	Symptomatic or untreated leptomeningeal disease.
	• Symptomatic brain metastases. Patients previously treated or untreated for brain metastases that are asymptomatic in the absence of corticosteroid therapy or on a stable dose of steroids for four weeks are allowed to enroll.
	Brain metastases must be stable at least 4 weeks with verification by imaging (e.g. brain MRI completed at screening demonstrating no current evidence of progressive brain metastases).
	• Patients are not permitted to receive enzyme inducing anti-epileptic drugs.
	• Known acute or chronic pancreatitis.
	• History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes);
	• Clinically significant cardiac disease including any of the following:
	  • CHF requiring treatment (NYH grade ≥ 2),
	  • LVEF < 50% as determined by MUGA scan or ECHO
	  • History or presence of clinically significant ventricular arrhythmias or atrial fibrillation
	  • Clinically significant resting bradycardia
	  • Unstable angina pectoris ≤ 3 months prior to starting study drug
	  • Acute Myocardial Infarction (AMI) ≤ 3 months prior to starting study drug,
	  • QTcF > 480 msec.
	Patients with any of the following laboratory values at Screening/baseline:
	• Absolute neutrophil count (ANC) <1,500/mm3 [1.5 x 109/L]
	• Platelets < 100,000/mm3 [100 x 109/L]
	• Hemoglobin < 9.0 g/dL
	• Serum creatinine >1.5 x ULN or calculated or directly measured CrCl < 50% LLN (lower limit of normal)
	• Serum total bilirubin >1.5 x ULN
	• AST/SGOT or ALT/SGPT > 2.5 x ULN, or > 5 x ULN if liver metastases are present

Additional Exclusion criteria (for triple combinations)	Patients who have developed brain metastases during Part I of the study may continue to Part II upon discussion with the Sponsor Medical Monitor. The brain metastasis must be either asymptomatic or treated and stable for at least 4 weeks and on a stable or tapering dose of steroids for at least 2 weeks. **Note: As of Protocol Amendment 06, enrollment to the BKM120-, BGJ398- and INC280-containing arms in Part II is closed. As of Amendment 07, enrollment to the LEE011-containing arm in Part II is closed.** **LGX818/MEK162/BKM120**: • Patients with fasting glucose > 120 mg/dL or 6.7 mmol/L, and HbA1c > 8 %. • Patient has any of the following mood disorders as judged by the Investigator or a Psychiatrist: • Patient has a score ≥ 12 on the PHQ-9 questionnaire • Patient has ≥ CTCAE grade 3 anxiety **LGX818/MEK162/BGJ398**: • History and/or current evidence of significant ectopic mineralization/ calcification with the exception of calcified lymph nodes and asymptomatic vascular calcification. • Current evidence of corneal disorder/ keratopathy incl. but not limited to bullous/ band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis etc., confirmed by ophthalmologic examination **LGX818/MEK162/LEE011**: • Patients with uncontrolled hypertension (please refer to WHO-ISH guidelines) are excluded from study. • QTcF ≥450 ms • Mean resting heart rate < 50 or >90 bpm • Patient with the following laboratory abnormalities unless corrected to within normal limits with supplements before the first dose of study medication: sodium, potassium, magnesium, total calcium (corrected for serum albumin), and phosphorus • Total bilirubin ≥ ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN. • Aspartate transaminase (AST) ≥ 2.5 × ULN, ≥ 5 × ULN in patients with liver metastasis • Alanine transaminase (ALT) ≥ 2.5 × ULN, ≥ 5 × ULN in patients with liver metastasis • Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome or any of the following before the first dose of the triple combination: • Risk factors for TdP including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia • Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be

	discontinued or replaced by safe alternative medication (e.g., within 5 half-lives or 7 days prior to starting study drug) • Inability to determine the QTcF interval. • Any heart disease that requires the use of a cardiac pacemaker or implantable cardioverter defibrillator ≤ 3 months prior to starting study drug. • Unstable atrial fibrillation (ventricular response >100 bpm). • Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II, and third degree AV block) • Systolic blood pressure (SBP) > 160 or < 90 mmHg • Patients who are currently receiving treatment with agents that are known to cause QTc prolongation in humans. See LEE011 Investigators Brochure for a complete list of agents that are known to cause QTc prolongation in humans. • Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2 according to the Modification of Diet in Renal Disease (MDRD) formula. • Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to Cycle 1 Day 1: • Concomitant medications, herbal supplements, and/or fruits (e.g., grapefruit, pummelos, star fruit, Seville oranges) and their juices that are strong inducers or inhibitors of CYP3A4/5 • Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5. • History of documented myocardial infarction (MI), angina pectoris, symptomatic pericarditis, or coronary artery bypass graft (CABG) within 6 months prior to study entry • Documented cardiomyopathy • Current evidence of brain metastasis or brain metastasis detected by mandatory CT/MRI at screening • PT/INR or aPTT > 1.5xULN **LGX818/MEK162/INC280**: • Patients unable to stop known CYP3A4, CYP1A2, CYP2C8 or CYP2C19 substrates with narrow therapeutic index. These medications should be stopped 7 days prior to first dose of study treatment (refer to Section 6.4.3 and Appendix 7 for prohibited medications for this combination treatment). • Patients receiving treatment with long-acting proton pump inhibitors, and unable to discontinue them 3 days prior to the start of study treatment and during the course of the study. • Asymptomatic serum amylase > CTCAE Grade 2 (1.5-2.0xULN). Patients with Grade 1 or Grade 2 serum amylase at the beginning of the study must be confirmed to have no signs or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.) • Serum lipase > ULN

Investigational and reference therapy	LGX818/MEK162 LGX818/MEK162 + BKM120 LGX818/MEK162 + BGJ398 LGX818/MEK162 + INC280 LGX818/MEK162 + LEE011
Efficacy assessments	Tumor response per RECIST v1.1: Overall Response Rate (ORR) (Part II), Progression Free Survival (PFS) (Part I and II), Duration of Response (DOR) (Part I and II) and Overall Survival (OS) (Part II), Time to Response (TTR) (Part I and II), Disease Control Rate (DCR) (Part I and II). As of Protocol Version 7, the Sponsor recommends assessing efficacy every 8 to 12 weeks or per institution local standard-of-care clinical practice.
Safety assessments	Physical examinations Vital signs Laboratory evaluations Cardiac assessments Dermatologic evaluations Ophthalmologic evaluations As of Protocol Version 7, for patients who have been on treatment in Part I for ≥ 36 months, safety evaluations should occur in accordance with local standard-of-care clinical practice and may receive treatment until treatment discontinuation criteria are met. It is recommended that safety evaluations occur approximately every 4 weeks, unless otherwise specified. Safety should be monitored by assessing physical examination, hematology, chemistry laboratory testing and other pertinent testing as required as part of the safety profile of the compound (dermatological examinations, ophthalmic exams, cardiac profiles) until discontinuation. Adverse events should be reviewed at every visit. Investigators will be required to record all Grade 3 or 4 AEs, including SAEs, in the clinical database. All SAEs are to be reported to the Sponsor or designee using the SAE form.
Other assessments	LGX818 and MEK162, or BKM120, or BGJ398, or INC280, or LEE011 pharmacokinetic evaluations Baseline molecular status in tumor tissue of potential predictive markers Changes from baseline in pharmacodynamic markers in tumor tissue Gene alteration/expression profiles (e.g. baseline, progression) in tumor tissue

Data analysis	The primary objective of the study is to assess the anti-tumor activity of LGX818/MEK162/LEE011 after progression on LGX818/MEK162 combination therapy. For patients receiving other triple combinations, an initial assessment of the anti-tumor activity of LGX818/MEK162 in combination with targeted agents after progression on LGX818/MEK162 combination therapy. Best Overall Response (BOR) assessed per RECIST v1.1 during Part II will be used to evaluate the tumor response in terms of Overall Response Rate (ORR) for combinations of LGX818, MEK162 and the third agents. This will be based on investigator-assessed tumor evaluations per RECIST v1.1 MTD/RP2D of LGX818/MEK162 in combination with targeted agents after progression on LGX818/MEK162 therapy will be assessed. Estimation of the MTD of the treatment will be based upon the estimation of the probability of DLT in Cycle 1 for patients in the dose-determining set (DDS), using an adaptive BLRM guided by the EWOC principle Safety and tolerability of LGX818/MEK162 and their combination with third target agents will be assessed for incidence and severity of adverse drug reactions and serious adverse drug reactions (as assessed by CTCAE Version 4.03), changes in hematology and chemistry values, physical examinations, vital signs, electrocardiogram, cardiac monitoring, ophthalmological and dermatological examinations. For Part I, the Full Analysis Set (FAS) consists of all patients who received at least one dose (partial or full) of LGX818 or MEK162. For Part II, the FAS consists of all patients who have received at least one dose of LGX818 or MEK162 or the assigned third agent following the assignment of the triple combination treatment. The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable pharmacokinetic (PK) data
Key words	BRAF inhibitor; RAF kinase inhibitor; LGX818; MEK162; Mek Inhibitor; BKM120; PI3K inhibitor; BGJ398; FGFR inhibitor; INC280; c-Met inhibitor; LEE011; CDK4/6 inhibitor; metastatic melanoma; BRAF; V600

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Melanoma

1.1.1.1 Drug resistance in melanoma

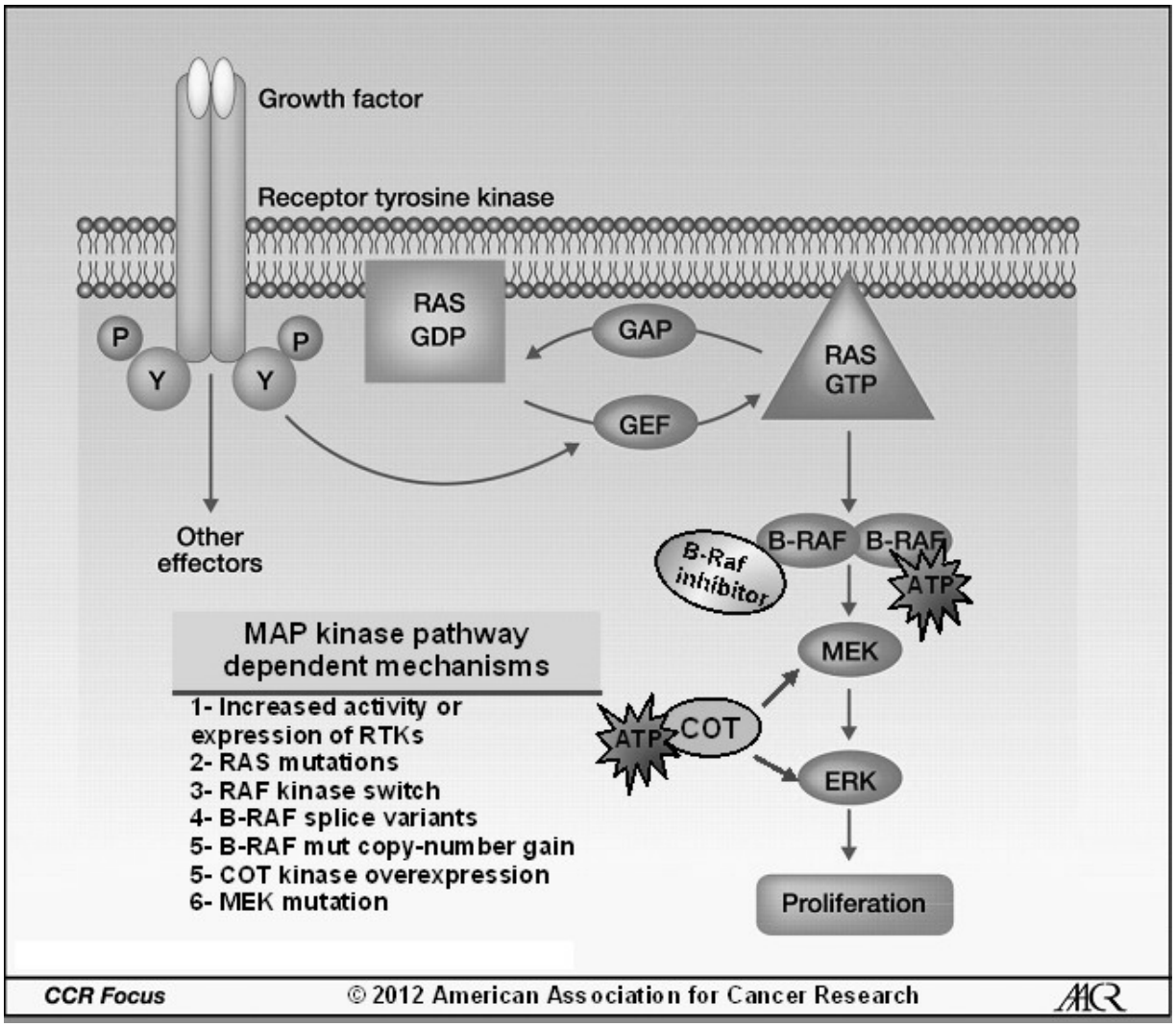
Melanoma is one of the most aggressive human malignancies. Its incidence has rapidly increased throughout the world in the last few decades (in the order of 3-7% per year for fair skin Caucasian population); (Ferlay et al 2010), faster than that of all solid tumors, constituting a significant and growing health burden. It is estimated that 76,250 men and women will be diagnosed with melanoma of the skin in 2012 in the United States alone (Siegel et al 2012). Overall incidence rates in USA have increased for both men and women, whereas death rates have increased in men (+3.3% 2001-2006) but have decreased in women (-0.6% 1992-2006) (annual percent change in age–standardized rates). Similarly, the number of new skin melanomas in the world, for all ages, in 2010 was 208,251 men and women (Jemal 2011; Ferlay 2010). Although the majority of early stage patients can be treated with surgical resection, and have excellent survival rates (approximately 90% at 5 years), many will develop disseminated disease. The prognosis for patients with distant metastasis is, by contrast, very poor with survival rates ranging from 6.7% to 8% at 5 years, and a median survival of 6 to 9 months (Jemal et al 2009).

Currently, the existing therapeutic options for patients with melanoma comprise of 6 therapies approved by the Food and Drug Administration (FDA): dacarbazine (DTIC), interleukin-2 (IL-2), ipilimumab (anti-CTLA-4), vemurafenib and dabrafenib (BRAF inhibitors) as well as trametinib (MEK inhibitor). Single agent (s.a.) therapy with dacarbazine (DTIC), a cytotoxic chemotherapy, is generally well tolerated, but results in an overall response rate of only 10% and no survival benefit for patients with metastatic disease (median PFS of 2-3 months and OS of 6-10 months) (Anderson 1995, Serrone 2000, Chapman 1999). Ipilimumab (Yervoy® Bristol-Myers Squibb) was approved by the FDA (25 March 2011) for the treatment of unresectable or metastatic melanoma. The selective BRAF inhibitors vemurafenib (Zelboraf®, Roche) and dabrafenib (Tafinlar, GSK), were recently approved for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation. The selective MEK inhibitor trametinib (Mekinist, GSK) was recently approved for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E and V600K mutations.

In addition to approved therapies, the concept of a simultaneous, dual, vertical pathway inhibition of the RAF/MEK/ERK pathway to prevent the emergence of resistance to single agent small molecule inhibitor therapy (Emery 2009, Fremin 2010) is currently being explored by the combination treatment of a selective BRAF- and a MEK1/2-inhibitor in cancer patients with advanced BRAF mutation-positive tumor types. Results of the first phase I/II study Study NCT01072175 have been recently reported (Flaherty et al 2012a). A total of 247 patients with metastatic melanoma and BRAF V600 mutations were treated with dabrafenib +/- trametinib, and in the phase II part, 162 patients were randomly assigned to receive dabrafenib (150 mg) plus trametinib (1 or 2 mg) or dabrafenib monotherapy (150mg). ORR was 50 %, 76% and

54%, with a median PFS of 9.2 months, 9.4 and 5.8 months for dabrafenib plus trametinib (150/1, 150/2) and dabrafenib monotherapy respectively. Results from theNCT01072175 study also show that a selective BRAF inhibitor combines safely with a MEK inhibitor with a decreased occurrence of cutaneous side effect, such as rash and squamous cell carcinoma (SCC) of the skin in comparison to single agent therapy (Flaherty et al 2012a).

Figure 1-1 Main mechanisms of resistance to BRAF inhibitors



Adapted from Alcalá et al (2012).

Despite the demonstrated clinical efficacy of BRAF and MEK inhibitors, in most cases tumors become resistant to treatment. Although there are multiple paths to resistance, the main mechanisms result in reactivation of the RAF/MEK/ERK signaling pathway in the presence of an inhibitor (see Figure 1-1). This reactivation can occur via (i) increased activity of receptor tyrosine kinases (RTKs) via gene amplification, and overexpression and/or ligand production (Straussman 2012, Villanueva 2010, Wilson 2012), (ii) acquisition of mutations in the NRAS and MEK1 genes, (iii) bypass of BRAF via overexpression of kinases such as COT and RAF-1 (CRAF), (iv) expression of splice variants of the mutant BRAF allele, and (v) increased

expression of the mutant BRAF allele due to, e.g. gene amplification (Emery 2009, Johannessen 2010, Nazarian 2010, Poulikakos 2011, Shi 2012, Trunzer 2013). Consistent with the observation that RAF/MEK/ERK pathway re-activation underlies the majority of cases of BRAF inhibitor resistance, combining selective RAF and MEK inhibitors confers a more durable response than do single agent treatments, although most patients ultimately progression in this case as well. Although the mechanisms of resistance to combined inhibitor treatment are not well understood at present time, initial reports suggest that many of the same mechanisms that confer resistance to single agent RAF inhibitors, such as RTK activation and mutations in, e.g. MEK1/2 and NRAS, also confer resistance to RAF/MEK inhibitor combinations (Abel 2013, Wagle 2013, Villanueva 2013). In addition, activation of survival pathways such as the PIK3Cα signaling system that are distinct from the MAPK pathway, either via activation RTKs such as PDGFR-β and IGF-1R or loss of the PTEN gene have also been demonstrated to confer resistance to BRAF inhibitors, and by extension are likely to promote resistance to combinations of BRAF and MEK inhibitors as well (Johannessen 2010, Nazarian 2010, Villanueva 2010, Wilson 2012). The findings described above highlight the importance of identifying mechanisms of resistance in real time in order to initiate rational combination therapy soon after progression. By comparing the set of genetic alterations present in a progressing tumor at the time of relapse to the alterations present in the tumor prior to treatment, it should be possible to identify the likely molecular mechanisms underlying resistance. This comparison could then be used to direct the selection of a drug combination therapy for an individual patient that is most likely to overcome resistance. In this CLGX818X2109 study, a rational combination treatment approach informed by comparing the genetic profiles of relapsed and treatment naive tumors will be taken to expand and improve the therapeutic options for patients with BRAF-mutant advanced or metastatic melanoma that have very poor prognosis after the development of resistance to combined BRAF/MEK inhibitor treatment.

1.2 Introduction to investigational treatment(s)

1.2.1 Overview of combination treatments

1.2.1.1 Non-clinical experience

1.2.1.1.1 LGX818/MEK162

Re-activation of MAPK signaling in the presence of inhibitor occurs in the majority of cases of acquired resistance to BRAF inhibitors. Often, this re-activation is the direct result of molecular alterations in genes that encode components of the MAPK pathway such as NRAS, BRAF, and MEK1 (Nazarian 2010, Poulikakos 2011, Shi 2012, Wagle 2011). Clinical data for the dabrafenib/trametinib as well as the LGX818/MEK162 combination prove the hypothesis, that inhibition of more distal components of the MAPK pathway provides at least a partial benefit in treating BRAF mutant melanomas. In vitro, the combination of LGX818 and MEK162 either additively or synergistically inhibited the proliferation of a set of 16 BRAF mutant melanoma-derived cell line models (Report RD-2011-50576). In vivo, this combination significantly increased the conditional survival of mice implanted with a BRAF-mutant primary human melanoma xenograft. Although most single agents, and all combination treatments effectively inhibited tumor growth, increased survival resulted from reductions in the overall rates (and in

some cases complete prevention) of the emergence of resistant tumors in the combination relative to the single agent treatment groups (Data on file).

LGX818 (encorafenib, BRAFTOVI®) in combination with MEK162 (binimetinib, MEKTOVI®), has received marketing approval in several jurisdictions for the treatment of patients with *BRAF*-mutant melanoma, based on results from a Phase 3 clinical trial CMEK162B2301 (COLUMBUS).

For further details on non-clinical experiences, refer to the current [LGX818 and MEK162 Investigator's Brochures]

1.2.1.1.2 LGX818/MEK162 + BKM120

Signaling through the PIK3C pathway, induced via RTK activation, PTEN loss, or activating alleles of PIK3Cα may also contribute to both intrinsic and acquired resistance to BRAF inhibitors and combinations of BRAF and MEK1/2 inhibitors in BRAF-mutant melanoma (Hodis 2012, Paraiso 2011, Villanueva 2010, Villanueva 2013). This observation provides a rationale for pairing RAF inhibitors and RAF/MEK inhibitor combinations with PIK3C inhibitors in some instances of clinical resistance. The effects of combining LGX818 with the pan-PIK3C inhibitor BKM120 have been measured in a set of BRAF-mutant melanoma cell lines in vitro. In these studies the combination inhibited proliferation in a moderately synergistic manner in a subset of cell lines (data on file). In vivo, this combination strongly inhibited the growth of the A-375 melanoma tumors implanted orthotopically into the brain of immunocompromised mice. Moreover, the combination improved the conditional survival of mice relative to comparable single agent treatments (data on file).

Recently, (Villanueva et al 2013) reported that addition of a mTOR/PI3K inhibitor was able to overcome resistance to BRAF/MEKi combination in vivo. These data suggest that blockading PIK3CA-pathway signaling in combination with MAPK-pathway inhibition, either via single agent BRAF or combined BRAF/MEK1/2 inhibition may provide clinical benefit.

For further details on non-clinical experiences, refer to the current [LGX818 and BKM120 Investigator's Brochures]

1.2.1.1.3 LGX818/MEK162 + INC280

Stimulation of the MAPK and/or the PIK3C pathways via RTK activation has been shown to confer resistance to BRAF inhibitors in melanoma-derived cell lines in vitro, and has been linked to resistance in the clinic (Nazarian 2010, Straussman 2012, Vergani 2011, Villanueva 2010, Wilson 2012). In particular, activation of the c-MET and FGFR family of RTKs have proven to robustly promote resistance to BRAF inhibitors in several melanoma models in vitro (Straussman 2012, Wilson 2012) (Novartis data on file). In addition to conferring resistance to RAF inhibitors, activation of c-MET by its cognate ligand HGF has also been demonstrated to confer resistance to a combination of the RAF inhibitor LGX818 and MEK1/2 inhibitor MEK162 in BRAFV600E mutant cell lines in vitro. Critically, in cell lines rendered resistant to LGX818 and the LGX818/MEK162 combination by exogenously added HGF, the addition of the c-MET inhibitor INC280 completely restored sensitivity to LGX818 (Novartis data on file).

For further details on non-clinical experiences, refer to the current [LGX818 and MEK162 Investigator's Brochures]

1.2.1.1.4 LGX818/MEK162 + BGJ398

Ligand mediated activation of FGFRs can promote resistance to RAF inhibitors (Straussman 2012, Wilson 2012, RD-2013-50040). Moreover, FGFR activation is also able to confer resistance to the combination of LGX818 and MEK162 in BRAFV600E mutant models of melanoma (data on file). However, FGFR-activation-mediated resistance to both LGX818 and the combination of LGX818 and MEK162 could be prevented via addition of the selective FGFR inhibitor BGJ398, which does not affect the growth of BRAFV600E cell lines as a single agent. These data suggest that BGJ398 could be useful in instances of FGFR-mediated resistance to combined RAF and MEK inhibition in the clinic.

For further details on non-clinical experiences, refer to the current [LGX818, MEK162 and BGJ398 Investigator's Brochures]

1.2.1.1.5 LGX818/MEK162 + LEE011

Several lines of evidence suggest that targeting the CDK4 and CDK6 kinases may be an effective means to combat resistance to RAF inhibitors and/or combinations of RAF and MEK inhibitors. First, the CyclinD/CDK4/6 complex represents a key downstream convergence point for many mitogenic signaling pathways including the RAS/RAF/MEK/ERK pathway. Elevated levels of cyclinD induced by activated signaling through this pathway serves to increase CyclinD/CDK4/6 activity and in doing so promotes transition from the G1 to S phases of the cell cycle as this complex is responsible for phosphorylating, and thereby inactivating, the tumor suppressor pRB. The majority of cases of clinical resistance to RAF inhibitors result in reactivated signaling and by extension re-establish cell proliferation via the CyclinD/CDK4/6/pRB axis. Second, CDK4/6 inhibitors have been demonstrated to effectively combine with inhibitors of RAF and MEK in preclinical models of melanoma that harbor BRAF and NRAS mutation, respectively, suggesting that such combinations behave in a manner akin to "dual vertical" pathway inhibition (Kwong et al 2012, RD-2012-50370, RD-2013-50169). Third, co-overexpression of the CDK4 and CCND1 genes is sufficient to confer resistance to BRAF inhibitors in BRAF-mutant cell lines in vitro (Smalley et al 2009).

Combinations between LGX818, MEK162 and LEE011 have been examined in a variety of $BRAF^{V600E}$ melanoma cell lines including models engineered to express alleles of the NRAS, BRAF and MEK1 genes, known to promote resistance to RAF inhibitors in the clinic. In both the parental and engineered models, the addition of LEE011 to the LGX818/MEK162 combination resulted in either additional synergistic or additive anti-proliferative effects. Collectively these data suggest that the CDK4/6 inhibitor LEE011 may be an effective means to combat resistance that emerges against the LGX818/ MEK162 as a result of pathway re-activation (RD-2013-50245).

For further details on non-clinical experiences, refer to the current [LGX818, MEK162 and LEE011 Investigator's Brochures]

1.2.1.2 Clinical experience

Clinical studies with combinations of MEK162

The experience with MEK162 in cancer patients in combination studies comprises 8 ongoing Phase I studies with overall 216 patients as of 7 January 2013. MEK162 is combined with a PI3K inhibitor in [CMEK162X2101] (MEK162 and BKM120), and it is combined with RAF inhibitors in [CMEK162X2110] (MEK162 and LGX818). In addition, as of October 2013 MEK162 is combined with LEE011 (inhibitor of CDK4/6), and enrolled 7 patients in [CMEK162X2114].

In combination studies, the most frequently reported AEs suspected to be related to study drug were diarrhea, CK elevation, dermatitis acneiform/rash, nausea/vomiting and fatigue.

For further details, please refer to the current [MEK162 Investigator's Brochure].

1.2.1.2.1 LGX818 + MEK162 and LGX818 + MEK162 + LEE011

The ongoing clinical study [CMEK162X2110] is an open label, dose finding, phase Ib/II study to determine the maximum tolerated dose (MTD) and/or recommended dose for Phase II (RP2D) of LGX818 in combination with MEK162 in patients with locally advanced or metastatic melanoma, mCRC or any other solid tumor positive for a V600 BRAF mutation.

As of March 8, 2013, enrolled patients were treated with LGX818 QD + MEK162 BID at the following dose levels (DLs): 50 mg + 45mg, 100 mg + 45 mg, 200 mg + 45 mg, 400 mg + 45 mg, 450 mg + 45 mg, and 600 mg + 45 mg (Kefford et al 2013).

At the time of data cutoff, 30 patients with BRAF V600 mutant tumors have been enrolled across 6 DLs. There were no dose-limiting toxicities (DLTs) in the first 5 DLs. One DLT was reported at the 600 mg + 45 mg DL (grade 3 alanine aminotransferase (ALT) elevation).

The MTD has not yet been determined in this study and the dose of 450mg QD LGX818 + 45mg BID MEK162 has been selected for further development.

The LGX818 + MEK162 + LEE011 arm has been recently added to this study and started enrolling patients.

A Phase 3 study comparing MEK162/LGX818 to LGX818 or Vemurafenib single agent has started in October 2013.

Safety

The combination of LGX818 and MEK162 in [CMEK162X2110] was well tolerated with no substantial increase in adverse events (AEs) for the combination vs single-agent therapy. The combination may decrease the severity and frequency of some on-target AEs common with BRAFi monotherapy including cutaneous toxicities (no events of HFSR, hyperkeratosis, and KA/SCC), myalgia, and arthralgia. No febrile or photosensitivity events have been reported to date. The most common AEs were grade 1/2 gastrointestinal toxicities, visual disturbances, headache, and fatigue. Five patients (16.7%) had grade 3 AEs suspected to be treatment related (2 with transaminase increases, 2 with lipase increase, 1 with retinal vein occlusion, and 1 with maculopapular rash).

In the on-going [CMEK162X2110] study, preliminary PK results indicated that there was no pharmacokinetic drug-drug interaction between LGX818 and MEK162. The PK exposures of LGX818 and MEK162 were similar to those observed in the corresponding monotherapy studies (see Section 1.2.3.2.1)

Efficacy

In [CMEK162X2110] the disease control rate was 100% for BRAFi naïve and 64% for BRAFi pretreated melanoma patients, 33% for mCRC (metastatic colorectal cancer) patients, and 100% for PTC (papillary thyroid carcinomas) patients. The overall response rate was 88% for BRAFi naïve and 18% for BRAFi pretreated melanoma patients and 67% for PTC patients.

For further details on clinical experience, refer to the current [MEK162 Investigator's Brochure].

1.2.1.2.2 BKM120 + MEK162

Study [CMEK162X2101] is a Phase Ib, open-label, multi-center, dose escalation and expansion study of an orally administered combination of MEK162 plus BKM120 in adult patients with selected advanced solid tumors. The study is still ongoing. As of 07 January 2013, 48 patients had received at least one dose of MEK162 in combination with BKM120. As of the data-cutoff date, 40 patients had discontinued from the study and 8 were still ongoing in the dose escalation phase. Seven dose levels were evaluated. The most frequently reported treatment-related AEs regardless of Grade occurring in ≥ 10% of patients were CK elevation (56%), diarrhea (54%) and AST elevation (50%). Twenty-five (25) out of 48 enrolled patients (52%) experienced at least one CTCAE Grade 3-4 AE suspected to be treatment related. The most common treatment-related CTCAE Grade 3-4 AEs were CK elevation (19%) and maculo-papular rash (10%). Thirty-five out of 48 enrolled patients (73%) experienced one or more AEs requiring a dose interruption and/or reduction. Fifteen out of 48 enrolled patients (31%) experienced one or more AEs leading to discontinuation from the study.

For further details on clinical experience, refer to the current [MEK162 Investigator's Brochure].

1.2.1.2.3 MEK162 + LEE011

[CMEK162X2114] is a phase Ib/II, multicenter dose escalation study of LEE011 in combination with MEK162 in adult patients with NRAS mutant melanoma. As of October 2013, 7 patients were enrolled and DLTs include CTCAE Grade 3 elevated creatinine and a CTCAE Grade 4 CPK elevation.

For further details on clinical experience, refer to the current [MEK162 and LEE011 Investigator's Brochures].

Clinical studies with combinations of LGX818

1.2.1.2.4 LGX818 + LEE011

[CLEE011X2105] is a phase Ib dose escalation study to estimate the MTD and/or RP2D for the combination of LEE011 and LGX818, followed by a Phase II study to assess the clinical

efficacy and to further evaluate the safety of the combination in patients with locally advanced or metastatic BRAF mutant melanoma. As of October 2013, 6 patients were enrolled; in two patients the following DLTs were observed: CTCAE Grade 3 myalgia and CTCAE Grade 3 acute liver injury. In another patient CTCAE Grade 2 elevated creatinine was reported.

For further details on clinical experience, refer to the current [LGX818 and LEE011 Investigator's Brochures]

1.2.1.2.5 LGX818 in combination with MEK162, BKM120, BGJ398, INC280 or LEE011

[CLGX818X2102] is a phase II, two part multi-center, open-label study in adult patients with locally advanced unresectable or metastatic BRAF V600 melanoma. Upon progression on single agent LGX818 in Part I of the study, patients are assigned to a combination treatment in Part II. Based on targeted sequencing of a tumor biopsy obtained at progression, patients are assigned to one of five combination arms: LGX818 + MEK162, BKM120, BGJ398, INC280, or LEE011 to assess the clinical efficacy and to further evaluate the safety of the drug combinations. As of 14th of November, this study has started enrolling patients.

For further details on clinical experience, refer to the current [LGX818 Investigator's Brochure]

1.2.1.3 Assessment of pharmacokinetic drug-drug interaction DDI

Brief summaries of the potential drug-drug interactions between different study drug combinations are listed in Table 1-1.

The single agent non clinical and clinical pharmacokinetics data are described in Section 1.2.

Table 1-1 Summary of drug-drug interaction assessment between combination partners

Combination	Potential Perpetrators	Potential Victims	Assessments
LGX818+MEK162	LGX818 is a CYP3A4 inducer.	LGX818 is a CYP3A4 substrate	No significant DDI observed so far in the LGX818 and MEK162 combination study MEK162X2110.
LGX818+MEK162+BKM120	LGX818 is a CYP3A4 inducer.	LGX818 and BKM120 are CYP3A4 substrates	Simcyp simulation predicted minimal DDI between LGX818 and BKM120. In the ongoing combination study CMEK162X2101, preliminary data showed no effect of BKM120 on the PK of MEK162 and its metabolite; mean Cmax and AUC of BKM120 were reduced by more than 50% when given in combination with MEK162
LGX818+ MEK162+BGJ398	BGJ398 is a TDI (time dependent inhibitor) of CYP3A4. LGX818 is a CYP3A4 inducer.	LGX818 and BGJ398 are CYP3A4 substrates	Simcyp simulation predicted minimal change in LGX818 exposure and reduced BGJ398 exposure. Change in the PK of MEK162 and its metabolite is expected to be minimal.
LGX818+ MEK162+INC280	INC280 is a strong TDI of CYP3A4. LGX818 is a CYP3A4 inducer.	LGX818 and INC280 are CYP3A4 substrates	Simcyp simulation predicted increased LGX818 exposure and reduced INC280 exposure. Change in the PK of MEK162 and its metabolite is expected to be minimal.
LGX818+ MEK162+LEE011	LEE011 is a TDI of CYP3A4. LGX818 is a CYP3A4 inducer.	LGX818 and LEE011 are CYP3A4 substrates	Simcyp simulation predicted increased LGX818 exposure and reduced LEE011 exposure. Change in the PK of MEK162 and its metabolite is expected to be minimal.

1.2.2 Overview of single agent LGX818

1.2.2.1 Non-clinical experience

1.2.2.1.1 Non-clinical pharmacodynamics

LGX818 is a highly selective ATP-competitive small molecule RAF kinase inhibitor, which suppresses the RAF/MEK/ERK pathway in tumor cells expressing BRAFV600E.

Similar to the *in vitro* profile of LGX818, its antitumor activity was restricted to tumors expressing BRAFV600E, while there was no anti-tumor effect in xenograft models expressing wild-type BRAF. Preclinical *in vivo* data suggest that LGX818 has a wide therapeutic index and that regression of BRAFV600E human melanoma tumor xenografts is associated with a strong and sustained inhibition of the RAF/MEK/ERK pathway.

For further details on pharmacodynamics, please refer to the current [LGX818 Investigator's Brochure].

1.2.2.1.2 Non-clinical pharmacokinetics and metabolism

The oral bioavailability (F) of encorafenib was ~40 to~50% in the mouse, rat, and dog. In the monkey ADME study F was low (22%). Encorafenib showed low plasma clearance (CL) in the rat and mouse and a moderate to high plasma clearance in the monkey and dog. The estimated volume of distribution at steady state (Vss) was low in the rodents and moderate in the dog and monkey. In the monkey 13-week toxicity study, encorafenib increased proportionally with dose and no accumulation upon multiple dosing.

Encorafenib is a substrate of P-glycoprotein (P-gp) with a high apparent passive permeability. Binding to human plasma proteins was ~86%.

Distribution into rat tissues was rapid. There was no distribution to the central nervous system (brain and spinal cord) and no retention in the melanin-rich tissues. For all species investigated, monohydroxylation, N-dealkylation and subsequent glucuronidation represented the major metabolic pathways. Glucuronidation, both direct and indirect, occurred more readily in human than in other species. Encorafenib is metabolized by CYP3A4, CYP2C19 and CYP2D6. CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%), followed by CYP2C19 and CYP2D6 (~16.0% and 0.71%, respectively).

The predominant route of excretion of [^{14}C] encorafenib in monkeys was via fecal excretion while the urinary excretion was a minor route of elimination. Encorafenib is predominantly excreted as metabolites.

In vitro experiments indicate that encorafenib is a relatively potent reversible inhibitor of UGT1A1, CYP2B6, CYP2C9, and CYP3A4/5, and also a time-dependent inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Finally, encorafenib was found to be a weak inhibitor of BCRP, and a potent inhibitor of renal transporters OCT2, OAT1, OAT3 and hepatic transporters OCT1,OATP1B1 and OATP1B3.

For further details on non-clinical pharmacokinetics and metabolism, please refer to the current [LGX818 Investigator's Brochure].

1.2.2.1.3 Safety pharmacology and toxicology

LGX818 was evaluated in rats and Cynomolgus monkeys in toxicology studies ranging from 1 to 4 weeks in duration. Overall, LGX818 was well tolerated at doses at which tumor regression was observed. Significant toxicities were mainly observed in the female rat at the highest dose of 400 mg/kg/day, a dose well above the MTD. Other findings included hyperplasia and

hyperkeratosis in the skin (plantar surface of feet) and non-glandular stomach in rat, which was apparent at all dose levels and presented with recovery 4 weeks after stopping treatment, and an absence of the later stages of spermatid maturation in the male rats. In the 13-week monkey toxicology study (No. 1370471) with LGX818, two monkeys treated at a dose of 60mg/kg/day presented retinal changes at the assessment on week 12. These non-clinical findings suggest a potential risk of retinal changes with LGX818. Preclinical cardiovascular safety pharmacology data did not indicate a clinical risk for QTc prolongation based on the findings of the hERG assay and ECG evaluation in the GLP 4-week monkey study. Also, there were no clinical signs in the 4-week GLP rat and monkey studies that would indicate an effect on the central nervous system or respiratory system.

No teratogenicity studies have been completed to date. There were no effects in a rat safety pharmacology study on the CNS or respiratory system.

For further details on non-clinical pharmacology and toxicology, please refer to the current [LGX818 Investigator's Brochure].

1.2.2.1.4 Genotoxicity study

For details on non-clinical pharmacology and toxicology, please refer to the current [LGX818 Investigator's Brochure].

1.2.2.2 Clinical experience

1.2.2.2.1 Clinical safety and efficacy

As of 11 May 2019, a total of 1549 healthy subjects and patients had received LGX818 either as a single agent or in combination with other targeted agents. These patients constitute the LGX818 safety population, which includes 97 healthy subjects, 7 subjects with hepatic impairment and 1445 patients with advanced cancer (410 patients who received single-agent LGX818 and 1046 patients who received encorafenib combination therapy, with 11 patients who received both single-agent LGX818 and LGX818 + MEK162 combination therapy and 4 patients who received LGX818 + MEK162 combination therapy in 2 different studies).

For further details, please refer to the current [LGX818 (encorafenib) Investigator's Brochure].

1.2.2.2.2 Clinical pharmacokinetics

The human ADME study in healthy subjects showed that encorafenib is at least 86% absorbed based on recovered radioactivity and has a preferential distribution to plasma as compared to blood. The predominant biotransformation reaction of encorafenib was N-dealkylation (other

major metabolic pathways involved hydroxylation, carbamate hydrolysis, indirect glucuronidation and glucose conjugate formation.). The most abundant circulating component was encorafenib, ranging from 17.9% to 36.4% of the radioactivity in plasma.

Encorafenib was mainly eliminated via metabolism, with low levels of unchanged encorafenib detected in urine and feces. The dose was equally recovered in urine and feces (47.2% in each matrix) and the renal clearance was estimated to be 1.8%.

Encorafenib as a single-agent in patients with locally advanced or metastatic BRAF-mutant melanoma [CLGX818X2101] in the dose-escalation phase showed that the Day 15 exposures were consistently decreased by 30 to 60% compared to those at Day 1, probably due to induction of CYP450 enzymes. AUC and Cmax ratios at steady state (Day 15) relative to Day 1 did not appear to change with dose. The dose expansion phase in patients with locally advanced or metastatic BRAF-mutant melanoma or metastatic colorectal cancer (mCRC) showed exposure of encorafenib in terms of Cmax and AUCtau was within the range observed at the 300-mg dose level for the dose-escalation phase. The results of the dose-proportionality assessment in patients with locally advanced or metastatic BRAF-mutant melanoma suggest that encorafenib exposure was approximately dose proportional over the dose range studied. In combination studies, when administered with binimetinib, PK parameters of encorafenib were similar to those observed in the single-agent study. When co-administered with cetuximab and BYL719, the mean Cmax and AUC of encorafenib at steady state were higher when co-administered with higher doses of BYL719. Encorafenib 200 mg in combination with 300 mg LEE011, showed that exposure of encorafenib was higher than single-agent data, though the available data is limited. When encorafenib 200 mg was dosed in combination with escalating doses of LEE011 and binimetinib 45 mg, the AUC and CL/F of encorafenib was higher on Day 1 at higher doses of LEE011. This was not observed at steady state. The possibility of drug-drug interactions in combinations requires further assessment.

For further details on clinical pharmacokinetics, please refer to the current [LGX818 Investigator's Brochure]

1.2.3 Overview of single agent MEK162

1.2.3.1 Non-clinical experience

1.2.3.1.1 Non-clinical pharmacodynamics

MEK162 is a potent and highly selective allosteric, ATP competitive inhibitor of MEK1/2. Overall, single agent anti-tumor activity of MEK162 has been demonstrated in vivo in xenograft models derived from a variety of cancer types including melanoma, CRC, pancreatic, and lung, that harbor an array of know oncogenic drivers including (but not limited to) activating lesions in BRAF, NRAS and KRAS.

Overall, MEK162 has demonstrated potent activity against MEK1/2 and broad anti-proliferative activity in vitro and in vivo.

For further details on pharmacodynamics, refer to the current [MEK162 Investigator's Brochure].

1.2.3.1.2 Non-clinical pharmacokinetics and metabolism

The oral bioavailability (F) in rat and monkey absorption, distribution, metabolism and excretion (ADME) studies is moderate (48%) and similar to the fraction absorbed (based on radioactivity excreted) suggesting a minimal first pass effect. Binimetinib shows a low total systemic plasma clearance and volume of distribution at steady state after intravenous (IV) administration. Mean plasma terminal half-life (T1/2) ranges from 2 to 9 hours in preclinical species.

In vitro experiments indicate that binimetinib has moderate to high membrane permeability and is a substrate of P-gp and BCRP.

Binimetinib is highly bound to plasma proteins (humans: 97.2%).

Binimetinib is more distributed in plasma than blood. The blood-to-plasma concentration ratios of binimetinib ranges from 0.652 to 0.994 in the species tested. In humans, the blood-to-plasma ratio is 0.718.

[^{14}C]-Binimetinib-derived radioactivity is absorbed and widely distributed to tissues in both pigmented rats and albino rats following a single oral (PO) dose.

With multiple routes of metabolism, binimetinib is metabolized primarily by glucuronidation pathways (mainly via UGT1A1, 1A3 and 1A9) and to a lesser extent by oxidation pathways (mainly via CYP1A2 and 2C19). UGT1A1 was shown to be the major contributor (90%) to the formation of the direct glucuronide.

Following IV dosing in the rat, fecal and urinary excretion accounts for 46% and 45% of total radioactivity, respectively. Approximately 15% of binimetinib is excreted unchanged in urine and 16 % in feces. Total recovery of radioactivity in the excreta of monkey is 99% and 85% following PO and IV dosing, respectively. The most abundant drug-related components in monkey excreta included binimetinib, the 2 glucuronides and the amide.

In vitro, binimetinib reversibly inhibits CYP2B6 and is a weak reversible inhibitor of CYP1A2 and CYP2C9. Binimetinib is not considered a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5. Binimetinib induces CYP3A, but this was not confirmed in a human DDI study.

For detailed information regarding non-clinical pharmacokinetics, refer to the [MEK162 Investigator's Brochure].

1.2.3.1.3 Non-clinical safety pharmacology and toxicology

Acute, subchronic, chronic and reproductive toxicity, genotoxicity and phototoxicity studies were completed to support the chronic administration of MEK162 to adult cancer patients. The toxic effects of MEK inhibitors in humans are similar to the toxic effects observed in monkeys. The toxic effects include gastro-intestinal intolerance and diarrhea, rash, central serous retinopathy (only seen in humans) and retinal vein occlusion (rarely seen in humans). In vitro and in vivo phototoxicity studies conducted in mice indicate that MEK162 has a very low risk of weak phototoxic potential at therapeutic doses. Furthermore, there has been no evidence of phototoxicity or photosensitivity in humans being treated with MEK162 for cancer or for rheumatoid arthritis. This includes 686 patients and healthy volunteers who have received at least one dose of MEK162 and is based on data as of January 7, 2013.

For details on non-clinical safety pharmacology and toxicology, refer to the current [MEK162 Investigator's Brochure].

1.2.3.1.4 Genotoxicity study

Teratogenic effects were seen in rats and rabbits. MEK162 should not be used in pregnant women and women of child-bearing potential must be advised to use highly effective contraception methods.

For details on non-clinical safety pharmacology and toxicology, refer to the current [MEK162 Investigator's Brochure].

1.2.3.2 Clinical experience

1.2.3.2.1 Clinical safety and efficacy

As of 20 January 2019, a total of 2907 healthy subjects and patients had received at least MEK162 either as a single agent or in combination with other targeted agents, standard chemotherapy agents or immunomodulating agents. These patients constitute the MEK162 safety population, which includes 229 healthy subjects, 17 subjects with hepatic dysfunction, 6 subjects with renal dysfunction, 164 patients with rheumatoid arthritis and 2491 patients with advanced cancer.

For further details, please refer to the current [MEK162 (binimetinib) Investigator's Brochure].

1.2.3.2.2 Clinical pharmacokinetics

The pharmacokinetics of binimetinib are characterized by moderate to high variability, accumulation of approximately 1.5-fold, and steady state concentrations reached within 15 days. Binimetinib has been shown to be approximately dose proportional (study [ARRY-162-111]). The human ADME study showed that about 50% of binimetinib dose is absorbed. The primary metabolic pathways include glurucronidation (up to 61.2% via UGT1A1), N-dealkylation, amide hydrolysis (up to 17.8% via CYP1A1 and CYP2C19). The excretion route is 31.7% of unchanged binimetinib in feces and 18.4% in urine. Estimated renal clearance of unchanged binimetinib is 6.3% of total dose. The impact of UGT1A1 inhibitors or inducers has not been clinically assessed.

Food-effect clinical studies have shown influence of food on PK of binimetinib is mild and not clinically relevant; therefore, binimetinib can be taken with food. A drug interaction study with binimetinib and midazolam was conducted; the results suggest that continuous intake of binimetinib produces no relevant CYP3A4 induction. Binimetinib solubility *in vitro* has been shown to be pH dependent but the effects of the impact of pH modifying agents on the PK of binimetinib *in vivo* is unknown. In vitro studies also demonstrated that binimetinib is a P-gp and BCRP substrate, but the effects of inhibitors of these substrates on the PK of binimetinib *in vivo* is unknown. In the cases where the extent of a drug interaction is unknown, it is recommended to co-administer drugs with caution.

A hepatic impairment study is on-going, preliminary results indicate that the exposure of binimetinib in healthy subjects and those with mild hepatic impairment is comparable. Exposure in moderate and severe hepatic impairment is to be determined.

For further details on clinical pharmacokinetics, refer to the current [MEK162 Investigator's Brochure].

1.2.4 Overview of single agent BKM120

1.2.4.1 Non-clinical experience

1.2.4.1.1 Non-clinical pharmacodynamics

NVP-BKM120 (BKM120) is a potent oral pan-class I PI3K inhibitor that is a 2,6-dimorpholino pyrimidine derivative. BKM120 inhibits wild-type PI3Kα (IC_{50}: 35 nM), with at least 50-fold selectivity towards this target compared to other protein kinases as well as against somatic PI3Kα activating mutants (H1047R-, E542K-, and E545K-p110α).

For further details on non-clinical pharmacodynamics, refer to the current [BKM120 Investigator's Brochure].

1.2.4.1.2 Non clinical pharmacokinetics and metabolism

In animals, BKM120 has moderate to high bioavailability, moderate volume of distribution and was found to cross the blood brain barrier in rats with a tissue-to-plasma ratio of about 2. BKM120 is moderately bound to plasma protein across all species examined (fup in human plasma of about 15%).

Oxidative metabolism of BKM120 is predominantly mediated by CYP3A4 (estimated fraction metabolized >0.9). Direct phase II metabolism (glucuronidation) via UGT1A4 is also observed in human liver microsomes supplemented with UDPGA. Recombinant human CYP1A1 also has the capacity to metabolize BKM120. However, its endogenous expression in the human liver is negligible and therefore it should not have any impact on hepatic BKM120 metabolism.

BKM120 was identified to be a weak reversible inhibitor of CYP3A4 (Ki 13.6 μM,) and it also weakly inhibited the CYP2C family (2C8, 2C9 and 2C19) with IC50 values ranging from 35-65 μM. BKM120 did not show time dependent inhibition of CYP450 enzymes. Experiments also showed a potential for BKM120 to induce UGT1A1 at concentrations between 0.5 and 100 μM.

BKM120 is neither an inhibitor nor a substrate of P- gp, MRP-2, BCRP, or OCT2. BKM120 can inhibit hMATE1 and hMATE2K in vitro at concentrations above 10 μM.

Further information on the non-clinical pharmacokinetics may be found in the [Investigator's Brochure for BKM120].

1.2.4.1.3 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 BKM120, 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 BKM120. However, these effects were minimal in both rats and dogs at the doses used in the 4-week studies.

Further information on the safety pharmacology and toxicology may be found in the [Investigator's Brochure for BKM120].

1.2.4.1.4 Genotoxicity study

No evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests in vitro with BKM120. However, a potential for genotoxicity was identified based on the observation of an aneugenic potential and was confirmed by fluorescence in situ hybridization of centromeric sequences within micronuclei induced in human peripheral lymphocytes in vitro. In summary, evidence of a genotoxic potential with BKM120 has been seen in vitro and in vivo and is likely due to an aneugenic effect.

1.2.4.2 Clinical experience

As of 15 September 2013, approximately 1469 patients and healthy volunteers have been enrolled into twenty two Novartis sponsored clinical studies of BKM120, including 3 blinded phase II and III studies.

The maximum tolerated dose (MTD) was determined to be 100 mg/day BKM120 in Caucasian, Japanese and Chinese patient population. The recommended Phase II dose (RP2D) was confirmed at 100mg daily for Caucasian and for Japanese population and is under evaluation in Chinese patients.

For further details, refer to the current [BKM120 Investigator's Brochure].

1.2.4.2.1 Clinical safety and efficacy

As of 15 September 2013, DLTs events were reported in 3 single agent trials. In [CBKM120X2101] (62 patients) 9 DLTs were observed in 9 patients: 2 grade 4 hyperglycemia (150 mg/d), 1 grade 3 hyperglycemia (100 mg/d), 1 grade 3 arthralgia (100 mg/d), 1 grade 3 abdominal pain upper (100 mg/d), 1 grade 3 rash (100 mg/d), 1 grade 3 mood altered (100 mg/d), 1 grade 2 mood altered (100 mg/d), 1 grade 2 mood altered (80 mg/d). In [CBKM120X1101] (15 patients) 1 DLT was observed: 1x grade 4 hepatic function abnormal (100 mg/d). In [CBKM120Z2102] (24 patients) 1 DLT was observed: 1 x grade 3 depression (80 mg/d). Most frequent events in single agent BKM120 studies (occurring in about ≥ 20% of patients) include, but may not be limited to: nausea, vomiting, diarrhea, decreased appetite, hyperglycemia, abdominal pain, constipation, asthenia, fatigue, macular-papular rash with or without pruritus, mucosal inflammation including stomatitis, increase in liver transaminases,

anxiety and depression. Other frequent events (about ≥10% of patients) include: anemia, altered mood, confusion, dizziness, headache, insomnia, dry skin, back pain, arthralgia, cough, peripheral edema, dyspepsia, fever, hypokalemia, hyponatremia, hypocalcemia, hypophosphatemia, eosinophilia, increase in blood alkaline phosphatase, lipase increase, dysgeusia and dyspnea. Other uncommon events are described in the current [BKM120 Investigator's Brochure].

In the [CBKM120X2101] study in adult patients with advanced solid malignancies, as of 15 September 2013 and among 83 patients analyzed, the best overall response according to RECIST criteria reported as per investigator assessment was as follows: partial response 1 patient (1.2%), stable disease 33 patients (39.8%), progressive disease 38 patients (45.8%), and unknown 11 patients (13.3%).

In the [CBKM120C2201] study in patients with advanced endometrial carcinoma, as of 15 September 2013, out of 70 patients analyzed, the best overall response distribution according to RECIST criteria reported as per investigator assessment was: complete response 1 patient (1.4%), partial response 1 patient (1.4%), stable disease 26 patients (37.1%), progressive disease 29 patients (41.4%), and unknown 13 patients (18.6%).

For further details on clinical efficacy data of BKM120, refer to the current [BKM120 Investigator's Brochure].

Liver toxicity

Approximately 25 to 45% of patients treated with single agent BKM120 reported liver toxicity (all grades, regardless of study drug relationship, 100 mg/d dose) based on a search of multiple MedDRA event terms (e.g. SMQ preferred terms). The incidence of grade 3 and 4 events was approximately 10 to 30%. Liver function test (LFT) alterations observed during ongoing and completed studies have been mostly transaminase enzyme increases (ALT and/or AST). Data suggest a slightly higher rate of grade 3 and 4 liver enzyme elevations in Japanese patients (44%) in the [CBKM120X1101] study, however, the number of patients treated at 100 mg in this study was limited (n=9). Transaminase elevations typically occur during the first 6 to 8 weeks of treatment start.

Although transaminase increases are relatively common, only a few of the patients had other simultaneous observations related to impaired liver function (e.g. bilirubin increase or clinical symptoms).

Based on these findings, guidelines to monitor and follow patients with LFT alterations (including dose and schedule modifications) have been implemented.

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 TBIL >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 TBIL >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.

1.2.4.2.2 Clinical pharmacokinetics and metabolism

The pharmacokinetic data reveals that BKM120 single agent is rapidly absorbed after oral administration with a median time to reach maximum concentration (Tmax) between 0.5 and 3 hours at steady-state. The variability in exposure and maximum plasma concentration (Cmax) at steady-state for the maximum tolerated dose (MTD) of 100 mg qd is moderate: 33% and 28% respectively. BKM120 accumulated in a linear fashion (~ 3-fold) and reached steady-state after 8 days of treatment. At steady-state the median accumulation half-life was estimated between 35.7 hours and 58.5 hours, calculated based on an accumulation ratio between 3 and 4-fold

For further details on pharmacokinetics and metabolism of BKM120, refer to the current [BKM120 Investigator's Brochure].

1.2.5 Overview of single agent BGJ398

1.2.5.1 Non-clinical experience

1.2.5.1.1 Non-clinical pharmacodynamics

BGJ398 is orally bio-available, selective and ATP competitive pan FGFR kinase inhibitor which has demonstrated anti-tumor activity in preclinical, *in vitro* and *in-vivo*-xenograft tumor models.

In mice, BGJ398 administered p.o. at doses of 10 to 50mg/kg qd for 7 days shows a significant, dose-dependent anti-tumor activity against NIH3T3/FGFR3S249C and NIH3T3/FGF-R3K650E xenografts, with stasis and regression at doses ≥ 30 mg/kg qd. In rats, BGJ398 led to a dose-dependent inhibition of RT112 tumor growth with tumor stasis/regression at 10mg/kg qd.

For further details on non-clinical pharmacodynamics, refer to the current [BGJ398 Investigator's Brochure].

1.2.5.1.2 Non-clinical and pharmacokinetics and metabolism

In all species tested, BGJ398 exhibited a high plasma CL and a large Vss. The compound is highly bound to plasma proteins (~ 98%) but does not preferentially distribute to red blood cells. BGJ398 is widely distributed to tissues in the rat and has a high affinity to melanin containing tissues.

In human liver microsomes, BJG398 is mainly metabolized by CYP3A4/5 with partial contribution by FMO3 (6%).The major circulating component in rat plasma after a single [^{14}C] BGJ398 dose was parent compound, accounting for 35.7% (i.v.) and 25.9% (p.o.). There were two main biotransformations in all species investigated: N-oxidation and N-deethylation to yield the pharmacologically active metabolites BQR917 and BHS697, respectively. The predominant reaction in dog was N-oxidation while N-deethylation was the main biotransformation product in rat and human. Minor reactions were observed in rat and human included glucuronic acid and glutathione conjugation. BGJ398 is a potent reversible inhibitor

of CYP3A4 (Ki 0.26µM). The compound also reversibly inhibits CYP2C9 and CYP2C19 with Ki values of 6.09µM and 4.1µM, respectively. BGJ398 was found not to be a CYP3A4 inducer at concentrations up to of 10 µM.

BGJ398 is a P-gp and BCRP substrate and also inhibits BCRP mediated transport with an IC50 value of 0.21µM.

The active metabolite CQM157 showed a reversible CYP inhibition profile similar to BGJ398. CQM157 was shown to be a potent inhibitor of CYP2C8, CYP2C9 and CYP3A4 (IC50 less than 10 µM) and CYP2C19 (IC50 12 µM). CQM157 was not a time dependent inhibitor of CYP1A2, 2C9, 2D6 and 3A4/5.CQM157 was found to be an inhibitor of P-gp with an IC50 of 2.7 µM and of BCRP with an IC50 of 3.4 µM and uptake transporters OATP1B1 with an IC50 of 3.5 µM and of OATP1B3 with an IC50 of 2.8 µM. Active metabolite BHS697 did not inhibit efflux transporters P-gp and BCRP and was an inhibitor of OATP1B1 (IC50 = 6.0 µM) and OATP1B3 (IC50 = 1.6).

For further details on nonclinical drug metabolism and pharmacokinetics, refer to the current [BGJ398 Investigator's Brochure].

1.2.5.1.3 Non-clinical safety and genotoxicity

In conclusion, multiple biological effects were observed in nonclinical safety studies and mainly consisted of effects on the phosphate and/or calcium homeostasis, corneal opacity associated with keratopathy, ectopic mineralization, changes in renal function parameters, bone growth plate thickening / retention of the primary spongiosa and a potential for QTc prolongation.

For further details on non- clinical safety pharmacology and toxicology, refer to the current [BGJ398 Investigator's Brochure].

1.2.5.2 Clinical experience

1.2.5.2.1 Clinical safety and efficacy

The treatment emergent adverse events as of the cutoff date of 24 September 2013 that were suspected to be related to BGJ398 that occurred in 20% or more of patients who received BGJ398 in [CBGJ398X2101] study are increases in phosphorous levels (71.3%) decreased appetite (26.6%), fatigue (25.5%), stomatitis (24.5%), and alopecia (21.3%). Twenty-eight percent of patients (26/94) experienced a least one suspected related grade 3 or 4 event, which is consistent with the value reported in the previous version of the IB (24.4%, 11/45 patients). Overall, most adverse events reported have been mild to moderate in severity, reversible, and unrelated to BGJ398.

Ten of the 94 patients who received BGJ398 experienced a total of 15 adverse events during the first cycle of treatment that met the protocol-defined DLT criteria. Of these events, four occurred in four patients enrolled in the dose escalation part of the study. The MTD has been determined as125mg QD.

None of the 18 patients treated with BGJ398 at 125 mg QD on the 3 week on/1 week off dosing regimen have experienced a DLT. Furthermore fewer dose interruptions due to

hyperphosphatemia occurred in patients enrolled to this cohort. Subsequently this intermittent schedule is considered the RP2D for BGJ398.

Preliminary antitumor efficacy has been detected in patients with FGFR1-amplified lung SCC, FGFR1-amplified squamous cell carcinoma of the head and neck, FGFR1-amplified breast cancer, FGFR3-mutated bladder cancer, and cholangiocarcinoma with FGFR2 gene fusion. While all patients who responded had increases in blood phosphorous levels, not all patients who experienced increases in blood phosphorous levels responded to treatment with BGJ398.

For further details on clinical efficacy, refer to the current [BGJ398 Investigator's Brochure].

1.2.5.2.2 Clinical pharmacokinetics

As of 24 September 2013, the pharmacokinetics (PK) of BGJ398 and active metabolites were evaluated following single and repeat daily doses in the ongoing phase 1 study ([CBGJ398X2101]).

The median apparent Tmax value across all dose levels tended to be 2-3 hours post-dose.

Accumulation was observed following multiple doses. The mean Cmax and AUC0-24 for Cycle 1 Day 1 at 125 mg was 111 ng/mL and 816 h.ng/mL and for Cycle 1 Day 15 was 318 ng/mL and 5301 h.ng/mL respectively. The mean AUC0-24 ratios between Cycle 1 Day 1 and Cycle 1 Day 15 ranged between 1.5 to 6.5, indicating some changes in BGJ398 exposure following multiple dosing. The inter-patient variability was moderate to high for BGJ398.

For further details on clinical pharmacokinetics, refer to the current [BGJ398 Investigator's Brochure].

1.2.6 Overview of single agent INC280

1.2.6.1 Non-clinical experience

1.2.6.1.1 Non-clinical pharmacodynamics

INC280 is a small ATP competitive, reversible inhibitor of the c-MET receptor tyrosine kinase. The proto-oncogene *c-MET*, a member of the receptor tyrosine kinase family, encodes the high-affinity receptor for hepatocyte growth factor (HGF), the only ligand for the receptor.

INC280 possesses potent inhibitory activity against the c-MET kinase in vitro (IC_{50} = 0.13 ± 0.05 nM) and is both ATP competitive and reversible (Liu et al 2011). INC280 is highly specific for c-MET with > 10,000-fold selectivity over a panel of 56 other human kinases tested.

Collectively, the data demonstrate that INC280 possesses potent in vitro and in vivo pharmacological activity against c-MET dependent advanced solid tumors.

More detailed information can be found in the current [INC280 investigator's brochure].

1.2.6.1.2 Non-clinical pharmacokinetics and metabolism

INC280 is highly bound to human plasma protein. After a single oral dose of [^{14}C]-INC280 in rats, radioactivity was widely and rapidly distributed into all tissues. INC280 penetrates the blood-brain barrier.

INC280 is predominantly metabolized by cytochromes P450. CYP3A4 is the major P450 enzyme to metabolize INC280 (~fm 99.6%) with very low contribution from other enzymes (~0.4%). Other than CYP3A4, the strong metabolic activity of recombinant CYP1A1 was also identified. The hydroxylated metabolite M8 and the imidazo-triazinone M16 were two prominent metabolites in hepatocyte incubations of all species except for the dog, and were the main metabolites observed in rat plasma, feces and urine. Information on metabolism and drug-drug interaction potential of M8 and M16 is not available.

INC280 showed inhibitory potency in vitro against CYP1A2 (IC50 = 20 µM; KI = 18.5 µM, k_{inact} = 0.033 min-1), 2C8 (IC50 = 1.7 µM), 2C9 (IC50 = 7.6 µM), 2C19 (IC50 = 11.3 µM) and 3A4/5 (IC50 = 9.9 µM; KI = 13.2 µM, k_{inact} = 0.030 min-1).

INC280 also displayed inhibition of MDR1/P-gp, MXR/BCRP, OATP1B1 and OATP1B3 mediated substrate efflux or uptake with IC50 values of 12, 16.4, 6.5 and 6.2 µM, respectively. For further details on non-clinical metabolism and pharmacokinetics, refer to the current [INC280 Investigator's Brochure].

1.2.6.1.3 Non-clinical safety and toxicology

Repeat dose toxicity studies conducted revealed the following target organs or systems: kidneys, pancreas, central nervous system (CNS), and potentially liver data are summarized in the IB. Additionally; INC280 has shown photosensitization potential in *in vitro* and *in vivo* assays.

For further details on non-clinical safety and toxicology, refer to the current [INC280 Investigator's Brochure].

1.2.6.1.4 Genotoxicity

INC280 is not genotoxic. INC280 is considered potentially teratogenic to human. Therefore, males must be willing to abide by protocol permitted methods of contraception to avoid fathering a child from the time of screening through follow-up. Women of child-bearing potential who agree to participate in initial clinical studies must agree to abide by permitted methods of contraception defined in the clinical protocol to avoid pregnancy from screening through follow-up.

For further details on genotoxicity, refer to the current [INC280 Investigator's Brochure].

1.2.6.2 Clinical experience

1.2.6.2.1 Clinical safety and efficacy

The INC280 film-coated tablet formulation has been developed and tested to improve patient convenience and compliance over the INC280 capsule formulation.

As of 28-Sep-2015 (cut-off date of the INC280 Investigator's Brochure, edition 6),

a total of 500 cancer patients and 90 non-cancer subjects have received INC280. A total of 271 patients with solid tumors have been treated with INC280 as a single agent (198 patients received the capsule formulation only, 66 patients received tablet formulation only, and 7

patients switched from capsule to tablet formulation during treatment with INC280), and 229 patients have been treated with INC280 in combination therapies (139 patients received the capsule formulation only and 90 patients received tablet formulation only). In addition, 90 non-cancer subjects have received INC280 (6 subjects received the capsule formulation only, 60 subjects received the tablet formulation only, and 24 subjects received both capsule and tablet formulations).

Overall, the majority of the reported AEs are of mild or moderate severity.

The most frequent AEs suspected to be related to INC280 of any grade reported in the [CINC280X2102] study, which is considered as the reference study for the safety profile of INC280 as a single agent, were nausea (38 patients [32.2%]), vomiting (31 patients [26.3%]), fatigue (29 patients [24.6%]), edema peripheral (27 patients [22.9%]) and decreased appetite (22 patients [18.6%]), and the majority were Grade 1/2. The most frequently occurring Grade 3/4 AEs suspected to be related to INC280 included fatigue (6 patients [5.1%]); lipase increased (4 patients [3.4%]); ALT increased (4 patients [3.4%]); AST increased (3 patients [2.5%]); anemia, nausea, neutropenia, dehydration and hypophagia (each in 2 patients [1.7%]); and thrombocytopenia, vomiting, diarrhea, edema peripheral, blood bilirubin increased, amylase increased, lymphocyte count decreased, decreased appetite, hypoalbuminemia, hypophosphatemia, hyperlipasemia, hyperlipidemia, cerebral venous thrombosis and rash maculopapular (each in 1 patient [0.8%]).

The MTD for INC280 capsules as single agent was not reached. The RP2D for INC280 as a single agent has been determined to be 600 mg BID in capsule formulation and 400 mg BID in tablet formulation.

A female patient experienced a serious, unexpected, possibly related adverse event of abnormal liver function tests during treatment with a combination of INC280 and gefitinib while enrolled in the [CINC280X2202] study. The initial Investigator Notification (IN) for the event was issued on 12 March 2015). The patient experienced concurrent elevations of total bilirubin >2×ULN and ALT/AST >3×ULN with alkaline phosphatase (ALP) <2×ULN. The patient permanently discontinued study drugs. The liver function alterations were reversible and improved after the discontinuation of both drugs. At the time of the follow-up Investigator Notification (IN), the outcome of the adverse event of abnormal liver function tests was reported as completely recovered. The investigator assessed the AE as suspected to be related to the combination of INC280 and gefitinib. This AE met the criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination. The recommended phase II dose (RP2D) of INC280 in combination therapy with gefitinib is 400mg BID in tablet formulation. The maximum tolerated dose (MTD) for single agent INC280 has not been defined.

For further details on clinical safety and efficacy, refer to the current IB [INC280 Investigator's Brochure].

1.2.6.2.2 Clinical pharmacokinetics

As of 28-Sep-2015, INC280 single agent steady state PK data are evaluable in four studies with tablet and/or capsule formulations ([CINC280X2101T], [CINC280X1101], [CINC280X2102] and [CINC280X2201]). Study [CINC280X2101T] only included Western patients, the majority of whom were Caucasian. Study [CINC280X1101] was performed in Japanese cancer patients while studies [CINC280X2102] and [CINC280X2201] included both Asian and Western cancer patients.

The mean plasma exposures (Cmax and AUC) of INC280 capsules were increased with dose following QD administration up to 600 mg/day in studies [CINC280X2101T] and [CINC280X1101], no further increase in the mean exposure was observed at 800 mg QD in [CINC280X1101]).

A single dose relative bioavailability study in healthy subjects, [CINC280X2103], was conducted to compare the relative bioavailability of INC280 tablets to INC280 capsules. The outcome of this study showed that following a single oral administration of 600 mg INC280 in healthy subjects, both formulations had similar Tmax values; tablets however provided higher systemic exposures at a dose of 600 mg. The AUC geometric mean ratios (tablet vs. capsule) were 2.4 to 2.6, and the Cmax geometric mean ratio (tablet vs. capsule) was 3.0. Additionally lower inter-subject variability was observed when administering the tablet formulation of INC280.

In clinical studies with cancer patients, the INC280 tablet formulation provided slightly higher exposures than the INC280 capsule formulation at the same doses tested, with generally lower inter-subject variability. The mean plasma exposures of INC280 tablet appeared to increase dose proportionally from 200 to 400 mg twice per day ([CINC280X1101] and [CINC280X2102]). The apparent terminal half-life T1/2 of INC280 estimated from [CINC280X1101] QD treatment is 4.4 h, ranging, from 2.8 to 9.0 across the cohorts. Steady state INC280 exposure is expected to be reached by the third day of consecutive dosing. Accumulation of INC280 tablet following repeated administration at 400 mg BID is low with an accumulation ratio of up to 2-fold in [CINC280X1101] and [CINC280X2102]; however, some subjects had higher accumulation ratios up to 10-fold in [CINC280X1101].

Study [CINC280X2102] investigated the MTD or RP2D, safety and tolerability of the INC280 capsule and tablet formulations in the cancer patient target population. The INC280 400 mg BID tablet formulation had comparable tolerability, safety profile, and exposure compared to the 600 mg BID capsule formulation. A comparison of exposure (Cmax and AUC0-12,ss) between tablets administered at 400 BID and capsules administered at 600 BID is shown below (Table 1-2).

Table 1-2 Comparison of INC280 exposure for 600 mg capsules versus 400 mg tablets in cancer patients from CINC280X2102

Dose Regimen (Dosage Form) [N]	Mean Cmax ± Standard Deviation [N]	Mean AUC0-12,ss ± Standard Deviation [N]
600 mg BID (capsule) [N=45]	4790 ± 3440 ng/mL [N=45]	24700 ± 13500 [N=21]
400 mg (tablet) [N=8]	5860 ± 2780 ng/mL [N=8]	25500 ± 14400 [N = 4]

In summary, the exposure data in the cancer patient target population [CINC280X2102] supports a dose ratio of approximately 3:2 (i.e., 600 mg capsules: 400 mg tablets) in the relevant treatment population for converting the capsule formulation to the tablet formulation.

For further details on clinical pharmacokinetics, refer to the current IB [INC280 Investigator's Brochure].

1.2.7 Overview of single agent LEE011

1.2.7.1 Non-clinical experience

1.2.7.1.1 Non-clinical pharmacodynamics

LEE011 is an orally bioavailable, small molecule inhibitor of CDK4/6. LEE011 exhibits highly specific inhibitory activity against CDK4/cyclin D1 and CDK6/cyclinD3 complexes, with concentrations resulting in 50% inhibition (IC50) values of 10 nM and 39 nM, respectively, in isolated enzyme assays. It is inactive against the majority of other kinases. LEE011 inhibits the growth of many tumor cell types *in vitro* and *in vivo*, including mantle cell lymphoma, liposarcoma, rhabdoid tumors, neuroblastoma, melanoma and carcinomas of the esophagus, breast, lung and pancreas. Furthermore, in patient-derived primary V600E BRAF mutated melanoma xenograft models, combining LEE011 with LGX818 (a potent and selective RAF inhibitor), both improved initial anti-tumor effects relative to LGX818 alone, and delayed/prevented the emergence of resistance to observed with single agent LGX818. Lastly, regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of LEE011 requires the presence of functional retinoblastoma protein (Rb). More detailed information can be found in the current [LEE011 investigator's brochure].

1.2.7.1.2 Non-clinical pharmacokinetics and metabolism

In human hepatocytes, LEE011 is mainly metabolized by CYP3A4 with partial contribution by FMO3 (15-26%). CYP3A4 metabolized LEE011 mainly by hydroxylation and N-demethylation, whereas FMO3 produced a hydroxylamine metabolite. In hepatocytes, LEQ803 (N-demethylation) was a major metabolite in the rat, monkey, and humans, and the only metabolite in dogs. This metabolite was found to interact with hERG channels in vitro. In the rat ADME studies, LEQ803 was found only in minor amounts. LEE011 is a time-dependent CYP3A4 inhibitor and a reversible inhibitor of CYP1A2. CYP2E1 was inhibited with an IC50 value of 62 µM. Time- dependent inhibition of CYP3A4 was observed with a KI value of 5 µM and a k_{inact} value of 0.0245 min^{-1}. LEE011 displayed no capacity to inhibit CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at concentrations up to 50 µM and was not

identified as time-dependent inhibitor of CYP1A2, CYP2C9, and CYP2D6. LEE011 is a low-affinity p-gp substrate.LEE011 was identified as inhibitor of the efflux transporter MDR1 and MXR with IC50 values of 143 µM and 24 µM, respectively. LEE011 inhibited the human BSEP (bile salt export pump) transporter with an IC50 value of 4.7 µM, but did not inhibit rat and dog BSEP at concentration up to 200 µM.

For further details on non-clinical pharmacokinetics, refer to the current [LEE011 Investigator's Brochure].

1.2.7.1.3 Non-clinical toxicology and genotoxicity

In vitro, LEE011 did not show mutagenic or phototoxic potential.

Safety pharmacology studies did not reveal any effects on CNS or respiratory functions. In the dog telemetry study, prolongation of the average QT and QTc was observed with the potential to induce PVCs at higher exposure levels. In rats and dogs, LEE011 induced bone marrow hypocellularity, lymphoid depletion, atrophy of the skin and intestinal mucosa, decreased bone formation and testicular atrophy. These are consistent with the mechanism of action of LEE011. Extensive distribution into the rat thyroid gland occurred following an oral dose of LEE011. Although no abnormalities of thyroid function were identified in the preclinical studies, this high distribution of LEE011 into the thyroid gland provides the rationale for monitoring thyroid function tests in patients enrolled into this first clinical trial of LEE011.

Based on its mechanism of action and preclinical toxicology studies, the major potential toxicities for LEE011 include myelosuppression, hepatic toxicity, and prolongation of the QT interval. The risk of these toxicities may be amplified by concomitant administration of strong inhibitors of CYP3A4.

For further details on non-clinical toxicology and genotoxicity, refer to the current [LEE011 Investigator's Brochure].

1.2.7.2 Clinical experience

LEE011 is currently being investigated as single agent in 3 studies: [CLEE011X1101], [CLEE011X2101], [CLEE011X2102] and in combination in 4 studies: [CLEE011X2105], [CLEE011X2106], [CLEE011X2107], [CMEK162X2114].

1.2.7.2.1 Clinical safety and efficacy

As of 2 July 2013, 78 patients have been treated with increasing doses of LEE011 orally, once daily for 21 days followed by a 1 week rest (28-day cycle). Doses ranging from the starting dose of 50 mg to 1200 mg were evaluated on this schedule. In addition, continuous dosing of LEE011 at 600 mg was evaluated (once daily for 28 days of a 28-day cycle). A total of 10 events meeting DLT criteria were observed at the indicated doses and include grade 3 mucositis/stomatitis (n=1) at 50 mg, grade 3 pulmonary embolism (n=1) at 280 mg, grade 3 hyponatremia (n=1) and prolonged grade 3/4 neutropenia (n=1) at 400 mg, prolonged grade 2 elevated creatinine (n=1) at 600 mg, grade 4 thrombocytopenia (n=1) at 750 mg, grade 3 asymptomatic QTcF prolongation with grade 3 neutropenia in one patient at 900 mg and grade 4 febrile neutropenia (n=1) and grade 4 thrombocytopenia (n=1) at 1200 mg. There was also 1 DLT, grade 3 neutropenia at 600 mg on the continuous dosing schedule. Grade 1/2 neutropenia

was observed at doses of 280 mg or higher (23%) and grade 3/4 neutropenia was seen at doses of 400 mg and higher (21%).

Asymptomatic grade 2 QTc prolongation was observed with increasing frequency starting at 600 mg with grade 3 prolongation in 2 patients. The majority of all reported adverse events were mild or moderate (grade 1-2) and reversible. There have been no deaths related to LEE011 reported. There have been no deaths related to LEE011 reported. The MTD of LEE011 is identified as 900 mg QD in a 3 weeks on/1 week off schedule while the RP2D is 600 mg QD in a 3 weeks on/1 week off schedule.

For further details on clinical safety and efficacy, refer to the current [LEE011 Investigator's Brochure]

1.2.7.2.2 Clinical pharmacokinetics

Following oral dosing, LEE011 is rapidly absorbed with median time to reach maximum plasma concentrations (Tmax) ranging from 1 to 5 hours (range of median Tmax values). LEE011 plasma exposure (maximum plasma concentration [Cmax] and AUC) exhibit slightly over-proportional increases in exposure across the dose range tested (50 to 1200 mg), with no clear evidence of time-dependent auto-inhibition of its clearance mediated by CYP3A4. Steady-state is generally reached by Day 8 and the arithmetic mean effective T1/2 based on accumulation ratio (i.e., T1/2, acc) range from 15.9 to 43.1, hours across the 50 to 1200 mg dose cohorts. The accumulation ratio based on AUC obtained in a dosing interval (Racc) across the studied doses ranged from 1.55- to 3.13-fold.

For further details on clinical pharmacokinetics, refer to the current [LEE011 Investigator's Brochure]

2 Rationale

2.1 Study rationale and purpose

About half of the patients with melanoma have an activating mutation in BRAF that results in the activation of the RAF/MEK/ERK pathway and plays an important role in the development of melanoma. The response to single agent BRAF or MEK inhibitors is often short lived (median PFS ~ 5 to 7 months), with resistance developing quickly. More recently, promising data have been reported for the vertical pathway inhibition of the RAF/MEK/ERK pathway with Dabrafenib and Trametinib leading to the FDA approval of this combination in January 2014. The decreased occurrence of SCC in the Dabrafenib/Trametinib combination trial, suggests that MEK inhibitors by acting downstream of RAF in the RAF/MEK/ERK pathway, may potentially block inappropriate signal transduction, originating either from the cell surface or due to RAS/RAF mutations, further strengthening the rationale for combining MEK inhibitors with BRAF inhibitors in the clinic (Heidorn 2010; Poulikakos 2010; Hatzivassiliou 2010).

Similar preliminary efficacy and tolerability has been seen for the combination of LGX818 and MEK162 with overall response rates of 88% for BRAFi naïve and 18% for BRAFi pretreated melanoma patients. The combination was well tolerated with no substantial increase in adverse events (AEs) for the combination vs single-agent therapy (Kefford et al 2013).

Despite further improvements of response and PFS for BRAF/MEK inhibitor combinations, virtually all patients eventually show progressive disease. Mechanisms for resistance to this combination are currently under investigation. It is however hypothesized that similar mechanisms are responsible for treatment failure after dual combination therapy as reported for single agent BRAF inhibitor treatment.

(Wagle et al 2013) recently reported on resistance mechanisms in 5 patients treated with the dabrafenib/trametinib combination and identified new MEK mutations in 2 patients as well as BRAF amplification in a third patient while no known resistance mechanisms could be identified in the two other patients. Similarly, in a second publication, (Villanueva et al 2013) identified MEK2 mutation and BRAF amplification as a resistance mechanism in a patient treated with the dabrafenib/trametinib combination.

This provides a strong rationale for a systemic analysis of the genetic alterations present in a patient's tumor at progression. By using the results of such analysis, it will be possible to characterize the possible mechanisms of resistance that emerge in an individual patient, and propose a tailored rational combination therapy to potentially circumvent resistance and achieve more prolonged responses. Such a combination approach would build on a backbone of BRAF/MEK inhibition and add a third agent based on the individual patient's resistance profile. The validity of this concept is supported by data from a xenograft model resistant to BRAF/MEK inhibitor combination, where persistent pS6 was observed and addition of a mTOR/PI3K inhibitor resulted in sustained tumor growth inhibition (Villanueva et al 2013).

The primary purpose of this study is to assess the anti-tumor activity of novel triple combinations of LGX818/MEK162 plus either BKM120, BGJ398, INC280 or LEE011 in patients who have progressed on prior BRAF and/or MEK inhibitor treatment.

In addition, safety and tolerability of the novel triple combinations will be assessed. The triple combination to be evaluated in an individual patient will be based on the molecular alteration(s) detected at progression after BRAF/MEK inhibitor combination treatment (see Table 4-1).

2.2 Rationale for the study design

This design was chosen in order to evaluate whether a selected combination partner for LGX818/MEK162, based on genetic alterations identified in a tumor at progression, can effectively overcome resistance to dual BRAF/MEK inhibition in adult patients with locally advanced or metastatic BRAF V600 melanoma. Tumor biopsies will be collected at baseline and at the time of progression following LGX818/MEK162 treatment in order to identify the molecular alteration(s) that predominate in an individual patient's tumor at progression. Molecular alterations identified in this manner would then be used to select the appropriate drug to combine with LGX818/MEK162.

Three different patient populations are eligible for participation in this study (see Figure 4-1):

a. Patients naïve to treatment with BRAF inhibitors (Group A).
b. Either patients who progressed after single agent BRAF or MEK inhibitors; or patients who progressed after combination of BRAF and MEK inhibitors other than the combination of LGX818/MEK162; or patients receiving LGX818 and/or MEK162, who have not progressed yet; or, in consultation with the Sponsor, patients who received any

BRAF and/or MEK inhibitor other than LGX818 and/or MEK162 and have not progressed yet (Group B).

c. Patients who progressed after LGX818/MEK162 combination therapy (Group C).

Treatment naïve patients (Group A) will receive the dual combination of LGX818/MEK162 during Part I until progression. In Part II, patients will be assigned to a rational combination treatment of LGX818/MEK162 and a third investigational agent.

For Group B:

- Patients who progressed after treatment with single agent BRAF or MEK inhibitor or after a BRAFi/MEKi combination therapy will enter Part II after a brief Run-in with the LGX818/MEK162 combination. However, if a response is achieved at the time of the first CT/MRI scan on LGX818/MEK162 the patient will remain on the LGX818/MEK162 combination.
- Patients who have been treated and not progressed on BRAF and/or MEK inhibitor regimen may enter the Run-in and continue LGX818/MEK162 combination until evidence of disease progression. At that time, a tumor biopsy will be taken and analyzed to guide assignment to a triple combination arm in Part II.

During the Run-in period, tolerability of the LGX818/MEK162 combination will be established. Patients who progressed after LGX818/MEK162 combination therapy (Group C) can be enrolled directly into a triple combination in Part II after analysis of their tumor sample after progression.

2.3 Rationale for dose and regimen selection

During Part I and the Run-in, patients will be treated with the LGX818/MEK162 combination at the recommended Phase 2 dose (RP2D) of 450mg QD LGX818 and 45mg BID MEK162.

During Part II, patients will be treated with LGX818/MEK162 in combination with a third targeted agent (i.e. LGX818/MEK162 + BKM120, LGX818/MEK162+BGJ398, LGX818/MEK162+INC280, LGX818/MEK162+LEE011). Please, see Section 6.2.1 and Section 6.2.2 for details on starting dose rationale and provisional dose levels. The escalation of the third agent and LGX818 in the respective triple combinations will be based on BLRM, unless a RP2D for that combination is already established.

If the proportion of patients eligible for one of the triple combinations is too low, it is possible that the trial will complete enrollment before a MTD/RP2D has been established for this combination.

The open-label dose escalation study design using a BLRM is a well-established method to estimate the MTD(s) and/or RP2D(s) in cancer patients. The adaptive BLRM will be guided by the escalation with overdose control (EWOC) principle to control the risk of DLT in future patients on study. The use of Bayesian response adaptive models for small datasets has been accepted by EMEA (“Guideline on clinical trials in small populations”, February 1, 2007) and endorsed by numerous publications (Babb 1998, Neuenschwander 2008, Neuenschwander 2010), and its development and appropriate use is one aspect of the FDA’s Critical Path Initiative.

Intra-patient dose escalation will be permitted after the first cycle for patients who have not experienced a DLT. Intra-patient dose escalation will also be guided by the BLRM with a modified EWOC criteria that reflects individual patient tolerability.

LGX818/MEK162 and LGX818/MEK162 + INC280 or BKM120 will be administered on a continuous schedule. In the triple combination arms of LGX818/MEK162 + LEE011 and BGJ398, LGX818/MEK162 will be administered on a continuous schedule while LEE011 and BGJ398 will be administered on a 3 weeks on 1 week off schedule (see Section 6.1.1) as it was found to improve tolerability.

2.4 Rationale for choice of combination drugs

Preclinical data suggest that simultaneous, triple inhibition of the RAF/MEK/PI3K pathway with the LGX818/MEK162/BKM120 combination could lead to increased clinical efficacy and possibly overcome early resistance to the BRAF/MEK combination in patients with BRAF V600 mutant advanced melanoma (see Section 1.2.1.1.2). Moreover, other mechanisms that reactivate MAPK signaling or activate alternate pathways such as PI3K/AKT signaling pathway may play a role in primary and/or acquired resistance to dual BRAF/MEK inhibition. Thus the antitumor activity of LGX818/MEK162 in combination with selected agents BKM120, BGJ398, INC280, and LEE011 that target PI3K, FGFR, c-met and CDK4/6 kinase respectively, will be assessed. The selection of the LGX818/MEK162 triple combination given to an individual patient will be based on the molecular alteration(s) identified in this patient's tumor sample upon progression on BRAF/MEK combination treatment (see Section 1.2.1.1).

2.5 Rationale for choice of comparators drugs

Not applicable

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 assess the anti-tumor activity of LGX818/MEK162 in combination with third targeted agents after progression on LGX818/MEK162 combination therapy.	Overall response rate (ORR)	Refer to Section 10.4.
Secondary To estimate the MTD/RP2D of triple combinations after progression on LGX818/MEK162 therapy	Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 of Combination Part (Part II)	Refer to Section 10.5.3.
To characterize the safety and tolerability of LGX818/MEK162 in combination with targeted agents	Adverse Events (AEs), serious AEs (SAEs), changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs), dose interruptions, reductions and dose intensity.	
To further assess anti-tumor activity of LGX818/MEK162 combination, and in combination with targeted agents after progression on LGX818/MEK162 combination	PFS, DOR, TTR, DCR, and OS (Part II only)	Refer to Section 10.5.2.
To characterize genomic alterations in tumor tissue at baseline and at tumor progression.	Genomic alteration status (e.g. mutation, amplification, deletion, overexpression, ligand activation and splice variants) of pre-defined markers	Refer to Section 10.5.5.
To determine the PK profiles of LGX818,MEK162 and the third agents when given in combination and to assess drug-drug interaction	Plasma concentration and derived parameters of LGX/MEK, and targeted agents	Refer to Section 10.5.4.


CCI

4 Study design

4.1 Description of study design

Note: As of Protocol Amendment 06, enrollment to the BKM120-, BGJ398- and INC280-containing arms in Part II is closed. As of Amendment 07, enrollment to the LEE011 arm in Part II is closed.

This is a multicenter, open-label, phase II study which will enroll approximately 140 patients with BRAF mutant locally advanced unresectable or metastatic melanoma.

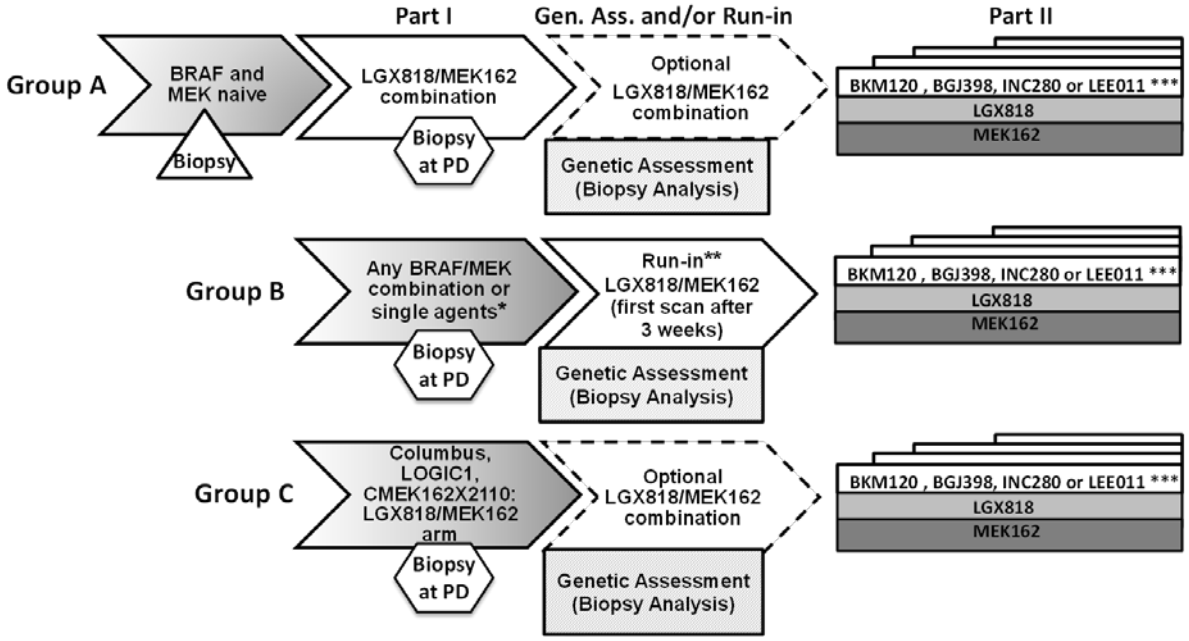
This study consists of two parts: in Part I, patients naïve to selective BRAF and MEK inhibitors will be treated with the LGX818/MEK162 combination until disease progression (as defined per RECIST v1.1). Based on the genetic assessment of a tumor biopsy obtained at progression of disease (PD), patients will enter Part II of the study for tailored combination treatment in one of four arms: LGX818/MEK162 + BKM120, BGJ398, INC280 or LEE011 (Figure 4-1). New triple combination arms will be introduced in the study via substantial protocol amendment which will require submission, review and approval by Health Authority (HA) and Ethic Committees (EC) or Institutional Review Boards (IRB) following local regulatory requirements. As of 10 July 2015, the triple combination of LGX818/MEK162 + BKM120 is no longer being explored, due to decreased exposure of BKM120 given with LGX818/MEK162 as compared to exposures achieved with single agent BKM120. It is assumed that this is attributable to LGX818, which is a known inducer of the CYP enzymes.

During Part I, patients will be treated with LGX818/MEK162 at RP2D of the dual combination.

In Part II, dose escalation for the triple combination will occur unless a RP2D for the respective combination is already established.

Non-naïve patients for BRAF and/or MEK inhibitor treatment who are relapsing will be enrolled into Part II. Depending on the previous treatment, patients may receive a brief Run-in with LGX818/MEK162 combination.

Figure 4-1 Study design



*Single agents: i.e. Vemurafenib, Dabrafenib, LGX818, Trametinib, MEK162; Combos: i.e. Dabrafenib/Trametinib, LGX818/MEK162 combination

**Patients who progressed on a previous BRAFi and/or MEKi regimen will continue on LGX818/MEK162 if PR is observed, followed by new Biopsy at progression. Patients who did not progress on their prior BRAFi/MEKi regimen may continue LGX818/MEK162 combination until evidence of disease progression at which point a tumor biopsy will be taken and analyzed to guide assignment to a triple combination arm in Part II.

***LEE011 cohort might start directly at the RP2D established in CMEK162X2110, if available.

Note: The triple combination arms containing BKM120, INC280, BGJ398 and LEE011 in Part II are closed to enrollment as these combinations are no longer being explored.

BRAF V600 mutant melanoma patients can enter different parts of this study (Part I, Run-in or Part II) according to their previous treatments:

Group A

Patients **naïve to selective BRAF and MEK inhibitors** will enter the **Part I** and be treated with LGX818/MEK162 combination at the RP2D of 450 mg/QD and 45 mg/BID, respectively, until disease progression (as defined per RECIST v1.1), or no clinical benefit. At the time of disease progression, newly obtained tumor sample will be analyzed for a selected panel of genes (Table 4-1) in order to assign patients to a triple combination arm in **Part II**.

Group B

Patients who progressed after treatment with single agent BRAF or MEK inhibitor or the combination of BRAF/MEK inhibitors (excluding LGX818/MEK162 combination) will receive LGX818/MEK162 combination in a brief Run-in phase (at least 3 weeks) followed by early disease assessment after 3 weeks. Patients achieving at least a PR from this treatment at the time of the first CT/MRI scan (during the Run-in phase) will continue on LGX818/MEK162 combination until progression. At this time, a newly obtained tumor biopsy will be mandatory

and patients will be assigned to a triple combination arm in Part II on the basis of the tumor sample's genetic assessment (Table 4-1). Patients not deriving clinical benefit from LGX818/MEK162 combination therapy will be assigned to a treatment arm in Part II on the basis of the analysis of their most recent tumor biopsy.

Patients who did not progress on their prior BRAF and/or MEK inhibitor regimen (including LGX818 and/or MEK162), may enter the Run-in and continue LGX818/MEK162 combination until evidence of disease progression at which point a tumor biopsy will be taken and analyzed to guide assignment to a triple combination arm in Part II.

Group C

Note: As of Amendment 07, the triple combination arms containing BKM120, INC280, BGJ398 and LEE011 in Part II are closed to enrollment as these combinations are no longer being explored, therefore no additional patients will be enrolled from Group C.

Patients who **progressed after treatment with LGX818/MEK162 combination** in other Sponsor studies (e.g. [CMEK162X2110], [CLGX818X2102] and [COLUMBUS] or IITs) are eligible to enter **Part II** directly on the basis of the molecular analysis of their last progressive tumor sample.

Important note: In Groups B and C, progressive disease (PD) after previous treatment should be documented per RECIST v1.1 and determined using radiological assessments.

During the molecular analysis, all patients (Groups A, B and C) may be treated with 450mg/QD of LGX818 and 45mg/BID of MEK162 or their last tolerated dose, not exceeding 450mg/QD of LGX818 and 45mg/BID of MEK162, until assigned to a triple combination arm, as indicated by Table 4-1. However, these patients must meet the related inclusion criteria (see Section 5.2) in order to continue to be treated with LGX818/MEK162 combination during the tumor genetic assessment. Moreover, patients should not discontinue LGX818/MEK162 combination for more than 6 weeks for AEs related to this combination prior to entering Part II of this study. All AEs related to LGX818/MEK162 combination should resolve to at least grade 2 before the first dose of triple combination.

Progressive disease assessment is deemed to be confirmed from the previous study (e.g. [COLUMBUS], [CMEK162X2110] and [CLGX818X2102] or IITs) and may be used as baseline tumor evaluation for Part II of this study, only if the time interval before start of Part II study treatment is no longer than 28 days.

Assignment of triple combination treatment

Table 4-1 Assignment of triple combination treatment based on molecular alteration(s) detected at progression under LGX818/MEK162 combination

Priority*	Molecular alteration identified on biopsy at progression**			Drug to be given in combination with LGX818/MEK162
	Amplification	Mutation	Loss	
1	CCND1 CDK4 B/CRAF No alteration in any gene listed in this table.	CDK4 MAP2K1/K2 N/KRAS HRAS	P16	LEE011***
2	HER2 IGF-1R EGFR	PTEN PIK3CA EGFR	PTEN	BKM120***
3	cMET			INC280***
4	FGFR1 FGFR2 FGFR3	FGFR1 FGFR2 FGFR3		BGJ398***

* Priority order may be revised based on data arising from this study or from other internal or external research.

** Other alterations arising from internal or external research may be considered in the future.

*** BKM120 (Amendment 03), BGJ398, INC280 (Amendment 06), and LEE011 (Amendment 07) triple combination arms were closed to enrollment as these combinations are no longer being explored.

Assignment to the specific triple combination is based on the results of genetic profiling of the tumor biopsy obtained at progression from LGX818/MEK162 combination, as described in Table 4-1.

If a patient is assigned to one triple combination arm due to his/her molecular alteration, but he/she meets the additional exclusion criteria for that arm, then the investigator and the Sponsor will come to agreement on which group is most appropriate for the patient.

If a patient does not fit any of the criteria specified in Table 4-1, or if the biopsy is medically contra-indicated for the patient, other relevant data may be considered, and the investigator and the Sponsor may decide to assign the patient to the LEE011 triple combination treatment group.

Molecular pre-screening

To enter the screening phase for Part I, Run-in and Part II of this study, patients must complete the molecular pre-screening assessment and provide written documentation of BRAF V600 mutation (see Section 7.1.1 for details).

Screening

Only once the BRAF V600 mutational status is known, the patient is allowed to sign the Main Study Informed Consent Form and start the screening for the appropriate study part. All screening evaluations are required to be performed before administration of study treatment.

Treatment periods

There will be two treatment parts: Part I and Part II:

Part I = LGX818/MEK162 combination treatment phase that will begin on Cycle 1 Day 1 until disease progression and initiation of triple combination treatment.

Part II = triple combination treatment that should be initiated once the genetic alterations from tumor biopsy collection at the time of progression are known.

Important note: patients in group B will have to undergo a three-week Run-in period with LGX818/MEK162. Please, see the flowchart in Figure 7-1.

Study treatment will be administered as 21-day cycles (except LGX818/MEK162/LEE011 and LGX818/MEK162/BGJ398 combination arm of 28-day cycles) and will continue until disease progression (on triple combination treatment), unacceptable toxicity, withdrawal of informed consent, or death.

Eligible patients may continue treatment beyond the data cutoff.

Once a patient has received 3 cycles of treatment a reduced schedule of assessments for the subsequent cycles will be followed. Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5 define the reduced schedule of assessments.

Since the safety and efficacy of the dual combination of binimetinib and encorafenib has been extensively assessed, patients who have been on treatment in Part I for ≥ 36 months will be followed as per local standard-of-care practice for patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors and only limited data will be collected (see Section 7.2).

30-day safety follow-up assessments

Patients must complete the safety follow-up assessments 30 days after the last dose of the study treatment (see also Section 7.1.5 and Section 7.1.6). For patients who have been on treatment in Part I for ≥ 36 months, the 30 day follow-up will include a review of concomitant medications and assessment of compliance with administration of LGX818 (encorafenib) and MEK162 (binimetinib). There will also be review of AEs with recording of all Grade 3 or 4 AEs and all SAEs (SAEs, follow-up of SAEs to continue as described in Section 8). Other safety evaluations may be conducted if clinically indicated.

Disease progression, survival follow-up assessments

Patients enrolled in Part I, Run-in and Part II of the study who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease. All patients enrolled in the Part II of the study will be followed for survival (Section 7.1.6.3).

4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned. However, the dose-escalations are planned for Part II. The dose-escalation design foresees that decisions based on the DLT data are taken before the end of the study. More precisely, after each cohort in the dose-escalation phase, the next dose combination has to be chosen depending on the observed data. Details of this procedure and the process for communication with Investigators are provided in Section 6.2.3.

4.3 Definition of end of the study

End of study (Last Patient Last Visit [LPLV]) will occur once all patients have discontinued treatment and all eligible patients (patients who have not withdrawn consent and are not lost to follow-up) have completed their 30-day follow-up visit.

4.4 Early study termination

The study can be terminated at any time for any reason by the Sponsor. Should this be necessary, the patient should be seen as soon as possible. The same assessments for a prematurely withdrawn patient should be performed as described in Section 7.1.6.1. 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 Population

5.1 Patient population

Study CLGX818X2109 will be conducted in adult patients with locally advanced or metastatic melanoma harboring a confirmed BRAF V600 mutation. Moreover patients fitting group **A**, **B** or **C** (see Section 4.1), and meeting all the inclusion criteria in Section 5.2 are eligible to start with either LGX818/MEK162 combination or with one of the triple combinations (LGX818/MEK162 + third agent, as described in Figure 4-1)

Patients enrolled in this study are not permitted to participate in parallel investigational drug or device studies. Additionally, patients who have been permanently discontinued from study medication must not be re-enrolled for a second course of 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.

5.2 Inclusion criteria (Group A, B and C)

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

1. **For Group A only**: patients who are **naïve** to selective BRAF and MEK inhibitors and might have received other allowed treatments such as chemotherapy, biological therapy (e.g., antibodies) (see related exclusion criterion in Section 5.3)
2. Patients (male and female) age ≥ 18 years

3. Able to understand and voluntarily sign the informed consent form prior to any screening procedure, and ability to comply with the study visit schedule and other protocol requirements.
4. Histologically confirmed diagnosis of unresectable stage III or metastatic melanoma (stage IIIC to IV per American Joint Committee on Cancer [AJCC]).
5. Documented evidence of BRAF V600 mutation.
6. **For Group A only**: Patients must provide either archival or newly obtained tumor sample at baseline. In addition, patients must agree to a mandatory biopsy at the time of progression from LGX818/MEK162 combination, if not medically contraindicated.
7. Evidence of measurable disease, as determined by RECIST v1.1.
   Note: Lesions in areas of prior radiotherapy or other locoregional therapies (e.g., percutaneous ablation) should not be considered measurable, unless lesion progression has been documented since the therapy.
8. ECOG Performance Status ≤ 2.
9. Negative serum pregnancy test within 72 hours prior to the first dose of study treatment in all women of childbearing potential.
10. **For Group B only**: Patients who progressed after treatment with single agent BRAF or MEK inhibitor or the combination of BRAF/MEK inhibitors (excluding LGX818/MEK162 combination) and patients who did not progress on their prior BRAF and/or MEK inhibitor regimen (including LGX818 and/or MEK162 inhibitor), but did not tolerate this treatment, may enter the Run-in (Group B) upon consultation with the Sponsor.
11. **For Group B only**: Patients with progressive disease following any single or double-agent BRAF and MEK inhibitors other than LGX818 and /or MEK162 must discontinue these treatments for a period of at least five half-lives before the first day of dosing in the Run-in, and the drug related AE's from the previous treatment must have normalized to at least grade 2.
12. **For Group B only**: The most recent biopsy sample collected, either before starting treatment with any BRAF and/or MEK inhibitor, or after progression from any previous BRAF and/or MEK inhibitor (other than LGX818 and MEK162 combination) must be available before entering the Run-in. In addition, patients must agree to a biopsy at the time of progression from LGX818/MEK162 combination (see Figure 7-1), if necessary and not medically contraindicated.

Additional inclusion criteria for Part II (Group C)

Group C patients are eligible for inclusion in the triple combination part (Part II) of this study, if they meet the above inclusion criteria from N. 2 to N. 9 and **all** of the following criteria:

13. Progressive disease documented per RECIST v 1.1 and determined using radiological assessments, following prior treatment with LGX818/MEK162 combination.
14. A pre-LGX818/MEK162 combination archival tumor sample must be available.
15. A biopsy sample at disease progression, post-LGX818/MEK162 combination, must be either already available from previous studies or collectable at screening/baseline of this study. This tumor sample will be analyzed in order to determine which third

investigational drug patients will be administered as described in Section 4.1 of the protocol.

16. Patients are allowed to continue receiving LGX818/MEK162 combination (at their highest tolerated doses) during their tumor genetic assessment if all inclusion and exclusion criteria (Section 5.3) are met at Screening as well as the following conditions:
    - Absence of symptoms and signs indicating clinically significant progressive disease not compatible with continued participation in this study,
    - No clinically significant decline in ECOG performance status,
    - Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.
17. Progressive disease documentation, produced at the last tumor assessment in the previous study, must be provided. The last progressive disease assessment visit must have been performed within 4 weeks (28 days) from the scheduled first dose administration in this study. If this is not the case, a new tumor assessment should be performed.

5.3 Exclusion criteria

Enrollment in Part I and Run-in

Patients eligible for Part I or Run-in of this study must NOT meet **any** of the following criteria:

1. Symptomatic or untreated leptomeningeal disease.
2. Symptomatic brain metastasis. Patients previously treated or untreated for brain metastasis that are asymptomatic in the absence of corticosteroid therapy or on a stable dose of steroids for four weeks are allowed to enroll. Brain metastases must be stable at least 4 weeks with verification by imaging (e.g. brain MRI completed at screening demonstrating no current evidence of progressive brain metastases).
3. Patients are not permitted to receive enzyme inducing anti-epileptic drugs.
4. Known acute or chronic pancreatitis.
5. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes);
6. Clinically significant cardiac disease including any of the following:
    - CHF requiring treatment (NYH grade ≥ 2)
    - LVEF < 50% as determined by MUGA scan or ECHO or uncontrolled hypertension (please refer to WHO-ISH guidelines)
    - History or presence of clinically significant ventricular arrhythmias or uncontrolled atrial fibrillation
    - Clinically significant resting bradycardia
    - Unstable angina pectoris ≤ 3 months prior to starting study drug
    - Acute Myocardial Infarction (AMI) ≤ 3 months prior to starting study drug
    - QTcF > 480 msec.
7. Patients with any of the following laboratory values at Screening/baseline:
    - Absolute neutrophil count (ANC) <1,500/mm^3 [1.5 x 10^9/L]

- Platelets < 100,000/mm^3 [100 x 10^9/L]
- Hemoglobin < 9.0 g/dL
- Serum creatinine >1.5 x ULN or calculated or directly measured CrCl < 50% LLN (lower limit of normal)
- Serum total bilirubin >1.5 x ULN
- AST/SGOT or ALT/SGPT > 3 x ULN, or > 5 x ULN if liver metastases are present

8. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
9. Patients treated with warfarin or other coumadin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed.
10. Previous or concurrent malignancy. Exceptions: adequately treated basal cell or squamous cell skin cancer; in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to study entry; or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to first dose administration.
11. **Pregnant or nursing (lactating) women**, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum hCG laboratory test.
    Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, are not allowed to participate in this study UNLESS they are using highly effective methods of contraception throughout the study and for 3 months after study drug discontinuation. Highly effective contraception methods include:
    - Total abstinence when this is in line with the preferred and usual lifestyle of the patient or
    - Male or female sterilization
    - Combination of any two of the following (a+b)
        a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        b. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

    Post-menopausal women are allowed to participate in this study. 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 six months of spontaneous amenorrhea with serum Follicle-Stimulating Hormone (FSH) levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. 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.
12. **Sexually active males** must use a condom during intercourse while taking the drug and for 3 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

13. History of thromboembolic or cerebrovascular events within the last 6 months, including transient ischemic attack, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism.
14. Patients who have received radiation therapy (that includes > 30% of the bone marrow reserve), chemotherapy, biological therapy (e.g., antibodies) within ≤ 4 weeks (6 weeks for nitrosourea, mitomycin-C), or who have been treated with continuous or intermittent small molecule therapeutics or investigational agents within 5-half-lives of the agent (or ≤ 4 weeks when half-life is unknown) prior to starting study drug, or, who have not recovered from the side effects of such therapy (except alopecia).
15. Patients who have undergone any major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery.
16. Known Human Immunodeficiency Virus (HIV) infection.
17. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study.
18. Patients unable to stop treatment with strong CYP3A4 inhibitors and CYP2C9 substrates with narrow therapeutic index (e.g. warfarin, phenytoin). These medications should be stopped 7 days prior to first dose of study treatment (refer to Section 6.4.3 and Appendix 7 for prohibited medications for this combination treatment).

Enrollment in Part II

Note: Enrollment to the BKM120- (Amendment 03), BGJ398- and INC280- (Amendment 06) and LEE011 (Amendment 07)-containing arms in Part II is closed.

Patients are NOT eligible for enrollment in Part II of this study if they meet any exclusion criteria listed above, and/or any applicable additional exclusion criteria listed below. Please note, patients who have developed brain metastases during Part I of the study may continue to Part II upon discussion with the Sponsor Medical Monitor. The brain metastasis must be either asymptomatic or treated and stable for at least 4 weeks and on a stable or tapering dose of steroids for at least 2 weeks. Patients with brain metastasis are not eligible for the combination with LEE011.

19. Patients who discontinued LGX818/MEK162 for more than 6 weeks prior to the scheduled first dose of triple combination (Part II), and AEs related to the above treatment are not resolved to at least grade 2.

Additional exclusion criteria for Part II for selected triple combination

LGX818/MEK162 + INC280: This arm is closed to enrollment as this combination is no longer being explored (Amendment 06).

20. Patients unable to stop known CYP3A4, CYP1A2, CYP2C8 or CYP2C19 substrates with narrow therapeutic index. These medications should be stopped 7 days prior to first dose of study treatment (refer to Section 6.4.3 and Appendix 7 for prohibited medications for this combination treatment).

21. Patients receiving treatment with long acting proton pump inhibitors, and unable to discontinue them 3 days prior to the start of study treatment and during the course of the study.
22. Asymptomatic serum amylase > CTCAE Grade 2 (1.5-2.0xULN). Patients with Grade 1 or Grade 2 serum amylase at the beginning of the study must be confirmed to have no signs or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.)
23. Serum lipase > ULN

LGX818/MEK162 + BKM120: This arm was closed to enrollment due to DDI between LGX818 and BKM120 (Amendment 03).

24. Patients with fasting glucose > 120 mg/dL or 6.7 mmol/L, and HbA1c > 8 %.
25. Patient has any of the following mood disorders as judged by the Investigator or a Psychiatrist:
    - Patient has a score ≥ 12 on the PHQ-9 questionnaire
    - 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)
    - Patient has a GAD-7 mood scale score ≥ 15
    - 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.
    - Patient has ≥ CTCAE grade 3 anxiety
26. Patients with uncontrolled hypertension (please refer to WHO-ISH guidelines)
27. Patient is 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 randomization. Please refer to Section 6.4.3 and Appendix 7 for a list of prohibited drugs.
    Patients currently receiving treatment with strong and moderate inhibitors or inducers of isoenzyme CYP3A. 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 randomization is allowed. Please refer to Appendix 7 for prohibited medication of this combination treatment.

LGX818/MEK162 + BGJ398: This arm is closed to enrollment as this combination is no longer being explored (Amendment 06).

28. History and/or current evidence of significant ectopic mineralization/ calcification with the exception of calcified lymph nodes and asymptomatic vascular calcification.

29. Current evidence of corneal disorder/ keratopathy incl. but not limited to bullous/ band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis etc., confirmed by ophthalmologic examination
30. Patients with current evidence of endocrine alteration of calcium/phosphate homeostasis.
31. History of congenital long QT- syndrome and/or hypokalemia CTCAE Grade ≥ 3 and/or magnesium levels below the clinically relevant lower limits before the first dose of triple combination.
32. QTcF > 470 msec
33. Use of medications that are known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes 7 days prior to first dose. (Refer to Appendix 7)
34. Ionized (i) calcium (Ca) > ULN
35. Serum inorganic phosphorus (Pi) > ULN
36. Patients who are currently receiving treatment with agents that are known CYP3A4 strong inducers or inhibitors. (Refer to Appendix 7 for prohibited medications).

LGX818/MEK162 + LEE011: This arm is closed to enrollment as this combination is no longer being explored (Amendment 07).

37. Uncontrolled hypertension (please refer to WHO-ISH guidelines) are excluded from study.
38. Current evidence of brain metastasis or brain metastasis detected by mandatory CT/MRI at screening
39. PT/INR or aPTT > 1.5xULN
40. QTcF ≥450 ms on screening ECG
41. Mean resting heart rate < 50 or > 90 bpm (determined from ECG)
42. Patients with abnormalities of the following laboratory tests unless corrected to within normal limits with supplements before the first dose of study medication:
    - Sodium
    - Potassium
    - Magnesium
    - Total Calcium (corrected for serum albumin)
    - Phosphorus
43. Total bilirubin ≥ ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN.
44. Aspartate transaminase (AST) ≥ 2.5 × ULN, ≥ 5 × ULN in patients with liver metastasis
45. Alanine transaminase (ALT) ≥ 2.5 × ULN, ≥ 5 × ULN in patients with liver metastasis
46. Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome or any of the following before the first dose of the triple combination:
    - Risk factors for TdP including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
    - Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication (e.g., within 5 half-lives or 7 days prior to starting study drug)

- Inability to determine the QTcF interval.

47. Any heart disease that requires the use of a cardiac pacemaker or implantable cardioverter defibrillator ≤ 3 months prior to starting study drug.
48. Unstable atrial fibrillation (ventricular response >100 bpm).
49. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II, and third degree AV block)
50. History of documented myocardial infarction (MI), angina pectoris, symptomatic pericarditis, or coronary artery bypass graft (CABG) within 6 months prior to study entry
51. Documented cardiomyopathy
52. Systolic blood pressure (SBP) > 160 or < 90 mmHg
53. Patients who are currently receiving treatment with agents that are known to cause QTc prolongation in humans. See LEE011 Investigators Brochure for a complete list of agents that are known to cause QTc prolongation in humans.
54. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) formula.
55. Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to Cycle 1 Day 1:

- Concomitant medications, herbal supplements, and/or fruits (e.g., grapefruit, pummelos, star fruit, Seville oranges) and their juices that are strong inducers or inhibitors of CYP3A4/5
- Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.

6 Treatment

6.1 Study treatment

The investigational drugs to be used in this study are LGX818, MEK162, BKM120, BGJ398, INC280, and LEE011.

The study treatments are:

- Part I : dual combination LGX818 (QD) and MEK162 (BID)
- Part II: triple combinations:
  - LGX818 (QD) and MEK162 (BID) and BKM120 (QD) LGX818 (QD) and MEK162 (BID) and BGJ398 (QD)LGX818 (QD) and MEK162 (BID) and INC280 (BID)LGX818 (QD) and MEK162 (BID) and LEE011 (QD) (the triple combinations containing BKM120, BGJ398, INC280, and LEE011 are no longer being explored).

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Starting Dose and Schedule
LGX818	Capsule for oral use	450 mg QD (Part I), or highest tolerated dose (Run-in or Part II) 200 mg QD (in combination with INC280 and LEE011 in Part II) (continuous)
MEK162	Tablet for oral use	45mg BID (Part I) or highest tolerated dose (Run-in or Part II) (continuous)
BKM120***	Capsule for oral use	60 mg QD (Part II) (continuous)
BGJ398***	Capsule for oral use	75 mg QD (Part II) (three week on, one week off)
INC280***	Capsule for oral use	200 mg BID (Part II) (continuous)
INC280***	Tablets for oral use*	400 mg BID (Part II) (continuous)
LEE011***	Capsule for oral use	100 mg QD (Part II) (three week on, one week off)
*Note: For INC280, tablets will be provided when available. *** BKM120 (Amendment 03), BGJ398, and INC280 (Amendment 06) and LEE011 (Amendment 07) triple combination arms were closed to enrollment.		

For all treatments the first dose of study drug defines Day 1 of Cycle.

For Part I a complete treatment cycle is defined as 21 days of daily continuous treatment with LGX818/MEK162 combination.

For Part II a complete treatment cycle is defined as 21 days continuous treatment for LGX818/MEK162 plus BKM120 or INC280.

For LGX818/MEK162 plus LEE011 or plus BGJ398 a complete treatment cycle is defined as 28 days.

LEE011 or BGJ398 will be taken for 21 consecutive days followed by a 7-day planned break (called also 3 weeks on, 1 week off schedule), while LGX818 and MEK162 are always taken on a continuous schedule.

6.1.1.1 Instructions for administration of LGX818, MEK162, INC280, BKM120, LEE011 and BGJ398

Study treatments will be administered as a flat-fixed dose, and not by body weight or body surface area. On all dose administration days patients can take the dual combination (LGX818 and MEK162) or the triple combination (LGX818 and MEK162 and LEE011) with or without food.

LGX818 capsules will be co-administered orally, once daily (QD), with MEK162 tablets, twice daily (BID).

BKM120 will be administered orally on a daily schedule (QD). LEE011 and BGJ398 will be administered orally, once daily for 21 days followed by a 1 week rest (QD). INC280 will be administered orally, twice daily (BID, 21-day cycle)

- **QD Dosing**: Patients should be instructed to take LGX818 or BKM120 or BGJ398 or LEE011 capsules daily in the morning.
- **BID Dosing**: MEK162 and INC280 will be administered orally on a twice daily schedule (BID). The doses of MEK162, or INC280, should be taken 12 ± 2 hours apart.
- Note that all drugs (LGX818 + MEK162, or LGX818 + MEK162 + INC280) should be taken together in the morning and only the BID administered drug (MEK162 or INC280) should be taken in the evening.

Instructions for administration on days when PK sampling is performed:

Pre-dose PK samples should be collected just prior to intake of dose. Exact dates and clock times of administration of the first capsule or tablet of LGX818, MEK162 and third agent will be recorded on the appropriate eCRF.

For combination arm LGX818/MEK162 with BKM120 only:

Instructions for administration on days when a fasting plasma glucose monitoring is performed: On the days of fasting plasma glucose monitoring, patients must be fasting overnight for at least 8 hours prior to the blood collection. A light breakfast/snack may be consumed after fasting plasma glucose draw. Nonetheless, study drugs should be administered on an empty stomach and eating is not allowed for one hour after drug administration. Please, note that if the patient has eaten, he/she must wait two hours until taking the drug

6.1.1.1.1 General instructions

- Patients must be instructed to take MEK162, LGX818, and the 3rd combination agent for Part II, together with a large glass of water (~250 ml) daily in the morning at approximately the same time every day.
- Patient must take the third agent immediately after LGX818/MEK162 (Part II).
- Doses should be taken at approximately the same time each day, except on the days when blood collection is scheduled at the clinic, at which time the patients should take their morning doses at the clinic.
- On days when blood collection is scheduled at the clinic, patients will take oral study drugs in the clinic under the supervision of the investigator or designee. On all other days patients will take oral study drugs at home.
- At each visit, responsible site personnel will ensure that the patient is provided with the correct amount of study drug(s) for the duration of the treatment cycle.
- Patients will be instructed to return unused study drugs to the site at the end of each cycle.
- Patients should be instructed to swallow the capsules/tablets whole and not to chew, crush or open them.
- If the patient forgets to take a dose, then he/she should take the dose within 6 hrs from the normally scheduled dose time. If more than 6 hours has passed from the previous dose, then the dose should be withheld that day and the patient should continue treatment with the next scheduled dose.
- Patients must avoid consumption of grapefruit, pomelos, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7

days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

- 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 and/or diarrhea (or increased stool frequency) must be noted in the AE section of the eCRF. In addition, on the days of full PK sampling, the onset time of any episodes of vomiting within the first 4 hours post-dosing on that day must be noted in the corresponding Dose Administration Record PK page of the eCRF.
- During the entire duration of treatment with INC280, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a sunlamp or tanning bed).

6.1.2 Ancillary treatments

6.1.2.1 Phosphate-lowering therapy for LGX818/MEK162 + BGJ398 combination

Since the administration of BGJ398 may be associated with hyperphosphatemia and given the potential role of phosphorus and calcium in vascular calcifications, accepted limits of serum phosphorus and tCa x Pi have been predefined.

The in-vivo-solubility product of tCa x Pi is about 58mg2/dL2 and higher values involve a significant risk of calcium phosphate precipitation. Phosphorus retention of serum Pi > 6.5 mg/dL is associated with a significantly increased mortality rate of ESRD patients and several studies in this population have reported that tCa x Pi values > 55-60 mg2/dL2 significantly increase the risk of cardiovascular calcification, suggesting that these levels should be the upper limit of acceptability.

For the purpose of this study, in LGX818/MEK162 + BGJ398 combination arm, prophylactic phosphate lowering therapy is recommended according to institutional standards.

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

See Section 6.1.5.

6.1.5 Treatment duration

Patients enrolled in Part I and Run-in (Group A and B) of CLGX818X2109 study will be treated with LGX818/MEK162 combination until progression and/or experiencing unacceptable toxicity, and/or the treatment is discontinued at the discretion of the investigator or withdrawal of consent. In particular, pre-treated patients with BRAF and MEK inhibitors single or dual-agent treatment (Group B) will enter the Run-in part and will be treated with LGX818/MEK162 combination at RP2D for at least 3 weeks (one cycle).

At disease progression from LGX818/MEK162 combination, all patients (Groups A, B and C) will be requested to provide a tumor biopsy in order to be assigned to a triple combination in

Part II (LGX818/MEK162 double agent + third agent) according to the genetic alterations profile identified in the biopsy sample. During this time, patients progressing on LGX818/MEK162 combination (Group A, B and C) can continue to be treated with LGX818/MEK162 combination at the RP2D or highest tolerated dose, until assigned to the appropriate triple-agent therapy arm, as indicated by Table 4-1, and after discussion between the Investigators and the Sponsor. The following criteria must be met:

- Absence of symptoms and signs indicating clinically significant PD not compatible with continued participation in this study,
- No clinically relevant decline in ECOG performance status,
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Moreover, patients should not discontinue LGX818/MEK162 combination for more than 6 weeks for AEs, or any other reason, related to treatment with LGX818/MEK162 combination prior to entering Part II of this study. All AEs should resolve to at least grade 2 before commencing treatment in Part II. Please, refer to Section 6.3.1 for additional guidance on treatment discontinuation

In all cases, continued treatment beyond progression of disease will be allowed in Parts I and II only if a patient meets the above listed criteria and only under special circumstances, for example, cystic lesions, mixed responses, and new brain metastasis which are treatable with stereotactic radiotherapy or surgery, but not requiring whole brain radiotherapy. It is judged by the investigator, in agreement with the Sponsor, whether or not a patient may remain on study treatment as long as he/she continues to benefit from the study drug treatment per investigator assessment.

Patients treated in Part II of the study (LGX818/MEK162 double agent + third agent) who do not tolerate therapy with the third agent may be retreated with LGX818/MEK162 upon discussion with the Sponsor Medical Monitor.

At the time of the data cutoff for the primary analysis, those patients who are continuing to receive clinical benefit may continue to be treated with the current combination, or, if progressing on LGX818/MEK162 combination, they are allowed to receive a triple combination treatment in Part II. Reduced schedule of assessments will be followed from Cycle 3 onward as defined in Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5.

For patients who have been on treatment in Part I for ≥ 36 months, safety evaluations should occur in accordance with local standard-of-care clinical practice and may receive treatment until treatment discontinuation criteria are met.

It is recommended that safety evaluations occur approximately every 4 weeks, unless otherwise specified. Safety should be monitored by assessing physical examination, hematology, chemistry laboratory testing and other pertinent testing as required as part of the safety profile of the compound (dermatological examinations, ophthalmic exams, cardiac profiles) until discontinuation. Adverse events should be reviewed at every visit. Investigators will be required to record all Grade 3 or 4 AEs, including SAEs, in the clinical database. All SAEs are to be reported to the Sponsor or designee using the SAE form.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

Part I

The RP2D for the LGX818 and MEK162 dual combination has been determined as 450 mg LGX818 QD and 45 mg MEK162 BID ([MEK162X2110]). This dose will be used for patients enrolled in the first part of this trial.

Part II

In the second part of this trial, the starting doses for LGX818 are set at 450 mg QD for the triple combinations with BGJ398 and BKM120, and at 200 mg QD for the triple combinations with INC280 and LEE011. MEK162 starting doses are kept at 45 mg BID for all the triple combinations (see Table 6-2).

LGX818/MEK162 + BKM120

Note: Due to the DDI between LGX818 and BKM120 (Amendment 03), the BKM120-containing arm is closed to enrollment as this combination is no longer being explored.

Qualitative DDI assessment (Section 1.2.1.3) predicts potential decrease in BKM120 exposure and no significant impact on LGX818 and MEK162 exposure when LGX818, MEK162 and BKM120 are co-administered. Quantitative analysis using SimCYP simulation predicted no change in LGX818 or BKM120 exposure when the two drugs are co-administered. Preliminary PK data from the ongoing clinical study using combination of MEK162 and BKM120 [CMEK162X2101] showed that the pharmacokinetics of MEK162 and its metabolite were not altered by BKM120. When combined with MEK162, overall BKM120 systemic drug exposure was found to be lower than expected from the single agent data. Therefore the starting dose for this triple combination is selected to be the currently established RP2D for LGX818/MEK162 combination and 60% of the BKM120 single agent MTD (i.e. 100mg): 450 mg QD LGX818, 45 mg BID MEK162 and 60mg QD BKM120.

LGX818/MEK162 + BGJ398

Note: The BGJ398-containing arm is closed to enrollment as this combination is no longer being explored (Amendment 06).

Qualitative DDI assessment (Section 1.2.1.3) predicts potential decrease in BGJ398 exposure and no significant impact on LGX818 and MEK162 exposure when LGX818, MEK162 and BGJ398 are co-administered. Quantitative DDI assessment using SimCYP simulation predicts minimal changes in LGX818 exposure when co-administered with BGJ398. At LGX818 dose of 450 mg QD, it predicts 17% decrease in BGJ398 AUC and minimal change in BGJ398 Cmax at BGJ398 75 mg QD, and 24% decrease in AUC and minimal change in Cmax at BGJ398 125 mg QD (MTD of BGJ398 as single agent). Therefore the starting dose for the triple combination is selected to be the currently established RP2D for LGX818/MEK162 combination and 60% of the BGJ398 MTD (i.e. 125mg): 450 mg QD LGX818, 45 mg BID MEK162, and 75 mg QD BGJ398.

LGX818/MEK162 + INC280

Note: The INC280-containing arm is closed to enrollment as this combination is no longer being explored (Amendment 06).

Qualitative DDI assessment (Section 1.2.1.3) predicts potential decrease in INC280 exposure, increase in LGX818 exposure, and no significant change in MEK162 exposure when LGX818, MEK162 and INC280 are co-administered. Quantitative DDI assessment using SimCYP simulation predicts 100% and 50% increase in AUC and Cmax of LGX818, respectively, as well as 57% and 38% decrease in AUC and Cmax of INC280, respectively when 450 mg QD LGX818 and 200 mg BID INC280 are co-administered. Moreover, quantitative DDI assessment using SimCYP simulation predicts 144% and 61% increase in AUC and Cmax of LGX818, respectively, as well as 50% and 33% decrease in AUC and Cmax of INC280, respectively when 200 mg QD LGX818 and 200 mg BID INC280 are co-administered. Based on that, the starting dose for the triple combination is selected to be 200 mg QD LGX818, 45 mg BID MEK162, and 200 mg BID INC280 capsules. This is 44% of the RP2D of LGX818 in combination with MEK162 and 1/3 of the RP2D of INC280 (600 mg BID).

LGX818/MEK162 + LEE011

The LEE011-containing arm is closed to enrollment as this combination is no longer being explored (Amendment 07).

Qualitative DDI assessment (Section 1.2.1.3) predicts potential decrease in LEE011exposure when it is co-administered with LGX818/MEK162, potential increase in LGX818 exposure, and no significant impact on MEK162 exposure when LGX818, MEK162 and LEE011 are co-administered. Quantitative DDI assessment using Simcyp simulation predicts 29% and 14% increase in AUC and Cmax of LGX818, respectively, as well as 47% and 30% decrease in AUC and Cmax of LEE011, respectively when 450 mg QD LGX818 and 200 mg QD LEE011 are co-administered. Moreover, quantitative DDI assessment using Simcyp simulation predicts 43% and 18% increase in AUC and Cmax of LGX818, respectively, as well as 40% and 26% decrease in AUC and Cmax of LEE011, respectively when 200 mg QD LGX818 and 200 mg QD LEE011 are co-administered. Therefore, the starting dose for this triple combination is selected to be 200 mg QD LGX818, 45 mg BID MEK162, and 100 mg QD LEE011. This is 44% of the RP2D of LGX818 in combination with MEK162 and ~11% of the MTD of LEE011 dose (i.e. 900 mg QD). If the RP2D/MTD for LGX818/MEK162/LEE011 triple combination is established in [CMEK162X2110], that dose will be administered in the LEE011 arm of this study.

In this study, the pharmacokinetics of all combination partners as well as their active metabolites (if applicable) will be evaluated as soon as possible at steady-state and compared with those obtained in the respective monotherapy studies for assessment of the potential drug-drug interaction.

Before the first patient is dosed in any combination, the Bayesian model for this combination will be updated with the most recent data from the ongoing double or triple agent trial, to confirm that the proposed starting doses for LGX818/MEK162 and triple agent are still appropriate (i.e. fulfills the EWOC criteria). If the proposed starting dose does not meet the criteria, a lower dose combination that satisfies the EWOC criteria will be used. In addition,

emerging clinical data from other combination trials may also be considered for the purpose of selecting a starting dose. However, patients will be treated at the determined triple combination MTD/RP2D if it becomes available from other clinical trials. This is to allow treating patients directly at the most appropriate dose without intra-patient dose escalation once results become available for each triple combination arm.

6.2.2 Provisional dose levels

Table 6-2 and Table 6-3 describe the starting doses and the provisional dose levels of study treatments for the combinations that may be evaluated during this trial. Additional dose levels not currently specified may be added and additional patients may be enrolled at a dose level already tested if such changes are deemed necessary to provide optimal safety and tolerability, pharmacokinetic, and pharmacodynamic data, and satisfy the EWOC criteria.

Table 6-2 Provisional dose levels for LGX818 and MEK162 (Part I and Part II)

Dose level* (mg)	LGX818 QD (Part I and Part II in combo with BKM120 or BGJ398)***	MEK162 BID (Part I and Part II in combo with each third agent)	LGX818 QD (Part II in combo with INC280 or LEE011)***
-2**	150	15	50
-1**	300	30	100
1 (starting dose)	450 (RP2D)	45 (RP2D)	200
+1	-	-	-
+2	-		-

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Dose level may be added below the MTD in order to better understand safety, PK or PD. Doses can be modified individually (see Section 6.3.1 for details)

**Dose level -1 and -2 will also be used for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -2 is permitted for this study.

***Triple combination arms containing BKM120 (Amendment 03), INC280, BGJ398 (Amendment 06), and LEE011 (Amendment 07) are closed to enrollment as these combinations are no longer being explored.

Table 6-3 Provisional dose levels for third agents (Part II)

Dose level[1] (mg)	BKM120 QD*	BGJ398 QD*	INC280 BID (capsules)*	INC280 BID (tablets)*	LEE011 QD*
-2[2]	30	25	50		-
-1[2]	40	50	100		50
1 (starting dose)	60	75	200		100[3]
2a				200	
2b	80	100	400	300	200
3	100 (MTD)[4]	125 (MTD)[4]	600 (RP2D)[4,5]	400 (RP2D)[4,5]	300
4	-	-	-		400

1. It is possible for additional and/or intermediate dose levels to be added during the course of the study Dose level may be added below the MTD in order to better understand safety, PK or PD.

2. Dose level -1 and -2 will also be used for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -2 is permitted for this study.

3. Note that the starting dose for LEE011 may be higher. The LEE011 starting dose will be at or below a dose used for a completed cohort of the [CMEK162X2110] study. This dose level must satisfy the EWOC criteria under the BLRM used in [CMEK162X2110] as well as the EWOC criteria under the BLRM used in this study.

4. Note that escalation beyond the single agent MTD/RP2D may be considered if satisfying the EWOC criteria.

5. INC280 capsules will be used in dose level 3. Due to a change in formulation, subsequent dose levels will evaluate the INC280 tablets. The 600 mg BID capsule dose is equivalent in the relevant patient population to the 400 mg BID tablet dose.

* Triple combination arms containing BKM120 (Amendment 03), INC280, BGJ398 (Amendment 06) and LEE011 (Amendment 07) are closed to enrollment as these combinations are no longer being explored .

6.2.2.1 INC280 Dose Escalation: Capsule and Tablet Formulations

Note: The INC280-containing arm is closed to enrollment as this combination is no longer being explored (Amendment 06).

For detailed relative bioavailability of INC280 capsules and INC280 tablets refer to Section 1.2.6.2.2.

The exposure data in cancer patients [CINC280X2102] suggest a dose ratio of approximately 3:2 (capsules:tablets) for converting the capsule formulation to the tablet formulation. Once the INC280 capsule formulation RP2D (600 mg BID) in combination with LGX818 and MEK 162 has been completed, no further escalations with the capsule formulation will be investigated. Subsequent recruitment of patients will occur at the tablet formulation RP2D (400 mg BID) in combination with LGX818 and MEK162 with no further escalation beyond the tablet formulation RP2D (400 mg BID).

Ongoing patients will continue with capsule formulation unless otherwise authorized by the Sponsor Medical Monitor. Patients will have the opportunity to switch from the INC280 capsule formulation to the INC280 tablet formulation only if the capsule formulation is no longer available. The investigators are required to consult with the Sponsor Medical Monitor to

determine the appropriate dose conversion based on the current available PK and safety data for the table formulation.

6.2.3 Guidelines for dose escalation and determination of MTDs

6.2.3.1 MTD definition

The MTD for a combination treatment is defined as the highest combination drug dosage not causing medically unacceptable, dose-limiting toxicity (DLT) in 35% or more of the treated patients in the first cycle of treatment. AEs and laboratory abnormalities considered to be DLTs are defined in Table 6-4. Note that more than one MTD may be identified for a given combination treatment.

For each combination treatment, the applied adaptive Bayesian methodology provides an estimate of the dose levels for each third agent not exceeding the MTD. Typically the MTD is a tested dose with maximum probability of targeted toxicity (DLT rate between 16% to less than 35%). The use of the EWOC principle limits the risk that a potential next dose will exceed the MTD (Section 10.5.3.2).

6.2.3.2 Implementation of dose escalation decisions

The BKM120- (Amendment 03), INC280-, BGJ398- (Amendment 06), and LEE011 (Amendment 07)-containing arms are closed to enrollment as these combinations are no longer being explored.

The dose escalation process will be implemented stepwise and will proceed with cohorts of at least 3 patients at the current dose of triple combination arm in Part II (see also Section 10.8).

In particular, LGX818/MEK162 in combination with LEE011 will be administered at the MTD/R2PD found in the [CMEK162X2110] study, if available. In that case, no further dose escalations will be performed.

The decision to escalate to a higher dose level will occur after evaluation of individual patients' tolerability of the triple combination during the first 21 days of the cycle (except for LGX818/MEK162 + LEE011 and LGX818/MEK162 + BGJ398 combination arms which will be 28 days) upon agreement between the investigators and the Sponsor.

Patients must complete a minimum of one cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions. Dose escalation decisions will occur when at least 3 patients treated at a dose level not tested before have met these criteria. However, if only 2 patients are evaluable and neither patient has experienced a treatment-related toxicity > CTCAE grade 1, dose escalation decisions may be considered.

To implement dose escalation decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK and PD information will all be evaluated by the Investigators and Sponsor study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the

investigator receives written confirmation from the Sponsor indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

The recommended combination doses for the next patients will be guided by the Bayesian logistic regression model (BLRM) with EWOC principle.

The adaptive Bayesian methodology provides an estimate of all dose levels of the combination that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval (16 to less than 35%) and will always satisfy the EWOC principle. For the escalations of BKM120, BGJ398, and INC280, the next dose will not exceed a 100% increase from the previous dose. Should escalation of LEE011 be required in this study, the next dose may exceed a 100% increase from the previous dose, but only if that dose both satisfies the EWOC criteria for the BLRM used in this study, and is a dose that has been used and shown to satisfy the EWOC criteria in the LGX818/MEK162/LEE011 dose escalation taking place in the [CMEK162X2110] study. Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data if necessary. To better define the dose-toxicity relationship additional patients may be enrolled to the current dose level, to a preceding dose level, or to an intermediate dose level before proceeding with further dose escalation.

If the first two patients in a previously untested dose level experience a DLT, enrollment to that dose will stop, the BLRM will be updated and the next patients will be enrolled at the next lower dose level or an intermediate dose level that satisfies the EWOC criteria. If the two consecutive patients treated at a previously tested dose level experience a DLT, further enrollment will stop, the BLRM will be updated with this new information and re-evaluation of the available safety, PK, and PD data will occur. By incorporating all information available, additional patients may be enrolled into the current dose only if the combination still meets the EWOC criteria and as agreed by Investigators and Sponsor personnel. Alternatively, if recruitment to the same dose may not resume, new patients may be recruited to a lower dose combination as agreed by Investigators and Sponsor personnel and if the BLRM predicts that the risk for this lower dose combination to exceed the MTD remains below 35% (EWOC). Re-escalation may then occur if data in subsequent patients supports this (EWOC criteria are satisfied) and Investigators and Sponsor personnel agree.

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first cycle of treatment, then the BRLM will be updated with this new information before any additional patients are enrolled at that higher dose level.

The dose-escalation in each combination arm will continue until identification of the MTD or completion of the study (if the required total number of patients has been enrolled). Identification of the MTD will occur when the following conditions are met:

1. At least six patients have been treated at this dose
2. This dose satisfies one of the following conditions:
    a. The posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
    b. A minimum of 12 patients have already been treated with the combination.

3. It is the dose recommended for patients, either per the model or by review of all clinical data by the Sponsor and Investigators in a dose-escalation teleconference.

Patients may enter the Part II of the study at an LGX818 dose below 450 mg QD, and at a MEK162 dose lower than 45 mg BID if they previously required a dose reduction, but data from at least 3 patients treated at the assigned dose level of LGX818, MEK162 and third agent are required before escalation to the next dose level is allowed. Please note that doses of LGX818 higher than 200mg may be explored in the triple combination arms with LEE011 or INC280, if permissible by BLRM.

6.2.3.3 Intra-patient dose escalation

The BKM120- (Amendment 03), INC280-, BGJ398- (Amendment 06) and LEE011- (Amendment 07)-containing arms are closed to enrollment as these combinations are no longer being explored.

Intra-patient dose escalation is not permitted at any time within the Part I of treatment with LGX818/MEK162 combination because this combination is administered at the RP2D.

Intra-patient dose escalation of the third agent in the combination treatment is permitted during Part II. Intra-patient dose escalation will not be permitted for patients in the LGX818/MEK162 + LEE011 arm in the event that an RP2D of this combination has been declared in study [CMEK162X2110]; in this case these patients will be treated at the declared RP2D.

In order for a patient to be treated at a higher dose of BKM120, BGJ398, INC280, or LEE011, he or she must have tolerated the lower dose combination for at least 1 cycle of therapy (e.g., he or she must not have experienced at the lower dose originally assigned, a toxicity of CTCAE grade ≥ 2 for which relationship to study drug cannot be ruled out). Moreover, the new higher dose of triple combination which the patient is to be treated with, must meet the modified EWOC criteria used for intra-patient escalation.

Patients will have the opportunity to switch from the INC280 capsule formulation to the INC280 tablet formulation only if the capsule formulation is no longer available. The investigators are required to consult with the Sponsor Medical Monitor to determine the appropriate dose conversion based on the current available PK and safety data for the tablet formulation.

The intra-patient dose escalation will be limited to 50% and will be guided by the BLRM according to the following modified EWOC criterion which reflects individual patient tolerability: a patient will be able to intra-escalate to a dose for which there is less than a 40% chance of excessive toxicity. Furthermore, if treatment-related toxicities of CTCAE grade 2 are observed in 2 or more patients at a dose level or if any patient experiences a grade 3 or greater toxicity, then the increase in dose of the third agent will be $\leq 25\%$ for any subsequent increase in dose. (See Appendix 1)

Should any of the other combinations have a RP2D identified from an alternative study, then this will be used for all patients transitioning from double-agent (Part I) into that particular triple combination (Part II) from the time it is identified and no intra-patient escalation will be permitted above this dose. Any patients ongoing with that combination at the time the RP2D is identified may be escalated to the RP2D at the end of their ongoing cycle if, after review of the safety data, both the investigator and the Sponsor agree.

These changes must be recorded on the Dosage Administration Record CRF.

6.2.4 Definitions of dose limiting toxicities (DLTs)

The BKM120- (Amendment 03), INC280-, BGJ398- (Amendment 06) and LEE011 (Amendment 07)-containing arms are closed to enrollment as these combinations are no longer being explored.

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first cycle (first 21 days for BKM120, and INC280, 28 days for LEE011 and BGJ398) of treatment initiation and meets any of the criteria included in Table 6-4.

The rules for treatment re-initiation and dose modification of LGX818, MEK162, BKM120, BGJ398, INC280 or LEE011 treatment are outlined in Section 6.3.

National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 will be used for all grading, unless otherwise noted. For the purpose of dose escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the Sponsor immediately of any unexpected ≥ CTCAE grade 3 adverse events or laboratory abnormalities.

Table 6-4 Criteria for defining dose-limiting toxicities

	Toxicity	**Any of the following criteria:**
Hematologic	Blood and lymphatic system disorders[a]	Febrile neutropenia (ANC < 1.0 x 10^9/L with fever ≥ 38.5°C)[b]
	Investigations (Blood)	Absolute Neutrophil count CTCAE Grade 3 for > 7 consecutive days
		Absolute Neutrophil count CTCAE Grade 4
		Platelet count CTCAE Grade 3 with signs of bleeding
		Platelet count CTCAE Grade 4
Dermatologic	Skin and subcutaneous tissue disorders: Rash, HFSR and/or photosensitivity	Rash, HFSR or photosensitivity CTCAE Grade 3 despite skin toxicity treatment (as per local practice)
		Rash, HFSR or photosensitivity CTCAE Grade 4
GI	Gastrointestinal disorders	Diarrhea CTCAE Grade 3 ≥ 48 hrs, despite the use of optimal anti-diarrhea therapy
		Nausea or vomiting CTCAE Grade 3 ≥ 48 hrs, despite the use of optimal anti-emetic therapy
		Grade 4
	Pancreas	Pancreatitis CTCAE Grade 3
Renal	Investigations (Renal)	Serum creatinine CTCAE Grade ≥ 3

	Toxicity	**Any of the following criteria:**
Hepatic	Investigations (Hepatic)	Blood bilirubin (total bilirubin) CTCAE Grade ≥ 3
		AST or ALT CTCAE Grade 3 in conjunction with blood (total) bilirubin CTCAE Grade ≥ 2 of any duration
		AST or ALT CTCAE Grade 3 for > 7 consecutive days.
		AST or ALT CTCAE Grade 4.
		Serum alkaline phosphatase CTCAE Grade 4 > 7 consecutive days
Hepatic – for INC280 combination therapy only	Investigations (Hepatic)	Isolated* total bilirubin Grade 2 > 7 consecutive days Isolated* total bilirubin Grade ≥ 3 Isolated* AST or ALT Grade ≥ 3 for > 7 consecutive days AST or ALT Grade 4 For patients with normal baseline ALT or AST or total bilirubin value: AST or ALT > 3 x ULN combined** with total bilirubin >2.0 x ULN without evidence of cholestasis*** OR For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, **combined with** [total bilirubin > 2 x baseline AND > 2.0 x ULN] * "Isolated total bilirubin" increase defined as: total bilirubin increase without ALT or AST increase; "isolated AST or ALT" increase defined as: AST or ALT increase without total bilirubin increase ** "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold *** "Cholestasis" defined as: ALP elevation [>2xULN and R value < 2] in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis)
		Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury)

	Toxicity	Any of the following criteria:
Metabolic	Investigations (Metabolic)	Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade ≥ 3 > 7 consecutive days
		Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 4
Cardiac	Cardiac disorders	CTCAE Grade ≥ 3
	Vascular disorders	Persistent hypertension CTCAE Grade ≥ 3 requiring more than one drug or more intensive therapy than previously
Investigations (Cardiac)	Investigations (Cardiac)	Serum CK/CPK CTCAE Grade 3 for > 14 consecutive days if clinically significant (symptomatic)
		Serum CK/CPK CTCAE Grade 4 for > 14 consecutive days
		Serum CK-MB CTCAE grade 4
		QTcF interval ≥ 501 ms on at least two separate ECGs (only for triple combination)
Ophthalmologic	Eye disorders - RVO	Any grade
	Eye disorders- Retinal events and Uveitis	CTCAE Grade 3, if not resolved within 21 days
		CTCAE Grade 4
	Eye disorders- any other	CTCAE Grade 3, if not resolved within 21 days
		CTCAE Grade 4
General disorders	Fatigue	Fatigue CTCAE Grade 3 for > 7 consecutive days
		CTCAE Grade 4 fatigue (asthenia)
	Edema	Edema CTCAE Grade 3 for > 14 consecutive days
Other Adverse Events[c]		Any other CTCAE Grade ≥ 3 toxicity (except cutaneous SCC[c], CTCAE Grade 3 alopecia, CTCAE Grade 3 fatigue/asthenia <7 days,

[a] ≥ CTCAE grade 3 anemia will not be considered a DLT unless judged to be a hemolytic process secondary to study drug. ≥ CTCAE grade 3 lymphopenia will not be considered a DLT unless clinically significant.

[b] Not according to CTCAEv4.03

[c] Cutaneous SCC has been reported to be an on-target side-effect that is manageable and will not be considered a DLT.

	Toxicity	Any of the following criteria:
Specific criteria for defining dose-limiting toxicities in combination arm with BKM120		
Endocrine		A grade 3 hyperglycemic event (> 250 mg/dL) should result in continuous dosing (case-by-case basis) of the drug, but the patient should have immediate access to consultation with an endocrinologist or specialist. If the event continues for > 2 week after consultation and management, consider this a DLT. (Busaidy et al 2012)
Pneumonitis		CTCAE grade ≥3 symptomatic pneumonitis
Psychiatric	Mood alteration	CTCAE grade 2 mood alteration that does not resolve to ≤ grade 1 within 14 days despite medical treatment (for Anxiety only, if worsened from baseline)
		CTCAE grade ≥ 3 mood alteration
	Psychiatric disorders: Agitation, anxiety, depression, suicide ideation	Psychiatric disorders: Agitation, anxiety, depression, suicide ideation CTCAE Grade 2 despite mood stabilizing therapy for at least 14 days; for anxiety only, if worsened from baseline. Psychiatric disorders CTCAE Grade ≥ 3
Specific criteria for defining dose-limiting toxicities in combination arm with BGJ398		
Renal	Investigations (Renal)	Creatinine CTCAE Grade 2 for > 7 consecutive days.
Metabolic	Investigations (Metabolic)	Hyperphosphatemia (serum-high) Serum Pi>7.0mg/dL for > 7 consecutive days despite phosphorus lowering therapy for at least 14 days Serum Pi > 9.0 mg/dL, despite phosphorus lowering therapy for at least 14 days Serum Pi > 10.0 mg/dL
		Hypercalcemia (serum-high) Serum calcium CTCAE Grade 2 for > 7 consecutive days. Serum calcium CTCAE Grade ≥ 3.
Ocular/visual		Clinical evidence of corneal disorder/ disease of any grade (CTCAE grade ≥ 2) including but not limited to corneal edema, abrasion, bullous/band keratopathy, inflammation/ ulceration, keratoconjunctivitis confirmed by ophthalmologic examination during any cycle.
Specific criteria for defining dose-limiting toxicities in combination arm with INC280		
Any Neurological Toxicity		Grade ≥ 2

6.3 Dose modifications

6.3.1 Dose modification and dose delay

If a patient develops a toxicity, the dose may be adjusted or delayed as outlined in this section. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03). All dosing interruptions and changes must be recorded on the Dosage Administration Record eCRF. If a patient experiences a DLT, study treatment should be interrupted and the toxicity should be followed, as described in Section 6.3.3. Each patient is only allowed a maximum of two dose reductions after which the patient will be discontinued from the study treatment. In addition, a patient should discontinue treatment with the LGX818/MEK162 combination or LGX818/MEK162 + third agent combination if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity. However, the patient may continue to receive study treatment at the next lower dose level, if appropriate, at the discretion of the Investigator and in discussion with the Sponsor. If, after interruption of treatment and resolution, treatment is resumed at the same dose following the criteria in Table 6-5, Table 6-6, Table 6-7, Table 6-8, Table 6-9 and Table 6-10 and the same toxicity recurs with the same or worse severity, next treatment re-initiation must resume at the next lower dose level irrespective of duration. For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles. Table 6-5 lists the dose modification guidelines for LEE011.

Table 6-5 LEE011 dose modification guidelines

	Dose	Number of Capsules and Strength
Starting dose	600 mg	3 x 200 mg capsules
First dose reduction	400 mg	2 x 200 mg capsules
Second dose reduction	200 mg	1 x 200 mg capsules

If a patient requires a dose delay of > 21 consecutive days of LGX818, MEK162, BKM120, BGJ398, LEE011, or INC280 from the intended day of the next scheduled dose, then the patient should be discontinued from the study treatment. In exceptional situations, if the patient is clearly benefiting from the study treatment (i.e. stable disease, partial response, complete response), and in the opinion of the investigator no safety concerns are present, after discussion with the Sponsor Medical Monitor, the patient may remain on the study treatment at a dose level adjusted based on safety.

Treatment discontinuation

In addition, a patient must discontinue study treatment if, after treatment is resumed at a lower dose, the same toxicity reoccurs with the worse severity during the first cycle (except for hyperglycemia, hyperphosphatemia, or for CK not clinically significant elevation, where explicit rules are provided in appendices, and for skin lesions such as SCC/KA, squamous cell carcinoma/keratoacanthoma). If after resolution, treatment is resumed at the same dose following the criteria in Table 6-5 to Table 6-10, and the same toxicity reoccurs with the same severity, next treatment re-initiation must resume at the next lower dose level irrespective of duration.

For each patient, once a dose level reduction of LGX818, MEK162, BKM120, BGJ398, LEE011, or INC280 has occurred, the dose level may not be re-escalated during subsequent treatment cycles with the study drugs. Dose reduction for LGX818 MEK162, BKM120, BGJ398, LEE011, or INC280 means treatment at the next lower, previously tested dose level of the respective study drug.

In the LGX818/MEK162 combination part of the study, treatment beyond progression is allowed for the assignment of the combination treatment (see Section 6.1.5).

Table 6-6 Criteria for interruption and re-initiation of LGX818/MEK162 combination treatment

Recommended Dose Modifications for LGX818/MEK162 combination	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
No toxicity	Maintain dose level
Blood and lymphatic system disorder	
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)[b]	Omit dose until resolved, then ↓ 1 dose level of LGX818 and MEK162
Investigations (Blood)	
Neutropenia (neutrophil count (ANC) decreased)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) or Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level of LGX818 and MEK162
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Omit dose of LGX818 and MEK162 until resolved to ≤ Grade 2, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 - If resolved in > 7 days, then ↓ 1 dose level* of LGX818 and maintain dose level of MEK162
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose of LGX818 and MEK162 until resolved to ≤ Grade 2, then ↓ 1 dose level* of LGX818 and MEK162
Thrombocytopenia (platelet count decreased)	
Grade 1 (PLT < LLN - 75 x 10^9/L) or Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level of LGX818 and MEK162
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose of LGX818 and MEK162 until resolved to ≤ Grade 1, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 - If resolved in > 7 days and/or with signs of bleeding, then ↓ 1 dose level* of LGX818 and MEK162
Grade 4 (PLT < 25 x 10^9/L)	Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment.

Recommended Dose Modifications for LGX818/MEK162 combination	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Gastrointestinal disorders	
Diarrhea Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose level of LGX818 and MEK162, but initiate anti-diarrhea treatment (see Appendix 3). Omit dose of LGX818 and MEK162 until resolved to Grade ≤ 1 and then maintain dose level of LGX818 and MEK162 - For 2nd occurrence of diarrhea Grade 2 within 15 days, omit dose of LGX818 and MEK162 until resolved to Grade ≤ 1, then reduce MEK162 by 1 dose level* and maintain dose level of LGX818 Omit dose of LGX818 and MEK162 until resolved to Grade ≤ 1, then reduce dose of LGX818 and MEK162 by 1 dose level*. Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment. Note: Anti-diarrhea medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.
Nausea/Vomiting Grade 1 or 2 Grade 3 Grade 4	 Maintain dose level of LGX818 and MEK162 Omit dose of LGX818 and MEK162 until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment. Note: Omit dose for ≥ grade 3 vomiting or nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Pancreatitis Grade 1 or 2 Grade ≥ 3	 Maintain dose level of LGX818 and MEK162 Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment
Investigations (Renal)	
Serum creatinine Grade 1 (> ULN – 1.5 x ULN) Grade 2 (> 1.5 - 3.0 x ULN) Grade ≥3 (> 3.0 x ULN)	 Maintain dose level of LGX818 and MEK162 Omit dose of LGX818 and MEK162 until resolved to ≤ Grade 1, then maintain dose level of LGX818 and MEK162 Omit dose of LGX818 and MEK162 and discontinue patient from study treatment.

Recommended Dose Modifications for LGX818/MEK162 combination	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Hepatic)	
Bilirubin Grade 1 (> ULN – 1.5 x ULN) Grade 2 (> 1.5 – 3.0 x ULN) Grade ≥ 3 (> 3.0 x ULN)	 Maintain dose level of LGX818 and MEK162 Omit dose of LGX818 and MEK162 until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162 Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment. Note: If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level* and continue treatment at the discretion of the investigator.
AST or ALT Grade 1 Grade 2 or Grade 3 Grade 4	 Maintain dose level of LGX818 and MEK162 Omit dose of LGX818 and MEK162 until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162 Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment.
AST or ALT and Bilirubin AST or ALT > 3.0 - 5.0 x ULN and total blood bilirubin ≥ Grade 2 AST or ALT > 5.0 x ULN and total blood bilirubin ≥ Grade 2	Omit dose of LGX818 and MEK162 until resolved to Grade ≤ 1, then - If resolved in ≤ 7 days, ↓ 1 dose level* of LGX818 and MEK162 - If resolved in > 7 days, discontinue patient from study drug treatment. Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment.

Recommended Dose Modifications for LGX818/MEK162 combination	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation Grade 1 (> ULN - 1.5 x ULN) or Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level of LGX818 and MEK162
Grade 3 (> 2.0 - 5.0 x ULN)	Omit dose of LGX818 and MEK162 until resolved to Grade ≤ 2, then : - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162
Grade 4 (> 5.0 x ULN)	Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment. Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any grade ≥ 3 of amylase and/or lipase. In cases of asymptomatic elevations of lipase and/or amylase with imaging study which does not show damage to pancreas, liver, and gallbladder, if the patient is benefiting from study therapy, they may remain on-study at a reduced dose following discussion between investigator and Sponsor. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.
Cardiac disorders	
Cardiac general Grade 1 or 2	Maintain dose level of LGX818 and MEK162
Grade 3	Omit dose of LGX818 and MEK162, until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162
Grade 4	Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment.

Recommended Dose Modifications for LGX818/MEK162 combination	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Cardiac)	
Creatine phosphokinase (CPK)	
Grade 1 (> ULN – 2.5 x ULN) or Grade 2 (> 2.5 - 5.0 x ULN)	Maintain dose level of LGX818 and MEK162
Grade 3 (> 5.0 - 10.0 x ULN)	If asymptomatic: Maintain dose level of LGX818 and MEK162 If symptomatic: Omit dose of MEK162 and maintain dose of LGX818 until resolved to Grade ≤ 1, then: - If resolved in ≤ 14 days, then ↓ 1 dose level* of MEK 162 and maintain dose level of LGX818[2] - If resolved in > 14 days, then discontinue patient from study drug treatment with LGX818 and MEK162
Grade 4 (> 10.0 x ULN)	Omit dose of MEK162 and maintain dose of LGX818 until resolved to CTCAE Grade ≤ 1, then: - If resolved in ≤ 14 days, then ↓ 1 dose level of MEK162 and maintain dose level of LGX818 - If resolved in > 14 days, then discontinue patient from study drug treatment with LGX818 and MEK162
LV systolic dysfunction (not according CTCAE)	
Asymptomatic decrease of > 10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal and CTCAE Grade 2	Omit dose of MEK162 until LVEF recovers (defined as ≥ LLN and decrease ≤ 10% compared to baseline). - If the LVEF recovers ≤ 21 days, then ↓ 1 dose level of MEK162, maintain dose of LGX818 and monitor LVEF 2 weeks after restarting on MEK162, every 4 weeks for 12 weeks and subsequently as per protocol - If the LVEF recovers >21 days, then discontinue patient from study drug treatment with MEK162 and LGX818, and closely monitor LVEF until resolution (or for 16 weeks).
Grade ≥ 3	Omit dose of MEK162 and LGX818 and discontinue patient from study drug treatment.
Vascular disorders	
Hypertension	
Grade 1 or 2	Maintain dose level of LGX818 and MEK162
Grade 3 (requiring more than one drug or more intensive therapy than previously)	Omit dose of LGX818 and MEK162, until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162
Grade 4 (life-threatening)	Omit dose of LGX818 and MEK162, and discontinue patient from study drug treatment

Recommended Dose Modifications for LGX818/MEK162 combination	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Eye disorders	
Eye disorders – RVO[e]	Note: Results of ophthalmic examinations must be made available upon request. This includes scans/images of fluorescein angiography.
Any Grade	Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment[c]
Eye disorders – Retinal events, Uveitis[e]	Note: Results and images of ophthalmic examinations must be made available upon request. This includes scans/images of OCTs.
Grade 1	Maintain dose of LGX818 and MEK162 and increase frequency of ophthalmic monitoring by ophthalmologist to at least every 14 days
Grade 2	Maintain dose of LGX818 and MEK162 and refer the patient to ophthalmologist within one week. Reassess the patient weekly (ophthalmic examination) until resolution to Grade ≤ 1: - If resolved to Grade ≤ 1 in ≤ 21 days, maintain dose of LGX818 and MEK162 - If not resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of LGX818 and MEK162 At any time if symptoms worsen, or persist with the same severity for more than 7 days, reduce 1 dose level[d] of LGX818 and MEK162
Grade 3	Interrupt dose of LGX818 and MEK162 and refer the patient to ophthalmologist monitoring within one week[e]: - If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[b] of LGX818 and MEK162 - If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue LGX818 and MEK162, and refer the patient to ophthalmologist monitoring
Grade 4	Permanently discontinue LGX818 and MEK162, and refer the patient to ophthalmologist monitoring[e]

Recommended Dose Modifications for LGX818/MEK162 combination	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Eye disorders – any other (i.e. retinal detachment)	
Grade 1 or 2	Maintain dose level of LGX818 and MEK162 and increase frequency of ophthalmic monitoring to at least every 14 days. At any time if symptoms worsen, or persist with the same severity for more than 7 days, reduce 1 dose level[d] of LGX818 and MEK162
Grade 3	Interrupt dose of LGX818 and MEK162 and refer patient to ophthalmologist monitoring within one week[e]: - If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of LGX818 and MEK162 - If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue LGX818 and MEK162, and refer the patient to ophthalmologist monitoring[e]
Grade 4	Permanently discontinue LGX818 and MEK162, and refer the patient to ophthalmologist Monitoring[e]
Skin and subcutaneous tissue disorders	
Rash/ HFSR/ photosensitivity	
Grade 1	Maintain dose level of LGX818 and MEK162, but consider initiating appropriate skin toxicity therapy (see Appendix 4)
Grade 2	Maintain dose level of LGX818 and MEK162, but initiate/intensify appropriate skin toxicity therapy
Grade 3, despite skin toxicity therapy	Omit dose of LGX818 and MEK162, until resolved to Grade ≤ 1 then: - If resolved in ≤ 7 days, ↓ 1 dose level* of LGX818 and MEK162 - If resolved in > 7 days, discontinue patient from study drug treatment with LGX818 and MEK162 (see Appendix 4)
Grade 4, despite skin toxicity therapy	Omit dose LGX818 and MEK162, and discontinue patient from study drug treatment with LGX818 and MEK162
General disorders and administration site conditions	
Fatigue	
Grade 1 or 2	Maintain dose level of LGX818 and MEK162
Grade 3	Omit dose of LGX818 and MEK162, until resolved to Grade ≤ 1, then : - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162

Recommended Dose Modifications for LGX818/MEK162 combination	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Edema Grade 1 or 2 Grade 3	 Maintain dose level of LGX818 and MEK162 Omit dose of LGX818 and MEK162 until resolved to Grade ≤ 1, then : - If resolved in ≤ 14 days, ↓ 1 dose level* of MEK162 and maintain dose of LGX818 - If resolved in > 14 days, discontinue patient from study drug treatment with LGX818 and MEK162
Other adverse events[c]	
Grade 1 or 2 Grade 3 Grade 4	Maintain dose level of LGX818 and MEK162 Omit dose of LGX818 and MEK162, until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment
[a] All dose modifications should be based on the worst preceding toxicity. [b] Not CTCAE grading [c] except: 1) lymphopenia unless clinically significant, 2) occurrence of KA and/or cutaneous SCC, 3) alkaline phosphatase, 4) AEs not considered clinically significant like alopecia. [d] Dose reduction below 50 mg QD for LGX818, and below 15 mg BID for MEK162 is not allowed [e] Ophthalmic monitoring mandated for retinal event, posterior uveitis, RVO: further evaluation with specialized retinal imaging (e.g. ocular coherence tomography, angiography) * ↓ 1 dose level refers to: next lower dose level of LGX818, MEK162 (please see Table 6-2).	

Table 6-7 Criteria for interruption and re-initiation of LGX818 and MEK162 in combination with third agent (BGJ398, INC280, BKM120 or LEE011)

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
No toxicity	Maintain dose level
Blood and lymphatic system disorder	
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)[b]	Omit dose until resolved, then ↓ 1 dose level
If the third agent is LEE011:	
Grade 3 ANC <1.0 x 10^9/L with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than one hour	Omit dose of LGX818 and MEK162 and LEE011 until improvement of ANC ≥ 1.0 x 10^9/L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue LGX818 and MEK162 and third agent if it is LEE011.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue LGX818 and MEK162 and LEE011.
Investigations (Blood)	
Neutropenia (neutrophil count (ANC) decreased)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) or Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level of LGX818 and MEK162 and third agent
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Omit dose of LGX818 and MEK162 and third agent until resolved to ≤ Grade 2, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 and third agent - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and LEE011 and maintain dose level of MEK162 and third agent (if not LEE011)
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose of LGX818 and MEK162 and third agent until resolved to ≤ Grade 2, ↓ 1 dose level* of LGX818 and MEK162 and third agent

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Thrombocytopenia (platelet count decreased)	
Grade 1 (PLT < LLN - 75 x 10^9/L) or Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level of LGX818 and MEK162 and third agent
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose of LGX818 and MEK162 and third agent until resolved to ≤ Grade 1, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 and third agent. - If resolved in > 7 days and/or with signs of bleeding, ↓ 1 dose level* of LGX818 and MEK162 and third agent
Grade 4 (PLT < 25 x 10^9/L)	Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment.
Gastrointestinal disorders	
Diarrhea	
Grade 1	Maintain dose level of LGX818 and MEK162 and third agent, but initiate anti-diarrhea treatment.
Grade 2	Omit dose of LGX818 and MEK162 and third agent until resolved to Grade ≤ 1 and then maintain dose level of LGX818 and MEK162 and third agent - For 2nd occurrence of diarrhea Grade 2 within 15 days, omit dose of LGX818 and MEK162 and third agent until resolved to Grade ≤ 1, then reduce MEK162 by 1 dose level* and maintain dose level of LGX818 and third agent. If in the opinion of the investigator the toxicity is unrelated to LGX818 but may be related to MEK162 and the third agent, maintain dose level of LGX818 and reduce MEK162 and third agent by 1 dose level.
Grade 3	Omit dose of LGX818 and MEK162 and third agent until resolved to Grade ≤ 1, then reduce dose of LGX818 and MEK162 and third agent by 1 dose level*.
Grade 4	Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment. Note: Anti-diarrhea medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.
Nausea/Vomiting	
Grade 1 or 2	Maintain dose level of LGX818 and MEK162 and third agent
Grade 3	Omit dose of LGX818 and MEK162 and third agent, until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 and third agent
Grade 4	Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment. Note: Omit dose for ≥ grade 3 vomiting or nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Pancreatitis Grade 2 Grade ≥ 3	 Maintain dose level of LGX818 and MEK162 and third agent Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment
Investigations (Renal)	
Serum creatinine Grade 1 (> ULN – 1.5 x ULN) Grade 2 (> 1.5 - 3.0 x ULN) Grade ≥3 (> 3.0 x ULN)	 Maintain dose level of LGX818 and MEK162 (and INC280, BKM120 and LEE011). For BGJ398 triple combination, please, also refer to Section 6.3.1 Table 6-8. Omit dose of LGX818 and MEK162 and third agent until resolved to ≤ Grade 1, then maintain dose level of LGX818 and MEK162 and third agent. Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study treatment.
Grade ≥2 renal impairment	Discontinue treatment and follow-up patient for safety assessments.
Investigations (Hepatic*)- for BGJ398, BKM120 only**	
Bilirubin Grade 1 (> ULN – 1.5 x ULN) Grade 2 (> 1.5 – 3.0 x ULN) Grade ≥ 3 (> 3.0 x ULN)	 Maintain dose level of LGX818 and MEK162 and third agent Omit dose of LGX818 and MEK162 and third agent until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 and third agent- If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162 and third agent Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment. Note: If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level* of LGX818 and MEK162 and Third agent and continue treatment at the discretion of the investigator.

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
AST or ALT	
Grade 1	Maintain dose level of LGX818 and MEK162 and third agent.
Grade 2 or Grade 3	Omit dose of LGX818 and MEK162 and third agent until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 and third agent. - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162 and third agent.
Grade 4	Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment.
AST or ALT and Bilirubin	
AST or ALT > 3.0 - 5.0 x ULN and total blood bilirubin ≥ Grade 2	Omit dose of LGX818 and MEK162 and third agent until resolved to Grade ≤ 1, then - If resolved in ≤ 7 days, ↓ 1 dose level* of LGX818 and MEK162 and third agent - If resolved in > 7 days, discontinue patient from study drug treatment.
AST or ALT > 5.0 x ULN and total blood bilirubin ≥ Grade 2[c]	Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment.

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Hepatic)- for LEE011 only**	
Total Bilirubin without ALT/AST increase above baseline value (confirmed 48-72hr later) Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level of LGX818 and MEK162 and LEE011 with LFTs monitored bi-weekly.
Grade 2 (> 1.5 – 3.0 x ULN)	Omit dose of LGX818 and MEK162 and LEE011 until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 and LEE011 - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162 and LEE011 - If resolved in > 28 days, discontinue patient from all study drug treatment Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption.
Grade ≥ 3 (> 3.0 x ULN)	Omit dose of LGX818 and MEK162 and LEE011 and discontinue patient from all study drug treatment. Note: If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level* of LGX818 and MEK162 and LEE011 and continue treatment at the discretion of the investigator. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption.
Grade 4 (> 10.0 x ULN)	Discontinue patient from all study drug treatment.

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Hepatic)- for LEE011 only (con't).**	
AST or ALT without bilirubin elevation > 2 ULN (confirmed 48-72hr later) Grade 1	Maintain dose level of LGX818 and MEK162 and LEE011. Monitor LFT bi-weekly.
Grade 2 (> 3.0 – 5.0 x ULN)	Omit dose of LGX818 and MEK162 and LEE011 until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 and LEE011. - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162 and LEE011. - If resolved in > 28 days, discontinue patient from all study drug treatment Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption.
Grade 3 (> 5.0 – 20.0 x ULN)	Omit dose of LGX818 and MEK162 and third agent until resolved to ≤ baseline grade, then lower 1 dose level of dose level of LGX818 and MEK162 and LEE011. If recovery to ≤ baseline grade is > 28 days, discontinue patient from all study drug treatment. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption. If toxicity recurs, discontinue patient from all study drug treatment.
Grade 4 (> 20.0 x ULN)	Discontinue patient from all study drug treatment.

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Hepatic)- for LEE011 only (con't).**	
AST or ALT and Bilirubin For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis Or For patient with elevated AST or ALT or total bilirubin at baseline: baseline: (AST or ALT > 2 x baseline AND > 3.0 x ULN) OR (AST or ALT 8.0 x ULN)- whichever is lower- combined with (total bilirubin > 2 x baseline AND > 2.0 x ULN)	Discontinue patient from all study drug treatment.

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Hepatic)- for INC280 only**	
Isolated Bilirubin increase Grade 1 (> ULN – 1.5 x ULN) Grade 2 (> 1.5 – 3.0 x ULN)	Maintain dose level of LGX818 and MEK162 and INC280 with LFTs*** monitored Omit dose of LGX818 and MEK162 and INC280 with weekly monitoring of LFTs***, or more frequently as clinically indicated, until resolved to ≤ Grade 1, then -If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 and INC280 -If resolved in > 7 days, ↓ 1 dose level of LGX818 and MEK162 and INC280
Grade ≥ 3 (> 3.0 x ULN -10.0xULN)	Omit dose of LGX818 and MEK162 and INC280 with weekly monitoring of LFTs***, or more frequently as clinically indicated, until resolved to ≤ Grade 1, then -If resolved in ≤ 7 days, ↓ 1 dose level of LGX818 and MEK162 and INC280 If resolved in > 7 days, discontinue patient from study drug treatment
Grade 4 (> 10.0 x ULN)	Discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs***), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT increase Grade 1 or 2 (> ULN - 5.0 x ULN) Grade 3 (>5.0 x ULN - 20.0 x ULN)	Maintain dose level of LGX818 and MEK162 and INC280 with LFTs monitored Omit/delay dose of LGX818 and MEK162 and INC280 until resolved to ≤ Grade 1 or ≤ grade 2 if grade 2 elevation at baseline, then -If resolved in ≤ 7 days, resume treatment at the same dose level -If resolved in > 7 days, resume treatment at ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	Permanently discontinue patient from study drug treatment

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Investigations (Hepatic)- for INC280 only**	
Combined elevations of AST or ALT, and Total Bilirubin[b,d] For patients with normal baseline ALT or AST or total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis[e] OR For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, **combined with** [total bilirubin > 2 x baseline AND > 2.0 x ULN]	Permanently discontinue patient from study drug treatment. Repeat LFTs as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.2.8 for additional follow-up evaluations as applicable.
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation Grade 1 (> ULN - 1.5 x ULN) or Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level of LGX818 and MEK162 and third agent
Grade 3 (> 2.0 - 5.0 x ULN)	Omit dose of LGX818 and MEK162 and third agent until resolved to Grade ≤ 2, then : - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 and third agent - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162 and third agent.
Grade 4 (> 5.0 x ULN)	Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment. Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any grade ≥ 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Cardiac disorders	
Cardiac general	
Grade 1 or 2	Maintain dose level of LGX818 and MEK162 and third agent
Grade 3	Omit dose of LGX818 and MEK162 and third agent, until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 and third agent
Grade 4	Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment.
Investigations (Cardiac)	
Creatine phosphokinase (CPK)	
Grade 1 (> ULN – 2.5 x ULN) or Grade 2 (> 2.5 - 5.0 x ULN)	Maintain dose level of LGX818 and MEK162 and third agent
Grade 3 (> 5.0 - 10.0 x ULN)	If asymptomatic: Maintain dose level of LGX818 and MEK162 and third agent If symptomatic: Omit dose of MEK162 and maintain dose of LGX818[1] and third agent until resolved to Grade ≤ 1, then: - If resolved in ≤ 14 days, ↓ 1 dose level* of MEK 162 and maintain dose level of LGX818[2] and third agent - If resolved in > 14 days, discontinue patient from study drug treatment with LGX818 and MEK162 and third agent
Grade 4 (> 10.0 x ULN)	Omit dose of MEK162 and maintain dose of LGX818[1] and third agent until resolved to CTCAE Grade ≤ 1, then: - If resolved in ≤ 14 days, ↓ 1 dose level of MEK162 and maintain dose level of LGX818[2] and third agent - If resolved in > 14 days, discontinue patient from study drug treatment with LGX818 and MEK162 and third agent

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
LV systolic dysfunction (not according CTCAE)	
Asymptomatic decrease of > 10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal and CTCAE grade 2	Omit dose of MEK162 until LVEF recovers (defined as ≥ LLN and decrease ≤ 10% compared to baseline). - If the LVEF recovers ≤ 21 days, then ↓ 1 dose level of MEK162, maintain dose of LGX818 and third agent and monitor LVEF 2 weeks after restarting on MEK162, every 4 weeks for 12 weeks and subsequently as per protocol - If the LVEF recovers > 21 days, then discontinue patient from study drug treatment with MEK162 and LGX818 and third agent, and closely monitor LVEF until resolution (or for 16 weeks).
Grade ≥ 3	Omit dose of MEK162 and LGX818 and third agent and discontinue patient from study drug treatment.
Electrocardiogram QTcF interval prolonged (only for LEE011) For all grades	Check the quality of the ECG and the QT value and repeat if needed. Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, **hold LEE011**, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. Check compliance with correct dose and administration of LEE011.
Grade 1 QTcF 450-480 ms[h]	Perform all the steps "For All Grades" and check compliance with correct dose and administration of LEE011. No dose adjustment required
Grade 2 QTcF 481-500 ms[h]	Omit dose of LGX818 and MEK162 and LEE011. Perform all the steps above "For All Grades." Perform repeat triplicate ECGs within one hour after the first QTcF of ≥ 481 ms. If QTcF < 481 ms, restart study treatment with LEE011 dose reduced by 1 dose level. If QTcF remains ≥ 481 ms, repeat ECG as clinically indicated until the QTcF returns to < 481 ms and then restart study treatment with LEE011 dose reduced by 1 dose level.

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Electrocardiogram QTcF interval prolonged (only for LEE011 con't.) Grade 3[h] QTcF interval ≥ 501 ms on at least two separate ECGs	If QTcF ≥ 481 ms recurs, again ↓ 1 dose level* of LEE011. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms. Omit dose of LGX818 and MEK162 and LEE011. Perform all the steps above for "For All Grades." Transmit ECG immediately and confirm prolongation/abnormalities with central assessment. Perform repeat triplicate ECGs one hour after the first QTcF of ≥ 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms. • If QTcF returns to < 481 ms, LEE011 will be reduced by 1 dose level (Table 6-5). • If QTcF remains ≥ 481 ms after performing steps as directed in "For All Grades," discontinue LEE011. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms If QTcF of ≥ 501 ms recurs, discontinue all study treatment
Grade 4[h] QT/QTcF ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Discontinue patient from LGX818, MEK162, and LEE011 treatment. Perform all the steps above for "For All Grades." Transmit ECG immediately and confirm prolongation/abnormalities with central assessment. Obtain local cardiologist (or qualified specialist) consultation and perform repeat cardiac monitoring as indicated until the QTcF returns to <481 ms..

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Electrocardiogram QTcF interval prolonged (only for BGJ398, INC280 and BKM120)	
Grade 1 or 2	Maintain dose level
Grade 3 (QTcF interval ≥ 501 ms on at least two separate ECGs)	Omit dose of LGX818 and MEK162 and third agent Perform frequent ECGs until the QTcF is < 501 msec. Address electrolyte, calcium and magnesium abnormalities. Restart LGX818, MEK162 and either BGJ398, INC280 or BKM120 at the same dose level. If QTcF is not < 501 ms within 5 days reduce LGX818, MEK162 and either BGJ398, INC280 or BKM120 by 1 dose level. If findings recur at the lower dose, omit dose of LGX818 and MEK162 and third agent until resolve to ≤ Grade 1, and restart at the next lower dose.
Grade 4	Discontinue patient from LGX818 and MEK162 and third agent
Vascular disorders	
Hypertension	
Grade 1 or 2	Maintain dose level of LGX818 and MEK162 and third agent
Grade 3 (requiring more than one drug or more intensive therapy than previously)	Omit dose of LGX818 and MEK162 and third agent, until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 and third agent
Grade 4 (life-threatening)	Omit dose of LGX818 and MEK162 and third agent, and discontinue patient from study drug treatment
Eye disorders	
Eye disorders – Retinal events, Uveitis[i]	Note: Results and images of ophthalmic examinations must be made available upon request. This includes scans/images of OCTs.

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Grade 1	Maintain dose of LGX818/MEK162 and combination partner and increase frequency of ophthalmic monitoring by ophthalmologist to at least every 14 days
Grade 2	Maintain dose of LGX818/ MEK162 and combination partner and refer the patient to ophthalmologist within one week. Reassess the patient weekly (ophthalmic examination) until resolution to Grade ≤ 1: - If resolved to Grade ≤ 1 in ≤ 21 days, maintain dose of LGX818/ MEK162 and combination partner - If not resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of LGX818 and MEK162 and maintain combination partner At any time if symptoms worsen, or persist with the same severity for more than 7 days, reduce 1 dose level[d] of LGX818/ MEK162 and maintain combination partner
Grade 3	Interrupt dose of LGX818 and MEK162 and refer the patient to ophthalmologist monitoring within one week[i]: - If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose levelb of LGX818/ MEK162 and maintain combination partner - If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue LGX818/MEK162 and combination partner, and refer the patient to ophthalmologist monitoring
Grade 4	Permanently discontinue LGX818/ MEK162 and combination partner, and refer the patient to ophthalmologist monitoring[i]
Eye disorders – RVO[i] Any Grade	Note: Results of ophthalmic examinations must be made available upon request. Omit dose of LGX818 and MEK162 and third agent and discontinue patient from study drug treatment

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
Eye disorders (con't.)	
Eye disorders – any other (i.e. retinal detachment)	
Grade 1 or 2	Maintain dose level of LGX818 and MEK162 and increase frequency of ophthalmic monitoring to at least every 14 days. At any time if symptoms worsen, or persist with the same severity for more than 7 days, reduce 1 dose level[d] of LGX818/ MEK162 and maintain combination partner
Grade 3	Interrupt dose of LGX818 and MEK162 and refer patient to ophthalmologist monitoring within one week[i]: - If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of LGX818/ MEK162 and maintain combination partner - If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue LGX818/ MEK162 and combination partner and refer the patient to ophthalmologist monitoring[i]
Grade 4	Permanently discontinue LGX818/ MEK162 and combination partner, and refer the patient to ophthalmologist Monitoring[i]
Skin and subcutaneous tissue disorders	
Rash/ HFSR/ photosensitivity	
Grade 1	Maintain dose level of LGX818 and MEK162 (and BGJ398, INC280 and LEE011), but consider initiating appropriate skin toxicity therapy (see Appendix 4). For BKM120 triple combination, please, refer to Table 6-10 for the specific dose modification recommendation (see also Appendix 4).
Grade 2	Maintain dose level of LGX818 and MEK162 and third agent, but initiate/intensify appropriate skin toxicity therapy (see Appendix 4)
Grade 3, despite skin toxicity therapy	Omit dose of LGX818 and MEK162 and third agent, until resolved to Grade ≤ 1 then: - If resolved in ≤ 7 days, ↓ 1 dose level* of LGX818 and MEK162 - If resolved in > 7 days, discontinue patient from study drug treatment with LGX818 and MEK162 and third agent
Grade 4, despite skin toxicity therapy	Omit dose LGX818 and MEK162 and third agent, and discontinue patient from study drug treatment with LGX818 and MEK162 and third agent

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**
General disorders and administration site conditions	
Fatigue Grade 1 or 2 Grade 3	 Maintain dose level of LGX818 and MEK162 and third agent Omit dose of LGX818 and MEK162 and third agent, until resolved to Grade ≤ 1, then : - If resolved in ≤ 7 days, maintain dose level of LGX818 and MEK162 and third agent - If resolved in > 7 days, ↓ 1 dose level* of LGX818 and MEK162 and third agent
Other adverse events[j]	
Grade 1 or 2 Grade 3 Grade 4	Maintain dose level of LGX818 and MEK162 and third agent Omit dose of LGX818 and MEK162 and third agent, until resolved to Grade ≤ 1, then ↓ 1 dose level* of LGX818 and MEK162 and third agent Omit dose of LGX818 and MEK162 and third agent, and discontinue patient from study drug treatment

Recommended Dose Modifications for LGX818 and MEK162 in combination with a third agent (BGJ398, INC280, BKM120 or LEE011)	
Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)[a]	**Recommended Dose Modifications any time during a cycle of therapy**

[a] All dose modifications should be based on the worst preceding toxicity.

[b] Not CTCAE grading

[c] All patients with ALT or AST >5.0x ULN and total bilirubin > 1.5x ULN in the absence of cholestasis must immediately be withdrawn from study treatment and every attempt should be made to carry out the **liver event follow-up assessments** as described below in Section 6.3.2.5 and Section 6.3.2.6.

[d] "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

[e] "Cholestasis" defined as: ALP elevation (> 2.0 x ULN and R value (ALT/ALP in x ULN) < 2.0) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis

[f] If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction

[g] Dose reduction below 50 mg QD for LGX818, and below 15 mg BID for MEK162 is not allowed

[h] All values refer to the average of triplicate measurements.

[i] Ophthalmic monitoring mandated for retinal event, posterior uveitis, RVO: further evaluation with specialized retinal imaging (e.g. ocular coherence tomography, angiography).

[j] except: 1) lymphopenia unless clinically significant, 2) occurrence of KA and/or cutaneous SCC, 3) alkaline phosphatase, 4) AEs not considered clinically significant like alopecia.

* ↓ 1 dose level refers to: next lower dose level of LGX818, MEK162 and third agents (please see Table 6-2 and Table 6-3).

** Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.

*** LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin ≥ grade 2), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT.

Table 6-8 Specific criteria for interruption and re-initiation of BKM120 treatment in LGX818/MEK162 + BKM120 triple combination

Recommended Dose Modifications for BKM120 in combination with LGX818/MEK162	
Worst toxicity grade[a] (value)	Recommended Dose Modifications any time during a cycle of therapy
No toxicity	Maintain dose level
Metabolism and Nutrition disorders	
Hyperglycemia - Fasting Plasma Glucose (FPG)	According Management of Metabolic Effects Associated With Anticancer Agents Targeting the PI3K-Akt-mTOR Pathway, (Busaidy et al 2012)
Grade 1 (> ULN - 160 mg/dL) [ULN - 8.9. mmol/L]	Maintain dose level of LGX818/MEK162 and BKM120 If appropriate in clinical context, refer to nutritionist for dietary education on diabetic diet, increase aerobic exercise, and refer to diabetes educator for comprehensive diabetic education on nonpharmaceutical interventions or therapeutic lifestyle change (TLC)
Grade 2 (> 160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	Maintain dose level of LGX818/MEK162 and BKM120 Initiate plasma glucose (PG) monitoring and PG lowering therapy (Metformin*). After 2 weeks: If fasting glucose grade 2 or random glucose > 200 mg/dL, continue metformin*, add sulfonylurea and titrate. After additional 1 week: If fasting glucose > 160 mg/dL or random glucose > 200 mg/dL, continue two oral agents and add basal insulin. Stop oral agents. Begin basal bolus insulin four injections/day.
Asymptomatic Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	Maintain dose level of LGX818/MEK162 and BKM120 Start home glucose monitoring before meals twice per day and TLC. Begin metformin* and sulfonylurea and rapidly titrate. After 1 week: If fasting glucose > 160 mg/dL or random glucose > 200 mg/dL, add basal insulin to oral agents, and titrate basal insulin to fasting glucose. After additional 1 week: If fasting glucose > 160 mg/dL or random glucose > 200 mg/dL, stop oral agents; add premeal insulin, and check glucose before meals three times a day (TID) and at every bed time (QHS).

Recommended Dose Modifications for BKM120 in combination with LGX818/MEK162	
Worst toxicity grade[a] (value)	Recommended Dose Modifications any time during a cycle of therapy
Symptomatic Grade 3, (> 250 - 500 mg/dL) [> 13.9 – 27.8 mmol/L], or asymptomatic grade 4: fasting glucose > 500 mg/dL [27.8 mmol/L]	Consider intravenous fluids (IVF) and/or admit if hypovolemic signs/symptoms, diabetes consultation, four-injection basal bolus insulin regimen, check home glucose before meals TID and QHS After 1 week: If fasting or random glucose > 250 mg/dL, DLT and hold BKM120. Restart when glucose < 250 mg/dL and no symptoms The occurrence of grade 3 hyperglycemia (> 250 mg/dL) or asymptomatic grade 4 hyperglycemia (> 500 mg/dL) should result in a rapid review by the team endocrinologist (by telephone or in person) or the respective algorithm should be followed.
Symptomatic Grade 4: fasting glucose > 500 mg/dL [27.8 mmol/L]	The study drug BKM120 should be held without attempting intervention if a patient experiences a symptomatic grade 4 (>500 mg/dL) hyperglycemic event and refer to endocrinology or diabetes treating specialist.
Any hyperglycemia leading to diabetic keto-acidosis, hospitalization for intravenous insulin infusion, or non-ketotic coma.	Omit dose of LGX818/MEK162 and BKM120 and discontinue patient from study drug treatment.
	(*) Do not use metformin if creatine > 1.3 mg/dL (women) or > 1.4 mg/dL (men) or if any state of decreased tissue perfusion or hemodynamic instability is present (eg, heart failure); hold metformin for computed tomography scans; GI symptoms may occur with initiation but usually subside after first week.
Stomatitis/Oral mucositis	
Grade 1 / Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash
Intolerable Grade 2 or Grade 3	First occurrence: hold BKM120 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 BKM120 until ≤ G1 and ↓ 1 dose level.
Grade 4	Permanently discontinue patient from BKM120.
Skin and subcutaneous tissue disorders	
Rash/HFSR/photosensitivity	
Grade 1	Maintain dose level of LGX818/MEK162 + BKM120; but consider initiating appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids, and low-dose systemic corticosteroids) (see Appendix 4)

Recommended Dose Modifications for BKM120 in combination with LGX818/MEK162	
Worst toxicity grade[a] (value)	Recommended Dose Modifications any time during a cycle of therapy
Grade 2	First occurrence: Omit dose of LGX818/MEK162 + BKM120 until resolved to grade ≤ 1 then: • If resolved in ≤ 2 weeks, maintain dose level. • If resolved in more than 2 weeks, ↓ 1 dose level LGX818/MEK162 + BKM120. Second occurrence: ↓ 1 dose level of LGX818/MEK162 + BKM120. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids) (see Appendix 4)
Grade 3, despite skin toxicity therapy	First occurrence: omit dose of LGX818/MEK162 + BKM120 until resolved to CTCAE Grade ≤ 1; then ↓ 1 dose level. Second occurrence: permanently discontinue patient from LGX818/MEK162 + BKM120 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) if clinically appropriate.
Grade 4, despite skin toxicity therapy	Permanently discontinue patient from LGX818/MEK162 + BKM120. 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) if clinically appropriate.
Psychiatric disorders	
Mood alteration (Depression, Anxiety) (for BKM120 combination arm only)	Questionnaire scores should be considered when assigning the AE Grade but psychiatric consult, if required, may determine the grade (refer to Section 7.2.2.7).
Grade 1* (or Grade 2 anxiety if present at Cycle 1 Day-1 of BKM120 combination arm)	Maintain dose level Consider psychiatric consultation at the investigator's discretion and introduce optimal management
Grade 2* (for Anxiety only, if worsened from Cycle 1 Day-1 of BKM120 combination arm)	Omit BKM120 dose until resolved to ≤ Grade 1 or baseline status Consider psychiatric consultation at the investigator's discretion and introduce optimal management First event: if the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then maintain the 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 BKM120 dose until resolved to ≤ Grade 1 or baseline status, then ↓ 1 dose level (co-medicate) Psychiatric consultation should be performed Introduce optimal management

Recommended Dose Modifications for BKM120 in combination with LGX818/MEK162	
Worst toxicity grade[a] (value)	Recommended Dose Modifications any time during a cycle of therapy
Grade 4*	Permanently discontinue patient from BKM120 Psychiatric consultation should be performed Introduce optimal management
* Note: For all grades, if question 9 on the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit study drug and refer patient for psychiatric consult regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued.	
Pneumonitis	Please see Section 6.3.2.4 and Table 6-12.
[*]↓ 1 dose level refers to: next lower dose level previously treated. [a] All dose modifications should be based on the worst preceding toxicity. Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03).	

Table 6-9 Specific criteria for interruption and re-initiation of BGJ398 treatment in LGX818/MEK162 + BGJ398 triple combination

Recommended Dose Modifications for BGJ398 in combination with LGX818/MEK162	
Worst toxicity grade[a] (value)	Recommended Dose Modifications any time during a cycle of therapy
No toxicity	Maintain dose level
Investigations (Renal)	
Serum creatinine	For elevations of serum creatinine associated with hyperphosphatemia, see below guidelines for management of elevated phosphate. For serum creatinine elevation see the recommended dose modification for LGX818/MEK162 + third agent (Table 6-6).
Ocular	
Corneal disorder/disease* Grade ≥ 2 *confirmed by ophthalmologic examination	Omit dose and discontinue patient from study.
Investigations (metabolic)	
Hyperphosphatemia (For serum creatinine = Grade 2 with any degree of hyperphosphatemia)	Hold dose to allow for resolution to <=Grade 1 or baseline, and subsequently reduce BGJ398 dose and maintain MEK162 and LGX818 dose.
Serum phosphorus ULN ≤ 5.5 mg/dL.	Maintain dose level. Serum phosphorus lowering therapy consisting of dietary phosphate intake restriction and oral phosphate binders should be applied prophylactically as follows: From Cycle Day 1 (it could be started in the evening of C1D1): -Restriction of dietary phosphate intake to 600 - 800 mg/day, if BMI ≥ 21kg/m2. -Sevelamer 1 tablet (800mg) per meal; i.e. 3 x 800 mg/day
Serum phosphorus > 5.5 - 7.0 mg/dL.	Maintain dose level, increase the dose of sevelamer up to 1200mg every 8 hours.
Serum phosphorus > 7.0 - 9.0 mg/dL despite phosphorus lowering therapy for at least 14 days.	At >7.0 mg/dL maintain dose level and: - Increase the dose of sevelamer up to 1600mg (2 tablets per meal) every 8 hours. If serum phosphorus increases further despite phosphorus lowering therapy over at least 14 days the BGJ398 dose must be held until resolution to ≤5.5 mg/dL, subsequently BGJ398 dose reduced (maintain dose level of LGX818/MEK162), and permanently discontinued if not decreased to ≤ 5.5 mg/dL within 7 days after suspending BGJ398. All patients will continue to be followed-up until resolution to serum phosphorus ≤ 5.5 mg/dL or baseline or stabilization.

Recommended Dose Modifications for BGJ398 in combination with LGX818/MEK162	
Worst toxicity grade[a] (value)	Recommended Dose Modifications any time during a cycle of therapy
Serum phosphorus > 9.0 mg/dL	Omit dose until resolution to ≤5.5 mg/dL, subsequently dose reduce (maintain dose level of LGX818/MEK162), and permanently discontinue if not decreased to ≤ 5.5 mg/dL within 7 days after suspending BGJ398. All patients will continue to be followed-up until resolution to serum phosphorus ≤ 5.5 mg/dL or baseline or stabilization.
Serum Pi > 10.0 mg/dL	Omit dose and discontinue patient from study
Hypercalcemia	
Serum calcium CTCAE Grade 1	Maintain dose level.
Serum calcium CTCAE Grade 2	Omit dose until resolved to ≤ CTCAE Grade 1or baseline, then: -If resolved by ≤ 7 days after suspending BGJ398, maintain dose level. -If resolved by > 7 days after suspending BGJ398, ↓ 1 dose level (maintain dose level of LGX818/MEK162),.
Serum calcium CTCAE Grade ≥ 3	Omit dose and discontinue patient from study.
[*]↓ 1 dose level refers to: next lower dose level previously treated. [a] All dose modifications should be based on the worst preceding toxicity. Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03).	

Table 6-10 Specific criteria for interruption and re-initiation of INC280 treatment in LGX818/MEK162 + INC280 triple combination

Recommended Dose Modifications for INC280 in combination with LGX818/MEK162	
Worst toxicity grade[a] (value)	**Recommended Dose Modifications any time during a cycle of therapy**
No toxicity	Maintain dose level
Any Neurological Toxicity	
Grade ≥ 2	Discontinue dose. Neurological assessments must be repeated at least twice a week until resolution to < CTCAE grade 1. Unscheduled MRI and gadolinium enhanced T1 imaging may also be conducted to evaluate patients for intramyelinic edema like lesions, brain metastases and other unanticipated CNS occurrences. An EEG may be performed to monitor for physiological changes in brain activity.
[*]↓ 1 dose level refers to: next lower dose level previously treated. [a] All dose modifications should be based on the worst preceding toxicity. Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03).	

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts such as an ophthalmologist or dermatologist should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study drug combination induced toxicities are provided in sub-sections below.

6.3.2.1 Management of hand foot skin reaction (HFSR)

As HFSR has been reported in some patients during LGX818 treatment, it is recommended that patients are educated prior to starting study treatment which activities to avoid and on supportive measures for prevention and/or management of HFSR. Recommendations are summarized below in Table 6-11. Furthermore the patient should be treated at the first symptoms according the institutional standards of care. A visit to a podiatrist may also be recommended at the discretion of the investigator.

Table 6-11 Supportive care for the prevention and management of HFSR

Stage	Recommendations
Prior to treatment	Educate the patient about the early signs and symptoms of HFSR and discuss the importance of early reporting.
Prevention of HFSR	Monitor the patient for signs and symptoms of HFSR. Instruct the patient to: • Apply emollient cream regularly to hands and feet • Avoid skin irritants (e.g. perfumes, alcohol, harsh cleaning agents) • Wear cotton socks or gloves to bed to enhance the absorption of creams • Avoid tight, irritating or ill-fitting clothing and shoes[a] • Avoid the use of band aides or other types of adhesive bandages or tape • Avoid repetitive activity or staying in one position for long periods of time • Keep the skin uncovered when possible to minimize perspiration • Wear rubber gloves while doing dishes • Pat (do not rub) skin dry with towels • Avoid extremes of temperature, pressure and friction • Avoid performing mechanically stressful manual work • Minimize exposure to strong, direct sunlight • Elevate affected limbs
Treatment of HFSR	1) Ensure that patient follows treatment interruption or dosage reduction guidelines 2) Monitor the patient for progression/resolution of HFSR 3) Prescribe analgesics if necessary 4) Instruct the patient to: • Continue the use of prevention strategies • Cushion sore skin • Submerge hands and feet in cool water baths or apply cold compresses for relief

[a] Wear loose-fitting clothing made of soft, natural fabrics and shoes that are wide and comfortable. Avoid tight belts, panties and bras.

This Table is adapted from (Von Moos et al 2008).

6.3.2.2 Follow up evaluations for appearance of keratoacanthoma (KA) and/or squamous cell carcinoma (SCC)

The skin of patients treated with the LGX818/MEK162 combination or LGX818/MEK162 + third agent combination will be examined regularly to monitor for the possible development of KA and/or SCC, as these have been reported to occur under selective BRAF inhibitor treatment. Dermatologic evaluations for this adverse effect will be performed at Screening/baseline, every 2 months thereafter and at End of Study Treatment.

In case of occurrence of KA and/or SCC, patients will undergo complete surgical excision of the skin lesion following institutional standards.

6.3.2.3 Follow up evaluations for appearance of visual toxicity

The patients treated with the LGX818/MEK162 combination or LGX818/MEK162 + third agent combination will be examined regularly to monitor for the possible development of visual toxicity. Ophthalmologic examinations to check for this adverse effect will be performed in Part I, Run-in and Part II at the timepoint s indicated in Section 7.2.2.5.7. Patients developing a CTCAE grade 1 or 2 retinal disorders (eg. retinal detachment) can be maintained on the study drug combination as is detailed in Table 6-5 and Table 6-6. For these patients it is recommended to follow up the event with an ophthalmological exam every two weeks for 8 weeks, and subsequently at approximately a 4-weeks interval. The study drug dosages of patients developing retinal event (eg. uveitis or retinal detachment) > CTCAE grade 2 should be interrupted/modified according to Table 6-5 and Table 6-6 and should be followed as described above. Patients developing a CTCAE grade 1 uveitis) can be maintained on the study drug combination as is detailed in Table 6-5 and Table 6-6. For these patients it is recommended to follow up the event with an ophthalmological exam every two weeks for 8 weeks, and subsequently at approximately a 4-weeks interval. For patients developing a CTCAE grade 2 uveitis, drug dosages should be modified according to what is described in Table 6-5 and Table 6-6, and the ophthalmological monitoring detailed above should be followed. The study drug dosages of patients developing uveitis ≥ CTCAE grade 3 should be interrupted/modified according to Table 6-5 and Table 6-6 and should be followed as described above.

6.3.2.4 Management of pneumonitis in patients receiving BKM120

All patients participating in clinical trials with BKM120 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). Pulmonary function tests and radiology assessment 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 6-12 should be followed. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment.

Table 6-12 Management of pneumonitis

Worst Grade Pneumonitis	Recommended/Required Investigations	Management of Pneumonitis	BKM120 Dose Adjustment
Grade 1	CT scans with lung windows. Repeat at least every 6 weeks until return to within normal limits.	No specific therapy is required	Administer 100% of BKM120 dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, Carbon monoxide diffusing capacity (DLCO), and room air O2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or Bronchoalveolar lavage (BAL).	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce BKM120 dose by 1 dose level (see Table 6-3) 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 BKM120 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 BKM120.

6.3.2.5 Management of hepatotoxicity (ALT and/or AST >5.0x ULN and total bilirubin >1.5x ULN) in patients receiving BKM120

Criteria for interruption and re-initiation of BKM120 treatment in case of the occurrence of AST, ALT or bilirubin increase are detailed in Section 6.3 Dose Modification (Table 6-7).

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 >5.0 x ULN and total bilirubin > 1.5x 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 treatment, 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. Record the date/time of the PK blood sample draw and the date/time of the last dose of BKM120 prior to blood sample draw on the eCRF
- Verify and record the use of concomitant medications, acetaminophen, 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.

6.3.2.6 Additional follow-up for hepatic toxicities in patients receiving LEE011

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2 x ULN), alkaline phosphatase (fractionated if alkaline

phosphatase is grade 2 or higher) and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

Close observation is recommended in case of AST, ALT, and/or bilirubin increase requiring dose interruption, which involves:

- Repeating liver enzyme and serum bilirubin tests **two or three times weekly**. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases, including history of any pre-existing liver conditions or risk factors.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.
- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.
- Considering a liver biopsy, as clinically indicated to assess pathological change and degree of potential liver injury.

6.3.2.7 Additional follow-up for hepatic toxicities in patients receiving INC280

In case of isolated elevations in total bilirubin, AST or ALT, additional follow-up evaluations are recommended as outlined in Table 6-13:

Table 6-13 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
HEPATIC	
Isolated total bilirubin elevation	
CTCAE Grade 1	Monitor LFTs per protocol or more frequently if clinically indicated
CTCAE Grade 2	Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN
CTCAE Grade 3	Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in > 7 days, after discontinuing the patient from INC280 permanently, the patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks
CTCAE Grade 4	After discontinuing the patient from INC280 permanently, the patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 week

TOXICITY	FOLLOW-UP EVALUATION
HEPATIC	
Isolated AST/ALT elevation	
CTCAE Grade 2 For patients with baseline value ≤ 3.0 x ULN	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
For patients with baseline value > 3.0 - 5.0 x ULN	Monitor LFTs per protocol or more frequently if clinically indicated
CTCAE Grade 3 -For elevation > 5.0 - 10.0 x ULN: For patients with baseline value ≤ 3.0 x ULN	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
For patients with baseline value > 3.0 - 5.0 x ULN:	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs, weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
CTCAE Grade 3 For AST/ALT elevation > 10.0 - 20.0 x ULN:	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline
CTCAE Grade 4	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
*Note: this table refers only to the evaluation schedule to monitor selected toxicities. Refer to Table for dose modifications required for applicable toxicities	

6.3.2.8 Follow up on potential drug-induced liver injury cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL values; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: ALP elevation > 2.0 x ULN with R value (ALT/ALP in x ULN) < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed

history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (eg, biliary tract) may be warranted.
- Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperglycemia, skin toxicity and diarrhea are provided in Appendices. Refer to preclinical toxicity and or clinical data found in the Investigator's Brochures of the study drugs.

6.3.3.1 Anticipated risks and safety considerations of the study drug combinations

6.3.3.1.1 LGX818/MEK162 combination

Note: INC280-, BKM120- and BKM120-containing arms are closed to enrollment as these combinations are no longer being explored (Amendment 06).

Main adverse events for LGX818/MEK162

The most common AEs observed in the on-going [CMEK162X2110] were grade 1/2 gastrointestinal toxicities, visual disturbances, headache, and fatigue. Five patients (16.7%) had Grade 3 AEs suspected to be treatment related (2 with transaminase increases, 2 with lipase increase, 1 with retinal vein occlusion, and 1 with maculopapular rash) (see Section 1.2.1.2.1).

6.3.3.1.2 LGX818/MEK162 + BKM120 combination

Main anticipated adverse events for LGX818/MEK162 + BKM120

The most frequently reported treatment-related AEs in MEK162 + BKM120 combination study [CMEK162X2101] were CK elevation (56%), diarrhea (54%) and AST elevation (50%).

Preliminary clinical data available from ongoing [CMEK162X2101] study with MEK162 and BKM120 as combination showed that the most frequently reported treatment-related AEs were CK elevation (56%), diarrhea (54%) and AST elevation (50%) (see Section 1.2.1.2.2).

Based on the most frequent observed adverse events described above for LGX818 and MEK162 dual combination and single agent and for MEK162 and BKM120 as dual combination and single agent (see also current LGX818, MEK162 and BKM120 Investigator Brochure), overlapping toxicities, which may potentially be dose-limiting, includes skin (i.e. rash) and fatigue/asthenia, CK and AST elevation, diarrhea and maculopapular rash for the proposed combination.

6.3.3.1.3 LGX818/MEK162 + INC280

Main anticipated adverse events for LGX818/MEK162 + INC280

Fatigue, headache, nausea, tremor, vomiting and pain in extremity are associated with INC280 as single agent.

Based on the most frequent observed adverse events described above for the LGX818 and MEK162 dual combination (see also current LGX818 or MEK162 Investigator Brochure) and for INC280 as single agent, overlapping toxicities, which may potentially be dose-limiting, includes fatigue, nausea, peripheral edema and pain in extremity for the proposed combination.

6.3.3.1.4 LGX818/MEK162 + BGJ398

Main anticipated adverse events for LGX818/MEK162 + BGJ398

Hyperphosphatemia, diarrhea, nausea, pain in extremity, fatigue/asthenia, mucositis/stomatitis, decreased appetite, blood, dyspepsia, dry mouth, transaminase increase and lipase increase are associated with BGJ398.

Based on the most frequent observed adverse events described for the LGX818 and MEK162 dual combination (see current LGX818 or MEK162 Investigator Brochure) and for BGJ398 as single agent, overlapping toxicities, which may potentially be dose-limiting, includes fatigue/asthenia, nausea and myalgia/arthralgia, corneal or retinal adverse events, headache and confusional state for the proposed combination.

6.3.3.1.5 LGX818/MEK162 + LEE011

Main anticipated adverse events for LGX818/MEK162 + LEE011

Mucositis, vomiting, hematological toxicities (i.e. neutropenia, leucopenia, thrombocytopenia), and rash are associated with LEE011.

Based on the most frequent observed adverse events described above for the LGX818 and MEK162 dual combination (see current LGX818 or MEK162 Investigator Brochure) and for LEE011 (See current [LEE011 Investigators Brochure]), overlapping toxicities can be expected for gastrointestinal events (such as nausea, vomiting, diarrhea), as well as fatigue.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, unless otherwise specified in the IBs.

Patients receiving medications outlined below must be carefully monitored for potentiating of toxicity due to any individual concomitant medication, and may require dose titration of the drug substance. Investigators should use caution when prescribing co-medications, as clinical experience with these compounds in patients with cancer is often limited. Investigators should contact the Sponsor when they are unsure whether a drug should be prescribed to a patient in the clinical study. All concomitant medications and dietary supplements must be documented on the eCRFs. Refer to Appendix 7 for a list of medications to be used with caution as mentioned above.

Antiemetics

Use of antiemetics is allowed. Prophylactic antiemetics should be started only once the patient experiences nausea or vomiting and at the discretion of the investigator. It is recommended that patients use drugs that do not cause QT prolongation. Note that some anti-emetics have a known risk for Torsade de Pointes (TdP) (Appendix 7).

Bisphosphonates

The use of bisphosphonates regardless of indication is allowed for the LGX818 and MEK162 dual combination and triplet combinations other than LEE011 (prophylactic treatment is not allowed for bisphosphonates with LEE011) provided patients have been on stable doses for at least 2 weeks prior to study entry. Stable doses should be maintained during the treatment period. Patients requiring initiation of bisphosphonates during the course of the study should be discontinued due to progressive disease unless disease progression can be completely ruled out and this is clearly documented in the patients' source documentation.

Oral antidiabetics

Patients who develop diabetes mellitus during the study should be treated according to the ADA (American Diabetes Association) guidance. It is recommended to start treatment with glimepiride, glibenclamide or metformin. Patients receiving oral antidiabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, must be carefully monitored for hypoglycemia as BKM120 has been found to be a moderate reversible inhibitor of these enzymes (Appendix 7).

Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially increasing the risk of reducing drug exposure for CYP3A substrates to subtherapeutic levels. The following forms of corticosteroid treatment are permitted:

- Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);
- A short duration (< 5 days) of systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g., for chronic obstructive pulmonary disease, or as an antiemetic).

6.4.2 Permitted concomitant therapy requiring caution and/or action throughout the study

6.4.2.1 Permitted concomitant therapy requiring caution and/or action throughout the study based on LGX818 and MEK162 DDI potential (Part I and Part II)

CYP and UGT substrates and inhibitors

LGX818 has been identified to be primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19 in vitro. Moderate inhibitors of CYP3A4 and strong inhibitors of CYP2C19 (see Appendix 7) should be taken with caution when co-administered with LGX818.

MEK162 has been identified to be primarily metabolized by UGT1A1 in vitro. It is advised that inhibitors and inducers of UGT1A1 should be taken with caution when co-administered with MEK162. Patients should be closely monitored for the occurrence of adverse events. Please refer to Table 14-22 for a list of these known drugs but this list may not be exhaustive

MEK162 is a substrate for many CYP isoforms, in particular CYP1A2 and CYP2C19. The risk of metabolic interaction caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution should be used in patients receiving concomitant treatment with other drugs that are either potent inhibitors or inducers of these enzymes.

LGX818 is a reversible inhibitor of UGT1A1, CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, and CYP3A and a time-dependent inhibitor of CYP3A4 at clinically relevant plasma concentrations. Permitted medications to be used with caution in this study include those that are sensitive substrates of these UGT and CYP enzymes or those substrates that have a narrow therapeutic index (NTI) except those prohibited in Section 6.4.3.

There is a potential for LGX818 to induce CYP2B6, CYP2C9, and CYP3A4. Induction of these enzymes may result in reduced efficacy for drugs that are major substrates for these CYP enzymes. Additionally, CYP3A4 induction may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least one form of non-hormonal contraception is needed during the participation in this study. See study exclusion criterion for use of contraception methods required for this study.

Transporter substrates and inhibitors

In vitro data showed that LGX818 is a substrate of P-gp. Thus, the use of drugs that are known to inhibit or induce P-gp and/or BCRP should be used with caution. LGX818 is a P-gp and BCRP inhibitor. It is also a potent inhibitor of the renal transporters, OAT1, OAT3, and OCT2 and the hepatic transporter OATP1B1 and OATP1B3. The co-administration of drugs that are

known to be sensitive or NTI substrates of BCRP, P-gp, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 should be used with caution.

In vitro data showed that MEK162 is a substrate of P-gp and BCRP and thus the use of drugs that are known to inhibit these transporters should be used with caution.

Hematopoietic growth factors

Hematopoietic growth factors (e.g. erythropoietin, G-colony stimulating factor (CSF) and GM-CSF) are not to be administered prophylactically. Use of these drugs should be reserved for patients requiring this therapy as per the labeling of these agents or as dictated by local practice (see also the guidelines established by the American Society of Clinical Oncology).

Drugs with a conditional or possible risk to induce Torsade de Pointes

If a patient requires the concomitant use of any medication with a possible or conditional risk for TdP (Appendix 7), then investigators, at their discretion, may co-administer such medications with LGX818/MEK162, LGX818/MEK162 + INC280 or LGX818/MEK162 + BGJ398. For LGX818/MEK162 + BKM120 and LGX818/MEK162 + LEE011 see Section 6.4.3. Patients receiving such medications must however be monitored.

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, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications.

6.4.2.2 Additional permitted concomitant therapy requiring caution and/or action during Part II

In addition to the cautions and/or actions to be taken throughout the study based on LGX818 and MEK162 DDI potential (see Section 1.2.1.3), the following cautions and/or actions must be taken when administering the triple combinations with BKM120, BGJ398, INC280, or LEE011.

6.4.2.3 Additional permitted concomitant therapy requiring caution and/or action during triple combination with BKM120

In vitro metabolism studies performed to examine the direct and metabolism-dependent inhibition of P450 enzymes showed that BKM120 is a weak, reversible inhibitor of CYP3A4/5 and a weak inhibitor of CYP2C8/2C9/2C19. Note that with the data available, we are not able 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, except those were prohibited in Section 6.4.3. Patients receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate. Particularly, caution is advised when BKM120 is co-administered with:

- drugs which are substrates for CYP3A4, CYP2C8, CYP2C9 or CYP2C19 and which have a narrow therapeutic index

- oral anti-diabetics which are metabolized by CYP2C8 or CYP2C9, possibly resulting in hypoglycemia.

6.4.2.4 Permitted concomitant therapy requiring caution and/or action during triple combination with BGJ398

In vitro data show that BGJ398 is a likely inhibitor of BCRP (IC50 = 0.21 µM), suggesting an increased risk for drug-drug interactions with BCRP substrates. In the absence of data confirming whether such an interaction occurs in patients, investigators at their discretion may co-administer known BCRP substrates. However, patients receiving such medications must be carefully monitored for potentiation of toxicity and may require dose titration or reduction of the BCRP substrate. (including but not limited to rosuvastatin, sulfasalazine, zidovudine and lamivudine).

In *in-vitro*-assays, BGJ398 was shown to inhibit the cytochrome P450 isoenzyme CYP3A4 with a Ki = 0.26µM, thereby suggesting an increased risk of drug interactions with concomitant medications that are also metabolized by CYP3A4. Accumulation of BGJ398 following multiple dosing in patients likely due to auto-inhibition of CYP3A4 mediated clearance pathways was observed. No clinical DDI studies for BGJ398 have been done. Concomitant medications known to be metabolized by CYP3A4 should be administered with caution. Patients receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the CYP3A4 substrate. In particular, caution is advised when BGJ398 is to be co-administered with CYP3A substrates with a narrow therapeutic index, including but not limited to alfentanil, fentanyl, astemizole, cisapride, diergotamine, ergotamine, pimozide, quinidine and terfenadine.

6.4.2.5 Permitted concomitant therapy requiring caution and/or action during triple combination with INC280

Medications that are weak and moderate inducers or inhibitors of CYP3A4 are permitted but should be administered with caution. Refer to Appendix 7 for a list of these medications.

Short acting gastric acid modulators containing aluminium hydroxide and magnesium hydroxide, (e.g., Maalox®) or calcium carbonate (e.g., TUMS®) can be taken. However, it is recommended to take these drugs at least 4 hours before or 4 hours after administration of INC280. H2 receptor antagonists should be avoided when possible. If patients have to take H2 receptor antagonists during the course of this study, patients should take INC280 at least 2 hours before H2 receptor antagonists administration. In addition, the interval of H2 receptor antagonist administration to next dose schedule of INC280 should be at least 8 hours apart. For example, if patient take twice daily dose of H2 receptor antagonist and twice daily dose of INC280, patient can take morning dose of INC280 at 8 am and morning dose of H2 receptor antagonist at 10 am. Afternoon dose of INC280 should be taken approximately 12 hours after the morning dose (8pm) and evening dose of H2 receptor antagonist can be taken at 10pm.

6.4.2.6 Permitted concomitant therapy requiring caution and/or action during triple combination with LEE011

Medications to be used with caution during triplet combination treatment with LEE011 in this study are listed below (see Appendix 7, this list is not comprehensive and is only meant to be

used as a guide. Please contact the medical monitor with any questions). These medications should be excluded from patient use if possible. If they must be given based on the investigator's judgment, then use with caution and consider a LEE011 interruption if the concomitant medication is only needed for a short time.

- Moderate inhibitors or inducers of CYP3A4/5 (may increase or decrease LEE011 exposure, respectively)
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index (LEE011 may increase exposure to these medications)
- Strong inhibitors of BSEP (based on *in vitro* data co-administration with LEE011 may lead to intrahepatic cholestasis)
- Medications that carry a possible risk for QT prolongation (may precipitate QT prolongation and TdP)
- Sensitive substrates of the renal transporters, MATE1, OCT2 and BCRP (has a potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements).

6.4.3 Prohibited concomitant therapy

Prohibited concomitant therapy for LGX818/MEK162 combination

Other investigational and antineoplastic therapies

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy (that includes > 30% of the bone marrow reserve) and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study. Patients requiring antineoplastic therapy after Part I but prior to Part II of the study may receive treatment upon discussion with the Sponsor medical monitor, as long as guidelines specified in Exclusion Criterion 14 are adhered to.

Herbal medications

Herbal preparations/medications are not allowed throughout the study. Patients should stop using these herbal medications 7 days prior to first dose of study treatment.

Warfarin and Coumadin derivatives

Therapeutic doses of warfarin sodium (Coumadin®) or any other Coumadin-derivative anticoagulants are not permitted. Warfarin has a narrow therapeutic range and LGX818, BGJ398 and INC280 are possible inhibitors of 2C9, the major metabolizing enzyme of warfarin. Therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

Strong inhibitors of CYP3A4

LGX818 has been identified to be primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19 in vitro. Systemic use of strong inhibitors of CYP3A4 is prohibited. Below lists current examples of strong CYP3A4 inhibitors that are not permitted (see Appendix 7):

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
- Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
- Antivirals: boceprevir, telaprevir
- Others: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone

These medications should be stopped 7 days prior to first dose of study treatment.

Enzyme inducing anti-epileptic drugs (EIAEDs)

Use of EIAEDs is not permitted. Below lists current examples of enzyme-inducing anti-epileptic drugs that are prohibited: carbamazepine, ethotoin, felbamate, fosphenytoin Phenobarbital, phenytoin, primidone, topiramate.

Additional prohibited concomitant therapy for LGX818/MEK162 + BKM120 combination

- *In vitro* metabolism studies suggest that oxidative metabolism of BKM120 is predominantly mediated by CYP3A4, with only minor contributions of CYP1A1 and UGT1A4. Co-administration with strong and moderate CYP3A4 inhibitors and CYP3A4 inducers (except LGX818) is prohibited.
- Drugs with a known risk for TdP as well as sensitive CYP3A substrates with a possible or conditional risk for TdP are prohibited. Please see Appendix 7 for a list of prohibited medication for this combination.

Additional prohibited concomitant therapy LGX818/MEK162 + LEE011 combination

- Prophylactic treatment of bisphosphonates is not allowed with LEE011.
- Strong inhibitors or inducers of CYP3A4/5 (may significantly increase or decrease LEE011 exposure, respectively)
- Substrates of CYP3A4/5 with a narrow therapeutic index (LEE011 may increase exposure to these medications resulting in toxicity to these medications)
- Medications with a known risk for QT prolongation and/or TdP (may precipitate QT prolongation and TdP in combination with LEE011). See Appendix 7 and LEE011 Investigators Brochure for a complete list of agents that are known to cause QTc prolongation in humans.
- Other investigational and antineoplastic therapies
- Herbal preparations/medications that are strong inhibitors or inducers of CYP3A4/5. These include but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

Please see Appendix 7 for a list of prohibited medication for this combination.

Additional prohibited concomitant therapy LGX818/MEK162 + BGJ398 combination

- Use of medications that are known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes is prohibited and these medications must be stopped 7 days prior to first dose.
- Treatment with agents that are known strong inducers or inhibitors CYP3A4 are prohibited. Caution should be used during administration of moderate inhibitors. Please see Appendix 7 for a list of prohibited medication for this combination

Additional prohibited concomitant therapy LGX818/MEK162 + INC280 combination

- Known CYP3A4, CYP1A2, CYP2C8 or CYP2C19 substrates with narrow therapeutic index.
- Long acting proton pump inhibitors

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a 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 his/her entire participation in the trial. The Patient Number consists of the Center Number (Center No.) (as assigned by the Sponsor to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the Molecular pre-screening Informed Consent Form (if applicable) or Study Informed Consent Form, the patient is assigned to the next sequential Patient Number available to the investigator.

Once assigned, the Patient No. must not be reused for any other subject and the Patient No. for that individual must not be changed.

6.5.2 Treatment assignment or randomization

6.5.3 Part I

No randomization will be performed in this study.

6.5.4 Part II

Patients will be assigned to one of the 4 treatment arms according the molecular alterations detected at progression under LGX818/MEK162 combination treatment (see Table 4-1).

Note: Enrollment to the BKM120- (Amendment 03), BGJ398-, INC280- (Amendment 06) and LEE011 (Amendment 07)-containing arms in Part II is closed.

6.5.5 Treatment blinding

Not applicable.

6.6 Study drug preparation and dispensation

Note: Enrollment to the BKM120- (Amendment 03), BGJ398-, INC280-, (Amendment 06) and LEE011(Amendment 07)-containing arms in Part II is closed.

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

All medication will be provided by the Sponsor and other drug strengths may become available.

LGX818 will be supplied as capsules of 50 mg, and 100 mg dosage strength.

MEK162 is supplied as tablets of dosage strength 15 mg.

BKM120 is supplied as capsules of dosage strength 10 mg, and 50 mg.

BGJ398 is supplied as capsules of dosage strengths 25 mg and 100 mg.

INC280 is supplied as capsules of dosage strength 50 mg or tablets of dosage strength 100 mg and 200 mg.

LEE011 is supplied as capsules of dosage strength of 50 mg, and 200 mg

LGX818, BKM120, BGJ398, and LEE011 will be dosed **once a day** on a flat scale of mg/day and not adjusted to body weight or body surface area.

MEK162 and INC280 will be dosed on a flat scale of mg **twice a day** and not individually adjusted by weight or body surface area.

6.6.1 Study drug packaging and labeling

Study Drug labels will comply with the legal requirements of each country and will be printed in the local language. They will supply no information about the patient. The storage conditions for study drug will be described on the study drug label.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, LGX818, MEK162, BKM120, BGJ398, INC280 and LEE011 should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochures].

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of LGX818 and MEK162, BKM120, BGJ398, INC280, and LEE011 in plasma.

At the day of a scheduled visit to the clinic, the patient will take LGX818 + MEK162, or LGX818 + MEK162 + BKM120, or LGX818 + MEK162 + BGJ398, or LGX818 + MEK162 + INC280, or LGX818 + MEK162 + LEE011 at the clinic under supervision of the Investigator or designee. The time of dose administrations must be recorded in the Dosage Administration Record eCRF.

For all other study days, the patient will take LGX818 + MEK162, or LGX818 + MEK162 + BKM120, or LGX818 + MEK162 + BGJ398, or LGX818 + MEK162 + INC280, or LGX818 + MEK162 + LEE011 at home. The dose administrations must be recorded in the Dosage Administration Record eCRF.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. 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 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 log to the Sponsor monitor or to the Sponsor address provided in the investigator folder at each site.

6.6.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

The assessments are listed in Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5 and are indicated 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).

Patients in Group A and B will enter the screening phase (Part I or Run-in) and move to the treatment phase (Part I or Run-in), if eligible to be treated, or continue to be treated, with LGX818/MEK162 combination. Once the patients progressed on the double combination, a new biopsy sample will be collected for the genetic assessment. At the time when the genetic assessment results are available, the patients will go through the End of Study Treatment

assessments (Part I and Run-in), which will include some specific assessments (e.g. HbA1c, fasting glucose, thyroid function and others in Table 7-1 and Table 7-2) to determine the patients' eligibility for the assigned triple combination. If eligible, the patients in Group A and B will move from the End of Study Treatment visit (Part I or Run-in) to the treatment phase (Part II). Therefore, the safety and tolerability, as well as the tumor evaluation, End of Study Treatment assessments (Part I or Run-in) will be considered the baseline assessments for Part II. All Safety and tolerability assessments must be completed within 14 days before the first triple combination dose, with the exception of pregnancy test, which must be performed within 72 hours before the first triple combination dose. For patients in Group C progressing while treated with LGX818/MEK162 combination in other studies (e.g. [CMEK162X2110] and [COLUMBUS]), and patients in Group B, who already received LGX818/MEK162 in other studies (e.g. [CMEK162X2110], and [COLUMBUS]), the End of Study Treatment assessments (e.g. tumor evaluation) performed in the previous study will be used as baseline assessments for this study.

For all patients the screening assessments must be completed within 14 days before the first study treatment dose, with the exception of pregnancy test, which must be performed within 72 hours before the first study treatment dose. Part I Screening/baseline CT/MRI scans must be completed within 21 days prior to the first study treatment dose.

Assessments which are indicated to be performed at Screening/baseline, or at End of Study Treatment (Part I and Run-in) for patients moving to treatment phase Part II, and on Cycle 1 Day 1, need to be repeated at Cycle 1 Day 1 only if the Screening/baseline assessments, or the End of Study Treatment assessments, were performed more than 3 days before Day 1 Cycle 1.

For all patients the last CT/MRI must be completed within 28 days before receiving the first triple combination treatment dose. If the time interval between the last CTI/MRI tumor evaluation assessment documenting the disease progression and the first dose of the triple combination is more than 4 weeks (28 days), a new tumor evaluation should be performed.

For PK sampling the samples may be obtained on the day of dosing +/- 3 days from the scheduled date (except for Day1 PK profile, which must take place on Day 1). All samples from the same PK profile (e.g. C1D15 PK samples) should be shifted together (e.g., if visit for C1D15 actually occurs on C1D16, all the PK samples for this PK profile should be shifted of one day, accordingly, and all <24hr PK samples will be taken on C1D16 and 24 hr sample on C1D17).

For all other on-treatment visits, there is a ± 3-day window on assessments to take into account scheduling over public or religious holidays if not explicitly specified otherwise. For on-study imaging assessments a ± 7 day window is allowed. Every effort must be made to follow the schedule outlined in Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5.

Table 7-1 Part I - Visit evaluation schedule for patients enrolled in Group A

Note: For patients on dual combination treatment for ≥ 36 months, refer to Table 7-5.

Part I			**Screening Phase**		**Treatment Phase**							
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow up[7]**	**Disease Progression Follow-up**
Day of cycle				**-14 to-1**	**1**	**15**	**8**	**21**	**15**		**30 days from last dose**	
Molecular pre-screening Informed Consent	D	7.1.1 & 4.1.	X									
Main study Informed Consent	D	7.1.2.		X								
Documented BRAF V600 mutation	D	7.1.1 & 4.1.	X									
Demography	D	7.1.2.3.	X									
Inclusion/exclusion criteria	D	5.2 & 5.3.		X								
Additional exclusion criteria for third agent (only patients moving to Part II)	D	5.2 & 5.3.								X		
Relevant medical history/current medical conditions	D	7.1.2.3.		X								
Diagnosis and extent of cancer	D	7.1.2.3.		X								
Prior antineoplastic therapy	D	7.1.2.3.		X								
Prior/concomitant medications	D	7.1.2.3.		X	**Continuous**							
Physical examination	S	7.2.2.1.		X	X	X	X	X	X	X		
ECOG performance status (WHO)	D	7.2.2.2.		X	X		X		X	X		

Part I			**Screening Phase**		**Treatment Phase**							
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow up[7]**	**Disease Progression Follow-up**
Day of cycle				**-14 to-1**	**1**	**15**	**8**	**21**	**15**		**30 days from last dose**	
Height	D	7.2.2.3.		X								
Weight	D	7.2.2.3.		X	X		X			X		
Vital signs	D	7.2.2.4.		X	X	X	X	X	X	X		
Laboratory Assessments		7.2.2.5.										
Hematology	D	7.2.2.5.1.		X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2.		X	X	X	X	X	X	X		
Coagulation	D	7.2.2.5.3.		X		If clinically relevant				X		
Ophthalmologic examination	D	7.2.2.5.7.		X			X		X[2]	X		
Urinalysis	D	7.2.2.5.5.		X	If clinically relevant							
Pregnancy test	D	7.2.2.5.8.		X	X		X		X	X		
Dermatologic evaluation	D	7.2.2.5.6.		X						X		
HbA1c (only patients moving to BKM120 arm Part II)	D	7.2.2.5.4.								X		
Fasting plasma glucose (only patients moving to BKM120 arm Part II)	D	7.2.2.5.4.								X		
Thyroid Function (only patients moving to LEE011 arm Part II)	D	7.2.2.5.9.								X		

Part I			**Screening Phase**		**Treatment Phase**							
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow up[7]**	**Disease Progression Follow-up**
Day of cycle				**-14 to-1**	**1**	**15**	**8**	**21**	**15**		**30 days from last dose**	
Imaging		7.2.1.										
Brain CT/MRI with contrast (patients assigned to LEE011 arm in Part II)	D	7.2.1.								X		
Brain CT/MRI with contrast (patients with baseline brain metastases)	D	7.2.1.		X					Every 6 weeks	X		
Tumor evaluation (RECIST) - CT/MRI Color photography if skin lesions are present	D	7.2.1.		X				X	Every 6 weeks, every 6-12 weeks after ≥ 24 months of treatment[3]	X		Every 9 weeks, every 9-12 weeks after ≥ 24 months of treat-ment[4]

Part I			**Screening Phase**		**Treatment Phase**							
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow up[7]**	**Disease Progression Follow-up**
Day of cycle				**-14 to-1**	**1**	**15**	**8**	**21**	**15**		**30 days from last dose**	
ECG[5] (triplicate only at Day 1 Cycle1)	D	7.2.2.6.1.		X	X	X	X	X	X C3, C5 every 2 cycles, every 3 cycles after ≥ 24 months of treatment	X		
Cardiac imaging	D	7.2.2.6.2.		X			X		C5, C8, C11 and every 3 cycles thereafter	X		
GAD-7 and PHQ-9 Questionnaires (only patients moving to BKM120 arm Part II)	D	7.2.2.7.								X		
Additional Ophthalmologic exam (only patients moving to BGJ398 arm Part II)	D	7.2.2.5.7.								X		
Safety		7.2.2.										
Adverse events	D		X[6]	X	Continuous							
Biomarkers		7.2.4.										
Collection of archival paraffin blocks/slides & corresponding pathology report	D		X, if needed	X, if not collected at molecular screening								

Part I			**Screening Phase**		**Treatment Phase**							
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow up[7]**	**Disease Progression Follow-up**
Day of cycle				**-14 to-1**	**1**	**15**	**8**	**21**	**15**		**30 days from last dose**	
Collection of newly obtained tumor sample from biopsy	D	7.2.4.	X, if needed	X, if not collected at molecular screening	At progression							
Report genetic assessments results of progression biopsy (only patients moving to Part II)	D	7.2.4.								X		
CCI												
Study Drug Administration												
LGX818 QD/MEK162 BID administration	D	6.1.1.			**Continuous**							
PK Blood Sampling	D	7.2.3.			X	X	X pre-dose	X pre-dose	X Up to C5 only	X		
Meal Record	D	7.2.3.1.				X						
Antineoplastic therapies since discontinuation of study treatment	D	7.1.6.2.								X	X	X

Part I			Screening Phase		Treatment Phase							
	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1		Cycle 2		Subsequent Cycles	End of Study Treatment [1]	Safety Follow up[7]	Disease Progression Follow-up
Day of cycle				**-14 to-1**	**1**	**15**	**8**	**21**	**15**		**30 days from last dose**	

1. EOT assessments will take place for patients who discontinue study treatment during Part I and will not move into Part II of the trial, and for patients moving to Part II at the time the genetic assessment results are available. EOT for patients permanently discontinuing the study treatment will occur within 14 days of the last dose of study treatment or within 14 days of date of decision to discontinue study treatment.

2. Patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE within the past 12 months should be evaluated only for visual acuity at each scheduled patient visit and at End of Study Treatment visit. A full ophthalmic examination is required if clinically indicated and at End of Study Treatment visit.

3. Patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months will have CT/MRI scans every 6-12 weeks (+/- 7 days).

4. Patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression will have CT/MRI scans every 9-12 weeks (+/- 7 days).

5. All ECGs should be taken before a blood sample or at least 0.5 hours after a blood sample.

6. To collect only the Pre-screening Procedure Related SAEs.

7. Following the 30-day follow-up, when clinically appropriate, it is recommended patients be monitored with physical examinations, dermatological examinations, and chest CT scans for cutaneous and non-cutaneuous secondary malignancies for up to 6 months after the last LGX818 dose or until initiation of another antineoplastic therapy.

Table 7-2 Run-in Visit evaluation schedule for patients enrolled in Group B

Note: For patients on dual combination treatment for ≥ 36 months, refer to Table 7-5.

Run-in			Screening Phase		Treatment Phase								
	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1			Cycle 2		Subsequent Cycles	End of Study Treatment [1]	Safety Follow-up[7]	Disease Progression Follow-up
Day of cycle				**-14 to-1**	**1**	**15**	**21**	**8**	**21**	**15**		**30 days from last dose**	
Molecular pre-screening Informed Consent	D	7.1.1 & 4.1.	X										
Main study Informed Consent	D	7.1.2.		X									
Documented BRAF V600 mutation	D	7.1.1 & 4.1.	X										
Demography	D	7.1.2.3.	X										
Inclusion/exclusion criteria	D	5.2 & 5.3.		X									
Additional exclusion criteria for third agent (only patients moving to Part II)	D	5.2 & 5.3.									X		
Relevant medical history/current medical conditions	D	7.1.2.3.		X									
Diagnosis and extent of cancer	D	7.1.2.3.		X									
Prior antineoplastic therapy	D	7.1.2.3.		X									
Prior/concomitant medications	D	7.1.2.3.		X	Continuous								
Physical examination	S	7.2.2.1.		X	X	X	X	X	X	X	X		

Run-in			**Screening Phase**		**Treatment Phase**								
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**			**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow-up[7]**	**Disease Progression Follow-up**
Day of cycle				**-14 to-1**	**1**	**15**	**21**	**8**	**21**	**15**		**30 days from last dose**	
ECOG performance status (WHO)	D	7.2.2.2.		X	X			X		X	X		
Height	D	7.2.2.3.		X									
Weight	D	7.2.2.3.		X	X			X			X		
Vital signs	D	7.2.2.4.		X	X	X	X	X	X	X	X		
Laboratory Assessments		7.2.2.5.											
Hematology	D	7.2.2.5.1.		X	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2.		X	X	X	X	X	X	X	X		
Coagulation	D	7.2.2.5.3.		X		If clinically relevant					X		
Ophthalmologic examination	D	7.2.2.5.7.		X				X		X[2]	X		
Urinalysis	D	7.2.2.5.5.		X	If clinically relevant								
Pregnancy test	D	7.2.2.5.8.		X	X			X		X	X		
Dermatologic evaluation	D	7.2.2.5.6.		X							X		
HbA1c (only patients moving to BKM120 arm Part II)	D	7.2.2.5.4.									X		
Fasting plasma glucose (only patients moving to BKM120 arm Part II)	D	7.2.2.5.4.									X		

Run-in			**Screening Phase**		**Treatment Phase**								
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**			**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow-up[7]**	**Disease Progression Follow-up**
Day of cycle				**-14 to-1**	**1**	**15**	**21**	**8**	**21**	**15**		**30 days from last dose**	
Thyroid Function (only patients moving to LEE011 arm Part II)	D	7.2.2.5.9.									X		
Imaging		7.2.1.											
Brain CT/MRI with contrast (patients assigned to LEE011 arm in Part II)	D	7.2.1.									X		
Brain CT/MRI with contrast (patients with baseline brain metastases)	D	7.2.1.		X						Every 6 weeks	X		
Tumor evaluation (RECIST) - CT/MRI Color photography if skin lesions are present	D	7.2.1.		X			X			Every 6 weeks, every 6-12 weeks after ≥ 24 months of treatment[3]	X		Every 9 weeks, every 9-12 weeks after ≥ 24 months of treat-ment[4]

Run-in			**Screening Phase**		**Treatment Phase**								
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**			**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow-up[7]**	**Disease Progression Follow-up**
Day of cycle				**-14 to-1**	**1**	**15**	**21**	**8**	**21**	**15**		**30 days from last dose**	
ECG[5] (triplicate only at Day 1 Cycle1)	D	7.2.2.6.1.		X	X	X		X	X	X C3, C5 every 2 Cycles every 3 cycles after ≥ 24 months of treatment	X		
Cardiac imaging	D	7.2.2.6.2.		X				X		C5, C8, C11 and every 3 Cycles thereafter	X		
GAD-7 and PHQ-9 Questionnaires (only patients moving to BKM120 arm Part II)	D	7.2.2.7.									X		
Additional Ophthalmologic exam (only patients moving to BGJ398 arm Part II)	D	7.2.2.5.7.									X		
Safety		7.2.2.											
Adverse events	D		X[6]	X	Continuous								

Run-in			**Screening Phase**		**Treatment Phase**								
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**			**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow-up[7]**	**Disease Progression Follow-up**
Day of cycle				**-14 to-1**	**1**	**15**	**21**	**8**	**21**	**15**		**30 days from last dose**	
Biomarkers		7.2.4.											
Collection of archival paraffin blocks/slides & corresponding pathology report	D	7.2.4.	X (if needed)	X-if not collected at molecular screening									
Collection of newly obtained tumor sample from biopsy	D	7.2.4.	X (if needed)	X-if not collected at molecular screening	At Progression								
Report genetic assessments results of progression biopsy (only patients moving to Part II)	D	7.2.4.									X		
CCI BRAF	D	7.2.4.2.		X				X		X	X		
Study Drug Administration													
LGX818 QD/MEK162 BID administration	D	6.1.1.			Continuous								
PK Blood Sampling	D	7.2.3.			X	X		X pre-dose	X pre-dose	X Up to C5 only	X		
Meal Record	D	7.2.3.1.				X							
Antineoplastic therapies since discontinuation of study treatment	D	7.1.6.2.									X	X	X

Run-in			Screening Phase		Treatment Phase								
	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1			Cycle 2		Subsequent Cycles	End of Study Treatment [1]	Safety Follow-up[7]	Disease Progression Follow-up
Day of cycle				**-14 to-1**	**1**	**15**	**21**	**8**	**21**	**15**		**30 days from last dose**	

1. EOT assessments will take place for patients who discontinue study treatment during Part I and will not move into Part II of the trial, and for patients moving to Part II at the time the genetic assessment results are available. EOT for patients permanently discontinuing the study treatment will occur within 14 days of the last dose of study treatment or within 14 days of date of decision to discontinue study treatment

2. Patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE in the past 12 months should be evaluated only for visual acuity at each scheduled patient visit and at End of Study Treatment visit. A full ophthalmic examination is required if clinically indicated and at End of Study Treatment visit.

3. Patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months will have CT/MRI scans every 6-12 weeks (+/- 7 days).

4. Patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression will be followed up by CT/MRI scans every 9-12 weeks (+/- 7 days).

5. All ECGs should be taken before a blood sample or at least 0.5 hours after a blood sample.

6. To collect only the Pre-screening Procedure Related SAEs.

7. Following the 30-day follow-up, when clinically appropriate, it is recommended patients be monitored with physical examinations, dermatological examinations, and chest CT for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last encorafenib dose or until initiation of another antineoplastic therapy.

Table 7-3 Part II - Visit evaluation schedule for Part II (21 day cycles for triple combinations with INC280 and BKM120)

Note: As of Protocol Amendment 06, enrollment to the BKM120- and INC280-containing arms is closed.

Part II (21 days cycle)			Screening Phase Group C		Treatment Phase										
	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2		Subsequent Cycles	End of Study Treatment [1]	Safety Follow-up [2]	Disease Progression Follow-up	Survival Follow-up
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**1**	**15**	**1**				
Molecular pre-screening Informed Consent	D	7.1.2.	X												
Study Informed Consent	D			X											
Documented BRAF V600 mutation	D	7.1.1.	X												
Demography	D	7.1.2.3.	X												
Inclusion criteria /exclusion criteria	D	5.1; 5.2; 5.3.		X											
Relevant medical history/current medical conditions	D	7.1.2.3.		X											
Diagnosis and extent of cancer	D	7.1.2.3.		X											
Prior antineoplastic therapy	D	7.1.2.3.		X											
Prior/concomitant medications	D	7.1.2.3.		X	Continuous										
Physical examination	S	7.2.2.1.		X	X	X	X		X	X	X	X			
ECOG performance status (WHO)	D	7.2.2.2.		X	X				X		X	X			
Height	D	7.2.2.3.		X											
Weight	D	7.2.2.3.		X	X				X		X	X			

Part II (21 days cycle)			**Screening Phase Group C**		**Treatment Phase**										
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**				**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow-up [2]**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**1**	**15**	**1**				
Vital signs	D	7.2.2.4.		X	X	X	X		X	X	X	X			
Laboratory assessments		7.2.2.5.													
Hematology	D	7.2.2.5.1.		X	X	X	X		X	X	X	X			
Chemistry	D	7.2.2.5.2.		X	X	X	X		X	X	X	X			
Coagulation	D	7.2.2.5.3.		X		If clinically relevant						X			
HbA1c (BKM120 arm only)	D	7.2.2.5.4.		X					X		X	X			
											Every 3 Cycles				
Fasting plasma glucose (BKM120 arm only)	D	7.2.2.5.4.		X	X		X		X	X	X	X			
Hepatotoxicity follow up/ procedures (BKM120 arm only)	D	6.3.2.5.		As clinically indicated											
Urinalysis (and 24h urine collection if applicable)	D	7.2.2.5.5.		X					X		if clinically indicated	X			
Pregnancy test	D	7.2.2.5.8.		X	X				X		X	X			
Dermatologic evaluation	D	7.2.2.5.6.		X					X		X Every 2 Cycles	X			
Ophthalmologic examination		7.2.2.5.7.		X			X		X	X	X	X			
Imaging		7.2.1.													
Brain CT/MRI with contrast (patients with brain metastases)	D	7.2.1.		X	Every 9 weeks							X		X Every 9 weeks	

Part II (21 days cycle)			**Screening Phase Group C**		**Treatment Phase**										
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**				**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow-up [2]**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**1**	**15**	**1**				
Tumor evaluation (RECIST)-CT/MRI Color photography if skin lesions are present	D	7.2.1.		X	Every 9 weeks							X		X Every 9 weeks	
ECG (triplicate only at Day1 Cycle1)	D	7.2.2.6.1.		X	X	X	X		X	X	X Every 2 Cycles	X			
Cardiac imaging	D	7.2.2.6.2.		X[4]	X[4]				X[4]		X At C3 and every 3rd cycle	X			
GAD-7 and PHQ-9 Questionnaires (for BKM120 arm only)	D	7.2.2.7.		X			X		X		X	X			
Safety		7.2.2.													
Adverse events	D			Continuous											
Biomarkers		7.2.4.													
Report results of progression biopsy performed in previous studies	D	7.2.4.		X											
Collection of newly obtained tumor sample from biopsy, if applicable	D	7.2.4.	X, if needed	X, if needed			X					X at progression			

Part II (21 days cycle)			**Screening Phase Group C**		**Treatment Phase**										
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**				**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow-up [2]**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**1**	**15**	**1**				
Collection of archival paraffin blocks/slides & corresponding pathology report		7.2.4.		X											
CCI															
Study Drug administration															
LGX818 QD + MEK162 BID administration	D	6.1.1.			Continuous										
INC280 BID or BKM120 QD administration	D	6.1.1.			Continuous										
PK blood sampling	D	7.2.3.			X	X	X	X	X	X	X up to Cycle 5	X			
Meals record	D	7.2.3.1.					X								
Antineoplastic therapies since discontinuation of study treatment	D	7.1.6.2.										X	X	X	X
Survival Follow-up (Contact every 3 months)	D	7.1.6.3.													X

Part II (21 days cycle)			**Screening Phase Group C**		**Treatment Phase**										
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**				**Cycle 2**		**Subsequent Cycles**	**End of Study Treatment [1]**	**Safety Follow-up [2]**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**1**	**15**	**1**				

1. EOT will occur within 14 days of the last dose of study treatment or within 14 days of date of decision to discontinue study treatment
2. Safety follow-up will occur 30 days after the last dose
3. For patients in group C, who need to undertake a biopsy at screening and are going to continue treatment with LGX818/MEK162 combination, the screening assessments can be started at day -28 (instead of day -14) as described in Section 7.1.2.
4. Patients coming from Part I will perform the cardiac imaging at Day 1 of Cycle 1, Day 1 of Cycle 3 and every third cycle and at the End of Study Treatment visit. Patients coming from other trials will perform the cardiac imaging at Screening/baseline, Day 1 of Cycle 2, Day 1 of Cycle 3 and every third cycle and at the End of Study Treatment visit.

Table 7-4 Part II - Visit evaluation schedule for Part II (28 day cycles for LEE011 and BGJ398)

Note: As of Protocol Amendment 06, enrollment to the BGJ38-containing arm is closed. As of Amendment 07, enrollment to the LEE011 arm is closed.

Part II (28 days cycle)			**Screening Phase Group C**		**Treatment Phase**											
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**					**Cycle 2**		**Subsequent Cycles**		**End of Study Treatment[1]**	**Safety follow-up [2,7]**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**21**	**1**	**15**	**1**	**15[5]**				
Molecular pre-screening Informed Consent	D		X														
Main Study Informed Consent		7.1.2.		X													
Documented BRAF V600 mutation	D	7.1.1.	X														
Demography	D	7.1.2.3.		X													
Inclusion/ exclusion criteria	D	5.1; 5.2. 5.3.		X													
Relevant medical history/current medical conditions	D	7.1.2.3.		X													
Diagnosis and extent of cancer	D	7.1.2.3.		X													
Prior antineoplastic therapy	D	7.1.2.3.		X													
Prior/concomitant medications	D	7.1.2.3.		X	Continuous												

Part II (28 days cycle)			**Screening Phase Group C**		**Treatment Phase**												
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**					**Cycle 2**		**Subsequent Cycles**		**End of Study Treatment[1]**	**Safety follow-up [2,7]**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**21**	**1**	**15**	**1**	**15[5]**				
Physical examination	S	7.2.2.1.		X	X	X	X		X	X	X	X	X[5]	X			
ECOG performance status (WHO)	D	7.2.2.2.		X	X					X		X		X			
Height	D	7.2.2.3.		X													
Weight	D	7.2.2.3.		X	X					X		X		X			
Vital signs	D	7.2.2.4.		X	X	X	X		X	X	X	X	X[5]	X			
Laboratory assessments		7.2.2.5.															
Hematology	D	7.2.2.5.1.		X	X	X	X		X	X	X	X	X[5]	X			
Chemistry	D	7.2.2.5.2.		X	X	X	X		X	X	X	X	X[5]	X			
Coagulation	D	7.2.2.5.3.		X		If clinically relevant								X			
Thyroid Function (LEE011 arm only)	D	7.2.2.5.9.		X						X		X		X			
												Every 2 cycles from C3 only if clinically indicated					
Hepatotoxicity follow up/ procedures (LEE011 arm only)	D	6.3.2.6.		As clinically indicated													
Urinalysis	D	7.2.2.5.5.		X					X			if clinically indicated		X			
Pregnancy test	D	7.2.2.5.8.		X	X					X		X		X			
Dermatologic evaluation	D	7.2.2.5.6.		X						X		Every 2 Cycles		X			

Part II (28 days cycle)			**Screening Phase Group C**		**Treatment Phase**												
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**					**Cycle 2**		**Subsequent Cycles**		**End of Study Treatment[1]**	**Safety follow-up [2,7]**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**21**	**1**	**15**	**1**	**15[5]**				
Ophthalmologic examination	D	7.2.2.5.7.		X			X			X	X	X[6]		X			
Additional Ophthalmologic exam for BGJ398 arm only	D	7.2.2.5.7.		X			X			X	X	X	X[5]	X			
Imaging		7.2.1.															
Tumor evaluation (RECIST)-CT/MRI Color photography if skin lesions are present	D	7.2.1.		X	Every 9 weeks									X		X Every 9 weeks	
Brain CT/MRI with contrast (patients assigned to LEE011 arm and patients with history of brain metastases)	D	7.2.1.		X	Every 9 weeks									X		X Every 9 weeks	
ECG (triplicate only at Day1 Cycle1)	D	7.2.2.6.1.		X	X	X	X		X	X	X	X		X			
												Every 2 Cycles, then every 3 cycles after ≥ 24 months of treatment					
Cardiac imaging	D	7.2.2.6.2.		X[4]	X[4]					X[4]		X		X			
												At C3 and every 3rd cycle					

Part II (28 days cycle)			**Screening Phase Group C**		**Treatment Phase**												
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**					**Cycle 2**		**Subsequent Cycles**		**End of Study Treatment[1]**	**Safety follow-up [2,7]**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**21**	**1**	**15**	**1**	**15[5]**				
Safety		7.2.2.															
Adverse events	D		X	X	Continuous												
Biomarkers		7.2.4.															
Report results of progression biopsy in previous studies	D	7.2.4 and 4.1.		X													
Collection of newly obtained tumor sample from biopsy, if applicable	D	7.2.4 and 4.1.	X, if needed	X, if needed			X							X at progression			
Collection of archival paraffin blocks/slides or corresponding sequencing report.	D	7.2.4 and 4.1.		X													
CCI [redacted]																	
Study Drug administration																	
LGX818 QD + MEK162 BID administration	D	6.1.1.			Continuous												
BGJ398 QD or LEE011 QD administration	D	6.1.1.			3 weeks on 1 week off												
PK blood sampling	D	7.2.3.			X	X	X	X	X	X	X	X Up to Cycle 5		X			

Part II (28 days cycle)			**Screening Phase Group C**		**Treatment Phase**												
	Category	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**					**Cycle 2**		**Subsequent Cycles**		**End of Study Treatment[1]**	**Safety follow-up [2,7]**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of cycle				**-14 to-1[3]**	**1**	**8**	**15**	**16**	**21**	**1**	**15**	**1**	**15[5]**				
Meals record	D	7.2.3.1.					X										
Antineoplastic therapies since discontinuation of study treatment	D	7.1.6.2.												X	X	X	X
Survival Follow-up (Contact every 3 months)	D	7.1.6.3.															X

1. EOT will occur within 14 days of the last dose of study treatment or within 14 days of date of decision to discontinue study treatment
2. Safety follow-up will occur 30 days after the last dose
3. For patients in group C, who need to undertake a biopsy at screening and are going to continue treatment with LGX818/MEK162 combination, the screening assessments can be started at day -28 (instead of day -14) as described in Section 7.1.2.
4. Patients coming from Part I will perform the cardiac imaging at Day 1 of Cycle 1, Day 1 of Cycle 3 and every third cycle, and at the End of Study Treatment visit. Patients coming from other trials will perform the cardiac imaging at Screening/baseline, Day 1 of Cycle 2, and Day 1 of Cycle 3 and every third cycle, and at the End of Study Treatment visit.
5. Day15 visit will be only performed up to Cycle 4. After that, only Day 1 visit will be scheduled at each cycle from Cycle 5.
6. Patients who have received LGX818/MEK162 for ≥ 24 months (Cycle 25 Day 1 onward) without a retinal AE in the past 12 months should be evaluated only for visual acuity at each scheduled patient visit and at End of Study Treatment visit. A full ophthalmic examination is required if clinically indicated and at End of Study Treatment visit.
7. Following the 30-day follow-up, when clinically appropriate, it is recommended patients be monitored with physical examinations, dermatological examinations, and chest CT scans for cutaneous and non-cutaneous secondary malignancies for up to 6 months after the last LGX818 dose or until initiation of another antineoplastic therapy.

Table 7-5 Part I - LGX818 + MEK162 Visit Evaluation Schedule for patients on treatment ≥ 36 months (Amendment 07)

Part I Procedure or Assessment[1] (± 3-day window for procedures/assessments)	LGX818 + MEK162 Treatment					
			Starting Week 157 (≥ 36 months on treatment)		Treatment Discontinuation Visit	30-Day Safety Follow-up[13]
Day of Cycle	Category	Protocol Section	Per local standard of care (Recommended every 4 weeks)	Recommended every 8-12 weeks		
Physical Examination[2,13]	D	7.2.2.1.	X		X	
Vital Signs[3]	D	7.2.2.4.	X		X	
ECOG PS	D	7.2.2.2.	X		X	
Single ECG	D	7.2.2.6.1.	X		X	
Hematology[4]	D	7.2.2.5.1.	X		X	
Coagulation[5]	D	7.2.2.5.2.	X		X	
Clinical Chemistry[6]	D	7.2.2.5.3.	X		X	
Urinalysis	D	7.2.2.5.5.	X[7]		X[7]	
Pregnancy Test[8]	D	7.2.2.5.8.	X		X	
Cardiac Ejection Fraction[9]	D	7.2.2.6.2.		X	X	
Visual Acuity	D	7.2.2.5.7.	X		X	
Ophthalmic Examination	D	7.2.2.5.7.	(X)[10]	(X)[10]	(X)[10]	
Dermatological Examination[13]	D	7.2.2.5.6.			X	
LGX818+MEK162[11] **-** Dispense and/or Assess Compliance	D	6.1.1.	X[12]			
Review adverse events	D	8.1.	X		X	X
Review concomitant medications	D	7.1.2.3.	X		X	X
CCI [redacted] BRAF	D	7.2.4.	X		X	
Tumor Assessments	D	7.2.1.	Per institutional standard of care			

1 The minimally required procedures/assessments are indicated; these or any additional procedures/assessments can be repeated more frequently per standard of care or if clinically indicated. For all visits, there is a general ± 3-day window for assessments to take into account scheduling over public or religious holidays.

2 Body weight will be measured as part of the physical examination.

3 Including: blood pressure, pulse and temperature, as appropriate.

4 Including: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils/ANC, platelets, RBC, WBC.

5 Including: aPTT, INR/PT.

6 Including: ALT, AST, bilirubin (total and direct), albumin, alkaline phosphatase, BUN/urea, calcium, CK, creatinine, creatinine clearance (calculated), magnesium, potassium, sodium, total protein, troponin. For Grade 2 total CK that is also ≥ 3 × ULN or asymptomatic Grade 3 total CK: measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks and if total CK remains ≤ the grade which triggered increased monitoring, continue to assess CK, CK isoenzymes and myoglobin along with regularly scheduled clinical chemistry assessments.

7 To be done if clinically indicated.

8 Local urine test for women of childbearing potential only.

9 Assessed by ECHO or MUGA. The same method should be used throughout the study. Patients who develop signs/symptoms of CHF at any point during the study are required to have an evaluation by ECHO or MUGA.

10 Patients who have been on LGX818 + MEK162 treatment without a retinal AE within the past 12 months should be evaluated **only for visual acuity** at each scheduled patient visit and at End of Study Treatment visit. A full ophthalmic examination is required, **if clinically indicated**. Full ophthalmic examination includes: slit lamp examination; best corrected visual acuity for distance testing; automated visual field testing; IOP; and dilated fundoscopy with attention to retinal abnormalities, especially RPED, serous detachment of the retina and RVO. Patients with clinical suspicion of retinal abnormalities of any grade (i.e., RPED, serous detachment of the retina, RVO, photopsia, metamorphopsia, impairment of visual acuity, etc.) must be seen by an ophthalmologist as soon as possible and additional assessments with OCT (spectral domain OCT recommended) of the macula (for non-vascular abnormalities) and color fundus photography of the central 30 degrees and/or fluorescein angiography (for vascular abnormalities) are mandatory.

11 LGX818 + MEK162 dosed PO BID with water irrespective of food, continuously.

12 After Week 157, LGX818 and MEK162 will be dispensed every 12 weeks

13 Following the 30-day follow-up, when clinically appropriate, it is recommended patients be monitored with physical examinations, dermatological examinations, and chest CT scans for cutaneous and non-cutaneuous secondary malignancies for up to 6 months after the last LGX818 dose or until initiation of another antineoplastic therapy.

7.1.1 Molecular pre-screening

The molecular pre-screening informed consent must be signed prior to any study-related molecular pre-screening procedure.

To enter the screening phase for Part I, Run-in and Part II of this study, patients must complete the molecular pre-screening assessment if written documentation of BRAF V600 mutation is unavailable, or, there is a new lesion growing for which BRAF status may be of interest. Patients, for whom the BRAF mutational status was not already assessed outside of this study, must sign the molecular pre-screening informed consent and provide either an archival biopsy sample or consent to providing a new tumor biopsy sample, which will be locally analyzed for BRAF status (for patients enrolled at US sites, an FDA-approved test must be used). This does not apply to patients moving from Part I to Part II after progressing on LGX818/MEK162 combination. Once the mutation of the BRAF V600 codon (e.g. V600E/K/D/R) is confirmed by the designated local laboratory and documented by the site, the patient may begin the screening procedures.

In the case of patients previously treated with any BRAF and/or MEK inhibitors, and therefore eligible to be screened for participation into the Run-in or Part II, they should sign the pre-screening informed consent and provide an archival tumor sample collected pre-BRAF and/or MEK inhibitor treatment and a new, or archival, tumor sample collected at the time of relapse from the above treatment(s). The tumor samples will be fully characterized through a comprehensive genomic analysis performed at a Sponsor-delegated central laboratory.

7.1.2 Screening

Screening will start after the BRAF mutational status is documented.

For all patients in the study, the main study IRB/IEC approved Informed Consent Form (ICF) must be signed and dated before any screening procedures are performed (procedures which are part of the clinical routine during the initial diagnostic work-up of the patient may be performed before obtaining the ICF). A copy of the ICF must be given to the patient or to the person signing the form. The Investigator or designee must record the date when the study informed consent was signed in the medical records of the patient.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1, Table 7-2, Table 7-3 and Table 7-4. Part I Screening/baseline CT/MRI scans must be completed within 21 days prior to the first dose of study treatment. Part II Screening/baseline CT/MRI scans (Only Group C patients) must be completed, if not already performed within 28 days from the scan performed at progression. All other screening assessments must be completed, if not already performed within 14 days prior to the first dose with the exception of pregnancy test, which must be performed within 72 hours before the first dose.

For Groups B and C, patients enrolled from other LGX818/MEK162 combination studies (e.g. COLUMBUS, IIT), who had safety and tolerability assessments in the previous study at End of Study Treatment visit completed within 14 days prior to the first dose of the triple combination, data should be reported in CLGX818X2109 and be used as baseline assessments. Therefore,

for Groups B and C patients, safety and tumor assessments performed at last visits in the previous clinical trials should not be repeated at Screening, if fitting the above time windows to the first triple treatment dose (CT/MRI within 28 days and safety within 14 days of the first dose of triple combination). At screening, Group B patients will provide either a pre-BRAF and/or MEK inhibitors biopsy, or, a relapse biopsy from previous BRAF and/or MEK inhibitors. Group C patients at screening, will either provide a recent progression biopsy from previous LGX818/MEK162 trial, or, a new biopsy. Decision to continue receiving LGX818/MEK162 medications beyond progression, during the genetic assessment, will be taken by the investigator in the best interest of patients. The investigator will need to confirm patients' eligibility to continue receiving LGX818/MEK162 combination (see Section 5.1, Section 5.2 and Section 5.3). During this time, patients will be monitored according to Part I assessments as described in Table 7-1 (subsequent cycles). For patients in Group C, who need to undertake a biopsy at screening and are going to continue treatment with LGX818/MEK162 combination, the screening assessments can be started at day -28 (instead of day -14).

Patients in Group A and B who progressed while treated with LGX818/MEK162, will not perform the Screening Part II assessments before starting the triple combination treatment phase. These patients will perform the safety and tolerability assessments at the End of Study Treatment visit Part I (see Table 7-1 and Table 7-2 and Section 7.1.5).

Assessments which are indicated to be performed at Screening/baseline (Table 7-1, Table 7-2, Table 7-3 and Table 7-4), or at End of Treatment Part I (Table 7-1, Table 7-2) for patients moving to treatment phase Part II, and on Cycle 1 Day 1, need to be repeated at Cycle 1 Day 1 only if Screening/baseline assessments, or End of Treatment Part I assessments were performed more than 3 days before the first dose administration.

For all patients, screening examinations and assessments specifically required for triple combinations will be performed upon availability of the genetic assessment results from Sponsor-delegated central laboratory. **All results should be available at site and exclusion criteria for the specific triple combination arm must not be met in order to declare a patient eligible for receiving the selected triple combination.** If a patient does not meet all eligibility criteria (e.g. fails a laboratory assessment) a retest within the screening period is allowed. The same patient number should be kept. All assessments of initial screening are entered in eCRF and any repeat assessments are reported as unscheduled assessments.

7.1.2.1 Eligibility screening

When a patient is considered eligible for study treatment, the Investigator should complete the Patient Registration Form and send it to the Sponsor. The allocation of patients to the various treatment arms will be handled by the Sponsor.

7.1.2.2 Information to be collected on screening failures

Patients who sign the molecular prescreening informed consent and/or the main study informed consent, but fail to be started on study treatment for any reason will be considered a screen failure and data will be handled in the same manner. The reason for not being started on treatment will be entered on the applicable Screening Log eCRF page. The molecular pre-

screening failure or screening failure information will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, Dosage Administration Record (only for group C patients during the genetic assessment period) and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8.2 for SAE reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported (i.e., tumor biopsy).

Patients who have received study drug in Part I, or Run-in, and cannot continue onto Part II, because of unmet additional exclusion criteria for the triple combination (Part II), will be identified as not eligible for Part II only. Thus, they need to complete the End of Study Treatment visit (Part I, or Run-in)

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, prior concomitant medications, diagnosis and extent of tumor, baseline tumor mutation status and details of prior anti-neoplastic treatments.

7.1.3 Run-in period (only for Group B)

Patients who progressed after treatment with single agent BRAF and/or MEK inhibitor or the combination of BRAF/MEK inhibitors (excluding LGX818/MEK162 combination) will receive LGX818/MEK162 combination in a brief Run-in phase followed by early disease assessment (after 3 weeks). Patients achieving at least a PR from this treatment at the first CT/MRI scan may continue on LGX818/MEK162 combination until progression. At this time, a newly obtained tumor biopsy will be mandatory and patients will be assigned to a triple combination arm in Part II on the basis of the tumor sample's genetic assessment (Table 4-1). Patients not deriving clinical benefit from LGX818/MEK162 combination therapy will be assigned to a treatment arm in Part II on the basis of the analysis of their most recent tumor biopsy.

Patients who did not progress on their prior BRAF/MEK regimen (including LGX818 and /or MEK162), may enter the Run-in (Group B) and continue LGX818/MEK162 combination until evidence of disease progression at which point a tumor biopsy will be taken and analyzed to guide assignment to a triple combination arm in Part II.

7.1.4 Treatment period

Treatment period is divided into two parts:

Part I: BRAF and MEK inhibitor naïve patients will be dosed continuously with LGX818/MEK162 combination on 21-day (3 calendar weeks) cycles beginning on Day 1 of Cycle 1. There will be no scheduled break between cycles. Patients will receive LGX818/MEK162 combination until initiation of triple combination treatment after progression of disease or until unacceptable toxicity occurs, whichever comes first.

During the genetic assessment period patients will follow the same schedule of assessments for subsequent cycles of Part I or Run-in. However, only specific information will be collected such as dosing, AEs, concomitant medications until initiation of triple combination treatment.

Only patients in group B will go through a run-in period (LGX818/MEK162 combination) before entering Part II (see Section 4.1)

Part II: Patients, who received LGX818/MEK162 combination for at least 3 weeks and progressed, will enter in Part II to receive a triple combination treatment of LGX818/MEK162 + third agent, based upon the genetic alterations identified in the tumor biopsy at progression.

During the treatment period, the patient must follow the Investigators instructions with regards to contraception, concomitant medications, and dosing regimen (see Section 6.1.1 for dosing regimen guidelines).

For details of the frequency of the visits and assessments during the treatment period, refer to Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5.

7.1.5 End of Study Treatment visit including study completion and premature withdrawal

Patients permanently discontinuing the study treatment, as well as patients in Group A and B switching from LGX818/MEK162 to the triple combination treatment, must perform the End of Study Treatment assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4). For patients who permanently discontinue study treatment, this visit should take place ≤ 14 days after the last dose of study treatment, or after the decision to discontinue study treatment. For patients in Group A and B moving to Part II, this visit should take place as soon as the results of the progression biopsy genetic assessment are available and the patients can be assigned to a triple combination in Part II. However, at End of Study Treatment, CT/MRI scans must be completed, if not already performed within 28 days from the last CT/MRI scan, while other screening assessments must be completed, if not already performed within 14 days prior to the first dose with the exception of pregnancy test, which must be performed within 72 hours before the first dose. Moreover, the End of Study Treatment disposition CRF page should be completed, giving the date and reason for stopping the study treatment. End of Study Treatment/Premature withdrawal visit is not considered as the end of the study.

At a minimum, all patients who discontinue study treatment will be contacted to return 30 days after the last administration of the study treatment for safety follow up evaluations according to Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5.

Additionally, patients in Part I and Part II who discontinue study treatment for any reason prior to disease progression should also return for disease follow-up, but only patients enrolled in Part II will be subsequently followed for survival (Section 7.1.5 and Section 7.1.6) and should not be considered withdrawn from the study. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to obtain the follow-up information.

If a patient discontinues study treatment, but continues study assessments in the Follow-Up period, the patient remains on study until such time as he/she completes protocol criteria for

ending study assessments. At that time, the reason for study completion should be recorded on End of post-treatment evaluation follow-up).

7.1.5.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Adverse event
- Withdrawal of informed consent
- Lost to follow-up
- Progressive disease in the triple combination part of the study
- New therapy for study indication
- Any patient who becomes pregnant during study treatment will be immediately withdrawn.

7.1.5.2 Replacement policy

No patients will be replaced on the study.

7.1.6 Follow up period

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

7.1.6.1 30-day safety follow-up period

All patients must have safety evaluations for 30 days after the last dose of study treatment. Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing anti-neoplastic treatments will be collected for 30 days after the last dose of study drug. All AEs suspected to be related to study treatment should be followed up weekly, or as clinically indicated, until resolution or stabilization. For patients who have been on treatment in Part I for ≥ 36 months, the 30 day follow-up will include a review of concomitant medications and assessment of compliance with administration of LGX818 (encorafenib) and MEK162 (binimetinib). There will also be review of AEs with recording of all Grade 3 or 4 AEs and all SAEs (SAEs, follow-up of SAEs to continue as described in Section 8). Other safety evaluations may be conducted if clinically indicated.

Following the 30-day follow-up, when clinically appropriate, it is recommended patients be monitored with physical examinations, dermatological examinations and chest CT scans for cutaneous and non-cutaneuous secondary malignancies for up to 6 months after the last LGX818 dose or until initiation of another antineoplastic therapy.

7.1.6.2 Disease progression follow-up period

Patients enrolled in Part I, Run-in and Part II who discontinue study treatment for any reason other than disease progression will be followed up by CT/MRI scans every 9 weeks (+/- 7 days) as detailed in Table 7-1, Table 7-2, Table 7-3, Table 7-4, Table 7-5 and Section 7.2.1, until disease progression, death, removal of consent to follow, the initiation of subsequent anticancer therapies or until End of Study (see Section 4.3), whichever occurs first.

Patients enrolled in Part I and the Run-in phase, who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression will be followed up by CT/MRI scans every 9-12 weeks (+/- 7 days) as detailed in Table 7-1, Table 7-2 and Section 7.2.1, until disease progression, death, removal of consent to follow, the initiation of subsequent anticancer therapies or until End of Study (see Section 4.3), whichever occurs first.

7.1.6.3 Survival follow-up period

After Safety Follow-up, all patients enrolled in Part II of this study will be followed for survival every 3 months by contacting the patient (e.g., telephone calls, registered letters, etc.) until they have been followed for at least 18 months after the first dose of their treatment, or until death, or until End of Study (see Section 4.3), whichever occurs first. Newly started antineoplastic therapies during this follow-up period must be recorded on the Antineoplastic therapy since discontinuation.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be evaluated locally by the investigator according to the guideline based on RECIST version 1.1 (Appendix 8).

In the LGX818/MEK162 double-agent treatment, Part I, eligible patients will be evaluated for all potential sites of tumor lesions at Screening/baseline and every 6 weeks after starting study treatment until disease progression. Patients enrolled in Part I who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months will be evaluated for all potential sites of tumor lesions every 6-12 weeks (+/- 7 days) until disease progression.

Patients in Group B, eligible to enter the Run-in will be evaluated for all potential sites of tumor lesions after received at least 21 days (after one three-week cycle) of LGX818/MEK162 combination during the time of biopsy molecular analysis. For patients with PR or CR, the following assessments will be then executed every 6 weeks (every two three-week cycles) until disease progression. Patients in Group B who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months will be evaluated for all potential sites of tumor lesions every 6-12 weeks (+/- 7 days) until disease progression. If signs of tumor progression are observed, an unscheduled scan to assess progression may be performed upon investigator`s decision.

In the triple combination treatment part (Part II) of the study, each patient will be evaluated every 9 weeks after starting triple combination treatment until disease progression.

The Screening/baseline (Part I and Run-in) CT/MRI scan assessments may be performed within 21 days of treatment start for Part I and Run-in. The Screening/baseline Part II (only patients in Group C) and End of Study Treatment Part I and Run-in (only patients moving to Part II) CT/MRI scans assessments must be completed, if not already performed within 28 days of the previous CT/MRI scan. End of Study Treatment Part I and Run-in (only patients assigned to LEE011 arm in Part II) CT/MRI brain scans assessments must be completed, if not already performed within 28 days of the previous CT/MRI scan. At screening, patients in Group C, enrolled from other LGX818/MEK162 double agent studies (e.g. [CME162X2110], [COLUMBUS], IIT), can provide the last visit tumor evaluation data documenting the progressive disease as baseline assessment of CLGX818X2109 (Part II), if those tumor assessments have been performed within 28 days.

For patients in Group C assigned to LEE011 arm, the brain CT/MRI scans must be completed within 28 days before triple combination first dose.

On-study tumor assessments have a ± 7 day window, except for the first post-baseline tumor assessment. The first post-baseline tumor assessment should be performed 6 weeks (Part I), 3 weeks (Run-in) (± 3 days) and 9 weeks (Part II) +7 day window permitted after starting treatment. Patients enrolled in Part I and the Run-in phase, who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months will be evaluated for all potential sites of tumor lesions every 6-12 weeks (+/- 7 days) or per local standard-of-care clinical practice until disease progression. There will be a tumor assessment at the End of Study Treatment (± 3 days) if the patient discontinues for any reason other than disease progression and the last tumor assessment has been performed > 21 days prior to this day.

Patients included in Part I, Run-in and Part II of the study (triple combination part), who discontinue study treatment due to another reason than disease progression, should be followed up and undergo tumor assessments every 9 weeks (± 7 days) until disease progression or initiation of subsequent anti-neoplastic therapy, or death, whichever occurs first (Section 7.1.6). Patients enrolled in Part I and the Run-in phase, who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months and then discontinue study treatment for any reason other than disease progression will have CT/MRI scans every 9-12 weeks (+/- 7 days).

At Screening/baseline (Part I and Part II), the following should be performed:

- A CT/MRI scan with intravenous (IV) contrast of chest, abdomen and pelvis is required for all patients. This is the preferred radiologic technique for the study. However, if CT assessments require additional regulatory approval in a country, MRI is allowed for chest, abdomen, pelvis. 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 the abdomen and pelvis should be performed.
- In patients with a history of brain metastases, a brain MRI or CT scan must be performed.
- At screening in Part II, Group C patients assigned to LEE011 arm must perform a brain MRI or CT scan with contrast.
- If clinically indicated, a whole body bone scan (i.e., if bone metastases are suspected or known at baseline) should be performed. Sites may use a whole body bone imaging

method per their local standard of care (e.g., Tc99m bone scan, FDG-PET, NaF PET scan, or whole-body bone MRI). Skeletal lesions identified on a whole body bone scan at baseline, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan should be imaged at baseline using localized CT, MRI or x-ray and should be evaluated with same frequency as chest, abdomen, pelvis CT/MRI/X-ray.

- Color photography if skin lesions are present (it is recommended to include a ruler to estimate the size of the lesion).

Every effort must be made to assess each lesion that is measured at Screening/baseline by the same method throughout the study so that the comparison is consistent.

At all post-Screening/baseline assessments and End of Treatment (Part I, Run-in and Part II), the following should be performed:

- All patients are required to undergo chest, abdomen and pelvis CT/MRI scans.
- Brain MRI or CT scan, if metastases were documented at baseline
- At End of Treatment (Part I and Run-in), brain MRI or CT scan must be performed if patient is assigned to LEE011 arm in Part II.
- Skeletal lesions identified at baseline should continue to be imaged at subsequent scheduled visits using localized CT, MRI or x-ray (the method for any given lesion should be kept consistent across visits). After baseline, whole body bone scans need not be repeated, unless clinically indicated.
- Color photography of any skin lesions documented at baseline (it is recommended to include a ruler to estimate the size of the lesion).
- Additional imaging evaluations may be performed if there is symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical exam at any time.

Criteria required for determining partial or complete response should be present for at least 4 weeks. All complete and partial responses must be confirmed by a second assessment at least 4 weeks later. If off-schedule imaging evaluations are performed (e.g. to confirm response or if progression is suspected), every effort should be made to perform subsequent imaging evaluations in accordance with the original imaging schedule. If evidence of progressive disease is not unequivocal, every effort should be made to keep the patient on study medication for at least one additional imaging evaluation as long as it is clinically acceptable.

CT scans should be acquired with IV contrast. If a patient is known to have a medical contraindication to CT IV contrast agent or develops a contraindication during the study, a CT scan without IV contrast of the chest and MRI with IV contrast, if possible, of the abdomen and pelvis may be performed. A CT scan of the brain, preferably with IV contrast, may be performed if MRI is contra-indicated.

Chest x-ray or ultrasound should not be used for tumor response assessments in this study.

Any lesions that have been subjected to loco-regional therapies (e.g., radiotherapy, ablation, etc.) should not be considered measurable, unless they have clearly progressed since the

therapy. Previously treated lesions that have not progressed should be considered non-measurable and therefore, assessed as non-target lesions.

While FDG-PET scans are not required for this study, sites may perform combined PET/CT scans per their local standard of care, provided the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media. If acquired according to local standard of care, FDG-PET may be relied upon to document progressive disease in accordance with RECIST v1.1 (Appendix 8).

Each center should have a designated radiologist responsible for the interpretation of scans and response evaluations for study patients. Preferably, a single radiologist should perform all evaluations for an individual patient.

Table 7-6 Disease assessment collection plan

Procedure	Screening/Baseline and EOT	During Treatment and Follow-up
CT or MRI with contrast enhancement (Chest, Abdomen, Pelvis)	Mandated in Part I, Run-in and Part II	Part I: C2D21 and every 6 weeks during treatment. Run-in: First assessment after 3 weeks during Run-in, and after 6 weeks thereafter. Part I and Run-in: For patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 24 months, every 6-12 weeks. For patients who have been on the LGX818/MEK162 double-agent treatment for ≥ 36 months, every 8-12 weeks or per local standard-of-care. Every 9 weeks during Progressive Disease Follow-up. For patients who discontinue the LGX818/MEK162 double-agent treatment after ≥ 24 months without progressive disease, every 9-12 weeks. Part II: Every 9 weeks during treatment.. Every 9 weeks during Progressive Disease Follow-up
Whole bone scintigraphy	If clinically indicated	If clinically indicated
Brain CT or MRI (e.g. Brain)	Mandated in Part I for patients with a history of asymptomatic brain metastases. Mandated at EOT (Part I and Run-in) only for patients assigned to LEE011 arm and at Screening (Part II)	Every 6 weeks in Part I and Run-in (patients with history of brain metastasis). Every 9 weeks in Part II (patients with baseline brain metastasis and patients in LEE011 arm). Every 9 weeks during the disease follow-up period for patients in Part II.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing the procedures listed below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

For Group C patients enrolled from other LGX818/MEK162 combination studies (e.g. COLUMBUS, IIT), who had safety and tolerability assessments at End of Study Treatment visit completed within 14 days prior to the first dose of the triple combination, data should be reported in CLGX818X2109 and be used as baseline assessments.

7.2.2.1 Physical examination

A complete physical examination will be conducted at Screening/baseline and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam (examination of general appearance) will occur at all other visits indicated below unless the investigator considers a complete physical examination necessary.

Physical examinations will take place at the following visits irrespective of the time of dosing:

- Screening/Baseline (Part I, Run-in and Part II)
- Part I and Run-in Cycle 1: Days 1, 15
- Run-in Cycle 1: Day 21
- Part I and Run-in Cycle 2: Days 8, 21
- Part I and Run-in subsequent cycles: Day 15
- Part I and Run-in patients on treatment ≥ 36 months: Per local standard of care (recommended every 4 weeks) (Table 7-5).
- Part II (21 days cycle) Cycle 1: Days 1, 8, 15
- Part II (21 days cycle) Cycle 2: Days 1, 15
- All other Part II (21 days cycle) subsequent cycles: Day 1
- Part II (28 days cycle) Cycle 1: Days 1, 8, 15, 21
- Part II (28 days cycle) Cycle 2: Days 1, 15
- All other Part II (28 days cycle) subsequent cycles: Cycle 3 and 4 Days 1 and 15, from Cycle 5 only Day 1.
- End of Study Treatment (Part I, Run-in and Part II)

Significant findings that were present prior to the signing of study informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.2 Performance status

Assessment of ECOG Performance Status (WHO) will be performed at screening and on Day 1 of cycle 1 and once per cycle thereafter throughout the whole study period irrespective of the time of dosing. End of Study Treatment assessment will be performed.

Performance status should be obtained on the scheduled day, even if study medication is being held.

Table 7-7 ECOG performance status scale (WHO)

0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

Height information will be collected only at Screening/baseline, even for patients coming from other LGX818/MEK162 double agent studies (e.g. COLUMBUS, IIT). Weight information will be collected irrespective of the time of dosing according to the applicable visit evaluation schedule.

7.2.2.4 Vital signs

Vital signs (respiratory rate, pulse, blood pressure and temperature) will be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection and taken pre-dose.

Vital signs will be measured at screening, at every scheduled visit in Part I, Run-in, Part II 21-day cycle and 28-day cycle (with the exception of cycle 1 Day 16 and cycle 2 Day 8) and at End of Study Treatment as detailed in Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5.

7.2.2.5 Laboratory evaluations

Sites will use their local laboratories for the analysis of all safety lab samples collected at the timepoint s indicated in the Visit Schedule (Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5). More frequent assessments may be performed if clinically indicated, or at the investigator's discretion; these should be recorded on the Unscheduled Visit eCRFs.

Abnormal laboratory values that are clinically relevant (e.g., require an interruption or delay to study treatment, lead to clinical symptoms, or require therapeutic intervention) must be documented in the Adverse Event eCRF. If any abnormal laboratory value constitutes an AE, then these must be recorded on the Adverse Event eCRF.

The Sponsor will be provided with a copy of the site's local laboratory certification and tabulation of the normal ranges for each parameter required at study start and should be kept up to date on an ongoing basis. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, the Sponsor must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Table 7-8 Local clinical laboratory parameters collection plan

Hematology	RBC	Monocytes
	WBC	Eosinophils
	Platelets	Basophils
	Neutrophils/ANC	Hemoglobin Hemoglobin HbA1c (only for BKM120 arm)
	Lymphocytes	Hematocrit
Chemistry	Albumin	Sodium, Potassium, Magnesium, Calcium
	Total Protein	ALT (SGPT), AST (SGOT),
	Phosphate	Bicarbonate/CO_2
	Glucose (non-fasting) Fasting plasma glucose (only BKM120 arm)	Gamma-glutamyl-transferase (GGT) Lipase, Amylase
	LDH	TSH (free T4, and free T3)
	Alkaline Phosphatase	Total Bilirubin (direct and indirect bilirubin only need to be measured if total bilirubin is grade 2 or higher)
	Urea	Serum Creatinine
	Uric Acid	
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), Activated partial thromboplastin time (APTT), fibrinogen.	
Cardiac/Muscle Enzymes	Creatine Kinase (CK) If total CK ≥3 X ULN (≥ CTCAE Grade 2), then measure isoenzymes and myoglobin in blood or urine weekly until resolved to ≤ CTCAE Grade 1	
Pregnancy Test (for women of child-bearing potential)	Serum β-hCG test	
	urine pregnancy test to be performed locally	
Viral hepatitis serologic tests and other tests for hepatotoxicity follow-up (if clinically indicated for BKM120, INC280 & LEE011 arms)	HAAb, HBsAg, HBsAb HBcAb, HCV RNA, HDV RNA, EBV or HSV(where needed), HEAb, CMVAb, EBcAb, ALP, CPK, LDH, WBC (eosinophilia).	
Urinalysis	pH, protein, glucose, blood, ketones, and leukocytes	
	microscopic evaluations only if clinically indicated	

7.2.2.5.1 Hematology

The parameters listed in Table 7-7 will be measured pre-dose at screening, at every scheduled visit in Part I, Run-in, Part II 21-day cycle and 28-day cycle (with the exception of cycle 1 Day 16 and cycle 2 Day 8) and at End of Study Treatment as detailed in Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5.

7.2.2.5.2 Clinical chemistry

The parameters listed in Table 7-7, including CK, will be measured pre-dose at screening, at every scheduled visit in Part I, Run-in, Part II 21-day cycle and 28-day cycle (with the exception of cycle 1 Day 16 and cycle 2 Day 8) and at End of Study Treatment as detailed in Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5.

7.2.2.5.3 Coagulation

For Part I, Run-in and Part II, coagulation profiles will be performed pre-dose at:

- Screening/baseline
- If clinically relevant during treatment periods
- End of Study Treatment

7.2.2.5.4 Fasting glucose and hemoglobin HbA1c monitoring (for combination treatment arm with BKM120)

Fasting plasma glucose (fasting is defined as no caloric intake for at least 8 hrs prior to analysis) will be assessed pre-dose at:

- Part II: Screening/baseline
- Part II: Cycles 1 Days 1 and 15 and Cycles 2 Days 1 and 15 pre-dose (prior to snack/breakfast)
- Part II subsequent Cycles: Day1
- End of Study Treatment (in Part I and Run-in, only for patients that will be assigned to BKM120 arm, and in Part II, for all patients in BKM120 arm)

Hemoglobin HbA1c will be assessed pre-dose at:

- Part II: Screening/baseline
- Part II: Cycles 2 Day1
- Part II subsequent cycles: Day 1 of every 3 Cycles
- End of Study Treatment (in Part I and Run-in, only for patients that will be assigned to BKM120 arm, and in Part II, for all patients in BKM120 arm)

7.2.2.5.5 Urinalysis

Urine color and appearance should be evaluated. Abnormal findings will be followed up with a microscopic evaluation and/or additional assessments as clinically indicated. A microscopic evaluation (WBC/HPF, RBC/HPF, and any other evaluations depending on macroscopic

findings) need only be performed if the urinalysis result is abnormal (except for institutions where microscopic urinalysis is not available).

Urinalysis will be performed pre-dose at:

- Screening/baseline (Part I, Run-in and Part II)
- Part I and Run-in: only if clinically indicated
- Part II 28-day cycle: Cycle 1 Day 21
- Part II 28-day cycle: All subsequent cycles if clinically indicated
- Part II 21-day cycle: Cycle 2 Day 1
- Part II 21-day cycle: All subsequent cycles if clinically indicated
- End of Study Treatment (Part I, Run-in and Part II)

Note: If at Screening/baseline there is documentation of [+2] result or higher for protein from urinalysis, a 24-hour urine collection for total protein and measured creatinine clearance (CrCl) must be obtained. Whenever a 24-hour urine collection is performed, the total volume of urine must be recorded on the appropriate eCRF.

7.2.2.5.6 Dermatologic evaluation

Skin evaluations will be performed by dermatologists at Screening/baseline and End Study of treatment for Part I, Run-in and Part II. During Part II (21-day cycle and 28-day cycle), evaluations will take place at screening and Day 1 of Cycle 2 and every 2 cycles from Cycle 3 thereafter (±1 week) and at the End of Study Treatment visit to look for the appearance of squamous cell carcinoma of the skin or keratoacanthomas. This assessment can be done pre- or post-dose.

In the occurrence of these lesions, the lesions should be removed and the patient must be treated as per institutional practice.

Following the 30-day follow-up, when clinically appropriate, it is recommended patients be monitored with physical examinations, dermatological examinations and chest CT scans for cutaneous and non-cutaneuous secondary malignancies for up to 6 months after the last LGX818 dose or until initiation of another antineoplastic therapy.

7.2.2.5.7 Ophthalmologic evaluation

Routine testing

Full ophthalmic examination including slit lamp examination, best recorded visual acuity for distance testing, confrontational visual field testing, intraocular pressure (IOP) and dilated funduscopy with attention to retinal abnormalities, especially RPED and RVO, will be performed at the following timepoints and as clinically indicated:

- Screening/baseline (Part I, Run-in and Part II)
- Part I and Run-in: Cycle 2 Day 8 and for all the subsequent Cycles in Days 15*
- Part II 21-day cycle: Cycle 1 Day 15, Cycle 2 Day 1, Day 15 and for all the subsequent Cycles in Days 1

- Part II 28-day cycle: Cycle 1 Day 15, Cycle 2 Day 1, Day 15 and for all the subsequent Cycles in Days 1*
- End of Study Treatment (Part I, Run-in and Part II)*

* Patients who have been on LGX818/MEK162 for ≥ 24 months (Table 7-1 and Table 7-2) or ≥ 36 months (Table 7-5) in Part I and the Run-in phase without a retinal AE within the past 12 months should be evaluated for visual acuity at each scheduled patient visit and at the End of Study Treatment visit. A full ophthalmic examination is required if clinically indicated and at the End of Study Treatment visit.

Additional testing

Patients with clinical suspicion of retinal abnormalities (i.e. photopsia, metamorphopsia, impairment of visual acuity, etc.) or RVO, **must** complete at least one of the following additional assessments:

- For non-vascular abnormalities: optical coherence tomography of the macula (spectral domain is preferred)
- For vascular abnormalities: fluorescein angiography of the central 30 degrees.

Images of the ophthalmic exams, especially OCT and/or fluorescein angiography should be sent to the investigative site along with the results of the exam and be maintained in the patient's source document file. These images may be requested to be sent to the sponsor or designee.

Additional testing for BGJ398 arm only. As of Protocol Amendment 06, patients will no longer be enrolled in the LGX818/MEK162 + BGJ398 treatment arm.

Patients enrolled in the BGJ398 triple combination arm will undergo an additional examination such as specular microscopy (that enables a magnified, direct view of the corneal endothelium), corneal pachymetry that will be performed at screening, Cycle 1 Days 15 and Cycle 2 Days 1, 15 up to Cycle 4 and for all the subsequent cycles at Day 1, and at End of Study Treatment (in Part I and Run-in, only for patients that will be assigned to BGJ398 arm, and in Part II, for all patients in BGJ398 arm).

7.2.2.5.8 Pregnancy and assessments of fertility

All females of childbearing potential will have a serum pregnancy test ≤72 hrs before first dose of study drug at Screening/baseline and a urine or serum test performed during each study cycle on the first visit day and at the End of Study Treatment visit.

A positive urine pregnancy test requires immediate interruption of study treatment until serum β-HCG is performed and found to be negative. If positive, the patient must be discontinued from the study.

7.2.2.5.9 Thyroid function assessment only for LEE011 triple combination arm

TSH (free T4, and free T3 should also be measured only if clinically indicated) will be assessed at the following timepoints:

- Part II: Screening, Cycle 2 Day 1 and every 2 Cycles from Cycle 3 only if clinically indicated.
- End of Study Treatment (in Part I and Run-in, only for patients that will be assigned to LEE011 arm, and in Part II, for all patients in LEE011 arm)

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

At screening in Part I Run-in and Part II a standard 12 lead ECG (local assessment) will be performed to assess eligibility. For all patients, prior to the first administration of the LGX818/MEK162 combination and LGX818/MEK162 + third agent combination on Cycle 1 Day 1 (baseline), three sequential 12 lead ECGs, separated by at least 5-10 minutes, must be performed. The average of the triplicate ECG measurements will serve as the patient's baseline value for post-dose comparisons. Single ECGs will be performed for the other pre-dose ECGs during the study at the indicated timepoints, at EOT and if clinically indicated, as indicated in Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5 and listed below. All ECGs should be taken before a blood sample or at least 0.5 hours after a blood sample to avoid potential effects of blood-draw on ECG readout.

Interpretation of the screening/baseline tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient initials (where local regulations permit), subject 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 eCRF page. Clinically significant findings must be discussed with the Sponsor 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 eCRF page.

12-lead ECGs are to be conducted in Part I, Run-in and Part II at Screening and at pre-dose and 1.5 hrs (+/- 0.5 hr) post-dose, in addition for LEE011 triple combination arm at 4 hr (+/- 0.5 hr) post drug administration at the following timepoint s:

In Part I and Run-in

- Cycle 1 Days 1and15
- Cycle 2 Days 8 and 21
- Cycle 3 Day 15 and Day 15 every 2 cycles for all the subsequent cycles*

End of Study Treatment

In Part II 21-day cycle

- Cycle 1 Days 1, 8 and 15

- Cycle 2 Days 1 and 15
- Cycle 3 Day 1 and Day 1 of subsequent cycles every 2 cycles*
- End of Study Treatment

In Part II 28-day cycle

- Cycle 1 Day 1, 8, 15, 21
- Cycle 2 Days 1 and 15
- Cycle 3 Day 1 and Day 1 of subsequent cycles every 2 cycles*
- End of Study Treatment

*Patients who have been on study treatment for ≥ 24 months (Cycle 25 Day 1) will have ECGs every 3 cycles.

All ECGs (except the screening/baseline ECG) will be independently reviewed by a central laboratory. Instructions for the collection and transmission of ECGs to the independent reviewer will be provided in the Lab Manual. Significant findings must be recorded either as Medical History (if present before signing consent) or as Adverse Events (if newly occurring or worsening since signing consent). All patients treated in the study experiencing a grade 3 QTc interval prolongation, hypokalemia, hypomagnesaemia and oxygenation status should be monitored.

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

The left ventricular heart function will be evaluated by echocardiography (ECHO) or Multiple gated acquisition (MUGA).

For Part I and Run-in cardiac imaging will be performed at:

- Screening/baseline
- Cycle 2 Day 8
- Cycle 5 Day 15 and every third cycles for the subsequent cycles
- End of Study Treatment (only patients permanently discontinuing the study drug).

For Part II (21-day cycles and 28-day cycles) cardiac imaging will be performed:

- For patients coming from Part I: on Day 1 of Cycle 1, on Day 1 of Cycle 3 and every third cycle, and at the End of Study Treatment visit.
- For patients coming from other trials: at Screening/baseline, on Day 1 of Cycle 2, on Day 1 of Cycle 3 and every third cycle, and at the End of Study Treatment visit.

7.2.2.7 LGX818/MEK162 + BKM120 combination: Patient self-reported Mood Questionnaires

7.2.2.7.1 GAD-7 and PHQ-9 Questionnaires (for combination treatment arm with BKM120 – Part II)

The Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) will be collected to screen patients for the study Part II 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 6) 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 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) before the first dose (at EOT visit in Part I for patients that will be assigned to Part II in BKM120 arm and at Screening in Part II for Group C patients only), at cycle 1 day 15, day 1 of each subsequent cycle in addition to the EOT visit in Part II (See Table 7-3). 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.

On visits 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.

Table 7-9 PHQ-9/GAD-7 patient self-reported questionnaire collection plan (BKM120 triple combination arm only)

Patient Questionnaires	Cycle (Part II)	Day	Time
PHQ-9 GAD-7	Screening (Part II)	Day -14 to Day -1	Prior to any clinical assessments, study drug dosing, or diagnostic testing.
	Cycle 1 (Part II)	Day 15	
	Cycle 2 (Part II)	Day 1	
	Every subsequent cycle (Part II)	Day 1	
	End of treatment (Part II)	Day of end of treatment assessment	
	End of treatment (Part I or Run-in)	Day -14 to Day -1 (only for patients moving to Part II in BKM120 arm)	

Management of mood alterations

Patient self-rating mood questionnaires PHQ-9 (depression) and GAD-7 (anxiety) will be used:

- To support assessment of eligibility at Screening
- To monitor for and report as adverse events newly occurring or worsening mood alterations during the study

The severity classification table described in Table 7-10 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 7-10 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 of Part II (Group C patients) or at End of Treatment (Part I or Run-in, only patients in Group A and B moving to Part II), 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. 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.

During the treatment phase, patients who indicate a positive response by selecting '1, 2, or 3' to question number 9 in the PHQ-9 must omit treatment with study drug BKM120 and must be referred for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading 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.

Patients with symptoms of a mood disorder (anxiety or depression) ≥ grade 1 must be monitored on a weekly basis as long as the patient is receiving treatment with study drug. 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 are also provided in Appendix 6. Dosing modification guidelines for BKM120 are provided in Table 6-7. For additional information on AE reporting, please refer to Section 8.1.

7.2.3 Pharmacokinetics

Note: Enrollment to the BKM120- (Amendment 03), BGJ398-, INC280- (Amendment 06) and LEE011 (Amendment 07)-containing arms is closed.

During Part I and Run-in of the study, PK blood samples of LGX818 and MEK162 will be collected and the sampling schedules are listed in Table 7-11. During Part II of the study, the pharmacokinetics of LGX818, MEK162 (including its primary active metabolite AR00426032), LEE011 (including its active metabolite LEQ803), BGJ398 (including its active metabolite BHS697 and CQM157), BKM120, and INC280 will be assessed and the sampling schedules are listed in Table 7-12 to Table 7-17, respectively. PK samples will be collected and evaluated on all patients enrolled in both parts of the study for the first 5 cycles or until they withdraw consent.

In addition to the analysis mentioned above, metabolite profiling analyses on remaining plasma material may be performed using a non-validated, semi-quantitative or qualitative LC-MS/MS method, if deemed appropriate.

Plasma samples remaining from the analysis may be retained by the Sponsor for additional investigations (i.e. long term stability, reproducibility).

A detailed description of the planned pharmacokinetic analyses is given in Section 10.5.4.

7.2.3.1 Pharmacokinetic blood sample collection and handling

7.2.3.1.1 Blood collection plan

During Part I and Run-in, PK blood samples for LGX818 and MEK162 will be collected from all patients up to Cycle 5 according to the timepoints listed in Table 7-11. An end of study treatment sample will be collected if a patient withdraws from the study during Part I/Run-in and if a patient moves from Part I/Run-in treatment phase to Part II treatment phase.

During Part II (28-days cycle), PK blood samples for LGX818, MEK162 (including its primary active metabolite AR00426032), LEE011 (including its active metabolite LEQ803), BGJ398

(including its active metabolite BHS697 and CQM157), will be collected from all patients according to the timepoints listed in Table 7-12, Table 7-15 and Table 7-17. An end of study treatment sample will be collected as soon as possible after a patient withdraws from the study during Part II.

During Part II (21-days cycle), PK blood samples for LGX818, MEK162 (including its primary active metabolite AR00426032), INC280 and BKM120 will be collected from all patients up to Cycle 5 according to the timepoints listed in Table 7-13, Table 7-14 and Table 7-16. An end of study treatment sample will be collected as soon as possible after a patient withdraws from the study during Part II.

For all patients from whom PK samples are collected, exact dates and clock times of drug administration (first dose of LGX818/MEK162 and the first dose of the third agent) and actual PK blood draw will be recorded on the appropriate eCRF. Any sampling problems (e.g. patient took study drug before draw took place) must be noted in the comments section of the eCRF and on appropriate source documentation. The time of the last meal before dose administration should be recorded on PK sampling days for first cycles on Day 15 during both parts on the appropriate eCRF.

PK collection windows (+/- min/hr timepoint for the PK timepoints) are:

0.5 hour ± 10 min; 1 hour ± 10 min; 1.5 hour ± 15 min; 2 hour ± 15 min; 2.5 hour ± 15 min;

4 hour ± 30 min; 6 hour ± 30 min; 8 hour ± 60 min; 24 hour ± 2h

If vomiting or diarrhea occurs within 4 hrs following study drugs administration on the days of full PK blood sampling, the exact time (using the 24-h clock) of any vomiting or diarrhea episode should be recorded in a separate section of the eCRF in addition to recording this on the AE eCRF.

Complete instructions for sample collection, processing, handling and shipment for each compound will be provided in the [Laboratory Manual]

Table 7-11 Pharmacokinetic blood collection log for LGX818 and MEK162 during Part I/ Run-In (LGX818/MEK162 combination)

Treatment Period or Cycle	Day	Scheduled Time Point	Dose Reference ID LGX818	PK Sample No LGX818	Dose Reference ID MEK162	PK sample No MEK162	Sample Volume (ml)
1	1	1.5 hr post dose	100	100	700	700	3
1	15	Pre-dose*	101	101	701	701	3
1	15	1.5 hr post dose	101	102	701	702	3
2	8	Pre-dose*	102	103	702	703	3
2	21	Pre-dose*	103	104	703	704	3
3	15	Pre-dose*	104	105	704	705	3
4	15	Pre-dose*	105	106	705	706	3
5**	15	Pre-dose*	106	107	706	707	3
EOT	NA	EOT	107	108	707	708	3
NA	NA	Unscheduled***	NA	1001+	NA	7001+	3
Total							

*Collect PK sample immediately prior to the start of oral study drug(s) administration.

** Pre-dose PK samples will be collected up to Cycle 5 only.

***Applies only to samples collected before effective date of Protocol Amendment 06. Unscheduled PK samples will be uniquely, sequentially numbered

Table 7-12 Pharmacokinetic blood collection log for LGX818 and MEK162 during Part II (triple combination, 28 days cycle with LEE011 and BGJ398)

Combination Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID LGX818	PK Sample No LGX818	Dose Reference ID MEK162	PK sample No MEK162	Sample Volume (ml)
1	1	1.5 hr post dose	200	200	800	800	3
1	1	4 hr post dose$	200	217	800	817	3
1	8	Pre-dose*	201	201	801	801	3
1	15**	Pre-dose*	202	202	802	802	3
1	15	0.5 hr post dose	202	203	802	803	3
1	15	1.5 hr post dose	202	204	802	804	3
1	15	2.5 hr post dose	202	205	802	805	3
1	15	4 hr post dose	202	206	802	806	3
1	15	6 hr post dose	202	207	802	807	3
1	15	8 hr post dose	202	208	802	808	3
1	16	24 hr post dose immediately prior to dosing on C1D16	202/203	209	802/803	809	3
1	21	Pre-dose*	204	210	804	810	3
2	1	Pre-dose*	205	211	805	811	3
2	15	Pre-dose*	206	212	806	812	3
3	1	Pre-dose*	207	213	807	813	3
4	1	Pre-dose*	208	214	808	814	3
5***	1	Pre-dose*	209	215	809	815	3
EOT	NA	EOT	210	216	810	816	3
NA	NA	Unscheduled****		2001+	NA	8001+	3
Total							

*Collect PK sample immediately prior to the start of oral study drug(s) administration.

** Schedule PK collection together with collection fresh tumor biopsy (if applicable). If it is not possible to collect the tumor biopsy on D15 of first triple-agent combination cycle, then an additional unscheduled pre-dose PK sample should be collected on the day fresh tumor biopsy is collected

*** Pre-dose PK samples will be collected up to Cycle 5 only

****Applies only to samples collected before effective date of Protocol Amendment 06. Unscheduled PK samples will be uniquely, sequentially numbered.

$ This sample will only be collected for the LGX818 and LEE011 combination

Table 7-13 Pharmacokinetic blood collection log for LGX818 and MEK162 during Part II (triple combination, 21 days cycle with BKM120 and INC280)

Combination Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID LGX818	PK Sample No LGX818	Dose Reference ID MEK162	PK sample No MEK162	Sample Volume (ml)
1	1	1.5 hr post dose	200	200	800	800	3
1	8	Pre-dose*	201	201	801	801	3
1	15**	Pre-dose*	202	202	802	802	3
1	15	0.5 hr post dose	202	203	802	803	3
1	15	1.5 hr post dose	202	204	802	804	3
1	15	2.5 hr post dose	202	205	802	805	3
1	15	4 hr post dose	202	206	802	806	3
1	15	6 hr post dose	202	207	802	807	3
1	15	8 hr post dose	202	208	802	808	3
1	16	24 hr post dose immediately prior to dosing on C1D16	202/203	209	802/803	809	3
2	1	Pre-dose*	204	210	804	810	3
2	15	Pre-dose*	205	211	805	811	3
3	1	Pre-dose*	206	212	806	812	3
4	1	Pre-dose*	207	213	807	813	3
5***	1	Pre-dose*	208	214	808	814	3
EOT	NA	EOT	209	215	809	815	3
NA	NA	Unscheduled****		2001+	NA	8001+	3
Total							

*Collect PK sample immediately prior to the start of oral study drug(s) administration.

** Schedule PK collection together with collection fresh tumor biopsy (if applicable). If it is not possible to collect the tumor biopsy on D15 of first triple-agent combination cycle, then an additional unscheduled pre-dose PK sample should be collected on the day fresh tumor biopsy is collected

*** Pre-dose PK samples will be collected up to Cycle 5 only

****Unscheduled PK samples will be uniquely, sequentially numbered.

Table 7-14 Pharmacokinetic blood collection log for BKM120 during Part II (triple combination) (21 days cycle)

Combination Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID BKM120	PK Sample No BKM120	Sample Volume (ml)
1	1	1.5 hr post dose	300	300	3
1	8	Pre-dose*	301	301	3
1	15**	Pre-dose*	302	302	3
1	15	0.5 hr post dose	302	303	3
1	15	1.5 hr post dose	302	304	3
1	15	2.5 hr post dose	302	305	3
1	15	4 hr post dose	302	306	3
1	15	6 hr post dose	302	307	3
1	15	8 hr post dose	302	308	3
1	16	24 hr post dose immediately prior to dosing on C1D16	302/303	309	3
2	1	Pre-dose*	304	310	3
2	15	Pre-dose*	305	311	3
3	1	Pre-dose*	306	312	3
4	1	Pre-dose*	307	313	3
5***	1	Pre-dose*	308	314	3
EOT	NA		309	315	3
NA	NA	Unscheduled****	NA	3001+	3
Total					

*Collect PK sample immediately prior to the start of oral study drug(s) administration.

** Schedule PK collection together with collection fresh tumor biopsy (if applicable). If it is not possible to collect the tumor biopsy on D15 of first triple-agent combination cycle, then an additional unscheduled pre-dose PK sample should be collected on the day fresh tumor biopsy is collected.

*** Pre-dose PK samples will be collected up to Cycle 5 only.

****Unscheduled PK samples will be uniquely, sequentially numbered.

Table 7-15 Pharmacokinetic blood collection log for BGJ398 during Part II (triple combination) (28 days cycle)

Combination Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID BGJ938	PK Sample No BGJ398	Sample Volume (ml)
1	1	1.5 hr post dose	400	400	3
1	8	Pre-dose*	401	401	3
1	15**	Pre-dose*	402	402	3
1	15	0.5 hr post dose	402	403	3
1	15	1.5 hr post dose	402	404	3
1	15	2.5 hr post dose	402	405	3
1	15	4 hr post dose	402	406	3
1	15	6 hr post dose	402	407	3
1	15	8 hr post dose	402	408	3
1	16	24 hr post dose immediately prior to dosing on C1D16	402/403	409	3
1	21	Pre-dose*	404	410	3
2	1	Pre-dose*	405	411	3
2	15	Pre-dose*	406	412	3
3	1	Pre-dose*	407	413	3
4	1	Pre-dose*	408	414	3
5***	1	Pre-dose*	409	415	3
EOT	NA	EOT	410	416	3
NA	NA	Unscheduled****	NA	4001+	3
Total					

*Collect PK sample immediately prior to the start of oral study drug(s) administration.

** Schedule PK collection together with collection fresh tumor biopsy (if applicable). If it is not possible to collect the tumor biopsy on D15 of first triple-agent combination cycle, then an additional unscheduled pre-dose PK sample should be collected on the day fresh tumor biopsy and skin biopsy is collected.

*** Pre-dose PK samples will be collected up to Cycle 5 only.

****Unscheduled PK samples will be uniquely, sequentially numbered.

Table 7-16 Pharmacokinetic blood collection log for INC280 during Part II (triple combination) (21 days cycle)

Combination Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID INC280	PK Sample No INC280	Sample Volume (ml)
1	1	1.5 hr post dose	500	500	3
1	8	Pre-dose*	501	501	3
1	15**	Pre-dose*	502	502	3
1	15	0.5 hr post dose	502	503	3
1	15	1.5 hr post dose	502	504	3
1	15	2.5 hr post dose	502	505	3
1	15	4 hr post dose	502	506	3
1	15	6 hr post dose	502	507	3
1	15	8 hr post dose	502	508	3
1	16	24 hr post dose immediately prior to dosing on C1D16	502/503	509	3
2	1	Pre-dose*	504	510	3
2	15	Pre-dose*	505	511	3
3	1	Pre-dose*	506	512	3
4	1	Pre-dose*	507	513	3
5***	1	Pre-dose*	508	514	3
EOT	NA	EOT	509	515	3
NA	NA	Unscheduled****	NA	5001+	3
Total					

*Collect PK sample immediately prior to the start of oral study drug(s) administration.

** Schedule PK collection together with collection fresh tumor biopsy (if applicable). If it is not possible to collect the tumor biopsy on D15 of first triple-agent combination cycle, then an additional unscheduled pre-dose PK sample should be collected on the day fresh tumor biopsy is collected.

*** Pre-dose PK samples will be collected up to Cycle 5 only.

****Unscheduled PK samples will be uniquely, sequentially numbered.

Table 7-17 Pharmacokinetic blood collection log for LEE011 during Part II (triple combination) (28 days cycle)

Combination Treatment Cycle	Day	Scheduled Time Point	Dose Reference ID LEE011	PK Sample No LEE011	Sample Volume (ml)
1	1	1.5 hr post dose	600	600	3
1	1	4 hr post dose	600	617	3
1	8	Pre-dose*	601	601	3
1	15**	Pre-dose*	602	602	3
1	15	0.5 hr post dose	602	603	3
1	15	1.5 hr post dose	602	604	3
1	15	2.5 hr post dose	602	605	3
1	15	4 hr post dose	602	606	3
1	15	6 hr post dose	602	607	3
1	15	8 hr post dose	602	608	3
1	16	24 hr post dose immediately prior to dosing on C1D16	602/603	609	3
1	21	Pre-dose*	604	610	3
2	1	Pre-dose*	605	611	3
2	15	Pre-dose*	606	612	3
3	1	Pre-dose*	607	613	3
4	1	Pre-dose*	608	614	3
5***	1	Pre-dose*	609	615	3
EOT	NA	EOT	610	616	3
NA	NA	Unscheduled****	NA	6001+	3
Total					

*Collect PK sample immediately prior to the start of oral study drug(s) administration.

** Schedule PK collection together with collection fresh tumor biopsy (if applicable). If it is not possible to collect the tumor biopsy on D15 of first triple-agent combination cycle, then an additional unscheduled pre-dose PK sample should be collected on the day fresh tumor biopsy is collected.

*** Pre-dose PK samples will be collected up to Cycle 5 only.

****Applies only to samples collected before effective date of Protocol Amendment 06. Unscheduled PK samples will be uniquely, sequentially numbered.

7.2.3.2 Analytical method

LGX818

Plasma LGX818 concentrations will be measured at the Sponsor or a designated CRO using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay. The lower limit of quantitation (LLOQ) is currently 1.0 ng/mL.

MEK162

Plasma concentrations of MEK162 and its metabolite, AR00426032, will be measured at the Sponsor or a designated CRO using a validated LC/MS/MS assay. The lower limit of quantitation (LLOQ) is currently 1.0 ng/mL.

INC280

Plasma Concentrations of INC280 will be measured in plasma at the Sponsor or a designated CRO using a valid liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. The lower limit of quantitation (LLOQ) is currently 1.0 ng/mL.

BGJ398

Plasma concentrations for BGJ398 and its known pharmacologically active metabolites (i.e. BHS697 and CQM157) will be assayed at the Sponsor or a designated CRO using a validated liquid chromatography-tandem mass spectrometry method (LC-MS/MS). The lower limit of quantitation (LLOQ) is currently 1.0 ng/mL.

BKM120

BKM120 will be analyzed by liquid chromatography-tandem mass spectrometry, LC/MS/MS, for parent drug in plasma at the Sponsor or a designated CRO. The limit of quantitation is currently 0.25 ng/mL.

LEE011

The plasma samples from all patients will be assayed for concentrations of LEE011, LEQ803 and if needed any other clinically significant identified metabolites using a validated liquid chromatography-tandem mass spectrometry assay (LC/MS/MS). The lower limit of quantitation (LLOQ) is currently 5.0 ng/mL.

7.2.4 Biomarkers

As of Amendment 07, patients in Part I who have been on the combination treatment with LGX818/MEK162 for ≥ 36 months will no longer be required to provide a new tumor biopsy at disease progression.

Tumor samples will be collected pre-LGX818/MEK162 combination and at progression with both LGX818/MEK162 combination and triple combinations in order to fully characterize the tumor through a comprehensive genomic analysis (using technologies such as next generation sequencing). This will help to better understand the genomic profile of the patients' tumors and will allow assigning the drug to be given in combination with LGX818/MEK162 in Part II of the study.

In particular, biopsies will be performed for each patient groups as follows:

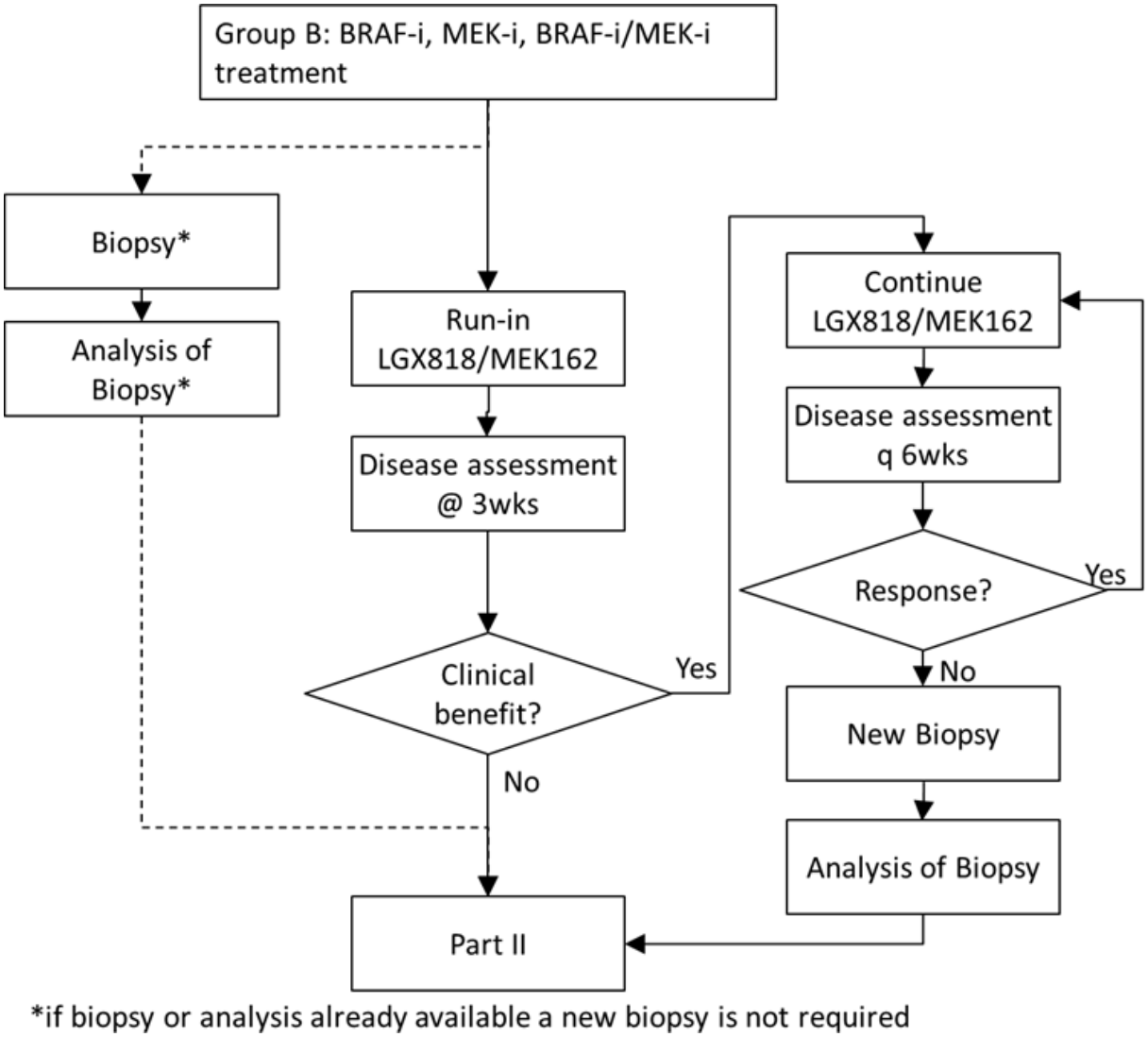
Patients in Group **A** will provide either an archival or a newly obtained tumor sample before entering Part I and receive LGX818/MEK162 combination therapy until disease progression.

At that time, patients will provide a new tumor biopsy sample to allow for assessment of genetic alterations as outlined in Table 4-1 and be assigned to a triple combination arm in Part II.

Patients in Group **B** will provide a biopsy sample at screening obtained either at progression from last treatment (i.e. BRAFi and/or MEKi), or, if they have not progressed yet, they will provide the most recent pre-BRAFi and/or MEKi biopsy sample. If not available, a new tumor sample must be obtained prior to entering the Run-in phase with LGX818/MEK162 combination. During Run-in, the first scan will be performed after 3 weeks treatment to assess patients' response. Patients achieving at least a PR from this treatment at the time of the first CT/MRI scan during the Run-in phase will continue on LGX818/MEK162 combination until progression. At this time, collection of a newly obtained tumor sample will be mandatory and patients will be assigned to a triple combination arm in Part II. Patients not deriving clinical benefit from LGX818/MEK162 combination therapy will be assigned to a treatment arm in Part II on the basis of the analysis of their most recent tumor biopsy.

Patients who did not progress on their prior BRAF and/or MEK inhibitor regimen (including LGX818 and/or MEK162 inhibitor), may enter the Run-in (Group B) and continue LGX818/MEK162 combination until evidence of disease progression at which point a tumor biopsy sample will be taken and analyzed to guide assignment to a triple combination arm in Part II.

Figure 7-1 Biopsy flow chart for patients in Group B



Patients in Group **C** should provide an archival biopsy sample collected pre-LGX818/MEK162 combination, or, the related DNA sequencing report produced by a Sponsor-designated Central Laboratory. Moreover, Group C patients entering this trial from other LGX818/MEK162 combination studies (e.g. [COLUMBUS], [CMEK162X2110] [CLGX818X2102] or IITs) will either provide a progression biopsy sample for genetic assessment, or, the related DNA sequencing report produced by a Sponsor-designated Central Laboratory. The molecular alteration identified will determine the assignment to one of the triple combination treatments in Part II (see Table 4-1). If a progression biopsy is not available, patients will be requested to provide a tumor biopsy at screening/baseline of Part II.

The newly obtained paired tumor samples collected before and during study treatments (Part 1 and Part II) will be used to investigate the pharmacodynamic effects of the triple drug combinations.

For all biomarker samples, the collection information must be captured on the Biomarker Assessment eCRF page(s) and Central Lab Requisition form(s).

Table 7-18 Biomarker sample collection plan and biomarker assessments

Sample Type	CCI	Visit	Time point	Markers to be assessed
Tumor samples				
Archival tumor sample & Corresponding Pathology Report	CCI	Requested from all patients if available Collected at molecular pre-screening (if needed) or at the screening/baseline visit otherwise	Anytime Part I, Run-in, Part II[3]	**Archival and/or Newly Obtained Tumor**: Molecular status (mutation/ amplification/ expression) of markers related to RAF/MEK/ERK pathway, PI3K/AKT pathway or cancer CCI CCI
Newly obtained tumor sample	CCI	Baseline - **required** Collected at molecular pre-screening (if needed) or at the screening/baseline visit otherwise	Prior to first dose Part I and Run-in Part II[4]	
		At time of progression under LGX818/MEK162 combination - **required**[1] At time of progression under LGX818/MEK162 + third agent combination To be collected preferably from a growing or new lesion	Pre-dose Part I And Part II	
		CCI		
CCI				
CCI				

3. Archival tumor sample is collected in Part II only from patients in Group C.
4. Newly obtained tumor biopsy is collected at molecular pre-screening or at the screening/baseline visit from patients in Group C, who cannot provide the progression biopsy from the previous study.

CCI

[redacted]

8 Safety monitoring and reporting

As of Amendment 07, for patients who have been on LGX818 + MEK162 for ≥ 36 months, only Grade 3 or 4 AEs and all SAEs will be recorded on the AE eCRF. Any AEs that meet these criteria until 30 days after the last dose of study drug must be recorded.

All SAEs are to be reported to the Sponsor or designee using the SAE form.

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

For patients whose BRAF status is unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

Patients whose BRAF status is known will sign the main study ICF.

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).

Except for screening failures, 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 Relevant Medical History/Current Medical Conditions CRF page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) 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, unless otherwise noted.

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 through 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:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates) or Ongoing after the 30 day Safety Follow-up.
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)

- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

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 (for example, as per RECIST criteria for solid tumors), should not be reported as a serious 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

For patients with unknown BRAF status and who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedure.

For patients with known BRAF status who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

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

Any SAEs experienced after this 30 days period (or 5 half-lives, whichever is longer) should only be reported to the Sponsor 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 the Sponsor or designee.

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 Sponsor study treatment, the Sponsor or designee may urgently require further information from the investigator for Health Authority reporting. The Sponsor or designee 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

Not applicable

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to the Sponsor or designee 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 Sponsor or designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatments, and

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 not be in place for this trial.

Instead, the Sponsor or designee will convene joint teleconferences with the participating Investigators of this study. Updated safety data on ongoing patients, including data in later cycles, will be discussed.

Inter-patient as well as intra- patient dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next patients will be guided by the BLRM (with EWOC) recommendation, and a medical review of available relevant clinical, PK, PD and laboratory data. The parties (i.e. study Investigators and the Sponsor) must reach a consensus on whether to declare MTD/RP2D of the combinations, escalate the dose any further, or whether to de-escalate and/or expand recruitment. The Sponsor or designee will prepare minutes from these meetings and circulate them to all concerned.

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.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Sponsor 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. Sponsor or designee 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 tumor tissue, except the pre-screening BRAF status assessment) samples drawn during the course of the study will be collected by investigational sites and analyzed by a Sponsor-delegated Central Laboratory.

All ECGs (except the screening/baseline ECG performed locally) collected during the study will be independently reviewed by a central laboratory.

9.4 Database management and quality control

For studies using eCRFs, Sponsor 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 are 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.

PK and biomarkers samples and ECG data (except screening baseline) will be processed centrally and the results will be sent electronically to the Sponsor (or a designated CRO).

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 the Sponsor and/or designated CRO.

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 data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data). Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

In all cases, data will be analyzed and/or presented separately for Part I and Part II. In Part II all outputs will be provided by triple combination arm unless otherwise stated.

Unless otherwise specified, baseline measurements/observations will be identified for each study part. The baseline for a study part is defined as the last available/valid assessment prior to the start of the study treatment for that study part. Consequently, the day of the 1st dose of the study treatment for a study part will be used as the reference date for all derivation of durations.

The study data will be analyzed and reported following end of study (see Section 4.3 for definition).

10.1 Analysis sets

For inclusion in any analysis set it is required that a patient has correctly consented and has received at least one dose of study treatment.

The following analysis sets will be used.

10.1.1 Full Analysis Set

For Part I, the Full Analysis Set (FAS) consists of all patients who received at least one dose (partial or full) of LGX818 or MEK162.

For Part II, the FAS consists of all patients who have received at least one dose of LGX818 or MEK162 or the assigned third agent following the assignment of the triple combination treatment.

Note that patients who were screened and/or are eligible but never started treatment for a study part will not be included in the FAS for that study part. This is considered as an acceptable deviation from the ITT principle in the context of a non-randomized exploratory study.

The FAS will be used for all listings of raw data. Unless otherwise specified, the FAS will be the default analysis set used for all analyses. Patients will be analyzed according to the treatment they have been assigned to.

10.1.2 Safety Set

The safety set for a study part consists of all patients from the FAS who had at least one valid post-baseline safety assessment. Please note that the statement that a patient had no adverse event on the Adverse Events eCRF constitutes a valid safety assessment.

For each study part, patients will be classified according to treatment received, where treatment received is defined as the following:

1. The treatment assigned if it was received at least once in the first cycle, or
2. The first treatment received when starting therapy with study treatment if the assigned treatment was never received.

The safety set will be the primary analysis set for all safety related endpoints except in summaries of DLTs and for the determination of the dose-DLT relationship where the dose-determining set will be used (Section 10.1.4).

10.1.3 Per-Protocol Set

The per-protocol set (PPS) consists of all Part II patients in the FAS who are compliant with the protocol in the following ways:

1. Diagnosis corresponds to that defined in inclusion criteria #5: histologically confirmed diagnosis of locally advanced or metastatic melanoma.

2. Stage of disease corresponds to that defined in inclusion criteria #5: stage IIIC to IV per American Joint Committee on Cancer [AJCC].
3. Prior treatment corresponds to that defined in exclusion criteria #13: Progressive disease following prior treatment with LGX818/MEK162 combination.
4. The patient was evaluated at least once for the primary efficacy variable or discontinued due to adverse event, unacceptable toxicity, Investigator's decision, patient's refusal, disease progression, or died prior to the first evaluation of the primary efficacy variable.
5. Patients will be evaluable for efficacy if they have at least one response assessed differently from 'unknown' or 'not assessed' under RECIST v1.1.

The Per-protocol set will be used in Part II in order to define the patients used in the sensitivity analysis of the primary endpoint.

10.1.4 Dose-determining analysis set

The dose-determining analysis set (DDS) consists of all patients from the Safety Set for Part II who have met the requirements for minimum safety evaluation and minimum exposure or experienced DLT during the first cycle of the assigned triple combination treatment.

To complete the minimum safety evaluations a patient must be observed for at least 1 cycle (21 days following the first dose of the combination treatment with BKM120, or INC280; 28 days for the combination with LEE011 or BGJ398) and considered to have sufficient safety data by both the Sponsor and Investigators to conclude that a DLT did not occur during this 1st cycle.

Patients meet the minimum exposure requirements if they have received at least 16 out of the 21 planned daily doses of the defined triple combinations.

10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable pharmacokinetic (PK) data. The PAS will be used for summaries of PK data (tables and figures) as well as for listings of derived parameters.

Note: Patients will be removed from the estimation of certain PK parameters on an individual basis, depending on, for example, the number of available blood samples and whether the PK parameter can be reliably estimated based on the available blood samples. These patients will be identified at the time of the analyses along with their reason for removal.

10.1.6 Other analysis sets

Not applicable

10.1.6.1 Efficacy/evaluable set

Not applicable

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including age, gender, height, weight, medical condition, disease characteristics, etc. will be summarized descriptively for all patients in the FAS. The summaries will be based on the assessments from the screening.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of LGX818, MEK162 (Part I and II) and the third assigned agent (Part II) treatment as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration) of each drug, will be listed and summarized by means of descriptive statistics in the clinical study report. The summary data will be presented for each treatment cycle individually, as well as for all study days as a single category.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will be listed by patient and summarized by ATC term by means of contingency tables.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized.

10.4 Primary objective

The primary objective of this study is to assess during Part II of the study the anti-tumor activity of LGX818 and MEK162 in combination with third targeted agents after progression on LGX818/MEK162 combination. Specific focus is placed on the LEE011 arm where it is expected that 30% of patients will be treated (see Section 10.4.2 and Section 10.8)

10.4.1 Variable

Best Overall Response (BOR) assessed per RECIST v1.1 during Part II will be used to evaluate the tumor response in terms of Overall Response Rate (ORR) for combinations of LGX818, MEK162 and the third agents. This will be based on investigator-assessed tumor evaluations per RECIST v1.1.

10.4.2 Statistical hypothesis, model, and method of analysis

BOR for all patients in the FAS (Part II) will be listed and summarized for each treatment combination. All patients from a combination arm will be pooled together irrespective of their initial planned combination treatment.

The ORR will be provided with a corresponding 95% confidence interval. Hence the summaries obtained will indicate whether progression can be reversed upon addition of a third targeted agent for which the initial dose may be titrated up when the triple combination treatment is tolerated. Consequently given that some patients will be treated below the MTD/RP2D prior to intra-patient dose-escalation, it is expected that the observed ORR will provide a conservative estimate of the true ORR for the final selected MTD/RP2D for each triple combination. Additional summaries by planned treatment may be generated if appropriate and if sample size allows.

In addition, since the LGX818+MEK162+LEE011 is expected to be the most used triple combination on study, and should be received by about 40 patients, a Bayesian inference will be performed to estimate the true ORR of this combination.

A minimally informative unimodal Beta prior distribution of the true ORR is derived as follows. A priori it is assumed that the true mean of the ORR equals 20%. A true ORR of 20% is the midpoint between limited and clinical relevant efficacy and serves as a compromise between a skeptical view assuming the treatment has only limited efficacy and an optimistic view assuming the treatment has clinically relevant efficacy. The parameter of the minimally informative Beta prior distribution of the ORR are then derived as a = 1/4 and b = 1.

At completion of the study, this prior distribution will be updated with all of the data available in the LGX818+MEK162+LEE011 combination arm. Once updated, the probabilities that the true ORR lies in the following categories will be reported:

- [0, 10%) unacceptable efficacy
- [10%, 20%) limited efficacy
- [20%, 30%) clinically relevant efficacy
- [30%, 100%] highly clinically significant efficacy

If the observed ORR is equal to or greater than 20%, then this will be considered as preliminary evidence of clinically relevant efficacy of the combination. If the observed ORR is less than 20% (i.e. $\leq$ 7 CR or PR out of 40), then insufficient efficacy will be concluded.

Note that for a sample size of n = 40 (see Section 10.8), if the observed ORR is greater than or equal to 20% (i.e. $\geq$ 8 CR or PR), then the true ORR has a posterior risk of less than 5% of being in the insufficient efficacy category.

If the number of patients recruited to any other triple-agent combination within Part 2 exceeds 30 patients this analysis will be performed for that combination in the same way as defined for the LGX818+MEK162+LEE011 combination.

10.4.3 Handling of missing values/censoring/discontinuations

As of the date of data-cutoff for the primary CSR for the purposes of reporting:

- Patients continuing to receive treatment will have time-to-event data (e.g. progression-free survival) censored at the date of last radiological disease assessment prior to the cut-off date.
- Continuing events (e.g. adverse events, concomitant therapies, etc.) will be summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing.

For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above paragraph.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study treatment, duration of exposure to study treatment and date of discontinuation for each patient.

Other missing data will simply be noted as missing on appropriate tables/listings.

10.4.4 Supportive analyses

The efficacy analysis for the LGX818/MEK162+LEE011 combination arm will also be performed using the PPS. Summaries in this arm by molecular alteration (see Table 4-1) will also be produced. In addition summaries for all patients enrolled in Part II pooled together will

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10.5 Secondary objectives

Please refer to Section 3 for the secondary objectives.

10.5.1 Key secondary efficacy objective(s)

Not applicable

10.5.2 Secondary efficacy objectives

As per the analysis of the primary efficacy endpoint, all patients from the same triple combination arm will be pooled together irrespective of their initial planned combination treatment dose level.

BOR will be listed and summarized for Part I, and then by combination arm for Part II. Exact 95% confidence intervals for ORR and DCR will also be derived

For each study part, Kaplan-Meier plots will be used to depict the progression-free survival for LGX818/MEK162 and their combination with third targeted agent (by combination arm). The corresponding median PFS as well as PFS rates at selected timepoints (e.g. 3 and 6 months) will be provided along with a 95% confidence interval when appropriate. OS, TTR and DOR will be summarized in a similar way by the triple combination treatment arm if appropriate.

10.5.3 Safety objectives

Safety and tolerability of LGX818/MEK162 and their combination with third target agents will be assessed for incidence and severity of adverse drug reactions and serious adverse drug reactions (as assessed by CTCAE Version 4.03), changes in hematology and chemistry values, physical examinations, vital signs, electrocardiogram, cardiac monitoring, ophthalmological and dermatological examinations.

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by study part and by initial received treatment group. The DDS will be used for all analyses of DLTs. The overall observation period 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 adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. 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 are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by treatment group and study arm.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and combination arm.

Bayesian Logistic Regression Model

An adaptive BLRM guided by the EWOC principle will guide the dose-escalation of each of the study drugs (BKM120, BGJ398, INC280, or LEE011) combined with LGX818 and MEK162 to its respective MTD(s)/RP2D(s). The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations and by (Rogatko et al 2007) and is one of the key elements of the FDA's Critical Path Initiative.

The definition of the BLRM, the prior distributions for the model parameters (based on currently available information about the targeted agents) and the associated prior distributions of DLT rates are provided in the appendix Section 14.1.

Note that any additional information on the dose-DLT relationship generated by on-going studies used to define the prior distribution will be incorporated before the first dose escalation is made within this study in order to reflect all relevant information at that time.

Summaries of the posterior distribution of model parameters and posterior distribution of DLT rates based on the DLT data from all patients enrolled in the study and included in the DDS will be produced.

For each triple combination, a 10-parameter BLRM is formulated in the following way: Let $\pi1(d1)$ be the probability of a DLT if LGX818 is given as a single agent on a q.d. schedule at dose d1 mg, and $\pi2(d2)$ the probability of a DLT if MEK162 is given as a single agent on a b.i.d. schedule at dose d2 mg, and $\pi3(d3)$ be the probability of a DLT if the third assigned agent is given as a single agent on its schedule at dose d3 mg (as described in Section 6.1.1).

The marginal dose-response relationships are then modeled as:

LGX818: $\text{logit}(\pi1(d1)) = \log(\alpha1) + \beta1\log(d1/d1^*)$

MEK162: $\text{logit}(\pi2(d2)) = \log(\alpha2) + \beta2\log(d2/d2^*)$

3rd agent: $\text{logit}(\pi3(d3)) = \log(\alpha3) + \beta3\log(d3/d3^*)$

where $\text{logit}(\pi.(d.)) = \log[\pi.(d.)/\{1- \pi.(d.)\}]$, d.* is the reference dose of each compound, and $\alpha1$, $\alpha2$, $\alpha3$, $\beta1$, $\beta2$, $\beta3 > 0$.

The dose-response relationship of the dual combinations is subsequently modeled as:

LGX818+MEK162: $\text{Odds}(\pi12(d1,d2))) = \pi12(d1,d2)/(1- \pi12(d1,d2))$

$= \exp(\eta12(d1/d1^*)(d2/d2^*))(\pi1(d1)+ \pi2(d2) – \pi1(d1)\pi2(d2))/((1- \pi1(d1))(1- \pi2(d2))),$

LGX818+3rd agent: $\text{Odds}(\pi13(d1,d3))) = \pi13(d1,d3)/(1- \pi13(d1,d3))$

$= \exp(\eta13\ (d1/d1^*)(d3/d3^*))(\pi1(d1)+ \pi3(d3) – \pi1(d1)\pi3(d3))/((1- \pi1(d1))(1- \pi3(d3))),$

MEK162+3rd agent: $\text{Odds}(\pi23(d2,d3))) = \pi23(d2,d3)/(2- \pi23(d2,d3))$

$= \exp(\eta23(d2/d2^*)(d3/d3^*))(\pi2(d2)+ \pi3(d3) – \pi2(d2)\pi3(d3))/((1- \pi2(d2))(1- \pi3(d3))),$

where $-\infty < \eta12, \eta13, \eta23 < \infty$ is a scalar.

The dose-response relationship of the triple combinations is then modeled as:

LGX818+MEK162+3rd agent:

$\text{Odds}(\pi123(d1,d2,d3))) = \pi123(d1,d2,d3)/(1- \pi123(d1,d2,d3))$

$= \exp(\eta123(d1/d1^*)(d2/d2^*)(d3/d3^*) + \eta12(d1/d1^*)(d2/d2^*) + \eta13\ (d1/d1^*)(d3/d3^*) + \eta23(d2/d2^*)(d3/d3^*))(\pi1(d1)+ \pi2(d2) + \pi3(d3) – \pi1(d1)\pi2(d2) – \pi1(d1)\pi3(d3) – \pi2(d2)\pi3(d3) + \pi1(d1)\pi2(d2)\pi3(d3))/((1- \pi1(d1))(1- \pi2(d2))\ (1- \pi3(d3))),$

where $-\infty < \eta123 < \infty$ is a scalar.

For further details on the statistical model, prior specification and operating characteristics, please refer to Section 14.1 Appendix 1.

Dose recommendation

Dose recommendation for the third target agent is conditional to the dose of LGX818 and MEK162 which may differ between patients entering Part II. This recommendation will be

based on posterior summaries of the DLT rate including the mean, median, standard deviation, 95% credible interval, and the probability that the true DLT rate for each dose combination lies in one of the following categories:

- [0%, 16%) under-dosing
- [16%, 35%) targeted toxicity
- [35%, 100%] excessive toxicity

Following the principle of EWOC, after each cohort of patients, the recommended dose combination is the one with the highest posterior probability of DLT in the target interval [16%, 35%) among the doses fulfilling the overdose criterion that there is less than 25% chance of excessive toxicity. The dose escalation for the triple combination is limited to 100%. A clinical synthesis of the available toxicity information (including AEs that are not DLTs), PK, PD, and efficacy information as well as the recommendations from the Bayesian model will be used to determine the dose combination for the next patients at a dose-escalation teleconference (see Section 6.2.3.2). The Investigators and Sponsor trial personnel will be involved in the decision making.

The final recommended MTD/RP2D for each combination will be based on considerations of the recommendation from the BLRM, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at all different dose combinations tested.

Summaries of the posterior distribution of model parameters and posterior distribution of DLT rates based on the DLT data from all patients enrolled in the study and included in the DDS will be produced. DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 4.03, type of AE, and by treatment. The DDS will be used for these summaries.

For further details of the BLRM model and results under a variety of scenarios, please refer to Section 14.1.1 and Section 14.1.2 of Appendix 1.

10.5.3.3 Laboratory abnormalities

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE, version 4.03. Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

For each laboratory test (e.g. hematology, biochemistry etc.) a listing of laboratory values will be provided by laboratory parameter, patient and treatment group. The frequency of notable lab abnormalities (i.e. newly occurring CTCAE grade 3 or 4 laboratory toxicities), will be reported by parameter, cycle and treatment group. Similarly, the frequency of all laboratory abnormalities will be tabulated by parameter, worst CTCAE v4.03 grade experienced, and treatment group. Laboratory data will be summarized by presenting grade shift tables for those parameters that can be classified using CTCAE version 4.03. All remaining data will be summarized by presenting shift tables based on normal ranges.

10.5.3.4 Other safety data

Data from other tests (e.g., electrocardiogram, ophthalmological assessments and vital signs) will be listed and summarized by treatment group, notable values will be flagged, and any other information collected will be listed and summarized as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Definitions of notably abnormal results have to part of the CDP, MAP, CSP and RAP.

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

10.5.3.5 Supportive analyses for secondary objectives

Any supportive analyses undertaken for estimation of the MTD/RP2D will be defined within the study RAP.

10.5.3.6 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed and summarized.

10.5.4 Pharmacokinetics

All patients who have at least one blood sample providing evaluable PK data for study treatment will be included in the PK data analysis. The PAS will be used. Missing/not collected values will be denoted as such in summary.

Pharmacokinetic variables and data analysis

Pharmacokinetic parameters for LGX818, MEK162 (including its primary active metabolite AR00426032), LEE011, BGJ398 (including its active metabolite BHS697 and CQM157), BKM120, and INC280 will be determined for all PK-evaluable patients using either non-compartmental method(s), using Phoenix WinNonlin® (Pharsight, Mountain View, CA), and/or compartmental method(s). The PK parameters listed in Table 10-1, but not limited to, will be estimated and reported, as appropriate. CCI

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The plasma concentration/time data will be summarized by treatment group and graphically presented. Descriptive graphical plots of individual and median plasma concentration (per treatment) along with its time course will be generated.

Table 10-1 Non compartmental pharmacokinetic parameters

Term	Definition
AUCtau, ss	Area under the concentration-time curve from time zero to time tau at steady-state [mass x time x volume-1]
Cmax	Maximum observed plasma concentration after drug administration (ng/mL)
Cmax, ss	The maximum (peak) observed plasma concentration after drug administration at steady state [mass x volume-1]
Tmax	Time to reach maximum (peak) plasma drug concentration (h)
Tmax, ss	The time to reach Cmax at steady state [time]
Ctrough	Measured concentration at the end of a dosing interval at steady-state (taken directly before next administration) (ng/mL)
Clast, ss	Last measurable plasma concentration at steady state [mass x volume-1]
T1/2, ss	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve at steady state [time].
CL,ss/F	Apparent total plasma clearance of drug after oral administration at steady state [volume x time-1]
Vz,ss/F	The apparent volume of distribution at the terminal elimination phase at steady state (volume)
Note: it is assumed that C1D15 is at steady state.	

10.5.4.1 Data handling principles

All concentrations of LGX818, MEK162, AR00426032, LEE011, BGJ398, BHS697, CQM157, BKM120 and INC280 below their respective LLOQs (lower limits of quantification) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of PK parameters.

Patients may be removed from the estimation of certain PK parameters on an individual basis when the PK parameters cannot be reliably estimated based on the available blood samples. These patients will be identified prior to the time of the data analysis. Only PK blood sample with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing will be excluded from the analysis.

10.5.5 Biomarkers

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Part I

Molecular status (mutation/amplification/expression) of markers relevant to the RAF/MEK/ERK and PI3K/AKT pathways CCI

CCI at screening/baseline and at progression with LGX818/MEK162 combination will be listed and summarized.

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10.7 Interim analysis

No formal interim analyses are planned. However, the dose-escalations planned for Part II foresee that decisions based on the current data are taken before the end of the study. More precisely, in each combination arm, the next combination of LGX818, MEK162 and the third targeted agent has to be chosen depending on the observed data. Details of this procedure and the process for communication with Investigators are provided in Section 6.2.

10.8 Sample size calculation

Part II LGX818/MEK162+LEE011 arm

About 140 patients are expected to enroll in Part II of the study to address the primary objective of the study. From these 140 patients, it is anticipated that about 30% of patients progressing on LGX818+MEK162 would be eligible to the LGX818+MEK162+LEE011 arm. With 140 patients recruited it would give 89% probability that the number of patients assigned to the LEE arm will be at least 36.

Based on the ORR (per RECIST 1.1) intervals described in Section 10.4.2, it was assessed how likely it is to wrongly declare activity as defined by observing at least "clinical relevant efficacy" (i.e. seeing at least 8 responses out of 40 patients) given the true ORR = 10%, and how likely it is to correctly declare activity given the true ORR = 30% when 40 patients are evaluated.

- If the true ORR = 10%, the probability to wrongly declare activity is 4.2%.
- If the true ORR = 30%, the probability to correctly declare activity is 94.5%.

Given a sample size of 40, if 8 responses are seen, the observed ORR is 20% with a 90% credible interval of (10.8%, 30.9%). This will be considered as preliminary evidence of antitumor activity of the treatment at the MTD/RDE within this arm.

Part II other arms

Note: Enrollment to the BKM120- (Amendment 03), BGJ398-, INC280- (Amendment 06), and LEE011 (Amendment 07)-containing arms is closed.

Dose escalation in Part II will proceed with groups of at least 3 evaluable patients receiving triple combination therapy at the current dose levels according to Table 6-2 and Table 6-3. At least six patients must be included at the MTD/RP2D level for each triple combination. Additional patients may be enrolled at any dose level below the current dose if this dose has not been tested before and if there are already 3 evaluable patients enrolled. Any dose level below the estimated MTD/RP2D may be expanded for further elaboration of safety and pharmacokinetic parameters as required. Approximately 100 patients are expected to be treated in total in the BKM120, BGJ398 and INC280 triple combination arms. The number of patients treated within each triple combination will depend upon the prevalence of the corresponding molecular alterations.

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 the Sponsor or designee monitors, auditors, Clinical Quality Assurance representatives, designated agents of the Sponsor, 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, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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.

The Sponsor or designee 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 the Sponsor before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Sponsor or designee's 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

The Sponsor 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 4.3 and Section 4.4.

11.5 Publication of study protocol and results

The Sponsor 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 Sponsor-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 the 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 the Sponsor. 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 the Sponsor 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 the Sponsor 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 the Sponsor 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 the Sponsor, 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, the Sponsor 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 - Operating characteristics of the Bayesian logistic regression mode and hypothetical dose escalation scenarios

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used to guide the dose escalation of each of the study drugs (BGJ398, BKM120, INC280, or LEE011) combined with LGX818 and MEK162 to their respective MTD(s)/RP2D(s) during Part II of the study. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by Rogatko (2007) and is one of the key elements of the FDA's Critical Path Initiative.

This section provides details of the statistical model, the derivation of prior distributions for the model parameters, and the properties of the adaptive design (dosing recommendations for hypothetical data scenarios).

14.1.1 Statistical model and prior distributions

This section is organized in the following way:

- A short motivation is provided.
- The single-agent prior distribution for each of the compound is derived.
- The prior distribution for each of the interaction parameters (eta) is derived.
- Numerical values and summary statistics at different dose levels are shown.

Motivation

For each combination, a 10-parameter BLRM (refer to the protocol Section 10.5.3.2 for detail) will be used to model the dose-limiting toxicity rate in the first cycle to assess the dose-toxicity relationship of BGJ398, BKM120, INC280 or LEE011 given in combination with LGX818 and MEK162.

Details regarding dose recommendation are described in Section 10.5.3.2 of the protocol. The Bayesian approach requires the specification of prior distributions for all model parameters, which comprise the single-agent parameters for LGX818, MEK162, BKM120, BGJ398, INC280 and LEE011, and for all the interaction parameters (See model definition in Section 10.5.3.2). Derivation of these is provided in the following subsections.

Intermediate and final parameter values are given in Table 14-2 and the data used to derive the informative priors are presented in Table 14-1. For some of the provisional dose levels, Table 14-3 summarizes the associated prior distribution of DLT rates corresponding to the priors.

LGX818

An informative bivariate normal prior for the model parameters ($\log(\alpha_1)$, $\log(\beta_1)$) is obtained as follows:

Patients involved in the dose escalation of a triple combination in Study Part II will have tolerated LGX818+MEK162 well. For this reason, the DLT rate is assumed to be very low:

- Assume that at 200 mg QD, the median probability of a DLT is 0.025 with 5th and 95th percentiles 0.0005 and 0.05 respectively.
- Assume that at 450 mg QD, the median probability of a DLT is 0.05 with 5th and 95th percentiles 0.001 and 0.10 respectively.

Based on the above specified medians and percentiles for the DLT rate at each dose, the optimal parameters of the bivariate normal distribution can be obtained following the procedure described by Neuenschwander et al (2008).

MEK162

An informative bivariate normal prior for the model parameters ($\log(\alpha_2)$, $\log(\beta_2)$) is obtained as follows:

Patients involved in the dose escalation of a triple combination in Study Part II will have tolerated LGX818+MEK162 well. For this reason, the DLT rate is assumed to be very low:

- Assume that at 30 mg QD, the median probability of a DLT is 0.025 with 5th and 95th percentiles 0.0005 and 0.05 respectively.
- Assume that at 45 mg QD, the median probability of a DLT is 0.05 with 5th and 95th percentiles 0.001 and 0.10 respectively.

Based on the above specified medians and percentiles for the DLT rate at each dose, the optimal parameters of the bivariate normal distribution can be obtained following the procedure described by Neuenschwander et al (2008).

The single-agent priors for BGJ398, BKM120, INC280 and LEE011 are derived from available historical data in a stepwise fashion. The details are listed below.

BGJ398

Currently available historical data from study [CBGJ398X2101] are used in order to derive the prior for the BLRM parameters. The bivariate normal prior for the model parameters is obtained as follows:

Step 1 The following non-informative prior for ($\log(\alpha_{BGJ})$, $\log(\beta_{BGJ})$) was used:

- The median DLT rate at the reference dose (75 mg QD) was assumed to be 0.15, i.e. $\text{mean}(\log(\alpha_{BGJ})) = \log(0.176)$.
- A doubling in dose was assumed to double the odds of DLT, i.e. $\text{mean}(\log(\beta_{BGJ})) = 0$.
- The standard deviation of $\log(\alpha_{BGJ})$ was set to 2, and the standard deviation of $\log(\beta_{BGJ})$ was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_{BGJ})$ and $\log(\beta_{BGJ})$ was set to 0.

Step 2 Data from 34 patients eligible for the dose-determining set of the study [CBGJ398X2101] were used to update the dose-toxicity profile (See Table 14-1).

Step 3 Heterogeneity between the historical and current study was incorporated by between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_{BGJ})$ and $\log(\beta_{BGJ})$. Both were set to follow a normal distribution. Mean log(0.25) and log(0.125) were chosen for τ_1 and τ_2 respectively, and stand deviation 0.01 were chosen for both τ_1 and τ_2, which correspond to moderate between-trial variability.

BKM120

Currently available historical data from study [CBKM120X2101] are used in order to derive the prior for the BLRM parameters. The bivariate normal prior for the model parameters is obtained as follows:

Step 1 The following non-informative prior for $(\log(\alpha_{BKM}), \log(\beta_{BKM}))$ was used:

- The median DLT rate at the reference dose (50 mg QD) was assumed to be 0.15, i.e. $\text{mean}(\log(\alpha_{BKM})) = \log(0.176)$.
- A doubling in dose was assumed to double the odds of DLT, i.e. $\text{mean}(\log(\beta_{BKM})) = 0$.
- The standard deviation of $\log(\alpha_{BKM})$ was set to 2, and the standard deviation of $\log(\beta_{BKM})$ was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_{BKM})$ and $\log(\beta_{BKM})$ was set to 0.

Step 2 Data from 40 patients eligible for the dose-determining set of the study [CBKM120X2101] were used to update the dose-toxicity profile (See Table 14-1).

Step 3 Heterogeneity between the historical and current study was incorporated by between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_{BKM})$ and $\log(\beta_{BKM})$. Both were set to follow a normal distribution. Mean log(0.25) and log(0.125) were chosen for τ_1 and τ_2 respectively, and stand deviation 0.01 were chosen for both τ_1 and τ_2, which correspond to moderate between-trial variability.

INC280

Currently available historical data from study [CINC398X2101], [CINC398X1101], and [CINC398X2102] are used in order to derive the prior for the BLRM parameters. The bivariate normal prior for the model parameters is obtained as follows:

Step 1 The following non-informative prior for $(\log(\alpha_{INC}), \log(\beta_{INC}))$ was used:

- The median DLT rate at the reference dose (200 mg BID) was assumed to be 0.15, i.e. $\text{mean}(\log(\alpha_{INC})) = \log(0.176)$.
- A doubling in dose was assumed to double the odds of DLT, i.e. $\text{mean}(\log(\beta_{INC})) = 0$.
- The standard deviation of $\log(\alpha_{INC})$ was set to 2, and the standard deviation of $\log(\beta_{INC})$ was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_{INC})$ and $\log(\beta_{INC})$ was set to 0.
- Since two schedules have been investigated for INC280, the difference in schedule is expressed by a covariate assumed to be normally distributed with mean 0.693 and standard deviation 0.541. This is based on the assumptions that at the reference dose

changing schedule from QD to BID lead to a 2-fold (median) and a 4-fold (90th percentile) increase in the odds of DLT.

Step 2 Data from 40 patients eligible for the dose-determining set of the study [CINC398X2101], 30 patients from [CINC398X1101], and 30 patients from [CINC398X2102] were used to update the dose-toxicity profile (See Table 14-1).

Step 3 Heterogeneity between the historical and current study was incorporated by between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_{INC})$ and $\log(\beta_{INC})$. Both were set to follow a normal distribution. Mean log(0.25) and log(0.125) were chosen for τ_1 and τ_2 respectively, and stand deviation 0.01 were chosen for both τ_1 and τ_2, which correspond to moderate between-trial variability.

LEE011

Currently available historical data from study [CLEE011X2101] are used in order to derive the prior for the BLRM parameters. The bivariate normal prior for the model parameters is obtained as follows:

Step 1 The following non-informative prior for $(\log(\alpha_{LEE}), \log(\beta_{LEE}))$ was used:

- The median DLT rate at the reference dose (400 mg QD) was assumed to be 0.15, i.e. $\text{mean}(\log(\alpha_{LEE})) = \log(0.176)$.
- A doubling in dose was assumed to double the odds of DLT, i.e. $\text{mean}(\log(\beta_{LEE})) = 0$.
- The standard deviation of $\log(\alpha_{LEE})$ was set to 2, and the standard deviation of $\log(\beta_{LEE})$ was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_{LEE})$ and $\log(\beta_{LEE})$ was set to 0.

Step 2 Data from 53 patients eligible for the dose-determining set of the study [CLEE011X2101] were used to update the dose-toxicity profile (See Table 14-1).

Step 3 Heterogeneity between the historical and current study was incorporated by between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_{LEE})$ and $\log(\beta_{LEE})$. Both were set to follow a normal distribution. Mean log(0.25) and log(0.125) were chosen for τ_1 and τ_2 respectively, and stand deviation 0.01 were chosen for both τ_1 and τ_2, which correspond to moderate between-trial variability.

Table 14-1 Data from single-agent trials used to derive priors for BGJ398, BKM120, INC280 and LEE011

Study	Schedule	Dose (mg/day)	No. of DLTs/No. of evaluable patients
[BGJ378X2101]	QD	5	0/3
	QD	10	0/2
	QD	20	0/4
	QD	40	0/5
	QD	60	0/3
	QD	100	1/6
	QD	125	1/10
	QD	150	2/4

Study	Schedule	Dose (mg/day)	No. of DLTs/No. of evaluable patients
[BKM120X2101]	QD	12.5	0/1
	QD	25	0/1
	QD	50	0/3
	QD	80	1/9
	QD	100	4/23
	QD	150	2/3
[INC280X2101]	QD	10	0/3
	QD	20	0/3
	QD	50	1/6
	QD	70	0/3
	BID	100	0/3
	QD	150	0/3
	QD	200	0/3
	QD	300	0/4
	QD	400	0/4
	BID	400	0/4
	BID	600	0/4
[INC280X1101]	QD	100	0/3
	QD	200	0/3
	QD	400	0/3
	QD	500	0/3
	QD	600	0/4
	QD	800	0/4
	BID	800	0/3
	BID	1200	1/3
[INC280X2102]	BID	200	0/4
	BID	400	1/4
	BID	500	1/4
	BID	700	0/3
	BID	900	1/8
	BID	1200	0/7
[LEE011X2101]	QD	50	1/4
	QD	70	0/2
	QD	140	0/3
	QD	260	0/4
	QD	280	1/4
	QD	350	0/5
	QD	400	1/4
	QD	600	1/12
	QD	750	2/10
	QD	900	1/13
	QD	1200	2/3

Interaction parameter

The prior reflecting the current uncertainty about the toxicity of the combination treatment is used for the parameter modeling the interactions. Based on the PK drug-drug interaction assessment (Section 6.2.1), the following assumptions are made for the interaction parameters.

LGX818 and MEK162:

- The parameter η is normally distributed and centered at 0, i.e. no increase in odds of DLT over independence at the combination starting dose.
- 97.5th percentile is log(2), i.e. 2 fold increase in odds of DLT over independence at the combination starting dose.

This assumes, *a priori*, that there will be a small interaction, but also allows for the potential of both synergism and antagonism of the safety profiles.

LGX818 and BGJ398, MEK162 and BGJ398, LGX818 and BKM120, MEK162 and BKM120, MEK162 and INC280, MEK162 and LEE011:

- The parameter η is normally distributed and centered at 0, i.e. no increase in odds of DLT over independence at the combination starting dose.
- 97.5th percentile is log(3), i.e. 3 fold increase in odds of DLT over independence at the combination starting dose.

This assumes, *a priori*, that there will be a small interaction, but also allows for the potential of both synergism and antagonism of the safety profiles.

LGX818 and INC280:

- The parameter η is normally distributed and centered at log(1.2), i.e. 20% increase in odds of DLT over independence at the combination starting dose.
- 97.5th percentile is log(3), i.e. 3 fold increase in odds of DLT over independence at the combination starting dose.

This assumes, *a priori*, that there will be a slight synergistic interaction, but also allows for the potential of both significant synergism and antagonism of the safety profiles.

LGX818 and LEE011:

- The parameter η is normally distributed and centered at log(1.1), i.e. 10% increase in odds of DLT over independence at the combination starting dose.
- 97.5th percentile is log(3), i.e. 3 fold increase in odds of DLT over independence at the combination starting dose.

This assumes, *a priori*, that there will be a slight synergistic interaction, but also allows for the potential of both significant synergism and antagonism of the safety profiles.

All three-way interactions:

- The parameter η is normally distributed and centered at 0, i.e. no increase in odds of DLT over independence at the combination starting dose.
- 97.5th percentile is log(2), i.e. 2 fold increase in odds of DLT over independence at the combination starting dose.

This assumes, *a priori*, that there will be a small interaction, but also allows for the potential of both synergism and antagonism of the safety profiles.

Numerical values and summary statistics

Table 14-2 summarizes the information for all model parameters: distributions for the single-agent parameters (weakly-informative prior, posterior from historical data, and discounted prior due to between-trial heterogeneity), and the prior for the interaction parameter. Table 14-3 summarizes the prior distribution of DLT rates corresponding to the prior. The doses not meeting the overdose criteria are bold in the table, i.e. doses not eligible at the start of the study (under the prior).

Table 14-2 Prior distributions of model parameters

Parameter	Means	Standard deviations	Correlation
Priors for LGX818 and MEK162			
$\log(\alpha_1)$, $\log(\beta_1)$	-3.200, 0.007	0.660, 0.060	0.582
$\log(\alpha_2)$, $\log(\beta_2)$	-1.859, 0.802	1.077, 1.307	0.963
Non-informative priors for BGJ398, BKM120, INC280 and LEE011 (Step 1)			
$\log(\alpha_{BGJ})$, $\log(\beta_{BGJ})$	-1.737, 0	2, 1	0
$\log(\alpha_{BKM})$, $\log(\beta_{BKM})$	-1.737, 0	2, 1	0
$\log(\alpha_{INC})$, $\log(\beta_{INC})$	-1.737, 0	2, 1	0
$\log(\alpha_{LEE})$, $\log(\beta_{LEE})$	-1.737, 0	2, 1	0
γ	0.693	0.541	NA
Posterior for BGJ398, BKM120, INC280 and LEE011 given available data (Step 2)			
$\log(\alpha_{BGJ})$, $\log(\beta_{BGJ})$	-2.600, 0.483	0.768, 0.745	-0.578
$\log(\alpha_{BKM})$, $\log(\beta_{BKM})$	-2.763, 0.382	0.932, 0.795	-0.794
$\log(\alpha_{INC,\ X2101})$, $\log(\beta_{INC,\ X2101})$	-3.273, -0.922	0.903, 0.702	-0.083
$\log(\alpha_{INC,\ X1101})$, $\log(\beta_{INC,\ X1101})$	-3.603, -0.355	1.135, 0.761	-0.536
$\log(\alpha_{INC,\ X2102})$, $\log(\beta_{INC,\ X2102})$	-2.921, -0.803	0.747, 0.709	-0.544
$\log(\alpha_{LEE})$, $\log(\beta_{LEE})$	-1.986, -0.789	0.382, 0.653	-0.266
Prior used for BGJ398, BKM120, INC280 and LEE011 (incorporating between-trial heterogeneity, Step 3)			
$\log(\alpha_{BGJ})$, $\log(\beta_{BGJ})$	-2.605, 0.494	0.851, 0.762	-0.508
$\log(\alpha_{BKM})$, $\log(\beta_{BKM})$	-2.772, 0.396	1.010, 0.824	-0.731
$\log(\alpha_{INC})$, $\log(\beta_{INC})$	-3.138, -0.709	0.573, 0.429	-0.351
$\log(\alpha_{LEE})$, $\log(\beta_{LEE})$	-1.987, -0.782	0.523, 0.684	-0.189
Priors for interaction terms			
$\eta_{LGX,\ MEK}$ (for BGJ398 or BKM120 arm)	0	0.472	NA
$\eta_{LGX,\ MEK}$ (for INC280 or LEE011 arm)	0	1.061	NA
$\eta_{LGX,\ BGJ}$	0	0.561	NA
$\eta_{MEK,\ BGJ}$	0	0.747	NA
$\eta_{LGX,\ BKM}$	0	0.467	NA
$\eta_{MEK,\ BKM}$	0	0.623	NA
$\eta_{LGX,\ INC}$	0.205	0.526	NA
$\eta_{MEK,\ INC}$	0	0.374	NA
$\eta_{LGX,\ LEE}$	0.858	4.607	NA
$\eta_{MEK,\ LEE}$	0	2.989	NA
$\eta_{LGX,\ MEK,\ BGJ}$	0	0.472	NA
$\eta_{LGX,\ MEK,\ BKM}$	0	0.393	NA
$\eta_{LGX,\ MEK,\ INC}$	0	0.530	NA
$\eta_{LGX,\ MEK,\ LEE}$	0	4.244	NA

Table 14-3 Summary of prior distribution of DLT rates for LGX818 = 450 mg (QD, for BGJ398 or BKM120 arm) / 200 mg (QD, for INC280 or LEE011 arm) and MEK162 = 45 mg (BID)

Dose of combination treatment (mg/day)	Prior probabilities that Pr(DLT) is in interval:			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.35)	[0.35, 1]			2.50%	50.00%	97.50%
BGJ398								
75	0.470	0.354	0.176	0.212	0.158	0.026	0.170	0.624
100	0.378	0.312	0.310	0.277	0.213	0.022	0.218	0.795
125	0.329	0.257	0.414	0.344	0.267	0.017	0.276	0.920
BKM120								
60	0.433	0.363	0.203	0.228	0.167	0.028	0.184	0.661
80	0.350	0.310	0.339	0.296	0.224	0.024	0.237	0.830
100	0.311	0.254	0.436	0.360	0.274	0.019	0.292	0.939
INC280								
400	0.518	0.358	0.124	0.189	0.136	0.028	0.155	0.545
800	0.420	0.235	0.344	0.292	0.254	0.010	0.209	0.883
1200	0.393	0.169	0.439	0.372	0.330	0.003	0.266	0.980
LEE011								
100	0.536	0.336	0.128	0.186	0.140	0.023	0.149	0.553
200	0.459	0.228	0.313	0.273	0.251	0.008	0.186	0. 877
300	0.436	0.158	0.405	0.344	0.326	0.002	0.223	0.977
400	0.428	0.121	0.451	0.393	0.371	0.001	0.259	0.996

Note: bold values indicate doses not meeting the overdose criterion (more than 25% chance of excessive toxicity) with the prior information only. For INC280, BID dosing is used, therefore, total daily doses shown in this table are twice the BID dose.

Details regarding dose recommendation are described in Section 10.5.2 of the protocol.

14.1.2 Hypothetical dose escalation scenarios

In order to show how well the BLRM model performs, different hypothetical dose escalation scenarios were investigated. The model should make reasonable dose recommendations during the study based on the observed DLTs. During the study, the decision to escalate dose after completion of a given cohort and the actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM per EWOC principle and medical review of available clinical and laboratory data. Details regarding dose recommendation using this model are described in Section 10.5.3 of the CSP.

Some scenarios to illustrate both inter-patient and intra-patient dose escalation up to the fourth dose cohort for each triple combination are listed in Table 14-4 to Table 14-7. It is assumed for most scenarios that each cohort has 3-6 evaluable patients. The maximum dose increment allowed in the scenarios did not exceed 100% for inter-patient dose escalation or 50% for intra-

patient dose escalation as per escalation rules defined in Section 6.2.3 of the CSP. The recommended next dose level satisfied the EWOC principle.

Note that the next dose level for the 3rd agent is selected in concordance with the provisional dose levels specified in Section 6.2.2 of the protocol wherever it is allowed, to mimic possible on-study escalation steps. However, for better examination of the performance of the model, several additional provisional dose levels are added.

Table 14-4 Hypothetical scenarios for on-study decisions with LGX818 = 450mg QD and MEK162 = 45mg BID in combination with BGJ398 (cohort size: 3)

Scenario	Dose of BGJ398 (mg/day)	Npat	Ntox	P(Over) NDC (inter-patient DE)	Next Dose Combination (inter-patient DE)	P(Over) NDC (intra-patient DE)	Next Dose Combination (intra-patient DE)
1	75	3	0	0.238	125	0.137	100
2	75	3	1	0.214	75	0.391	100
3	75	3	2	0.243	50	0.243	50
4	75 125	3 3	0 1	0.127	100	0.282	125
5	75 125	3 3	0 2	0.147	75	0.147	75
6	75 75	3 3	1 0	0.213	100	0.213	100
7	75 75	3 3	1 1	0.235	75	0.235	75
8	75 75	3 3	1 2	0.201	50	0.201	50
9	75 125 100	3 3 3	0 1 0	0.152	125	0.264	150
10	75 125 75	3 3 3	0 2 0	0.059	75	0.270	100
11	75 75 100	3 3 3	1 0 0	0.245	150	0.245	150
12	75 75 75	3 3 3	1 1 0	0.099	75	0.287	100

Table 14-5 Hypothetical scenarios for on-study decisions with LGX818 = 450mg QD and MEK162 = 45mg BID in combination with BKM120 (cohort size: 3)

Scenario	Dose of BKM120 (mg/day)	Npat	Ntox	P(Over) NDC (inter-patient DE)	Next Dose Combination (inter-patient DE)	P(Over) NDC (intra-patient DE)	Next Dose Combination (intra-patient DE)
1	60	3	0	0.217	90	0.217	90
2	60	3	1	0.235	60	0.330	70
3	60	3	2	0.186	30	0.298	40
4	60 80	3 3	0 1	0.203	80	0.346	100
5	60 80	3 3	0 2	0.201	60	0.352	70
6	60 60	3 3	1 0	0.230	80	0.301	90
7	60 60	3 3	1 1	0.156	50	0.369	70
8	60 60	3 3	1 2	0.224	40	0.362	50
9	60 80 80	3 3 3	0 1 0	0.182	100	0.280	120
10	60 80 60	3 3 3	0 2 0	0.203	70	0.363	80
11	60 60 80	3 3 3	1 0 0	0.247	120	0.247	120
12	60 60 50	3 3 3	1 1 0	0.240	70	0.335	80

Table 14-6 Hypothetical scenarios for on-study decisions with LGX818 = 200mg QD and MEK162 = 45mg BID in combination with INC280 (cohort size: 3)

Scenario	Dose of INC280 (mg/day)	Npat	Ntox	P(Over) NDC (inter-patient DE)	Next Dose Combination (inter-patient DE)	P(Over) NDC (intra-patient DE)	Next Dose Combination (intra-patient DE)
1	400	3	0	0.187	800	0.117	600
2	400	3	1	0.157	400	0.338	600
3	400	3	2	0.241	300	0.241	300
4	400 800	3 3	0 1	0.244	800	0.346	1000
5	400 800	3 3	0 2	0.125	400	0.272	500
6	400 400	3 3	1 0	0.241	700	0.186	600
7	400 400	3 3	1 1	0.179	400	0.299	500
8	400 400	3 3	1 2	0.206	300	0.206	300
9	400 800 800	3 3 3	0 1 0	0.249	1400	0.202	1200
10	400 800 400	3 3 3	0 2 0	0.154	500	0.284	600
11	400 400 700	3 3 3	1 0 0	0.226	1400	0.149	1000
12	400 400 400	3 3 3	1 1 0	0.248	600	0.248	600

Table 14-7 Hypothetical scenarios for on-study decisions with LGX818 = 200mg QD and MEK162 = 45mg BID in combination with LEE011 (cohort size: 3)

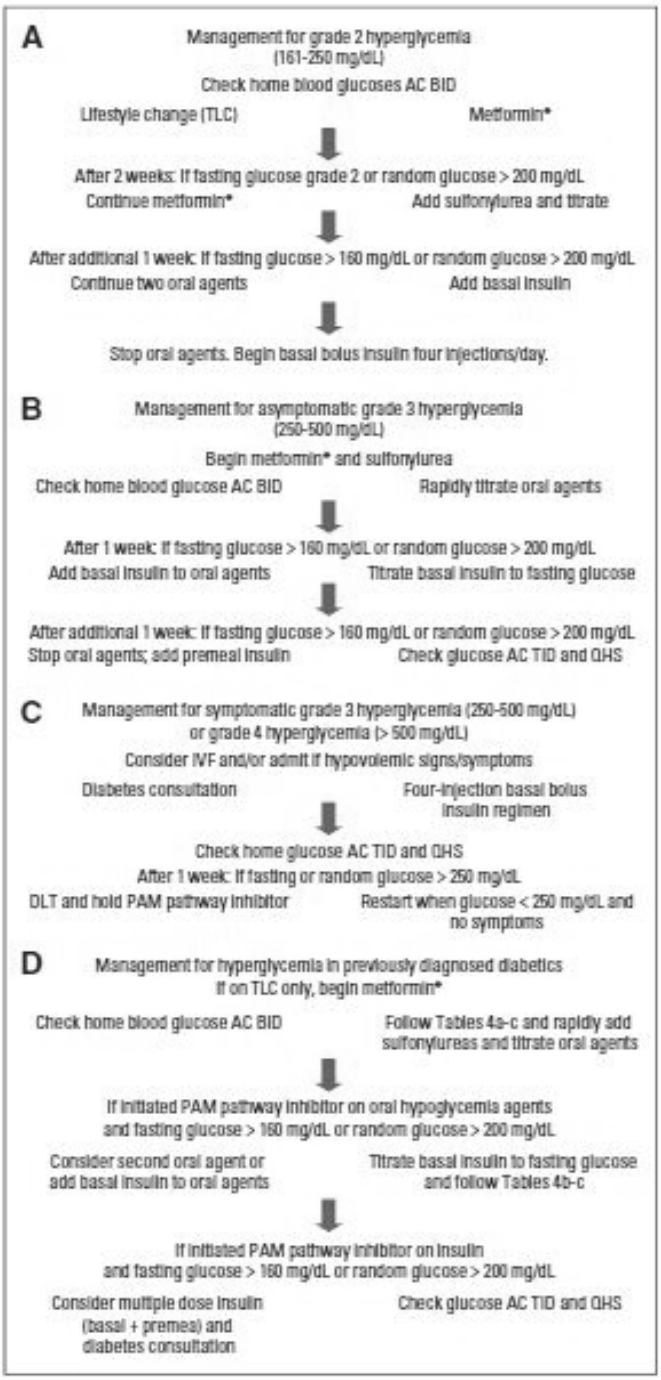
Scenario	Dose of LEE011 (mg/day)	Npat	Ntox	P(Over) NDC (inter-patient DE)	Next Dose Combination (inter-patient DE)	P(Over) NDC (intra-patient DE)	Next Dose Combination (intra-patient DE)
1	100	3	0	0.157	200	0.094	150
2	100	3	1	0.166	100	0.319	150
3	100	3	2	0.129	50	0.129	50
4	100 200	3 3	0 1	0.225	200	0.387	300
5	100 200	3 3	0 2	0.146	100	0.146	100
6	100 100	3 3	1 0	0.163	150	0.163	150
7	100 100	3 3	1 1	0.198	100	0.391	150
8	100 100	3 3	1 2	0.092	50	0.092	50
9	100 200 200	3 3 3	0 1 0	0.184	300	0.184	300
10	100 200 100	3 3 3	0 2 0	0.066	100	0.265	150
11	100 100 150	3 3 3	1 0 0	0.203	300	0.109	200
12	100 100 100	3 3 3	1 1 0	0.228	150	0.228	150

Within Table 14-4 to Table 14-7 "P(Over) NDC" represents the probability that the true DLT rate for the next recommended dose combination exceeds or equals to 35%. Note, the actual number of evaluable patients per cohort is variable (see Section 6.2.3) and the recommendations during the study will depend on the number of evaluable patients at each dose combination and the observed number of DLT.

In summary, the models are showing appropriate behaviors, leading to decisions that are in agreement with clinical sense: progressive increase of the 3rd compound doses if no DLT is observed, enrolling of a new cohort at the same dose combination when 1 DLT out of 3 patients is reported and decrease when more than 1 DLT out of 3 patients is reported in a cohort. Recommended dose levels for intra-patient dose escalation are usually higher compared to inter-patient dose escalation, when the increase is within 50%.

14.2 Appendix 2 - Guidelines for the treatment of study drug combination induced hyperglycemia

Figure 14-1 Algorithm for the treatment of study drug combination induced hyperglycemia



Management of (A) grade 2 hyperglycemia (161 to 250 mg/dL), (B) asymptomatic grade 3 hyperglycemia (250 to 500 mg/dL), (C) symptomatic grade 3 hyperglycemia (250 to 500 mg/dL) or grade 4 hyperglycemia (> 500 mg/dL), and (D) hyperglycemia in previously diagnosed diabetics.

NOTE. Recommendations based on experience and expertise of the panel. Some patients are able to stop insulin or sulfonylureas later with therapeutic lifestyle changes (TLC), after acute lowering of blood glucose or after discontinuation of phosphoinositide 3-kinase–Akt–mammalian target of rapamycin (PAM) pathway inhibitors. AC, before meals; DLT, dose-limiting toxicity; IVF, intravenous fluids; QHS, before every bedtime. (*) Do not use metformin if creatine > 1.3 mg/dL (women) or > 1.4 mg/dL (men) or if any state of decreased tissue perfusion or hemodynamic instability is present (eg, heart failure); hold metformin for computed tomography scans; GI symptoms may occur with initiation but usually subside after first week (Busaidy et al 2012).

14.3 Appendix 3 - Guidelines for the treatment of study drug combination induced diarrhea

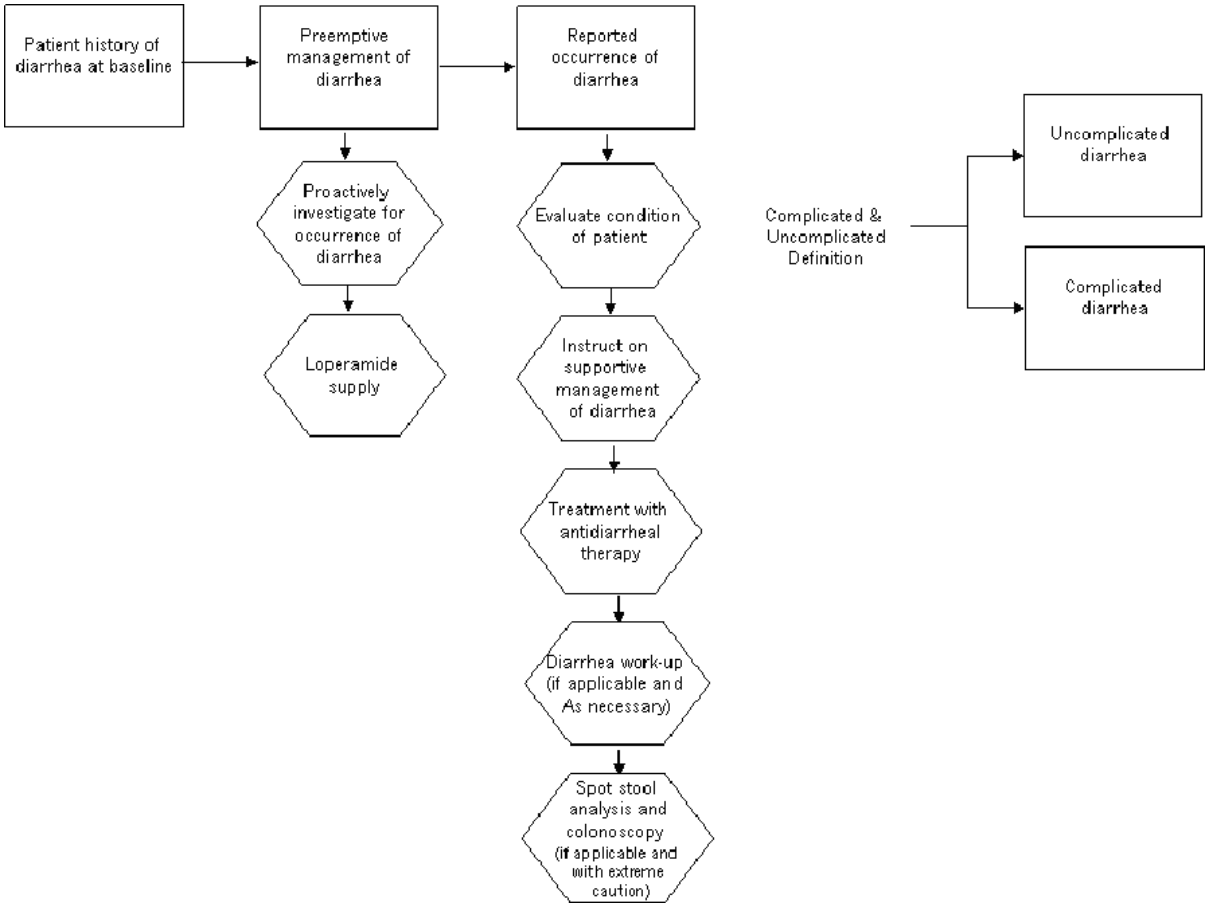
Anti-diarrhea therapy

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as well as proper management of diarrhea is mandatory. The following section outlines the recommended algorithm for management and treatment of study drug-induced diarrhea (Figure 14-2) (Benson 2004, Kornblau 2000, Wadler 1998).

Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. It is recommended that the anti-diarrhea treatment algorithm detailed in this document will be applied. All concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications/Non-drug Therapies eCRF. It is recommended that patients be provided loperamide tablets. It is mandatory that patients are instructed on the use of loperamide at cycle 1 in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide (initial administration of 4mg, then 2mg every 4 hrs (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the site should ensure that the patient understood the instructions. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms.

Refer to detailed guidelines for the treatment of persisting diarrhea grade 1 or 2 and severe diarrhea grade 3 or 4 below:

Figure 14-2 Algorithm for management and treatment of study drug-induced diarrhea



Patient history of diarrhea

At screening, the patient's history of diarrhea should be reviewed and the patient should be appropriately informed of drug-induced diarrhea and its management:

- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions;
- Stop all diarrheogenic agents at screening if possible, otherwise exclude from trial;
- Instruct patients regarding risk of developing diarrhea;
- Perform baseline clinical/laboratory studies according to the trial protocol (e.g. one could rule out carrier state of Salmonella spp., Clostridium difficile, Campylobacter spp., Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in immunosuppressed patients);

Explain the frequency of diarrhea and its relationship to NCI CTCAE grading (Table 14-8)

Table 14-8 NCI CTCAE v4.0 grading of diarrhea for patients without ileostomy/colostomy

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life threatening consequences; urgent intervention indicated	death

Preemptive management of diarrhea

Proactively investigate for occurrence of diarrhea

Educate patient

1. Remind patients at each visit to contact the site immediately upon the first sign of loose stool or symptoms of abdominal pain. Additionally, at the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea-related symptoms. If symptoms were experienced by the patient, then the site should question the patient regarding the actions taken for these symptoms and re-instruct as necessary.
2. In addition to dietary modification, the patients should be instructed on early warning signs (e.g. severe cramping → severe diarrhea, fever with diarrhea → infection). Patients should be instructed on what to report to the investigator if possible (i.e. number of stools, stool composition, stool volume) and how to report symptoms of life-threatening sequelae (eg, fever or dizziness on standing).
3. Contact the patient 2 times a week after the start of study treatments to detect diarrhea early during at least the first 2 cycles. If no problems occur, instruct the patient to call when a problem does arise.

Loperamide supply

- It is recommended that patients are provided a sufficient supply of loperamide tablets with the administration of study treatments at the start of each cycle in case the patient experiences diarrhea. When loperamide is provided to patients, it is mandatory that patients are instructed at each cycle in detail on the use of loperamide in order to manage signs or symptoms of diarrhea at home. The site should ensure that the patient understood the instructions.
- Patients should be instructed to start oral loperamide at the first sign of loose stool or symptoms of abdominal pain.

Multiple events of diarrhea may occur throughout the duration of treatment. When each occurrence of diarrhea is first reported, the following steps to manage the event are recommended:

Evaluate condition of patient

- Obtain history of onset and duration of diarrhea including a description of the number of stools and stool composition (e.g. watery, blood or mucus in stool);
- Assess patient for fever, abdominal pain/cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration);

Determine if diarrhea is complicated vs. uncomplicated (Table 14-9);

- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods).

For study treatment dose adjustment refer to Section 6.3.1.

Table 14-9 Uncomplicated vs. complicated diarrhea- defining symptoms

Uncomplicated	Complicated

• CTCAE Grade 1-2 diarrhea with no complicating signs and symptoms	• CTCAE Grade 3-4 diarrhea
	• CTCAE Grade 1-2 with the following complicating signs or symptoms:
	  • Moderate to severe cramping
	  • Grade ≥ 2 nausea/vomiting
	  • Decreased performance status
	  • Fever
	  • Sepsis
	  • Neutropenia
	  • Frank bleeding
	  • Dehydration
	  • Unresolved diarrhea after 48 hrs of treatment with loperamide (including high dose administration) and initiation of second-line treatment

Instruct on the supportive management of diarrhea (diet and other related concomitant medications)

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (like Metamucil®), and stool softeners (i.e, docusate sodium; Colace®)
- Stop high-osmolar food supplements such as i.e, Ensure® Plus and i.e, Jevity® Plus (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (like i.e, water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (i.e, bananas, rice, applesauce, toast)

Treatment with anti-diarrhea therapy

Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. It is strongly recommended that the following anti-diarrhea treatment algorithm outlined in Table 14-10 and Table 14-11 be used. Note: all concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications/Non-drug Therapies eCRF.

Loperamide is the first-line treatment of diarrhea (any Grade) in this recommended algorithm. Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea and related signs/symptoms. Upon treatment with any anti-diarrhea agents, the patient's response to treatment should be observed and appropriately documented in the source document and eCRF.

- Table 14-10 outlines the recommended treatment for diarrhea Grade 1 and 2.
- Table 14-11 outlines the recommended treatment for diarrhea Grade 3 and 4.

NOTE: Although the use of the Novartis product Sandostatin® (octreotide acetate) is included in the diarrhea management algorithm outlined in this protocol, please be advised it is not approved by the FDA or other health authorities for the treatment of chemotherapy-induced diarrhea (CID). The use of Sandostatin® or any other drug for the treatment of CID is at the discretion of the physician investigator. Please review the Sandostatin® full prescribing information for important safety information.

Diarrhea workup

If applicable and as necessary, perform appropriate tests (i.e., CBC and electrolytes, stool work-up, abdominal exam) for patients with persisting (> 48 hrs) CTCAE Grade 1-2 diarrhea not requiring hospitalization (AGA Technical Review on the Evaluation and Management of Chronic Diarrhea 1999). Patients with CTCAE Grade 3-4 diarrhea should have CBC, electrolytes and stool work-up completed with hospitalization.

1. **Spot stool analysis** [This may be obtained under discretion of the physician]
   - Collect stool and separate it from the urine (use special containers, analysis immediately, freeze samples for future analysis);
2. Analyze the following:
   - Blood from stool;
   - Fecal leukocytes (Wright's staining and microscopy);
   - C. difficile toxin;
   - Fecal cultures including the tests mentioned in section Patient history of diarrhea plus Shigella and pathogenic E.coli-enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water), infectious colitis.
3. Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

Table 14-10 Treatment of diarrhea Grade 1-2 (uncomplicated)

Timeline		Treatment
Initial Treatment		Treat with standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) or after each unformed stool.
12-24 hrs after initial onset of diarrhea	Diarrhea resolved	Continue instructions for dietary modification and gradually add solid foods to diet; Discontinue loperamide after 12-hrs diarrhea-free (Grade 0) interval.
	Diarrhea unresolved	If diarrhea Grade 1-2 (uncomplicated) Escalate to high dose loperamide: 2 mg every 2 hrs (max. of 16 mg/day) or after each unformed stool; Monitor patients' condition (to rule out dehydration, sepsis, ileus); Observe patient for response to anti-diarrhea treatment and reassess 12 to 24 hrs later. If patient progresses to complicated CTCAE Grade 1-2 (i.e. presence of fever, dehydration, neutropenia) or CTCAE Grade 3-4 with or without symptoms - refer to Table 14-4 for treatment guidance. Note: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.
24-28 hrs after the initial onset of diarrhea	Diarrhea resolved	Continue instructions for dietary modification and gradually add solid foods to diet; Discontinue loperamide and/or other treatment after 12-hrs diarrhea-free (Grade 0) interval. Note: Use of high-dose loperamide can result in paralytic ileus if administered in the absence of diarrhea
	Diarrhea unresolved	If diarrhea Grade 1-2 is still unresolved after 24 hrs high-dose loperamide (48 hrs total treatment with loperamide): Evaluated patient in an office/outpatient center for a medical/laboratory check and selected workup (see 'Diarrhea workup' within this section for additional recommended tests); Hospitalization may need to be considered. Replace fluids and electrolytes as appropriate. Discontinue loperamide and begin a second-line agent which can be an opiate or octreotide acetate: Opiates (choose a or b) Opium tincture (deodorized tincture of opium or opium 10% tincture) contains the equivalent of 10 mg/mL of morphine with a recommended dose of 0.6 mL up to four times a day. Treatment with opium tincture should be stopped 24 hrs after resolution of diarrhea to Grade 0. Paregoric (Camphorated Tincture of Opium®) contains the equivalent of 0.4 mg/mL morphine with a recommended dose of 5 mL in water up to four times a day. Treatment with Paregoric should be stopped 24 hrs after resolution of diarrhea to Grade 0. Important Note: Due to the differences in morphine content, special care must be taken to avoid potential overdose. Opium tincture is 25 times more concentrated (at 10 mg/mL of morphine) than Paregoric (at 0.4 mg/mL).

Timeline		Treatment
		If opium tincture is not available administration of codeine phosphate can be considered as an alternative. The recommendations below are provided as a general guidance however, physician discretion is advised. The use of codeine phosphate is not mentioned in the recommended guidelines for the treatment of CID published by Benson et al (2004), or by Wadler et al (1998), however, the WHO Model Formulary 2004 provides recommendations for codeine phosphate in the treatment of acute diarrhea. The recommended dose of codeine phosphate for the treatment of acute diarrhea is: Starting dose: 1 mg/kg every 6 hrs (may be increased up to 1.5 mg/kg every 6 hrs in the absence of a clinical improvement within 12 to 24 hrs). Maximum dose: 6mg/kg per 24 hrs. The doses and administration schedules above are recommended for the treatment of acute pain with codeine phosphate and may differ according to country. The WHO Model Formulary 2004 recommends 30 mg PO every 3-4 times daily. Treatment with codeine phosphate should be stopped 24 hrs after resolution of diarrhea to Grade 0. Octreotide acetate Recommended dose of octreotide acetate is 100-150 µg TID (every 8 hrs) with dose escalation up to 500 µg TID. Treatment should be administered until patient has experienced 24-hr diarrhea-free (Grade 0) interval. This recommendation is based upon published data supporting its use for CID (see Benson 2004). Important Note: Caution should be paid to a potential very quick decrease of water and electrolyte loss after the onset of treatment with octreotide acetate. It is advised to monitor the stool volume every 4 to 6 hrs and to adapt the administration of fluids and electrolytes accordingly. If diarrhea persists with the second-line agent (complicated CTCAE Grade 1-2 diarrhea) or has progressed to NCI CTCAE Grades 3-4, admit to hospital and employ measures described in Table 14-4.

Table 14-11 Treatment of diarrhea CTCAE Grade 3-4 or complicated diarrhea CTCAE Grade 1-2

Diarrhea Grade 3 or 4
Admit to hospital.
Stop loperamide and opiates if not already stopped.
Administer IV fluids and electrolytes as needed.
Administer SC octreotide acetate (100-150 µg TID - every 8 hrs)
NOTE: Caution should be paid to a potential very quick decrease of water and electrolyte loss after the onset of treatment with octreotide acetate. It is advised to monitor the stool volume every 4 to 6 hrs and to adapt the administration of fluids and electrolytes accordingly.
If there is no improvement in the diarrhea after 24 hrs, dose escalate octreotide acetate up to 500 µg TID SC until diarrhea is controlled.
Medical/laboratory check and selected workup if patient does not need hospitalization (see 'Diarrhea workup' within this section for additional recommended tests)
Monitor/Continue IV fluids and antibiotics as needed. Treatment should be discontinued within 24 hrs after the resolution of diarrhea.
For study drug dose adjustment see Criteria for dose modifications in the study protocol.

14.4 Appendix 4 - Guidelines for the treatment of study drug combination induced skin toxicity

14.4.1 Rash

Skin disorder/rash has been observed in the ongoing studies of single-agent LGX818, BKM120 and MEK162 and thus is recognized as a potential overlapping toxicity associated with the concurrent use of both compounds. The majority of these events were CTCAE Grade 1 or 2, but also dose-limiting as Grade 3 at the 80mg BID dose for MEK162.

The results of the STEPP study (Mitchell 2009; Piperdi 2009) support the use of pre-emptive skin treatment for patients at risk of treatment induced skin toxicity. In this study, the pre-emptive skin treatment regimen reduced the incidence of specific CTCAE Grade ≥ 2 skin toxicity by more than 50% as compared to the group who received only reactive skin toxicity treatment. In this study, patients will not initially receive prophylactic treatment for skin toxicity during Cycle 1. However, prophylactic treatment for skin toxicity may be introduced in subsequent cycles of treatment and in new patients if at least one patient has experienced CTCAE Grade 3 or greater skin toxicity, or if at least two patients have experienced such toxicities that are CTCAE Grade ≥ 2. Prophylactic supportive therapy for skin toxicity (i.e. initiated 24 hrs prior to study drug combination) including skin moisturizers, sunscreen (PABA free, SPF ≥ 15, UVA/UVB protection), topical steroid (1% hydrocortisone cream), and doxycycline (100 mg BID) may be initiated in all patients at the dose levels where these toxicities have been observed and may be advised to all further patients. Effective medications also include antihistamines, topical corticosteroids and low-dose systemic corticosteroids (the latter should be used with caution due to the increased risk of hyperglycemia).

The treatment algorithm is as follows:

Mild rash (CTCAE Grade 1)

- Treatment with LGX818/MEK162 or LGX818/MEK162 + BKM120 should be maintained at the current dose.
- Topical hydrocortisone (1% or 2.5% cream) for macular rash and/or topical clindamycin (1%) for pustular rash is recommended.
- The patient should be reassessed after 2 weeks.

Moderate rash (CTCAE Grade 2)

- Treatment with LGX818/ MEK162 should be maintained at the current dose, and the rash should be closely monitored for change in severity.
- Treatment with LGX818/MEK162 + BKM120 should be omitted, or reduced whether this is first occurrence, or second occurrence
- Doxycycline or minocycline are not recommended due to phototoxicity and could be replaced with oxytetracycline or lymecycline. However, if doxycycline or minocycline are used, precaution measurements should be taken (i.e., avoid direct exposure on sun, use of sunglasses, sunscreen, etc.). The recommendation is: topical clindamycin (1%) plus either

hydrocortisone (2.5% cream) or pimecrolimus (1% cream) plus oxytetracycline (500 mg twice daily) or lymecycline (408 mg QD).

Severe rash (CTCAE Grade 3-4)

CTCAE Grade 3

- The dose of LGX818/MEK162 should be omitted until resolved to CTCAE Grade ≤ 1, in line with protocol recommendations, and the rash should be closely monitored for any change in severity. If skin toxicity CTCAE Grade 3 is not resolved within 7 days, discontinue patient from study drug treatment.
- Treatment with LGX818/MEK162 + BKM120 should be omitted until resolved to CTCAE Grade ≤ 1, and then reduced, if this is the first occurrence, or omitted and patients discontinued from study drug treatment if this is the second occurrence.
- In addition to the interventions recommended for moderate rash, prednisolone may be given (with caution due to risk of hyperglycemia) as a reducing dose regimen (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day to 0).

CTCAE Grade 4

- If skin toxicity CTCAE Grade 4 occurs the dose of LGX818/MEK162 or LGX818/MEK162 + BKM120 should be omitted and patients discontinued from study drug treatment.

Table 14-12 Recommended treatment of skin toxicity

Mild Rash (Grade 1) Dry Skin Nail changes Pruritus Desquamation Acneiform	Topical hydrocortisone 1% or 2.5% and/or Clindamycin 1% gel
Moderate Rash (Grade 2) Dry Skin Nail changes Pruritus Desquamation Acneiform	Topical clindamycin (1%) plus either hydrocortisone (2.5% cream) or pimecrolimus (1% cream) plus oxytetracycline (500 mg twice daily) or lymecycline (408 mg QD).
Severe Rash (Grade 3-4) Dry Skin Nail changes Pruritus Desquamation Acneiform	Hydrocortisone 2.5% cream or Clindamycin 1% gel or Pimecrolimus 1% cream plus oxytetracycline (500 mg twice daily) or lymecycline (408 mg QD) plus prednisolone (with caution due to risk of hyperglycemia) (25 mg for 7 days, decreasing the dose by 5 mg/day every day).
Adapted from Thatcher (2009).	

14.4.2 Hand Foot Skin Reaction

As HFSR has been reported in some patients during LGX818 treatment, it is recommended that patients are educated prior to starting study treatment which activities to avoid and on supportive measures for prevention and/or management of HFSR. Recommendations are summarized below in Table 14-13. Furthermore the patient should be treated at the first symptoms according the institutional standards of care. A visit at a podiatrist may also be recommended at the discretion of the investigator.

Table 14-13 Supportive care for the prevention and management of HFSR

Stage	Recommendations
Prior to treatment	Educate the patient about the early signs and symptoms of HFSR and discuss the importance of early reporting.
Prevention of HFSR	Monitor the patient for signs and symptoms of HFSR. Instruct the patient to: • Apply emollient cream regularly to hands and feet • Avoid skin irritants (e.g. perfumes, alcohol, harsh cleaning agents) • Wear cotton socks or gloves to bed to enhance the absorption of creams • Avoid tight, irritating or ill-fitting clothing and shoes[a] • Avoid the use of band aides or other types of adhesive bandages or tape • Avoid repetitive activity or staying in one position for long periods of time • Keep the skin uncovered when possible to minimize perspiration • Wear rubber gloves while doing dishes • Pat (do not rub) skin dry with towels • Avoid extremes of temperature, pressure and friction • Avoid performing mechanically stressful manual work • Minimise exposure to strong, direct sunlight • Elevate affected limbs
Treatment of HFSR	1) Ensure that patient follows treatment interruption or dosage reduction guidelines 2) Monitor the patient for progression/resolution of HFSR 3) Prescribe analgesics if necessary 4) Instruct the patient to: • Continue the use of prevention strategies • Cushion sore skin • Submerge hands and feet in cool water baths or apply cold compresses for relief
[a] Wear loose-fitting clothing made of soft, natural fabrics and shoes that are wide and comfortable. Avoid tight belts, panties and bras. This Table is adapted from (Von Moos et al 2008).	

14.5 Appendix 5 - Phosphate-lowering therapy

Since the administration of BGJ398 may be associated with hyperphosphatemia and given the potential role of phosphorus and calcium in vascular calcifications, accepted limits of serum phosphorus and tCa x Pi have been predefined.

The *in-vivo*-solubility product of tCa x Pi is about $58mg^2/dLl^2$ and higher values involve a significant risk of calcium phosphate precipitation. Phosphorus retention of serum Pi > 6.5 mg/dL is associated with a significantly increased mortality rate of ESRD patients and several studies in this population have reported that tCa x Pi values > 55-$60mg^2/dL^2$ significantly increase the risk of cardiovascular calcification, suggesting that these levels should be the upper limit of acceptability.

The management of hyperphosphatemia includes reduction of phosphorus intake in sufficiently alimented cancer patients and increasing doses of the aluminum- and calcium-free phosphorus binder sevelamer and the phosphaturic agent acetazolamid, as described below.

If serum Pi > 5.5 mg/dL has been demonstrated, this parameter along with serum concentrations of ionized and total calcium as well as serum creatinine levels will continue to be monitored at least weekly. Serum 1,25-$(OH)_2$Vit D_3 and iPTH levels as well as urinary phosphate and calcium have to be determined as medically indicated. Serum phosphorus lowering therapy consisting dietary phosphate intake restriction, oral phosphate binders and phosphaturic agents should be applied as follows:

Serum Pi > 5.5 - 7.5 mg/dL:

- Restriction of dietary phosphate intake to 600 - 800 mg/day, if BMI ≥ 21kg/m2.
- Sevelamer 1 tablet (800mg) per meal; i.e. 3 x 800 mg/day.

Serum Pi > 7.5 - 9.0mg/dL :

- Restriction of dietary phosphate intake to 600 - 800 mg/day, if BMI ≥ 21kg/m2.
- Sevelamer 1- 2 tablets per meal; i.e. 3 x 1200 mg/day.

Serum Pi > 9.0 mg/dL :

- Restriction of dietary phosphate intake to 600 - 800 mg/day, if BMI ≥ 21kg/m2.
- Sevelamer 2 tablets per meal; i.e. 3 x 1600mg/day.
- Acetazolamide 2- 3x 250mg/day.

If serum phosphorus increases > 7.0mg/dL despite phosphorus lowering therapy over at least 14 days the BGJ398 dose must be reduced and eventually permanently discontinued if not decreased to ≤ 5.5 mg/dL within 7 days after suspending BGJ398. All patients will continue to be followed-up until resolution to serum phosphorus ≤ 5.5 mg/dL or baseline or stabilization

14.6 Appendix 6 - Guidelines for the treatment of study drug 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 6-9.

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 7.2.2.7.

If question 9 in the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit treatment with study drug and refer the patient for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading to 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 (e.g. Day 15 of Cycle 1, Day 1 and Day 15 of Cycles 2 and 3, Day 1 of each subsequent cycle, and at the End of Study 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

Table 14-14 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 the Sponsor to be used as source documents.

Table 14-15 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 the Sponsor to be used as source documents.

14.7 Appendix 7 - List of prohibited and concomitant medications to be used with caution

The substrates in Table 14-16 through Table 14-28 do not represent exhaustive lists of substrates, inducers or inhibitors.

Table 14-16 Prohibited concomitant therapy for LGX818/MEK162 combination

CYP2C9 substrates with narrow therapeutic index			
See Table 14-21.			
Strong CYP3A4 inhibitors			
See Table 14-22.			
Enzyme inducing anti-epileptic drugs (EIAEDs)			
carbamazepine	ethotoin	felbamate	fosphenytoin
phenytoin	primidone	topiramate	phenobarbital

Table 14-17 Additional prohibited concomitant therapy for LGX818/MEK162 + BKM120

Strong and Moderate CYP3A4/5 inhibitors
See Table 14-22.
Strong & Moderate CYP3A4/5 inducers
See Table 14-22.
Drugs with known risk for to QT interval prolongation or Torsades de Pointes (TdP) as well as sensitive CYP3A substrates with a possible or conditional risk for TdP
See Table 14-26.

Table 14-18 Additional prohibited concomitant therapy for LGX818/MEK162 + LEE011

Strong CYP3A4 inducers or inhibitors			
See Table 14-22.			
Substrates of CYP3A4/5 with a narrow therapeutic index (NTI)			
See Table 14-22.			
Medications with known QTc prolongation effect			
See Table 14-26.			
Drugs with known risk for Torsades de Pointes (TdP)			
See Table 14-26.			
Herbal preparations			
St. John's wort	Kava	Ephedra (ma huang),	Gingko biloba
Dehydroepiandrosterone (DHEA)	Yohimbe	Saw palmetto	Ginseng
Black cohosh			

Table 14-19 Additional prohibited concomitant therapy for LGX818/MEK162 + BGJ398

Strong CYP3A4 inducers and inhibitors
See Table 14-22.
Medications with known QTc prolongation effect
See Table 14-26.
Drugs with known risk for Torsades de Pointes (TdP)
See Table 14-26.

Table 14-20 Additional prohibited concomitant therapy for LGX818/MEK162 + INC280

CYP3A4, CYP1A2, CYP2C8 or CYP2C19 substrates with narrow therapeutic index
See Table 14-21.
Strong CYP43A4 inhibitors and inducers
See Table 14-23, Table 14-24
Long acting proton pump inhibitors
See Table 14-28.

Table 14-21 Narrow therapeutic index substrates and substrates of CYP3A4, CYP2B6, CYP2C8 and CYP2C9, CYPC19 and CYP1A2

This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. This might not be an exhaustive list.

Category	Drug Names
Narrow Therapeutic index substrates of CYP1A2	theophylline, tizanidine (also sensitive)
Sensitive Substrates of CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, selegiline, tacrine, tizanidine
Other Substrates of CYP1A2	clozapine, melatonin, ropivacaine
Narrow Therapeutic index substrates of CYP2B6	None reported to date
Sensitive Substrates of CYP2B6	bupropion, efavirenz
Other Substrates of CYP2B6	methadone, nevirapine, sibutramine
Narrow Therapeutic index substrates of CYP2C8	paclitaxel
Sensitive substrates of CYP2C8	repaglinide
Other Substrates of CYP2C8	amodiaquine, atorvastatin, buprenorphine, carbamazepine, enzalutamide, loperamide, montelukast, pioglitazone, rosiglitazone
Narrow Therapeutic index substrates of CYP2C9	phenytoin, warfarin (also sensitive)
Sensitive substrates of CYP2C9	celecoxib
Other Substrates of CYP2C9	diclofenac, losartan, tolbutamide
Narrow Therapeutic index substrates of CYP2C19	(S)-mephenytoin (also sensitive)
Sensitive substrates of CYP2C19	clobazam, dexlansoprazole, diazepam, gliclazide, lansoprazole, (R)-lansoprazole, (S)-lansoprazole, (R)-mephobarbital, omeprazole, (R)-omeprazole, pantoprazole, (+) pantoprazole, rabeprazole, tilidine
Other Substrates of CYP2C19	antipyrine, bosentan, dapasone, dexloxiglumide, diclofenac, esomeprazole, flurbiprofen, glyburide, losartan, moclobemide, ospemifene, phenytoin, pitavastatin, proguanil, quinidine, rabeprazolerosuvastatin, sildenafil, tolbutamide, voriconazole

Category	Drug Names
Narrow Therapeutic index substrates of CYP2D6	pimozide, thioridazine
Sensitive substrates of CYP2D6	atomoxetine, desipramine, dextromethorphan, doxepin, encainide, enclomiphene, methoxyphenamine, metoprolol, nebivolol, nefazodone, perhexiline,perphenazine, repinotan, resperidone, tolterodine, traxoprodil, trimipramine, tropisetronnicergoline, vernakalant
Other Substrates of CYP2D6	aripiprazole, brofaromine, buprenorphine, delavirdine, duloxetine, iloperidone, imipramine, methadone, nortriptyline, oxycodone, paroxetine, pimozide, propranolol, ramosetron, risperidone, tamsulosin, trazodone, venlafaxine
Narrow Therapeutic index substrates of CYP3A	Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, lomitapide, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine
Sensitive substrates of CYP3A	alpha-dihydroergocryptine, alfentanil, alisoporivir, almorexant, apixaban (doses < 2.5 mg only),aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, ibrutinib, indinavir, ivacaftor, levomethadyl, lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, ticagrelor, terfenadine, ticagrelor, tilidine,tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, vicriviroc, voclosporin.
Other substrates of CYP3A	alprazolam, ambrisentan, amlodipine, antipyrine, aripiprazole, artemether, avosentan, boceprevir, bosentan, buprenorphine, carbamazepine, dexloxiglumide, dextromethorphan, diazepam, docetaxel, enzalutamide, gemigliptin, halofantrine, imipramine, lansoprazole, lidocaine, linagliptin, loperamide, loratadine, losartan, lurasidone, macitentan, methadone,mirodenafil, montelukast, morphine, nelfinavir, netupitant, nevirapine, nifedipine, nilotinib, nitrendipine, omeprazole, ospemifene, oxycodone, paclitaxel, pazopanib, pioglitazone, quinine, ranolazine, repaglinide, rifabutin, ritonavir, roflumilast, saxagliptin, selegiline, sertraline, sibutramine, sotrastaurine, telaprevir, theophylline, tirilazad, tolterodine, udenafil, ulipristal, vincristine, voriconazole

[1] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

[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).

[3] Other substrates are these that have shown an *in vivo* ≥2-fold increase in AUC with co-administration of an inhibitor based on the University of Washington DDI database.

Table 14-22 List of inhibitors and inducers of UGT1A1 to be used with caution

The knowledge of UGTs is much more limited compared to that of CYP450s; hence, substrates are not classified as sensitive and inhibitors/inducers are not yet classified as strong/moderate/weak. This list might not be exhaustive.

Category	Drug Names
UGT1A1 inhibitors	atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib, *silybum marianum* (herbal also known as milk thistle), *valeriana officinalis* (herbal)
UGT1A1 inducers	carbamazepine, rifampicin, testosterone propiate, cigarette smoke

Table 14-23 List of CYP inhibitors

The information presented on inhibitors is a compilation of the University of Washington DDI database and FDA DDI guidance. This list might not be exhaustive.

Category	Drug Names
Strong inhibitors[1] of CYP1A2	ciprofloxacin, clinafloxacin, enoxacin, fluvoxamine[8], oltipraz, rofecoxib, zafirlukast
Moderate inhibitors[2] of CYP1A2	etintidine, idrocilamide,methoxsalen, mexiletine, oral contraceptives (drospirenone, norgestimate, ethinyl estradiol), pipemidic acid, phenylpropanolamine, propafenone, propranolol, thiabendazole, zileuton
Weak inhibitors[3] of CYP1A2	acyclovir, allopurinol,antofloxacin, artemisinin, caffeine, cimetidine, curcumin[5], daidzein[5], disulfiram, echinacea[4], famotidine, grapefruit juice[5], grepafloxacin, hormone replacement therapy (estradiol+levonogestrel), interferon alpha/beta, norfloxacin, pefloxacin, peginterferon alpha, simeprivir,terbinafine, thiabendazole, ticlopidine[9], verapamil, viloxazine, zileuton
Strong inhibitors of CYP2C19	fluconazole[7], fluvoxamine[8], fluoxetine, ticlopidine[9]
Moderate inhibitors of CYP2C19	Efavirenz, esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole
Weak inhibitors of CYP2C19	allicin (garlic derivative)[5], armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole, oral contraceptives[10], tipranavir/ritonavir, simeprivir, clopidogrel
Strong inhibitors of CYP3A	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelasib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, VIEKIRA PAK2, voriconazole

Category	Drug Names
Moderate inhibitors of CYP3A	amprenavir, aprepitant, atazanavir, atazanavir/ritonavir,, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, duranavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole[7], fosamprenavir, grapefruit juice[11], imatinib, lomitapide, netupitant,nilotinib, schisandra sphenanthera[4], tofisopam, verapamil
Weak inhibitors of CYP3A	almorexant, alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, berberine[4], bicalutamide, blueberry juice[5], cilostazol, cimetidine, clotrimazole, clozoxazone, cranberry juice[5], cyclosporine, delavirdine, evrolimus, fluoxetine, fluvoxamine[8], fosaprepritantranolaxine, ginkgo[4], goldenseal[4], isoniazid, ivacaftor, lacipidine, linagliptin, nilotinib, oral contraceptives, pazopanib, peppermint oil[5], propiverine, ranitidine, ranolazine, resveratrol[5], roxithromycin, Seville orange[5], simeprevir, tabimorelin, tacrolimus, ticagrelor, tolvaptan, sitaxentan, teriflunomide, tipranavir/ritonavir, zileuton□

1. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold.
2. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
3. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-foldbut equal to or more than 1.25-fold.
4. Herbal product.
5. Food product.
6. Gemfibrozil also inhibits OATP1B1.
7. Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
8. Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A;
9. Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2.
10. Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
11. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

Table 14-24 List of CYP inducers

The information presented on inducers is a compilation of the University of Washington DDI database and FDA DDI guidance. This list might not be exhaustive.

Category	Drug Names
Strong inducers[1] of CYP1A2	None reported to date
Moderate inducers[2] of CYP1A2	montelukast, phenytoin, smokers versus non-smokers, rifampin, ritonavir, teriflunomide
Weak inducers[3] of CYP1A2	moricizine, nelfinavir, omeprazole, phenobarbital, tipranivir/ritonavir
Weak inducers of CYP2C9	aprepitant, bosentan, eslicarbazepine, lopinavir/ritonavir, phenobarbital, secobarbital, St. John's Wort[5]

Category	Drug Names
Strong inducers of CYP2C19	None reported to date
Moderate inducers of CYP2C19	enzalutamide, rifampin, tipranavir/ritonavir
Weak inducers of CYP2C19	artemisinin, carbamazepine, efavirenz, ginko[5], glycyrrhizin[5] St. John's Wort[5]
Strong inducers of CYP3A	avasimibe, carbamazepine, enzalutamide, mitotane,phenytoin, rifampin, St. John's wort[5], rifabutin, phenobarbital
Moderate inducers of CYP3A	bosentan, efavirenz, etravirine, genistein[6], lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat[4], talviraline[4], thioridazine, tipranavir
Weak inducers of CYP3A	amprenavir, aprepitant, armodafinil, bexarotene, boceprevir, brivacetam, clobazam, danshen[5], dexamethasone, echinacea[5], eslicarbazepine, garlic[5], gingko (ginkgo biloba)5, ginseng[5], glycyrrhizin[5], methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, pleconaril[4], primidone, quercetin[6], raltegravir, ritonavir, rufinamide, sorafenib, Stribild (combo of elvitegravir, cobicistat, emtricitabine, and tenofovir), sulfinpyrazone, telaprevir, terbinafine, ticagleror, ticlopidine, topiramate, troglitazone[4], vinblastine, vemurafenib, vicriviroc/ritonavir

1. A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%.
2. A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%.
3. A weak inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 20-50%.
4. Drugs not available in the US Market.
5. Herbal product.
6. Food product.

Table 14-25 List of BSEP inhibitors, P-gp inhibitors/inducers and P-gp, BCRP, MATE1, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 substrates

Substrate and inhibitor information presented on drug transporter substrates and inhibitors is from a compilation of the University of Washington DDI database, the FDA DDI guidance, and the UCSF-FDA Transportal database. This list might not be exhaustive.

Category	Drug Names
Strong BSEP inhibitors	Alectinib, atazanavir, bromocriptine, bosentan, clofaziminie, cerivastatin, fusidate, glibenclamide, glyburide, nefazadone, paritaprevir, pioglitazone, reserpine, rosiglitazone, sulindac, troglitazone (TGZ-sulfate), valinomycin
NTI substrates of P-gp[1]	digoxin, quinidine, paclitaxel, cyclosporine, sirolimus, tacrolimus, fentanyl, phenytoin
Substrates of Pgp (≥2X AUC change)[2]	aliskiren, ambrisentan, atorvastatin, atorvastatin acid, azithromycin, cerivastatin, colchicine, CP-481,715, cyclosporine, dabigatran, digoxin, docetaxel, domperidone, doxorubicin, fentanyl, fexofenadine, lapatinib, linezolid, loperamide, maraviroc, nevirapine, paclitaxel, proguanil, quinidine, ranolazine, ritonavir, saquinavir, simvastatin, sirolimus, sofosbuvir, tacrolimus, ticagrelor, voclosporin
Substrates of Pgp mentioned in US label[3]	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, boceprevir, bosentan, carvedilol, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, doxepin, doxorubicin, eribulin, everolimus, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, levofloxacin, linagliptin, losartan, maraviroc, mirabegron, moxifloxacin, naloxegol, nateglinide, nintedanib, olodaterol, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, quinine, ranolazine, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, sirolimus, sitagliptin, sorafenib, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
P-gp inhibitors	alogliptin, amiodarone[4], azithromycin[4], canaglifozin, captopril[4], carvedilol[4], clarithromycin[4], conivaptan[4], cremophor RH40, curcumin, diltiazem[4], dronedarone[4], elacridar[4], erythromycin[4], felodipine[4], fluvoxamine[4], ginko[4,5], indinavir[4], indinavir/ritonavir[4], itraconazole[4], ketoconazole, lapatinib, lopinavir/ritonavir, mibefradil[4], milk thisle[4,5], mirabegron, nelfinavir[4], nifedipine[4], nitredipine[4], paroxetine[4], propafenone, quercetin,[4], quinidine[4], ranolazine[4], rifampin[4], ritonavir[4], sequinavir/ritonavir[4], *schisandra chinesis* extract[4,5], simepravir, St. John's wort extract[4,5], talinolol[4], telaprevir[4], telmisartan[4], ticagrelor[4], tipranavir/ritonavir[4], tolvaptan[4], valspodar, vandetanib, verapamil[4], voclosporin
P-gp Inducers	avasimibe, carbamazepine, efavirenz, genistein[2], phenytoin, quercetin[2], rifampin, St. Johns wort extract[5]
BCRP Substrates	atorvastatin daunorubicin, doxorubicin, ethinyl estradiol, hematoporphyrin, imatinib, methotrexate[6], mitoxantrone, pitavastatin[6], rosuvastatin[6], SN-38 (irinotecan), simvastatin, sulfasalazine, sofosbuvir[1], topotecan[1], sulfasalazine[1]

Category	Drug Names
MATE1 and OCT2 substrates3	Acyclovir, amantadine, amiloride, apricitabine, carboplatin, cisplatin, cephalexin, cephradine, cimetidine, dofetilde, famotidine, fexofenadine, furamidine, ganciclovir, glycopyrronium, Ipratropium, lamivudine, linagliptin, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), oxyplatin, pindolol, plisicainide, pramsorafenib, ranitidine, topotecan, tropisetron, trospium, umeclidinium, varenicline and zidovudine.
OAT1/3 substrates	adefovir, anagliptin, bumetanide, captopril, chlorothiazide, cidofovir, dapagliflozin, furosemide, ganciclovir, ibuprofen, beta-lactam antibiotics, methotrexate, olmesartan, pemetrexed, pravastatin, quinaprilat, ranitidine, rosuvastatin, tetracycline, topotecan-hydroxyl acid, valacyclovir, zidovudine, zonampanel, tenofovir
OCT1/2 substrates	6-beta-hydroxycortisol, amantadine, carboplatin, cisplatin, histamine, lamivudine, linagliptin, metformin, oxyp[latin, oxybutynin, phenformin, picoplatin, pramsorafenib, tropisetron, trospium, varenicline, umeclidinium
OATP1B1 substrates	ambrisentan, anacetrapib asunaprevir, atorvastatin, atrasentan, benzylpenicillin, bosentan, bromociptine ,caspofungin, cerivastatin, danoprevir, empangliflozin, enalapril, ezetimibe, fexofenadine, fimasartan, fluvastatin, maraviroc, methotrexate, olmesartan, pitavastatin, pravastatin, repaglinide, rifampicin, rosuvastatin, simvastatin acid, SN-38; temocapril, troglitazone, valsartan
OATP1B3 substrates	asunaprevir, atrasentan, bosentan, danoprevir, digoxin, docetaxel, empangliflozin, enalapril, erythromycin, fexofenadine, fluvastatin, imatinib, methotrexate, olmesartan, ouabain, paclitaxel, pitavastatin, pravastatin, rifampicin, rosuvastatin, telmisartan, SN-38; thyroxine (T4), valsartan

[1]These drugs have both a narrow therapeutic index and an *in vivo* DDI outcome ascribed at least in part ascribed to Pgp (inhibition or induction) that exceeds a 20% change in AUC.

[2]These drugs have *in vivo* DDI outcomes (inhibition) which are ≥2x increase in AUC and are at least in part ascribed to Pgp.

[3]The US labels for these drugs have specific language on *in vivo* Pgp substrate status.

[4]Dual P-gp and CYP3A4 inhibitor

[5]Herbal medication.

[6]Have been shown to have DDI *in vivo*, others are reported as substrates *in vitro*.

Table 14-26 List of QT prolonging drugs

TdP Risk	Generic Name
Known[1]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, cocaine, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol, procainamide, propofol, quinidine, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib
Possible[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine ,atazanavir, atomoxetine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, crizotinib,,clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gatifloxacin, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, , lapatinib, lenvatinib, leuprolide, loperamide,lithium, mifepristone, mirabegron, mirtazapine, moexipril, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimirtinib, ondansetron (p.o. only at 4 mg or 8 mg), oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, pipamperone, promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, sertindole, sorafenib, sunitinib, telavancin, tetrabenazine, tizanidine, tolterodine, toremifene, tramadol, trimipramine, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
Conditional[3]	amantadine, amisulpride, amitriptyline, amoxapine, chloral hydrate, diphenhydramine, doxepin, fluoxetine, furosemide (frusemide), galantamine, hydrochlorothiazide, Hydroxychloroquine hydroxyzine, indapamide, itraconazole, ivabradine (on non US mkt), ketoconazole, metoclopramide, metronidazole, nelfinavir, pantoprazole, paroxetine, posaconazole, quinine sulfate, ritonavir, sertraline, solifenacin, telaprevir, torsemide (torasemide), trazodone, voriconazole

[1] Known risk: Substantial evidence supports the conclusion that these drugs prolong the QT interval AND are clearly associated with a risk of TdP, even when taken as directed in official labeling

[2] Possible risk: Substantial evidence supports the conclusion that these drugs can cause QT prolongation BUT there is insufficient evidence at this time that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP.

[3] Conditional risk: Substantial evidence supports the conclusion that these drugs are associated with a risk of TdP BUT only under certain conditions (e.g. excessive dose, hypokalemia, congenital long QT or by causing a drug-drug interaction that results in excessive QT interval prolongation).

(Check website https://www.crediblemeds.org/healthcare-providers/drug-list for the most updated list)

Table 14-27 List of prohibited enzyme-inducing anti-epileptic drugs

enzyme-inducing anti-epileptic drugs
carbamazepine, ethotoin, felbamate, fosphenytoin, Phenobarbital, phenytoin, primidone, topiramate

Table 14-28 List of long acting proton pump inhibitors

Long acting proton pump inhibitors
omeprazole, pantoprazole, lansoprazole

14.8 Appendix 8 - Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1)

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Release date:	29-Nov-2011
Authors (Version 3.1):	PPD
Authors (Version 3):	PPD
Authors (Version 2):	PPD
Authors (Version 1):	PPD

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
GBM	Glioblastoma multiforme
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

14.1.1 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 14.1.2 and the definition of best response in Section 14.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.18 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 14.1.28 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.

14.1.2 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.

14.1.3 Definitions

14.1.4 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 14.1.26.

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.

14.1.5 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 14.1.26.

14.1.6 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 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.

14.1.7 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 14.1.4.
- **Nodal target**: See Section 14.1.4.

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.

14.1.8 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 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.9 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.

14.1.10 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.

14.1.11 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.

14.1.12 Determination of target lesion response

Table 14-1 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]

[1.] SOD for CR may not be zero when nodal lesions are part of target lesions

[2.] 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

[3.] Methodology change See Section 14.1.6.

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 timepoint 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 14-1 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.

14.1.13 Determination of non-target lesion response

Table 14-2 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.

[1.] 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 14.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.14 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 14.1.15).
- 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 14.1.6.

14.1.15 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 14-3.

Table 14-3 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

[1.] This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2.] Once confirmed PR was achieved, all these assessments are considered PR.
[3.] As defined in Section 14.1.8.

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.

14.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.17 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

- 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 timepoint 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 timepoint 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).

14.1.18 Time to event variables

The protocol should state which of the following variables is used in that study.

14.1.19 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.

14.1.20 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.

14.1.21 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.

14.1.22 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.

14.1.23 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.

14.1.24 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 14.1.23. 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.

14.1.25 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 14.1.26).

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.

14.1.26 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 14-4.

Table 14-4 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 14.1.8.

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.

14.1.27 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 14.1.25, 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 14-5 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)

[1]=Definitions can be found in Section 14.1.25.
[2]=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25.
[3]=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 14-5 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.

14.1.28 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).

14.1.29 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).

14.1.30 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)

14.1.31 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

14.1.32 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 the Sponsor 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 the Sponsor elects 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.

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 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.

14.1.35 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 14.1.25). 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.

14.1.36 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.

14.1.37 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)'.

14.1.38 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

14.1.39 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 14-5)
- 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 14.1.25. 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.

14.1.40 References (available upon request)

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SIGNATURE PAGE (SPONSOR)

I have read and understand the contents of the clinical protocol for Clinical Study CLGX818X2109 dated 16 December 2019 and agree to meet all obligations of Array BioPharma Inc. as detailed in all applicable regulations and guidelines. In addition, I will ensure that the Principal Investigators are informed of all relevant information that becomes available during the conduct of this study.

PPD

_ _____ 17th December 2019

PPD MD Date

PPD