CLINICAL STUDY PROTOCOL

SECOMBIT

"Sequential Combo Immuno and Target therapy (SECOMBIT) study"

"A three arms prospective, randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) and combo target therapy (LGX818/MEK162) in patients with metastatic melanoma and BRAF mutation"

Principal Investigators (PI): **Dr. Paolo A. Ascierto**
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Sponsor: Fondazione Melanoma (ONLUS)
c/o Istituto Tumori Napoli
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Via Mariano Semmola 80131 Naples, Italy

CONFIDENTIAL

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Sponsor representative

Signature

22/OCT/2015
Date

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18/NOV/2015
Date

PROTOCOL APPROVAL

CLINICAL STUDY PROTOCOL

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I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practices and local regulations and requirements.

Investigator:

Site Number: _____

Name: _____

Signature: _____

Date: _____

ADDITIONAL TRIAL PERSONNEL/SITE INFORMATION

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PROTOCOL SYNOPSIS

Study Title	A three arms prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) and combo target therapy (LGX818/MEK162) in patients with metastatic melanoma and BRAF mutation.
Study ID	**SECOMBIT** (Sequential Combo Immuno and Target therapy study)
Number of participant centers	Participating sites: Approximately 20 sites in Italy and Europe **Study coordinator:** Paolo Antonio Ascierto e-mail: paolo.ascierto@gmail.com Tel: +39 0815903431 Fax: +39 0815903841 Mobile: +39 338 7402333
Phase	II
Study Hypothesis	To evaluate the best sequencing approach with the combination of target agents (LGX818 plus MEK162) and the combination of immunomodulatory antibodies (ipilimumab plus nivolumab) in patients with metastatic melanoma and BRAF V600 mutation.
Background and rationale	The combination BRAF (B-raf murine sarcoma viral oncogene homolog B1) inhibitor plus mitogen-activated protein kinase (MEK) inhibitor seems to be more effective in the V600 BRAF mutated advanced melanoma patients compared to treatment with the BRAF inhibitors alone. In fact, a phase I-II study (*Flaherty et al, 2012*) showed a better overall response rate (ORR) and progression-free survival (PFS) in the combination arm (dabrafenib plus trametinib) respect to the single agent treatment (dabrafenib): 76% and 9.4 months versus 54% and 5.8 months respectively. Another phase I study with a similar combination (vemurafenib plus cobimetinib) showed an ORR of 85% in vemurafenib-naïve patients (*Martinez Garcia et al, 2012*) Recently, the results of a phase I study about the combination ipilimumab plus nivolumab have been reported (*Wolchock et al, 2013*). In this study at the selected schedule (ipilimumab 3 mg/kg and nivolumab 1 mg/kg), 53% of patients had an objective response, all with tumor reduction of 80% or more. Reponses were durable, although longer follow-up is needed. A recent phase I study has shown a high rate of liver toxicity with the combo ipilimumab plus vemurafenib (*Ribas et al, 2013*) which makes difficult a combination with these two different drugs. Moreover, a better efficacy of the sequencing treatment BRAF inhibitors/ipilimumab vs. the single agent treatment was also observed; for this reason it was also suggested to start immunotherapy treatment in the BRAF V600 mutated melanoma population as first option, in order to increase the percentage of patients who can benefit from the sequencing (*Ascierto et al, 2012*; *Ascierto et al, 2013*), considering the possibility of a fast progression of the disease after the BRAF inhibitors treatment (*Ascierto et al, 2012*).

	Taking into account these considerations, it seems impossible to think to combine all the four compounds (the target agents and immunomodulating monoclonal antibodies). The risk of a high rate of toxicity is realistic and would render this approach inapplicable. Sequencing with these different combinations seems to be more feasible. However, also in this case it would be important to start with the best combination in order to give to the patients the best chance to increase the overall survival. The aim of this prospective randomized phase II study is to evaluate the sequencing of these two different combinations and evaluate which is the best of these approaches.
Primary Objectives	To define the best sequencing combination treatment in primary efficacy variable overall survival (OS).
Secondary Objectives	To evaluate the effects of the two sequencing combination treatments on: • Total PFS; • Percentage of patients alive at 2 and 3 years; • Best overall response rate (BORR); • Duration of response (DoR); • Toxicity of the investigational medicinal products (IMPs) • Quality of life and general health status defined by: o Health-related quality of life (HRQoL), by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30); o General health status, by means of the European Quality of Life 5-Dimensions(EQ-5D) questionnaire; o Impairment of work productivity and activity, by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire; <u>Biological markers (biomarkers ancillary study)</u> The objective of the biomarkers ancillary study is to focus on understanding mechanisms of action/resistance. In particular, the ancillary study: • Will inform how to sequence targeted RAF/MEK agents with immunotherapy agents (i.e. ipilumumab and nivolumab) in melanoma; • Will be hypothesis-generating only.
Study plan	The study will be conducted according to an open-label, prospective, randomized, phase II design. Randomization will be stratified according to stage arranged in the 4 following strata: • IIIb/c – M1a • M1b • M1c with normal LDH • M1c with elevated LDH. Subjects will be assessed for response by computed tomography (CT) or Magnetic Resonance Imaging (MRI).

	All measurable and non-measurable lesions must be documented at screening (within 28 days prior to randomization) and re-assessed at each subsequent tumor evaluation (every 8 weeks for the first year, every 12 weeks while the patient is on study). Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis will be performed until disease progression after the second combo treatment per RECIST v1.1. Imaging of the neck should be included if clinically indicated. In the event positron emission tomography (PET)/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. All scans will be collected for a possible independent review. For patients who discontinue study treatment for reason other than investigator–determined disease progression, tumor assessments should continue to be performed as scheduled. For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed at baseline and throughout study treatment as clinically indicated. Color photographs with ruler/calipers will be taken at baseline and at all subsequent tumor assessment time points. The National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTC-AE) Version 4.03 will be used to evaluate the clinical safety of the treatment in this study. Patients will be assessed for AEs at each clinical visit and as necessary throughout the study. <u>Biomarkers ancillary study</u> A correlative biological study will be performed for the evaluation of biomarkers on the biological samples available (paraffin-embedded tissue, frozen tissue, blood, serum, etc.).
Sample size	A total of 230 patients will be enrolled to ensure a minimum of 207 randomized patients.
Study population	The study population will include patients of either sex aged ≥ 18 years with metastatic melanoma and BRAF V600 mutation not pretreated.
Inclusion criteria	1) Patients of either sex aged ≥ 18 years; 2) Histologically confirmed stage III (unresectable) or stage IV melanoma with the BRAF V600 mutation. Patients with mucosal melanoma (but not those with ocular melanoma) are eligible for study participation; 3) Treatment naïve patients. As previous systemic treatment for melanoma only interferon is permitted (note that prior adjuvant melanoma therapy is permitted if completed at least 6 weeks prior to randomization, and all related adverse events have either returned to baseline or stabilized). 4) Measurable disease by computed tomography (CT) or Magnetic Resonance Imaging (MRI) per RECIST 1.1 criteria; 5) Presence of BRAF V600E or V600K mutation in tumor tissue prior to enrollment; 6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1; 7) Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. An archive sample is mandatory at the screening visit; however, a fresh sample would be preferable;

	8) Female subjects of childbearing potential must have a negative pregnancy test result at Baseline and must practice a reliable method of contraception for the total study duration plus 23 weeks (i.e. 30 days plus the time required for nivolumab to undergo five half lives) after the last dose of nivolumab and ipilimumab; 9) Men who are sexually active with women of childbearing potential must practice a reliable method of contraception for the total study duration plus 31 weeks (i.e. 80 days plus the time required for nivolumab to undergo five half lives) after the last dose of nivolumab and ipilimumab; 10) Adequate bone marrow haematological function: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L AND platelet count $\geq 100 \times 10^9$/L AND haemoglobin ≥ 9 g/dL; 11) Adequate liver function: total bilirubin ≤ 1.5 x upper limit of normal (ULN) AND aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 X ULN (< 5 x ULN if liver metastases); 12) Adequate renal function: serum creatinine ≤ 1.5 mg/dL OR creatinine clearance $\geq$ 60 mL/min in males and $\geq$ 50 mL/min in females (calculated according to Cockroft-Gault formula); 13) Serum calcium levels, international normalised ratio (INR) and partial thromboplastin time were within normal limits; 14) Life expectancy of at least 3 months; 15) Ability to understand study-related patient information and provision of written informed consent for participation in the study.
Exclusion criteria	1) Active brain metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration; 2) Subjects with active, known or suspected autoimmune disease; 3) Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of treatment; 4) Prior treatment with an anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody; 5) Female subjects who are pregnant (positive pregnancy test), breast-feeding, or who are of childbearing potential and not practicing a reliable method of birth control; 6) Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the investigator's opinion makes it undesirable for the patient to participate in the study, or which would jeopardize compliance with the protocol, or would interfere with the results of the study; 7) Patients with a history of cardiovascular or interstitial lung disease and evidence or risk of retinal vein occlusion or central serous retinopathy (Patients with a history of cardiovascular or interstitial lung disease and evidence or risk of retinal vein occlusion or central serous retinopathy (Past or present evidence of rethinophaty central serous retinopathy - CSR -, occlusion of retinal - RVOo retinal degenerative disease) or ophthalmopathy, which according to the ophthalmologic

	evaluation at baseline could be considered a risk factor for CSR / RVO (eg. cupping of the optic disc, visual field defect, intraocular pressure - (eg: central IOP - > 21 mmHg).; 8) History of Gilbert's syndrome; 9) Inability to regularly access centre facilities for logistical or other reasons; 10) History of poor co-operation, non-compliance with medical treatment, or unreliability; 11) Participation in any interventional drug or medical device study within 30 days prior to treatment start. 12) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection; 13) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
Study treatment duration, dose and schedule	The following IMPs will be used in the study: • **Arm A**: Combo Target (LGX818 450 mg p.o. od + MEK162. 45 mg p.o bid) until PD; then Combo Immuno (nivolumab 1 mg/kg solution intravenously (IV) combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until progression of disease (PD). • **Arm B**: Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD; then Combo Target (LGX818 450 mg p.o.od + MEK162 45 mg p.o. bid) until PD. • **Arm C**: Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) for 8 weeks followed by Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD; then Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) until PD. Shift from the one combination therapy to the following one can be done (once the procedures of the new screening have been completed) in case of absence of AEs events from the previous combination therapy or in case of grade 1 AEs. In case of grade ≥ 2 AEs from the previous combination therapy, shift to the following combination therapy can be done only when the AE is resolved or has decreased in intensity to at least grade 1.
Primary endpoint	OS is primary endpoint of the study. OS will be calculated as the time from the date of randomization until the date of death from any cause. Any patient not know to have died at the time of data analysis will be censored at the time of the last recorded date on which the patient was know to be alive.
Secondary endpoints	• Total PFS, calculated from the date of randomization until the date of the second progression (i.e. the progression to second treatment); any progression or death will be considered as an event if patient cannot complete treatment sequence; • Percentage of patients alive at 2 and 3 years; • Best overall response rate (BORR); • Duration of response (DoR) calculated as the time from the date of first documented response (CR or PR) until the date of the first documented progression or death due

	to underlying cancer. If the patient with a CR or PR has no progression or death due to underlying cancer, the patient will be censored at the time of last adequate tumor assessment; • Biological markers (biomarkers ancillary study); • Health-related quality of life (HRQoL), by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30); • General health status, by means of the European Quality of Life 5-Dimensions (EQ-5D) questionnaire; • Impairment of work productivity and activity, by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire.
Safety endpoints	• Toxicity of the IMPs (NCI CTC-AE Version 4.03 criteria); • Adverse events (AEs) and serious adverse events (SAEs) • Vital signs (weight, BMI, heart rate, blood pressure); • Laboratory safety parameters (haematology, blood chemistry, urinalysis).
Biomarkers ancillary study endpoints	<u>Tumor tissue biomarkers:</u> • Immune status: CD3, CD8, and CD4 T cells; Activated T cells; T regulatory cells; Dendritic cells; • Resistance to immunotherapy agents: Checkpoint receptors/ligands; myeloid-derived suppressor cells (MDSCs); • Resistance to targeted agents: aberrations in MEK/PI3K pathways, cytokines that interact with tyrosine kinase receptors (VEGF, HGF and their cognate receptors); • Mutational load and neoantigen profile. <u>Peripheral blood biomarkers:</u> • Immune status/"Resistance" to immunotherapy agents: Activated T cells; Memory/Exhausted T cells; T regulatory cells; MDSCs; Inflammatory response; C-reactive protein (CRP); TCR Sequencing/Gene Expression analysis; • Response/Resistance to targeted agents: Apoptotic tumor cells (as measured by circulating tumor DNA); soluble hepatocyte growth factor (sHGF); serum vascular endothelial growth factor (sVEGF), soluble interleukin-2 receptor (sCD25); • Immunotherapy SNP Panel will be also assessed at baseline. Approximately 80-90 patients will take part in the ancillary study.
Statistical methods	<u>Sample size determination</u> This study is designed as a phase II, randomized trial with no formal comparative test. The sample size is discussed for the primary endpoint of the study (Overall Survival). For each arm a single-stage design will be used. We have assumed a median PFS of about 10 months for the combo target therapy (LGX818/MEK162) and a similar value for the combo immunotherapy (ipilimumab/nivolumab) derived from the aggregate clinical activity rate of 65% which, using an exponential distribution for PFS, could broadly give a median PFS of about 9.5 months. OS seems to be strictly correlated with total PFS.

	The null hypothesis is a median OS time of 15 months (i.e. percentage of surviving patients of 33% at 24 months). The altervative hypothesis is a median OS time of 23 months (i.e. percentage of surviving of 48% at 24 months). Using an exact 5% one-sided significance test at least 69 patients have to be randomized in each arm when the power of the study is 80%. For each arm the strategy will be further investigated if at least 30 patients, alive at 24 months, are observed. Taking in account a 10% drop-out rate, a total of 230 patients will be enrolled to ensure a minimum of 207 randomized patients.
	Data handling The Overall Survival (OS) will be calculated as the time from the date of randomization until the date of death from any cause. Any patient not know to have died at the time of data analysis will be censored at the time of the last recorded date on which the patient was know to be alive. Total Progression Free Survival (TPFS) will be calculated from the date of randomization to the date of the second progression (i.e. the progression to second treatment); any progression or death will be considered as an event if patient cannot complete treatment sequence. Duration of response (Dor) will be calculated as the time from the date of first documented response (CR or PR) until the date of the first documented progression or death due to underlying cancer. If the patient with a CR o PR has no progression death due to underlying cancer, the patient will be censored at the date of last adeguate tumor assessment. Statistical analysis A comprehensive Statistical Analysis Plan (SAP) will be prepared before database lock. All enrolled patients in the study will be considered for the Screened Population. All randomized will be considered the Intention-To-Treat population (ITT). The subset of patient of the ITT population receiving at least one dose of the study medication will define the Safety Population (SP). Analysis of efficacy endpoints will be performed in the ITT population whereas the safety analysis will be performed in the Safety Population. No comparative tests between the three arms will be performed and results will be presented as descriptive statistics. The standard summary statistics will be used for both continuous and discrete variables. The objective response rate (ORR) and the percentage of patients alive at 2 o 3 years will be reported with its 95% confidence interval (CI). The time-dependent endpoint will be analyzed according to the Kaplan-Meier method. Median with 95% confidence intervals will be derived from the K-M curves and presenting time-dependent endpoints as K-M plot (with a 95% CI over time). Cox's proportional hazard model will be used to assess the impact of known prognostic factors and treatment assigned. The list of the covariates to be included in the Cox's model will be presented and clinically justified in the statistical analysis plan.

	Safety and tolerability data will be presented by treatment received. Appropriate summaries of these data will be presented. Safety and tolerability will be assessed in terms of AEs, laboratory data, ECG data, vital signs and weight, which will be collected for all patients. AEs (both in terms of MedDRA preferred terms and CTCAE grade), laboratory data, ECG data, vital signs data and weight will be listed individually by the patient and summarised by treatment received.
Duration of the study	Treatment duration: until PD (2 years estimated) Study Start (First Patient First Visit Date): Febrary 2016 Recruitment end (Last Patient First Visit): September 2017 Study end (Last Patient Last Visit): Semptember 2020* *This date is dependent on the clinical course of the disease and may therefore occur earlier than indicated

LIST OF ABBREVIATIONS

AEs	Adverse Events
AESIs	Adverse Events of Special Interest
ALT	Alanine Transaminase (SGPT)
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase (SGOT)
ATP	Adenosin Triphosphate
AUC	Area Under the plasma concentration-time Curve
BCRP	Breast Cancer Resistant Protein
bid	Bis in die (twice daily)
BMI	Body Mass Index
BORR	Best Overall Response Rate
BRAF	B-raf murine sarcoma vioral oncogene homolog B1
BUN	Blood Urea Nitrogen
C/A/P	Chest/Abdomen/Pelvis
CI	Confidence Interval
CK	Creatin-kinase
Cmax	Maximum plasma concentration
CRP	C-reactive Protein
CT	Computed Tomography
CTC-AE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T Lymphocyte Antigen 4
DEHP	Di-(2-ethylexil-phthalate)
DILI	Drug-induced Liver Injury
DoR	Duration of Response
ECG	Electrocardiogram
EchO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC QLQ-C30	30-item European Organisation for Research and Treatment of Care quality of life questionnaire
EQ-5D	European Quality of Life 5-Dimensions
EOS	End of Study Visit
ERK	Extracellular Signal-Regulated Kinase
FDA	Food and Drug Administration

FFPE	Formalin-fixed Paraffin-embedded
HFSR	Hand Foot Skin Reaction
HCG	Human Chorionic Gonadotropine
HGF	Hepatocyte Growth Factor
HRQoL	Health-related Quality of Life
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB/IEC	Institutional Review Board / Independent Ethics Committee
IV	Intravenous
KA	Keratoacanthoma
Kg	Kilogram
LDH	Lactate dehydrogenase
LFT	Liver Function Tests
LLN	Lower Limit of Normal
LVEF	Left Ventricle Ejection Fraction
MAPK	Mitogen Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MDSCs	Myeloid-derived Suppressor Cells
MEK	Methyl Ethyl Ketone
mg	Milligram
ml	Millilitre
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
od	Once Daily
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PCN	Packaging Control Number
PD	Progression of Disease
PD-1	Programmed Death Receptor-1

PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetic
p.o.	Per os (oral route)
PS	Performance Status
PVC	Polyvinyl Chloride
RECIST	Response Evaluation Criteria In Solid Tumors
RL	Room Light
RT	Room Temperature
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma
sCD25	Soluble interleukin-2 receptor
SECOMBIT	Sequential Combo Immuno and target Therapy
sHGF	Soluble Hepatocyte Growth Factor
sICAM-1	Soluble Intercellular Adhesion Molecule-1
SUSAR	Suspected Unexpected Serious Adverse Reactions
sVEGF	Serum Vascular Growth factor
T3	Triiodotyroxine
T4	Tyroxine
TdP	Torsade de Points
TPFS	Total Progression-Free Survival
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor
WBC	White blood cell
WPAI:GH	Work Productivity and Activity Impairment: General Health

1. SCHEDULE ASSESSMENT

ARM A

ARM A Combo Target (LGX818 450 mg p.o. od + MEK162. 45 mg p.obid) until PD; then Combo Immuno (nivolumab 1 mg/kg solution intravenously (IV) combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until progression of disease (PD).															
	Screening1/ Baseline1[1]	**Treatment period[2]**												**End of Study Visit[3]**	**Follow-up Visit[4]**
		Combo Target LGX818+MEK162				**Screening 2/ Baseline2[13]**	**Combo Immuno**								
							Nivolumab+Ipilimumab				**Nivolumab**				
Day	**-28 to 0**	**1**	**29**	**57**	**Q 28 days up to PD**	**-28 to 0**	**1**	**21**	**42**	**63**	**75**	**87**	**Q14 days up to PD**		
Informed Consent[5]	X														
Demographics	X														
Medical History	X														
Physical Examination & Vital Signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	
Biochemistry	X	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	
Cardiac/Muscle Enzymes[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	Only if clinically indicated													
Endocrine Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BRAF Mutation testing[22]	X														
Serum Pregnancy Test[9]	X	A serum pregnancy test to be performed every 6 (± 1) weeks during the treatment period												X	X
Tumor Assessments (CT/MRI)[10]	X		Every 8 weeks for the first year, every 12 weeks thereafter while the patient is on study												X
Quality of life and general Health Status questionnaires [24]	X	X	X	X	X	X	X	X	X	X		X	X[24]	X	X
Biomarkers study: Biopsy[11]	X	X (4W)			X (PD)		X (4W)						X (PD)		
Biomarkers study: Blood Drawn[12]	X	X (4W)			X (PD)	X	X (4W)						X (PD)		
Ophthalmologic exam[14]	X					X									
Dermatologic evaluation[15]	X	A dermatologic evaluation will be performed at screening/baseline and every 8 weeks while the patient is on study													
ECG[7]	X	An ECG will be performed at screening/baseline, at the 2nd baseline, at the 1st month and every 12 weeks while the patient is on study													
Echocardiogram[16]	X	An echo will be performed at screening/baseline, at the 2nd baseline, at the 1st month and q12 weeks while the patient is on study													
AEs/SAEs[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[18]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Combo target dispensing & accountability[19]		X	X	X	X										
Combo Target Dosing Exception Diary[20]			X	X	X										
Combo immuno administration[21]							X	X	X	X	X	X	X		
Patient diary		X	X	X	X										

Table 1: Schedule of Assessments and Procedures in Arm A

Notes:
Day 1 = first dose of IMP
1. All screening/baseline assessments must be performed -28 to 0 days prior to the first administration of the IMP on Day 1 with the exception of the serum pregnancy test to be done within 24 hours. Results of tests or examinations (including tumor assessments) performed before obtaining informed consent and within the 28 Days prior to Day 1 may be used.
2. A window of 2 days prior to the scheduled visit date and 2 days after the scheduled visit date (- 2 days / + 2 days) is allowed for each visit, except for tumor evaluations for which a window of +/- 5 days will apply.
3. End of Study Visit (EOS) will be performed when the patient discontinues treatments regardless of when it occurs.
4. Follow up visit is to be performed within 28 days from discontinuation of treatments and thereafter every 12 weeks until 24 months for long term survival follow-up.
5. Informed consent must be obtained prior to perform any study procedure including screening/baseline assessments.
6. Height is taken at screening only. For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed at baseline and throughout study treatment as clinically indicated. Color photographs with ruler/calipers will be taken at baseline and at all subsequent tumor assessment time points.
7. A 12-lead ECG will be performed at screening/baseline, at the 2nd baseline, at the 1st month and every 12 weeks while the patient is on study
8. Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days; if it is necessary to repeat these blood tests, the results must be known before the patient receives treatments to ensure inclusion/exclusion criteria related to these tests are met.
9. Serum pregnancy test to be performed within 24 hours prior to Day 1. A serum pregnancy test to be performed every 6 (± 1) weeks during the treatment period and at end of study and follow-up visit.
10. All measurable and non-measurable lesions must be documented at screening (within 28 days prior to randomization) and re-assessed at each subsequent tumor evaluation (every 8 weeks for the first year, every 12 weeks while the patient is on study). Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis will be performed until disease progression after the second combo treatment per RECIST v1.1. Imaging of the neck should be included if clinically indicated. In the event PET/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. All scans w ill be collected for a possible independent review.
11. Biopsy of tumoral lesions for the biological study will be performed at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Target therapy; and at Week 4 and disease progression 2 (DP 2) during Combo Immuno therapy. Biopsy of tumoral lesions will be mandatory at baseline 1 and at the first disease progression (PD1), and will be optional at the other time-points.
12. Serum, plasma (for circulating tumor DNA) and whole blood for PBMC processing will be taken at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Target therapy; and at baseline 2, Week 4 and disease progression 2 (DP 2) during Combo Immuno therapy. Whole blood for SNP will be taken at baseline 1 only.
13. The second baseline visit will be performed -28 to 0 days prior to the first administration of the Combo Immuno treatment on Day 1.Shift from the one combination therapy to the following one can be done (once the procedures of the new screening have been completed) in case of absence of AEs events from the prevsious combination therapy or in case of grade 1 AEs. In case of grade ≥ 2 AEs from the previous combination therapy, shift to the following combination therapy can be done only when the AE is resolved or has decreased in intensity to at least grade 1.
14. An ophthalmologic examination will be performed at the screening/baseline visit, at the 2nd baseline visit and then when clinically indicated.
15. A dermatologic evaluation will be performed at the screening/baseline visit and every8 weeks while the patient is on study.
16. An echocardiogram will be performed at screening/baseline, at the 2nd baseline, at the 1st month and every 12 weeks while the patient is on study
17. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. All AEs (including SAEs) must be recorded from the time of first treatments administration. After the last treatment, any new, non-serious AEs which the Investigator considers may be related to treatments should be reported according Section 7 – Safety instruction and guidance
18. All concomitant medications during the study started within 14 Days prior to the screening visit and up to the end of study visit must be recorded.
19. Combo Target (LGX818 450 mg p.o.od + MEK162 45 mg p.o. bid) will be administered until PD.
20. Patients will keep a diary to record ONLY those occasions when a Combo Target dose was missed. The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
21. Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IVevery 2 weeks) will be administered until PD following the Combo Target and subsequent PD.
22. Presence of BRAF V600E or V600K mutation in tumor tissue prior to enrollment
23. Troponin, Creatine Kinase (CK). If total CK ≥3 X ULN, then measure isoenzymes and myoglobin in blood or urine weekly
24. Quality of life and general health status defined by: Health-related quality of life (HRQoL), by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30); General health status, by means of the European Quality of Life 5-Dimensions (EQ-5D) questionnaire; Impairment of work productivity and activity, by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire; every two administrations of nivolumab (i.e. every 28 days)

ARM B

ARM B Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD; then Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) until PD.															
	Screening/ Baseline1[1]	**Treatment period[2]**												**End of Study Visit[3]**	**Follow-up Visit[4]**
		Combo Immuno							**Baseline2[13]**	**Combo Target LGX818 + MEK162**					
		Nivolumab+Ipilimumab				**Nivolumab**									
Day	**-28 to 0**	**1**	**21**	**42**	**63**	**75**	**87**	**Q14 days up to PD**	**-28 to 0**	**1**	**29**	**57**	**Q 28 days up to PD**		
Informed Consent[5]	X														
Demographics	X														
Medical History	X														
Physical Examination & Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X[8]	X	X	X	X	X	X	X	X[8]	X	X	X	X	
Biochemistry	X	X[8]	X	X	X	X	X	X	X	X[8]	X	X	X	X	
Cardiac/Muscle Enzymes[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	Only if clinically indicated													
Endocrine Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BRAF Mutation testing[22]	X														
Serum Pregnancy Test[9]	X	A serum pregnancy test to be performed every 6 (± 1) weeks during the treatment period												X	X
Tumor Assessments (CT/MRI)[10]	X	Every 8 weeks for the first year, every 12 weeks thereafter while the patient is on study													X
Quality of life and general Health Status questionnaires [24]	X	X	X	X	X		X	X[24]	X	X	X	X	X	X	X
Biomarkers study: Biopsy[11]	X	X (4W)						X (PD)		X (4W)			X (PD)		
Biomarkers study: Blood Drawn[12]	X	X (4W)						X (PD)	X	X (4W)			X (PD)		
Ophthalmologic exam[14]	X							X							
Dermatologic evaluation[15]	X	A dermatologic evaluation will be performed at screening/baseline and every 8 weeks while the patient is on study													
Echocardiogram[16]	X	An echo will be performed at screening/baseline, at the 2nd baseline, at the 1st month and every 12 weeks while the patient is on study													
ECG[7]	X	An ECG will be performed at screening/baseline, at the 2nd baseline, at the 1st month and every 12 weeks while the patient is on study													
AEs/SAEs[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[18]	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Combo target dispensing & aqccountability[19]										X	X	X	X		
Combo Target Dosing Exception Diary[20]											X	X	X		
Combo immuno administration[21]		X	X	X	X	X	X	X							
Patient diary										X	X	X	X		

Table 2: Schedule of Assessments and Procedures in Arm B

Notes:
Day 1 = first dose of IMP
1. All screening/baseline assessments must be performed -28 to 0 days prior to the first administration of the IMP on Day 1 with the exception of the serum pregnancy test to be done within 24 hours. Results of tests or examinations (including tumor assessments) performed before obtaining informed consent and within the 28 Days prior to Day 1 may be used.
2. A window of 2 days prior to the scheduled visit date and 2 days after the scheduled visit date (- 2 days / + 2 days) is allowed for each visit, except for tumor evaluations for which a window of +/- 5 days will apply.
3. End of Study Visit (EOS) will be performed when the patient discontinues treatments regardless of when it occurs.
4. Follow up visit is to be performed within 28 days from discontinuation of treatments and thereafter every 12 weeks until 24 months for long term survival follow-up.
5. Informed consent must be obtained prior to perform any study procedure including screening/baseline assessments.
6. Height is taken at screening only. For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed at baseline and throughout study treatment as clinically indicated. Color photographs with ruler/calipers will be taken at baseline and all subsequent tumor assessment time points.
7. A 12-lead ECG will be performed at screening/baseline, at the 2nd baseline, at the 1st month and every 12 weeks while the patient is on study
8. Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days; if it is necessary to repeat these blood tests, the results must be known before the patient receives treatments to ensure inclusion/exclusion criteria related to these tests are met.
9. Serum pregnancy test to be performed within 24 hours prior to Day 1. A serum pregnancy test to be performed every 6 (± 1) weeks during the treatment period and at end of study and follow-up visit.
10. All measurable and non-measurable lesions must be documented at screening (within 28 days prior to randomization) and re-assessed at each subsequent tumor evaluation (every 8 weeks for the first year, every 12 weeks while the patient is on study). Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis will be performed until disease progression after the second combo treatment per RECIST v1.1. Imaging of the neck should be included if clinically indicated. In the event PET/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. All scans will be collected for a possible independent review.
11. Biopsy of tumoral lesions for the biological study will be performed at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Immuno therapy; and at Week 4 and disease progression 2 (DP 2) during Combo Target therapy. Biopsy of tumoral lesions will be mandatory at baseline 1 and at the first disease progression (PD1), and will be optional at the other time-points.
12. Serum, plasma (for circulating tumor DNA) and whole blood for PBMC processing will be taken at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Immuno therapy; and at baseline 2, Week 4 and disease progression 2 (DP 2) during Combo Target therapy. Whole blood for SNP will be taken at baseline 1 only.
13. The second baseline visit will be performed -28 to 0 days prior to the first administration of the Combo Target treatment on Day 1.Shift from the one combination therapy to the following one can be done (once the procedures of the new screening have been completed) in case of absence of AEs events from the prevsious combination therapy or in case of grade 1 AEs. In case of grade ≥ 2 AEs from the previous combination therapy, shift to the following combination therapy can be done only when the AE is resolved or has decreased in intensity to at least grade 1.
14. An ophthalmologic examination will be performed at the screening/baseline visit, at the 2nd baseline visit and then when clinically indicated.
15. A dermatologic evaluation will be performed at the screening/baseline visit and every8 weeks while the patient is on study.
16. An echocardiogram will be performed at screening/baseline, at the 2nd baseline, at the 1st month and every 12 weeks while the patient is on study
17. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. All AEs (including SAEs) must be recorded from the time of first treatments administration. After the last treatment, any new, non-serious AEs which the Investigator considers may be related to treatments should be reported according Section 7 – Safety instruction and guidance
18. All concomitant medications during the study started within 14 Days prior to the screening visit and up to the end of study visit must be recorded.
19. Combo Target (LGX818 450 mg p.o.od + MEK162 45 mg p.o. bid) will be administered until PD.
20. Patients will keep a diary to record ONLY those occasions when a Combo Target dose was missed. The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
21. Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) will be administered until PD following the Combo Target and subsequent PD.
22. Presence of BRAF V600E or V600K mutation in tumor tissue prior to enrolment.
23. Troponin, Creatine Kinase (CK). If total CK ≥3 X ULN, then measure isoenzymes and myoglobin in blood or urine weekly.
24. Quality of life and general health status defined by: Health-related quality of life (HRQoL), by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30); General health status, by means of the European Quality of Life 5-Dimensions (EQ-5D) questionnaire; Impairment of work productivity and activity, by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire; every two administrations of nivolumab (i.e. every 28 days)

ARM C

ARM C Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) for 8 weeks followed by Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD; then Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) until PD.																			
	Screening/ Baseline1[1]	**Treatment period[2]**																**End of Study Visit[3]**	**Follow-up Visit[4]**
		Combo-Target			**Baseline2[13]**	**Combo Immuno**							**Baseline3[14]**	**Combo Target LGX818+MEK162**					
						Nivolumab+Ipilimumab				**Nivolumab**									
Day	**-28 to 0**	**1**	**29**	**57**		**1**	**21**	**42**	**63**	**75**	**87**	**Q 14 days up to PD**		**1**	**29**	**57**	**Q 28 days up to PD**		
Informed Consent[5]	X																		
Demographics	X																		
Medical History	X																		
Physical Examination & Vital Signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry	X	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiac/Muscle Enzymes[24]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X	Only if clinically indicated																	
Endocrine Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
BRAF Mutation testing[23]	X																		
Serum Pregnancy Test[9]	X	A serum pregnancy test to be performed every 6 (± 1) weeks during the treatment period																X	X
Tumor Assessments (CT/MRI)[10]	X		Every 8 weeks for the first year, every 12 weeks thereafter while the patient is on study																X
Quality of life and general Health Status questionnaires [24]	X	X	X	X	X	X	X	X	X		X	X[25]	X	X	X	X	X	X	X
Biomarkers study: Biopsy[11]	X					X (4W)						X (PD)		X (4W)			X (PD)		
Biomarkers study: Blood Drawn[12]	X					X (4W)						X (PD)		X (4W)			X (PD)		
Ophthalmologic exam[15]	X				X								X						
Dermatologic evaluation[16]	X	A dermatologic evaluation will be performed at screening/baseline and every 8 weeks while the patient is on study																	
Echocardiogram[17]	X	An echo will be performed at screening/baseline, at the 2nd and 3rd baseline, at the 1st month and every 12 weeks while the patient is on study																	
ECG[7]	X	An ECG will be performed at screening/baseline, at the 2nd baseline, at the 1st month and every 12 weeks while the patient is on study																	X
AEs/SAEs[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[19]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Combo target dispensing & acountability[20]		X	X	X										X	X	X	X		
Combo Target Dosing Exception Diary[21]			X	X										X	X	X	X		
Combo immuno administration[22]						X	X	X	X	X	X	X							
Patient diary		X	X	X										X	X	X	X		

Table 3: Schedule of Assessments and Procedures in Arm C

Notes:
Day 1 = first dose of IMP
1. All screening/baseline assessments must be performed -28 to 0 days prior to the first administration of the IMPon Day 1 with the exception of the serum pregnancy test to be done within 24 hours. Results of tests or examinations (including tumor assessments) performed before obtaining informed consent and within the 28 Days prior to Day 1 may be used.
2. A window of 2 days prior to the scheduled visit date and 2 days after the scheduled visit date (- 2 days / + 2 days) is allowed for each visit, except for tumor evaluations for which a window of +/- 5 days will apply.
3. End of Study Visit (EOS) will be performed when the patient discontinues treatments regardless of when it occurs.
4. Follow up visit is to be performed within 28 days from discontinuation of treatments and thereafter every 12 weeks until 24 months for long term survival follow-up.
5. Informed consent must be obtained prior to perform any study procedure including screening/baseline assessments.
6. Height is taken at screening only. For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed at baseline and throughout study treatment as clinically indicated. Color photographs with ruler/calipers will be taken at baseline and at all subsequent tumor assessment time points.
7. A 12-lead ECG will be performed at screening/baseline, at the 2nd baseline, at the 1st month and every 12 weeks while the patient is on study
8. Hematology and biochemistry assessments do not need to be repeated on Day 1 if performed within 7 days; if it is necessary to repeat these blood tests, the results must be known before the patient receives treatments to ensure inclusion/exclusion criteria related to these tests are met.
9. Serum pregnancy test to be performed within 24 hoursprior to Day 1. A serum pregnancy test to be performed every 6 (± 1) weeks during the treatment period and at end of study and follow-up visit.
10. All measurable and non-measurable lesions must be documented at screening (within 28 days prior to randomization) and re-assessed at each subsequent tumor evaluation (every 8 weeks for the first year, every 12 weeks while the patient is on study). Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis will be performed until disease progression after the second combo treatment per RECIST v1.1. Imaging of the neck should be included if clinically indicated. In the event PET/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. All scans will be collected for a possible independent review.
11. Biopsy of tumoral lesions for the biological study will be performed at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Immuno therapy; and at Week 4 and disease progression 2 (DP 2) during the 2nd Combo Target therapy. Biopsy of tumoral lesions will be mandatory at baseline 1 and at the first disease progression (PD1), and will be optional at the other time-points.
12. Serum, plasma (for circulating tumor DNA) and whole blood for PBMC processing will be taken at baseline 1, at baseline 2, Week 4 and disease progression 1 (DP 1) during Combo Immuno therapy; and at baseline 3, Week 4 and disease progression 2 (DP 2) during the 2nd Combo Target therapy. Whole blood for SNP will be taken at baseline 1 only.
13. The second baseline visit will be performed -28 to 0 days prior to the first administration of the Combo Immuno treatment on Day 1.Shift from the one combination therapy to the following one can be done (once the procedures of the new screening have been completed) in case of absence of AEs events from the prevsious combination therapy or in case of grade 1 AEs. In case of grade ≥ 2 AEs from the previous combination therapy, shift to the following combination therapy can be done only when the AE is resolved or has decreased in intensity to at least grade 1.
14. The third baseline visit will be performed -28 to 0 days prior to the first administration of the second Combo Target treatment on Day 1.See rules for switching as above.
15. An ophthalmologic examination will be performed at the screening/baseline visit, at the 2nd baseline visit, at the 3rd baseline visit and then when clinically indicated.
16. A dermatologic evaluation will be performed at the screening/baseline visit and every8 weeks while the patient is on study.
17. An echocardiogram will be performed at screening/baseline, at the 2nd and 3rd baseline, at the 1st month and every 12 weeks while the patient is on study
18. During screening AEs are not recorded in the eCRF unless they are SAEs which are related to protocol-mandated procedures. All AEs (including SAEs) must be recorded from the time of first treatments administration. After the last treatment, any new, non-serious AEs which the Investigator considers may be related to treatments should be reported according Section 7 – Safety instruction and guidance
19. All concomitant medications during the study started within 14 Days prior to the screening visit and up to the end of study visit must be recorded.
20. Combo Target (LGX818 450 mg p.o.od + MEK162. 45 mg p.o bid) will be administered for initial 8 weeks and then will be administered until PD following the Combo Immuno and subsequent PD.
21. Patients will keep a diary to record ONLY those occasions when a Combo Target dose was missed. The patient will bring this diary with him/her to each study visit to allow missed doses to be recorded by the Investigator.
22. Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) will be administered until PD following the Combo Target and subsequent PD.
23. Presence of BRAF V600E or V600K mutation in tumor tissue prior to enrollment
24. Troponin, Creatine Kinase (CK). If total CK ≥3 X ULN, then measure isoenzymes and myoglobin in blood or urine weekly.
25. Quality of life and general health status defined by: Health-related quality of life (HRQoL), by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30); General health status, by means of the European Quality of Life 5-Dimensions (EQ-5D) questionnaire; Impairment of work productivity and activity, by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire; every two administrations of nivolumab (i.e. every 28 days)

2. BACKGROUND AND RATIONALE

2.1 Overview of disease epidemiology and current treatment

2.1.1 Epidemiology of melanoma

Melanoma is the most serious form of skin cancer and strikes adults of all ages. Both incidence of melanoma and mortality rate are rapidly increasing throughout the world, constituting a significant and growing health burden (*Ferlay et al, 2010*). The worldwide incidence of melanoma in 2010 was estimated at 208,251 (*Jemal et al, 2011*), and approximately 76,250 men and women were diagnosed with melanoma in 2012 in the United States alone (*American Cancer Society, 2012*)

About 80% of melanomas are detected in a localized stage, and can be treated with surgical resection. When detected early, the 5-year survival rate of melanoma is above 90%; however, when melanoma is diagnosed after distant metastasis, the prognosis is by contrast very poor.

The 5-year survival rate decreases to 15% with a median survival between 8 and 9 months (Jemal et al, 2011). Advanced melanoma is one of the most aggressive human malignancies. In 2012, an estimated 9,000 melanoma patients in the US have died from their disease (*American Cancer Society, 2012*).

2.1.2 Treatment options in patients with advanced melanoma

For the last 40 years, treatment progresses in advanced melanoma have been largely stagnant, with traditional options, such as chemotherapy, lacking substantial efficacy. This has changed in 2011 with the Food and Drug Administration (FDA) approval of novel immunotherapy, ipilimumab (Yervoy®, Bristol-Myers Squibb), an antibody against the cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4), although melanoma that has spread to distant sites remains rarely curable.

The discovery of the genetic underpinnings of melanoma and their characterization has uncovered potential targets for therapy, B-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations being principal among them. BRAF mutations have been identified as an important target in melanoma and discovery of oncogenic BRAF mutations highlighted the significant role of BRAF kinase in signalling pathways that control cellular proliferation. More than half of patients with metastatic melanoma have mutations that keep the BRAF protein constantly activated.

Mutations in BRAF exon 15 account for over 95% of activating BRAF mutations in metastatic melanoma. The two most common BRAF V600 mutations V600E and V600K have been reported to account for anywhere between 66-91% and 7-30% of BRAF V600 mutant metastatic melanoma patients respectively. Both BRAF

V600E and V600K mutant patients account for 92-98% of all BRAF V600 mutant metastatic melanoma patients (*Colombino et al, 2012*; *Jakob et al, 2011*; *Greaves et al, 2013*). These mutations constitutively activate BRAF and downstream signal transduction in the RAF/MEK/ERK pathway, which signals for cancer cell proliferation and survival. Moreover, oncogenic BRAF mutations generally correlate with poor prognosis in a variety of different tumor types.

The selective BRAF inhibitor vemurafenib was approved by the FDA (17 August 2011) for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation as detected by an FDA approved test. In February 2012, vemurafenib received approval in the European Union (EU) as a monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Although studies have shown that BRAF-targeted therapy is effective in BRAF mutant melanoma, data also indicate that the duration of response is often short lived, with resistance developing quickly, within approximately 6 months (*Flaherty et al, 2010*; *Sosman et al, 2012*; *Chapman et al, 2011*; *Hauschild et al, 2012*). Re-activation of mitogen activated protein kinase (MAPK) signalling occurs in the majority of cases of acquired resistance to BRAF inhibitors. In an attempt to delay resistance to BRAF inhibition, the combination of a selective BRAF- and a MEK1/2-inhibitor is currently being investigated by several clinical trials in patients with advanced BRAF mutant melanoma. Results of the first such phase I/II study [NCT01072175] of the combination of investigational agents dabrafenib and trametinib, and of the phase Ib dose escalation study [NCT01271803] of vemurafenib (Zelboraf®, Roche), in combination with an investigational MEK inhibitor GDC-0973 (Roche), have been recently reported (*Flaherty et al, 2012*). Median PFS was 9.4 months in the dabrafenib plus trametinib group vs. 5.8 months in the dabrafenib group (*Flaherty et al, 2012*).

Despite recent treatment breakthroughs, advanced melanoma remains an aggressive disease with a poor prognosis. There is a need to develop new treatment regimens to improve the duration of response and delay the emergence of resistance, expanding the therapeutic options for patients with unresectable or metastatic melanoma, including those with BRAF V600 mutation.

2.2 Introduction to investigational treatments and other study treatment(s)

2.2.1 LGX818

LGX818 (encorafenib) is a highly selective ATP-competitive small molecule RAF kinase inhibitor, which suppresses the RAF/MEK/ERK pathway in tumor cells expressing BRAF V600. The narrow kinase profile and potent anti-proliferative activity of LGX818 translates into a very wide therapeutic index in vivo.

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

The results of a phase I study assessing the maximum tolerated dose (MTD) and of the recommended dose phase II study of LGX818 in patients with locally advanced and metastatic BRAF mutated melanoma have confirmed the potency and the wide therapeutic index of LGX818 with clinical efficacy observed from the lowest tested dose of 50 mg/day up to the MTD of 450 mg/day.For further details, please refer to the current LGX818 Investigator's Brochure.

2.2.2 MEK162

MEK162 (binimetinib), previously named ARRY 438162, is a potent and selective allosteric, ATP (Adenosine Tri-Phosphate) non-competitive inhibitor of MEK1/2 that is active in inhibiting pERK and growth of BRAF mutant cancer cells in the low nanomolar range.

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. Given the embryo-lethal effects seen in rats and rabbits and the teratogenic effects seen in rabbits, MEK162 should not be used in pregnant women. Women of child-bearing potential must be advised to use highly effective contraception methods.

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

In oncology settings, MEK162 is currently being investigated both as a single agent and in combination with PI3K or RAF inhibitors in patients with selected advanced or metastatic solid tumors, including biliary cancer, colorectal cancer and melanoma.

The safety and efficacy of MEK162 as a single agent in patients with advanced melanoma have been evaluated in one Phase II study (CMEK162X2201), in which 45 mg and 60 mg bid dose levels have been investigated. In study CMEK162X2201, the most frequently treatment-related occurring events (≥ 20%) were dermatitis acneiform, diarrhea, peripheral edema, increase in creatin-kinase (CK) levels, nausea, fatigue and rash. The most common treatment-related Grade 3-4 AEs were CK increased, dermatitis acneiform and diarrhoea.

In the BRAF mutant population, the ORR was 20% (8 PR, 2 confirmed and 6 unconfirmed), and the median PFS was 3.6 months (CI: 2.0; 3.8) among the 41 patients treated with MEK162 at 45 mg bid (i.e. the recommended dose). In patients not previously treated with a BRAF inhibitor (n=34) the median PFS was 3.7 months. The majority of these patients received at least one prior anticancer treatment (*Ascierto et al, 2013*).For further details, please refer to the current MEK162 Investigator's Brochure.

2.2.3 LGX818 and MEK162 combination

PK data from the clinical study in BRAF mutated cancer patients up to doses of 600 mg od LGX818 in combination with 45 mg bid MEK162 show that, although the concentrations of MEK162 tended to be on the higher end of the variability range, the PK parameter of MEK162 remained unchanged when administered with 50 to 600 mg LGX818. Exposure to LGX818 on Day 15, as determined by Cmax and AUC, was 30 to 70% less compared with Day 1, likely due to CYP induction by LGX818 (auto-induction). PK characteristics of LGX818 when co-administered with MEK162 are similar to those observed when given as single agent.

Although clinical data from ongoing studies with LGX818 and MEK162 as single agents suggest that overlapping toxicities for the proposed combination, including effects on the skin (e.g. rash) and gastro-intestinal system (e.g. nausea) may potentially be dose-limiting, initial reports with a similar class of compounds have shown that selective BRAF inhibitor combines safely with MEK inhibitor with a decreased occurrence of skin

toxicities (rash, SCC). These data suggest that the combination of LGX818 with MEK162 may have an improved safety profile compared to the respective single agent therapies.

Soon after the initiation of clinical oncology trials with MEK inhibitors, it was observed that some participants developed an eye condition resembling central serous chorioretinopathy. A recently published article (Umer-Bloch et al, 2014) has examined the clinical features and management of MEK inhibitor-associated retinal syndromes in patients with advanced cutaneous melanoma treated with MEK162 in different Phase 1b or 2 clinical trials. Twenty patients on MEK162 monotherapy and 5 on MEK162 plus LGX818 underwent ophthalmological examinations at regular intervals, including determination of best corrected visual acuity, perimetry, colour vision testing, dilated fundus examination, and multimodal imaging. Grade 1-2 bilateral retinopathies with multiple lesions were observed in 13 of 20 patients on MEK162 monotherapy and in 2 of 5 patients on MEK162 plus LGX818. Retinopathy events appeared during the first 4 weeks, and in some cases, during the first few days of treatment. Patients reported mild and only short-lived visual symptoms. Optical coherence tomography revealed neuroretinal elevations. Central retinal thickness and volume showed dose-dependent increases after the start of treatment, followed by a marked decrease despite continued treatment, which was associated with symptom resolution. No vascular abnormalities were found with fluorescein and indocyanine green angiography. This analysis showed that treatment with MEK162 monotherapy or plus LGX818 induced transient retinopathy with multiple bilateral lesions in some patients. MEK162-induced retinopathy was usually mild, self-limiting, and tolerable as visual function was not seriously impaired.

2.2.4 Nivolumab

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds programmed death receptor-1 (PD-1). Blockade of PD-1 by monoclonal antibodies (mAbs) can enhance the anti--tumor immune response and result in tumor rejection.

In a recent study (*Topalian et al, 2014*), 107 patients with advanced melanoma enrolled between 2008 and 2012 received IV nivolumab in an outpatient setting every 2 weeks in 8-week treatment cycles for up to 96 weeks and were observed for overall survival, long-term safety, and response duration after treatment discontinuation. Nivolumab was administered at 1, 3, or 10 mg/kg during dose escalation. After completion of dose escalation, each dose cohort was expanded to accrue approximately 16 patients. Additional melanoma cohorts randomly assigned to 0.1, 0.3, and 1.0 mg/kg were enrolled. Median overall survival in nivolumab-treated patients (62% with two to five prior systemic therapies) was 16.8 months, and 1- and 2-year survival rates were 62% and 43%, respectively. Among 33 patients with objective tumor regressions (31%), the Kaplan-Meier estimated median response duration was 2 years. Seventeen patients discontinued therapy for reasons other than disease progression, and 12 (71%) of 17 maintained responses off-therapy for at least 16 weeks (range, 16 to 56+ weeks).

Objective response and toxicity rates were similar to those reported previously; in an extended analysis of all 306 patients treated on this trial (including those with other cancer types), exposure-adjusted toxicity rates were not cumulative.

In this study, OS following nivolumab treatment in patients with advanced treatment-refractory melanoma compares favourably with that in literature studies of similar patient populations. Responses were durable and persisted after drug discontinuation. Long-term safety was acceptable.

Based on its mechanism of action and data from animal studies, nivolumab can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with nivolumab and for at least 5 months after the last dose of nivolumab.

2.2.5 Ipilimumab

Ipilimumab is a recombinant, human monoclonal antibody that binds to the CTLA-4. Blockade of CTLA-4 augments T-cell activation and proliferation and ipilimumab works via T-cell mediated anti-tumor immune responses.

A variety of studies have demonstrated a clinically meaningful and statistically significant survival benefit with the use of ipilimumab in advanced melanoma.

A survival update at a follow-up of >5 years (5.5 to 6 years) for patients with advanced melanoma who previously received ipilimumab in phase II clinical trials has been recently published (*Lebbè et al, 2014*). Patients who previously received ipilimumab 0.3, 3, or 10 mg/kg in one of six phase II trials have been evaluated. Upon enrolment, patients initially received ipilimumab retreatment, extended maintenance therapy, or were followed for survival only. OS rates were evaluated in patients from 4 studies, and safety and best overall response during ipilimumab retreatment at 10 mg/kg were assessed in one study. Five-year OS rates for previously treated patients who received ipilimumab induction at 0.3, 3, or 10 mg/kg were 12.3%, 12.3% to 16.5%, and 15.5% to 28.4%, respectively. Five-year OS rates for treatment-naive patients who received ipilimumab induction at 3 or 10 mg/kg were 26.8% and 21.4% to 49.5%, respectively. Little to no change in OS was observed from year 5 up to year 6. The objective response rate among retreated patients was 23%. Grade 3/4 immune-related adverse events occurred in 25%, 5.9%, and 13.2% of retreated patients who initially received ipilimumab 0.3, 3, and 10 mg/kg, with the most common being observed in the skin (4.2%, 2.9%, 3.8%) and gastrointestinal tract (12.5%, 2.9%, 3.8%), respectively. At a follow-up of 5 to 6 years, ipilimumab continues to

demonstrate durable, long-term survival in a proportion of patients with advanced melanoma. In some patients, ipilimumab retreatment can re-establish disease control with a safety profile that is comparable to that observed during ipilimumab induction.

There are no adequate and well-controlled studies of ipilimumab in pregnant women. Ipilimumab is classified in pregnancy category C. Ipilimumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In a combined study of embryo-fetal and peri-postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition, at exposure levels either 2.6 or 7.2 times higher by AUC than the exposures at the clinical dose of 3 mg/kg of ipilimumab. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, the ipilimumab-treated groups experienced higher incidences of severe toxicities including abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner compared to controls. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus

2.2.6 Nivolumab and ipilimumab combination

Recently, the results of a phase I study about the combination ipilimumab plus nivolumab in patients with advances melanoma have been reported (*Wolchock et al, 2013*). In this study, IV doses of nivolumab and ipilimumab were administered every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen). The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. A total of 53 patients received concurrent therapy with nivolumab and ipilimumab, and 33 received sequenced treatment. The ORR for all patients in the concurrent-regimen group was 40%. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for ≥24 weeks) was observed in 65% of patients. At the maximum doses that were associated with an acceptable level of adverse events (nivolumab at a dose of 1 mg per kilogram of body weight and ipilimumab at a dose of 3 mg/kg), 53% of patients had an objective response, all with tumor reduction of 80% or more. Grade 3 or 4 adverse events related to therapy occurred in 53% of patients in the concurrent-regimen group but were qualitatively similar to previous experience with monotherapy and were generally reversible. Among patients in the sequenced-regimen group, 18% had grade 3 or 4 adverse events related to therapy and the objective-response rate was 20%. In this study, concurrent therapy with nivolumab and ipilimumab had a manageable safety profile and provided clinical activity that appears to be distinct from that in published data on monotherapy, with rapid and deep tumor regression in a substantial proportion of patients.

2.3 Study rationale

The combination BRAF inhibitor plus MEK inhibitor seems to be more effective in the V600 BRAF mutated advanced melanoma patients compared to treatment with the BRAF inhibitors alone. In fact, a phase I-II study (*Flaherty et al, 2012*) showed a better ORR and PFS in the combination arm (dabrafenib plus trametinib) respect to the single agent treatment (dabrafenib): 76% and 9.4 months versus 54% and 5.8 months respectively. Another phase I study with a similar combination (vemurafenib plus cobimetinib) showed an ORR of 85% in vemurafenib-naïve patients (*Martinez Garcia et al, 2012*)

The above reported phase I study on the combination ipilimumab plus nivolumab (*Wolchock et al, 2013*) has shown that more than half of patients treated at the selected schedule (ipilimumab 3 mg/kg and nivolumab 1 mg/kg) had an objective response, all with tumor reduction of ≥ 80%. Reponses were durable, although longer follow-up is needed.

A recent phase I study has shown a high rate of liver toxicity with the combo ipilimumab plus vemurafenib (*Ribas et al, 2013*) which makes difficult a combination with these two different drugs. Moreover, a better efficacy of the sequencing treatment BRAF inhibitors/ipilimumab vs. the single agent treatment was also observed; for this reason it was also suggested to start immunotherapy treatment in the BRAF V600 mutated melanoma population as first option, in order to increase the percentage of patients who can benefit from the sequencing (*Ascierto et al, 2012*; *Ascierto et al, 2013*), considering the possibility of a fast progression of the disease after the BRAF inhibitors treatment (*Ascierto et al, 2012*).

Taking into account these considerations, it seems impossible to think to combine all the four compounds (the target agents and immunomodulating monoclonal antibodies). The risk of a high rate of toxicity is realistic and would render this approach inapplicable.

Sequencing with these different combinations seems to be more feasible. However, also in this case it would be important to start with the best combination in order to give to the patients the best chance to increase the overall survival.
The aim of this prospective randomized phase II study is to evaluate the sequencing of these different combinations and evaluate which is the best of these approaches.

3. STUDY AIMS AND DESIGN

This prospective randomized phase II study is aimed at evaluating the effects of the sequencing of the two different tested combinations (Combo Target: LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid; Combo Immuno: nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) and at evaluating which is the best of the three tested approaches.

3.1 Objectives of the study

Primary Objectives

The primary objective is to define the best sequencing combination treatment in primary efficacy variable OS.

Secondary Objectives

The secondary objectives are to evaluate the effects of the two sequencing combination treatments on:

- Total PFS;
- Percentage of patients alive at 2 and 3 years;
- Best overall response rate (BORR);
- Duration of response (DoR);
- Biological markers (biomarkers ancillary study).
- Toxicity of the investigational medicinal products (IMPs).
- Quality of life and general health status defined by:
  - Health-related quality of life (HRQoL), by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30);
  - General health status, by means of the European Quality of Life 5-Dimensions (EQ-5D) questionnaire;
  - Impairment of work productivity and activity, by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire;

Biological markers (biomarkers ancillary study)

The objective of the biomarkers ancillary study (to be conducted in a subgroup of approximately 80-90 patients) is to focus on understanding mechanisms of action/resistance. In particular, the ancillarystudy will inform how to sequence targeted RAF/MEK agents with immunotherapy agents (i.e. ipilumumab and nivolumab) in melanoma and will be hypothesis-generating only.

3.2 Endpoints of the study

Primary Endpoint

OS is primary efficacy endpoint of the study. OS will be calculated as the time from the date of randomization until the date of death from any cause.

Any patient not know to have died at the time of data analysis will be censored at the time of the last recorded date on which the patient was know to be alive.

Secondary Endpoints

- Total PFS, calculated from the date of randomization until the date of the second progression (i.e. the progression to second treatment); any progression or death will be considered as an event if patient cannot complete treatment sequence;
- Percentage of patients alive at 2 and 3 years;
- Best overall response rate (BORR);
- Duration of response (DoR) calculated as the time from the date of the first documented response (CR or PR) until the date of the first documented progression or death due to underlying cancer. If the patient with a CR or PR has no progression or death due to underlying cancer, the patient will be censored at the date of last adeguate tumor assessment;
- Health-related quality of life (HRQoL), by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30);
- General health status, by means of the European Quality of Life 5-Dimensions (EQ-5D) questionnaire;
- Impairment of work productivity and activity, by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire;
- Biological markers (biomarkers ancillary study).

Biological markers (Biomarkers ancillary study)

<u>Tumor tissue biomarkers:</u>

- Immune status: CD3, CD8, and CD4 T cells; Activated T cells; T regulatory cells; Dendritic cells;
- Resistance to immunotherapy agents: Checkpoint receptors/ligands; myeloid-derived suppressor cells (MDSCs);
- Resistance to targeted agents: aberrations in MEK/PI3K pathways, cytokines that interact with tyrosine kinase receptors (VEGF, HGF and their cognate receptors);
- Mutational load and neoantigen profile.

Peripheral blood biomarkers:

- Immune status/"Resistance" to immunotherapy agents: Activated T cells; Memory/Exhausted T cells; T regulatory cells; MDSCs; Inflammatory response; C-reactive protein (CRP); TCR Sequencing/Gene Expression analysis;
- Response/Resistance to targeted agents: Apoptotic tumor cells (as measured by circulating tumor DNA); soluble hepatocyte growth factor (sHGF); serum vascular endothelial growth factor (sVEGF); soluble interleukine-2 receptor (sCD25);
- Immunotherapy SNP Panel will be also assessed at baseline.

Study Aim	Objectives	End point
Primary	The primary objective of this study is to define the best sequencing combination treatment in primary efficacy variable OS.	Overall Survival (OS) will be calculated as the time from the date of randomization until the date of death from any cause. Any patient not know to have died at the time of data analysis will be censored at the time of the last recorded date on which the patient was know to be alive.
Secondary	The secondary objectives of the study are to evaluate the effects of the two sequencing combination treatments on: • Total PFS; • Percentage of patients alive at 2 and 3 years; • Best overall response rate (BORR); • Duration of response (DoR); • Biological markers (biomarkers ancillary study); • Toxicity of the investigational medicinal products (IMPs); • Quality of life and general health status defined by: - Health-related quality of life (HRQoL), by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30); - General health status, by means of the European Quality of Life 5-Dimensions (EQ-5D) questionnaire; - Impairment of work productivity and activity, by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire.	• Total PFS, calculated from the date of randomization to the date of the second progression (i.e. the progression to second treatment); any progression or death will be considered as an event if patient cannot complete treatment sequence; • Percentage of patients alive at 2 and 3 years; • Best overall response rate (BORR); • Duration of response (DoR), calculated as the time from the date of first documented response (CR o PR) until the date of the first documented progression or death due to underlying cancer. If a patient with a CR o PR has no progression or death due to underlying cancer, the patient will be censored at the date of last adeguate tumor assessment; • Health-related quality of life (HRQoL), by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30); • General health status, by means of the European Quality of Life 5-Dimensions (EQ-5D) questionnaire; • Impairment of work productivity and activity, by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire; • Biological markers (biomarkers ancillary study).

Study Aim	Objectives	End point
Biomarkers Ancillary Study	The objective of the biomarkers ancillary study is to focus on understanding mechanisms of action/resistance. In particular, the ancillary study: • Will inform how to sequence targeted RAF/MEK agents with immunotherapy agents (i.e. ipilumumab and nivolumab) in melanoma; • Will be hypothesis-generating only.	Tumor tissue biomarkers: • Immune status: CD3, CD8, CD4, CD45RO and CD11c T cells; Activated T cells; T regulatory cells; Dendritic cells; • Resistance to immunotherapy agents: Checkpoint receptors/ligands; myeloid-derived suppressor cells (MDSCs); • Resistance to targeted agents: aberrations in MEK/PI3K pathways; mRNA expression (nanostring method). Peripheral blood biomarkers: • Immune status/"Resistance" to immunotherapy agents: Activated T cells; Memory/Exhausted T cells; T regulatory cells; MDSCs; Inflammatory response; CRP; TCR Sequencing/Gene Expression analysis; • Response/Resistance to targeted agents: Apoptotic tumor cells (as measured by circulating tumor DNA); soluble hepatocyte growth factor (sHGF); serum vascular endothelial growth factor (sVEGF); soluble intercellular adhesion molecule-1 (sICAM-1), soluble interleukine-2 receptor (sCD25); • Immunotherapy SNP Panel will be also assessed at baseline.

Table 4: Summary of study aim

3.3 Study Design

The study will be conducted according to an open-label, prospective, randomized, phase II design.

Randomization will be stratified according to stage arranged in the 4 following strata:

- IIIb/c – M1a
- M1b
- M1c with normal LDH
- M1c with elevated LDH.

Subjects will be assessed for response by computed tomography (CT) or Magnetic Resonance Imaging (MRI).

All measurable and non-measurable lesions must be documented at screening (within 28 days prior to randomization) and re-assessed at each subsequent tumor evaluation (every 8 weeks for the first year, every 12 weeks while the patient is on study). Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis will be performed until disease progression after the second combo treatment per RECIST v1.1. Imaging of the neck should be included if clinically indicated. In the event PET/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. All scans will be collected for a possible independent review.

For patients who discontinue study treatment for reason other than investigator–determined disease progression, tumor assessments should continue to be performed as scheduled.

For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed at baseline and throughout study treatment as clinically indicated. Color photographs with ruler/calipers will be taken at baseline and at all subsequent tumor assessment time points.

The National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTC-AE) Version 4.03 will be used to evaluate the clinical safety of the treatment in this study. Patients will be assessed for AEs at each clinical visit and as necessary throughout the study.

Biomarkers ancillary study

A correlative biological study will be performed for the evaluation of biomarkers on the biological samples available (paraffin-embedded tissue, frozen tissue, blood, serum, etc.). Approximately 80-90 patients will take part in the ancillary study.

3.4 Study Schedule

The following IMPs will be used in the study according the scheme shown in Figure 1:

- **Arm A**: Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) until PD; then Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD.
- **Arm B**: Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD; then Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) until PD.
- **Arm C**: Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) for 8 weeks followed by Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD; then Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) until PD.

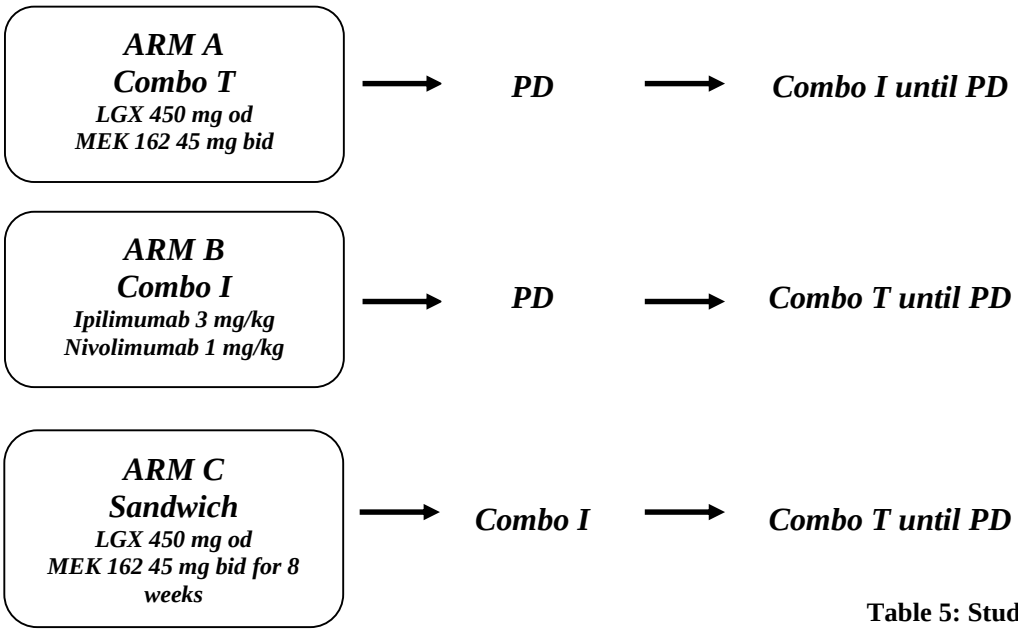

Table 5: Study treatment scheme

Shift from the one combination therapy to the following one can be done (once the procedures of the new screening have been completed) in case of absence of AEs events from the previous combination therapy or in case of grade 1 AEs. In case of grade ≥ 2 AEs from the previous combination therapy, shift to the following combination therapy can be done only when the AE is resolved or has decreased in intensity to at least grade 1. Treatment with any of the treatment schemes will be continued until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, consent withdrawal, death, reasons deemed by the treating physician or study termination by the Sponsor.

3.5 Schedule of Assessments and Procedures

All screening/baseline assessments as outlined in Tables 1 (arm A), 2 (arm B) and 3 (arm C) must be performed within 28 days prior to the first administration of study drugs on Day 1. Results of tests or examinations performed as standard of care before obtaining informed consent and within the 28 days prior to commencing study drugs may be used. All assessments during the study must be performed within a window – 2/+2 days of the day indicated on the schedule of assessment.

Eligibility for the study will be determined by the Investigator from the mandatory screening/baseline assessments performed during screening and according to the study inclusion/exclusion criteria.

First dosing of study drugs will be determined by the patient's eligibility and the laboratory assessments done on Day 1 prior to dosing.

Patients who discontinue study drugs for any reason (e.g. AEs, etc) other than disease progression will continue to be followed until disease progression. Follow-up will continue until the patient has documented disease progression, starts another cancer therapy or withdraws consent.

3.5.1 Screening Examination and Eligibility Screening Form

Written informed consent must be obtained before any study specific assessments or procedures are performed. All screening/baseline evaluations must be performed between Day -28 and -1. Patients who fulfill all the inclusion and none of the exclusion criteria will be accepted into the study.

3.5.2 Procedures for Enrolment of Eligible Patients

A patient who has fulfilled the entry criteria will be given an identifying number. Each identifying number will be unique to the patient for whom it is issued. A patient number will not be re-used if the patient leaves the study. Under no circumstances will patients who enroll in this study and have completed treatment as specified be permitted to re-enroll in the study. A Patient Enrolment and Identification Code List must be maintained by the Investigator.

Eligible patients will be then randomised in one of the three arms in a 1:1:1 ratio, i.e. an equal number of patients will be assigned to one of the three treatment schedules. In each arm and overall, the randomisation will be stratified according to the baseline value of LDH (normal or high – See section 3.3 of the protocol)

3.5.3 Clinical Assessments and Procedures

The following clinical assessments and procedures must be completed for all patients enrolled in this study at screening/baseline and during study visits. All assessments must be performed within a window of 2 days prior to the scheduled visit date and 2 days after the scheduled visit date (- 2 days / + 2 days) for each visit indicated on the schedule of assessment, except for tumor evaluations for which a window of +/- 5 days will apply.

Please refer to Tables 1 (arm A), 2 (Arm B) and 3 (arm C) for specific details and time points collected on clinical assessments and procedures outlined below.

Screening/Baseline:

- Informed Consent Form;
- Demographic data (age, gender, race);
- Medical history (including demographics, relevant medical history, previous and current diseases, prior therapies for melanoma including surgeries and relative responses, prior skin cancer history, therapies and procedures, all medications started within 14 days prior to screening visit);

- Physical exam including height (screening only) and weight and skin examination. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate. Tumor lesions accessible by physical examination should be recorded as well for biopsy purpose also. For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed at baseline and throughout study treatment as clinically indicated. Color photographs with ruler/calipers will be taken at baseline and at all subsequent tumor assessment time points;
- Vital signs (blood pressure, pulse, temperature, respiratory rate);
- A 12-lead ECG;
- ECOG PS;
- Ophthalmological and dermatological examination;
- Echocardiogram;
- Hematology (including hemoglobin, hematocrit, Platelet Count, WBC, ANC);
- Biochemistry (including glucose, BUN, creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, choloride, amylase, lipase, TSH, free T4, free T3,bicarbonate [if routinely performed on venous blood samples], total bilirubin with fractionation into direct and indirect (if total bilirubin elevated), alkaline phosphatase, AST [SGOT], ALT [SGPT]) and LDH;
- Serum pregnancy test (within 24 hours prior to commencement of dosing) for women of child-bearing potential confirmed by serum HCG laboratory test;
- Presence of BRAF V600E or V600K mutation in tumor tissue prior to enrolment;
- Cardiac/Muscle Enzymes: Troponin, Creatine Kinase (CK). If total CK ≥3 X ULN, then measure isoenzymes and myoglobin in blood or urine weekly;
- Urinalysis;
- Tumor assessments including measurable and non-measurable lesions (baseline brain CT or MRI, CT/MRI C/A/P, bone scan if clinically indicated);
- Assessment of HRQoL (EORTC QLQ-C30), general health status (EQ-5D) and impairment of work productivity and activity (WPAI:GH);
- Concomitant therapy;
- AEs (including SAEs) related to study-mandated procedures from time signed Informed Consent is obtained until first dose of study drugs;
- Biopsy of tumoral lesions for the biological study;
- Peripheral Blood Mononuclear Cells (PBMC) for the biological study.

During Study

- Physical exam at every visit;
- Vital signs (blood pressure, pulse, temperature, respiratory rate) at every visit;
- ECOG PS at every visit;
- A 12-lead ECG will be performed at at screening/baseline, at 2nd baseline at the 1th month and every 12 weeks while the patient is on study;
- The ophthalmologic examination will be performed at the 2nd baseline visit and then when clinically indicated;
- The dermatologic evaluation will be performed every 8 weeks while the patient is on study;
- The echocardiogram will be performed at screening/baseline, at the 2nd baseline (and 3rd baseline ARM C only), at the 1st month and every 12 weeks while the patient is on study;
- Hematology (including hemoglobin, hematocrit, platelet count, WBC, ANC) at every visit
- Biochemistry (including glucose, BUN, creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, choloride, amylase, lipase, TSH, free T4, free T3,bicarbonate [if routinely performed on venous blood samples], total bilirubin with fractionation into direct and indirect (if total bilirubin elevated), alkaline phosphatase, AST [SGOT], ALT [SGPT] and lactate dehydrogenase (LDH) at every visit;
- A serum pregnancy test to be performed every 6 (± 1) weeks during the treatment period;
- Cardiac/Muscle Enzymes: Troponin, Creatine Kinase (CK). If total CK ≥3 X ULN, then measure isoenzymes and myoglobin in blood or urine weekly;
- Urinalysis (only if clinically indicated);
- Biopsy of tumoral lesions for the biological study (if applicable);
- PBMCs for the biological study will be taken (if applicable).
- Tumor assessments of both measurable and non-measurable disease (baseline brain CT or MRI, CT/MRI C/A/P, bone scan if clinically indicated) every 8 weeks for the first year and every 12 weeks thereafter while the patient is on study;
- Assessment of HRQoL (EORTC QLQ-C30), general health status (EQ-5D) and impairment of work productivity and activity (WPAI:GH) will be performed every 28 days during the Combo Target therapy and at administration of nivolimumab+ipilimumab (i.e. every 21 days for 4 doses) and then every two administrations (i.e.every 28 days) of nivolimumab during the Combo Immuno therapy;
- Concomitant therapy throughout the study;
- AEs (including SAEs) throughout the study;
- IMP administration throughout the study.

End of Study Visit (when patient discontinues study drugs)

- Physical exam;
- Vital signs (blood pressure, pulse, temperature, respiratory rate);
- 12-lead ECG (if clinically indicated)
- ECOG PS
- Hematology (including hemoglobin, hematocrit, Platelet Count, WBC, ANC);
- Biochemistry (including glucose, BUN, creatinine or creatinine clearance, sodium, potassium, calcium, magnesium, choloride, amylase, lipase, TSH, free T4, free T3,bicarbonate [if routinely performed on venous blood samples], total bilirubin with fractionation into direct and indirect (if total bilirubin elevated), alkaline phosphatase, AST [SGOT], ALT [SGPT]) and LDH;
- Cardiac/Muscle Enzymes: Troponin, Creatine Kinase (CK). If total CK ≥3 X ULN, then measure isoenzymes and myoglobin in blood or urine weekly;
- Urinalysis;
- Serum pregnancy test;
- Tumor assessments if not performed within the prior 6 weeks (CT/MRI C/A/P, CT/MRI of brain as clinically indicated) including assessment of any tumor lesions accessible by physical examination;
- Assessment of HRQoL (EORTC QLQ-C30), general health status (EQ-5D) and impairment of work productivity and activity (WPAI:GH);
- Concomitant therapy;
- AEs (including SAEs);

Follow up visit within 28 days from discontinuation of study drugs

- Monitoring of AEs and SAEs
- Follow up for disease progression for those patients who have discontinued study drug for any reason (i.e. AE, etc) other than disease progression;
- Assessment of HRQoL (EORTC QLQ-C30), general health status (EQ-5D) and impairment of work productivity and activity (WPAI:GH);
- Serum pregnancy test;
- New anti-cancer therapy administration.

3.5.4 Biomarker study

Tumor biopsies and peripheral blood samples will be taken according to the following scheme (Table 6):

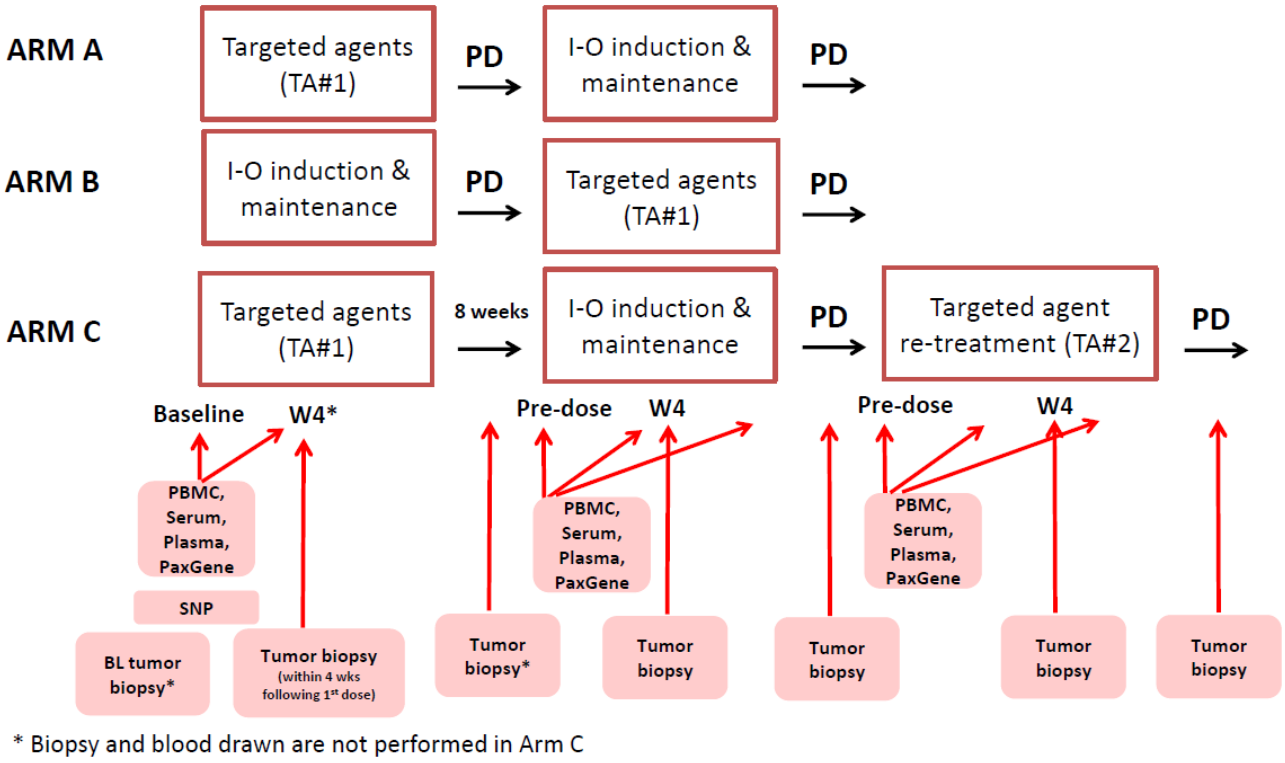

Table 6: Biomarker study treatment scheme

Note: Baseline tumor biopsies can be archival if is collected after prior systemic therapy; otherwise a fresh biopsy will be collected

Tumor biopsies:

The ancillary study requires tumor biopsies at baseline, on-treatment (within first 4 weeks after first dose), and upon progression when feasible.

In arm A, biopsy of tumoral lesions for the biological study will be performed at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Target therapy; and at Week 4 and disease progression 2 (DP 2) during Combo Immuno therapy. Biopsy of tumoral lesions will be mandatory at baseline 1 and at the first disease progression (PD1), and will be optional at the other time-points.

In arm B, biopsy of tumoral lesions for the biological study will be performed at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Immuno therapy; and at Week 4 and disease progression 2 (DP 2) during Combo Target therapy. Biopsy of tumoral lesions will be mandatory at baseline 1 and at the first disease progression (PD1), and will be optional at the other time-points.

In arm C, biopsy of tumoral lesions for the biological study will be performed at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Immuno therapy; and at Week 4 and disease progression 2 (DP 2) during the 2nd Combo Target therapy.

Biopsy of tumoral lesions will be mandatory at baseline 1 and at the first disease progression (PD1), and will be optional at the other time-points. A minimum of 15 x tissue sections will be collected for each patient/time point.

Fresh baseline biopsies will be performed in patients with easily accessible biopsy sites (subcutaneous and lymph nodes) and archived samples will be allowed for patients that cannot be biopsied. Procedures for sample collection and processing will be given to Investigators. Sites will be provided with appropriately containers with formalin. Sample will remain in the 10% Neutral Buffered Formalin for a minimum of 24-48 hours but no more than 96 hours. A matched paraffin embedded (FFPE) tissue block will be then stored ambient at the site until shipment.

Collection of the on-treatment sample should be encouraged, in order to obtain at least 30 (out of possible 138) matched pre- and on-treatment samples for Arm A/C and 30 (out of 69 patients) matched pre- and on-treatment samples for Arm B. Path assessments will be regularly performed to ensure that collected samples are of good quality.

Peripheral blood samples:

In arm A, peripheral blood samples will be taken at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Target therapy; and at baseline 2, Week 4 and disease progression 2 (DP 2) during Combo Immuno therapy.

In arm B, peripheral blood samples will be taken at baseline 1, Week 4 and disease progression 1 (DP 1) during Combo Immuno therapy; and at baseline 2, Week 4 and disease progression 2 (DP 2) during Combo Target therapy.

In arm C, peripheral blood samples will be taken at baseline 1, baseline 2 and Week 4 during Combo Immuno therapy; and at baseline 3 and Week 4 during the 2nd Combo Target therapy. In arm C, peripheral blood samples will be taken at baseline 1, at baseline 2, Week 4 and disease progression 1 (DP 1) during Combo Immuno therapy; and at baseline 3, Week 8 and disease progression 2 (DP 2) during the 2nd Combo Target therapy.

In all arms, whole blood for SNP will be taken at baseline 1 only.

3.5.5 Efficacy Assessments and biomarkers study

Biopsies

Biopsies at baseline, on-treatment (within first 8 weeks after first dose), and upon progression when feasible, will be obtained for patients with accessible tumors upon patient's consent to participate in the biomarker study. Accessible lesions are defined as tumor lesions which are easily biopsiable i.e. cutaneous, sub-cutaneous and palpable lymph nodes. Failure to obtain sufficient tumor sample, after making best efforts, will not be considered a protocol violation. Lesions with the biggest change in size, based on interval evaluation, are recommended to

be excised at time of progressive disease. Whenever possible, biopsies at progression should be obtained within 3 days of study drug discontinuation. This may require prolonging the treatment a short time after tumor evaluation demonstrates progressive disease.

A minimum of 15 x tissue sections will be collected for each patient/time point. Biopsies will be immediately transferred into the provided vials, filled with formalin. The biopsies will be fixed for 24±2 hours, transferred into 70% ethanol and then (always in ethanol) shipped to a central pathology lab for paraffin embedding. In cases where a reasonable size biopsy (e.g., excisional biopsy, 5 mm punch, or more than a single 14 gauge core biopsy) could be collected with formalin fixation, every effort should also be made to collect a fresh frozen biopsy at disease progression. Optimally both specimens should be available when biopsy is of a reasonable size.

The following tumor tissue biomarkers will be measured:

- Immune status: CD3, CD8, CD4, CD45RO and CD11c T cells; Activated T cells; T regulatory cells; Dendritic cells;
- Resistance to immunotherapy agents: Checkpoint receptors/ligands; myeloid-derived suppressor cells (MDSCs);
- Resistance to targeted agents: aberrations in MEK/PI3K pathways; mRNA expression (nanostring method).

Gene panel:

Using the Ion Torrent technology, the following gene-panel options (which have been already successfully tested on DNA samples from FFPE tissues) can be used for the assessment of the alterations into the MAPK-PI3K pathways

1. Hotspot regions in Ion Ampliseq Cancer Hotspot panel (~2,800 mutations of 50 oncogenes and tumor suppressor genes): 1 pool (10-15 ng per DNA sample)*

ABL1	*EGFR*	*GNAS*	*KRAS*	*PTPN11*
AKT1	*ERBB2*	*GNAQ*	*MET*	*RB1*
ALK	*ERBB4*	*HNF1A*	*MLH1*	*RET*
APC	*EZH2*	*HRAS*	*MPL*	*SMAD4*
ATM	*FBXW7*	*IDH1*	*NOTCH1*	*SMARCB1*
BRAF	*FGFR1*	*JAK2*	*NPM1*	*SMO*
CDH1	*FGFR2*	*JAK3*	*NRAS*	*SRC*
CDKN2A	*FGFR3*	*IDH2*	*PDGFRA*	*STK11*
CSF1R	*FLT3*	*KDR*	*PIK3CA*	*TP53*
CTNNB1	*GNA11*	*KIT*	*PTEN*	*VHL*

2. Exons within melanoma-associated genes from *Comprehensive Cancer Panel*: 3 pools (10-15 ng per pool, 30-45 ng per DNA sample)*

GENE	Position	GENE	Position
AKT3	chr1	HRAS	chr11
NRAS	chr1	ARID2	chr12
IDH1	chr2	CDK4	chr12
BAP1	chr3	KRAS	chr12
MITF	chr3	RB1	chr13
PIK3CA	chr3	AKT1	chr14
KDR	chr4	IDH2	chr15
KIT	chr4	MAP2K1	chr15
BRAF	chr7	ERBB2	chr17
MET	chr7	NF1	chr17
CDKN2A	chr9	TP53	chr17
GNAQ	chr9	AKT2	chr19
NOTCH1	chr9	GNA11	chr19
PPP6C	chr9	MAP2K2	chr19
PTEN	chr10	GNAS	chr20
CCND1	chr11	DDX3X	chrX

3. Exons within >400 oncogenes and tumor suppressor genes (*Comprehensive Cancer Panel*): 4 pools (10-15 ng per pool, 40-60 ng per DNA sample)*

**amount is referred to good quality DNA; thus, quantity of DNA from FFPE samples could be higher*

Study of peripheral blood biomarkers

Peripheral blood mononuclear cell (PBMC) samples will be collected for the biomarkers study.

The following peripheral blood biomarkers will be measured:

- Immune status/"Resistance" to immunotherapy agents: Activated T cells; Memory/Exhausted T cells; T regulatory cells; MDSCs; Inflammatory response; CRP; TCR Sequencing/Gene Expression analysis;
- Response/Resistance to targeted agents: Apoptotic tumor cells (as measured by circulating tumor DNA); soluble hepatocyte growth factor (sHGF); serum vascular endothelial growth factor (sVEGF); soluble intercellular adhesion molecule-1 (sICAM-1); soluble interleukine-2 receptor (sCD25).

Immunotherapy SNP Panel will be also assessed at baseline.

3.5.6 Tumor Response Criteria

Tumor evaluation will be assessed at screening/baseline (between Day -28 and -1) by means of CT or MRI of the chest, abdomen and pelvis (C/A/P), every 8 weeks for the first year and every 12 weeks thereafter while the patient is on study, and at the end of study visit. A window of +/-5 days of scheduled visit is allowed to complete tumor assessments at the required intervals.

Radiological tumor assessments of C/A/P will be done for measuring extent of disease. In addition, all patients must have a baseline brain CT and/or MRI to assess for brain metastasis. Patients with known or suspected bone metastases should undergo radionuclide bone scan or PET scan at baseline and as per institutional standard of care thereafter.

All measurable and non-measurable lesions must be documented at screening (within 28 days prior to randomization) and re-assessed at each subsequent tumor evaluation (every 8 weeks for the first year, every 12 weeks while the patient is on study). Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis will be performed until disease progression after the second combo treatment. Imaging of the neck should be included if clinically indicated. In the event PET/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. All scans will be collected for a possible independent review.

In case of a single new lesion treated with surgery or radiotherapy, if all the other sites are under response patients should be treated beyond progression with the first therapy. For switching to the next treatment there should be measurable disease and the progression should be evident even in the other lesions.

As indicated in Section 4.6, patients with PD and evidence of unoperable brain metastases without the involvement of other sites will not undergo the biopsy and will continue treatment according the protocol arm.

For patients who discontinue study treatment for reason other than investigator–determined disease progression, tumor assessments should continue to be performed as scheduled.

Tumor responses will be assessed by the Investigator according to RECIST Criteria (version 1.1). Both measurable and non-measurable lesions will be assessed by the Investigator. In the case of SD, measurements must have SD for at least 6 weeks. For assessing response in patients with measurable disease, the preferred radiologic tumor response assessment is the CT scan with oral and IV contrast. If IV contrast is contraindicated, a non-contrast chest CT will be done with abdominal/pelvic contrast enhanced MRI. If contrast enhanced MRI is contraindicated then non-contrast MRI will suffice. CT/MRI scans of extremities may be done as appropriate in individual patients. PET scan, bone scan, and ultrasound, are not adequate for RECIST response assessment. Patients should be assessed at designated time-points using a consistent imaging modality. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. If more than one method of assessment is used at baseline, select the most accurate method according to RECIST when recording data; in addition, this method should again be performed in all subsequent evaluations. Tumor measurements should be made by the same Investigator/radiologist for each patient during the study to the extent that this is feasible. Objective responses by RECIST (Version 1.1) should be confirmed by repeat assessments at least 4 weeks after initial documentation of response. Clinical lesions will only be considered measurable when they are superficial and > 10 mm diameter as assessed using calipers (e.g. skin

nodules). For skin lesions, documentation by color photography with ruler is required. CT scan is the preferred modality for skin lesions and should be used wherever possible.

3.5.7 Outcomes Research Assessments

Health-related Quality of Life

HRQoL will be evaluated by means of the 30-item European Organisation for Research and Treatment of Care quality of life questionnaire (EORTC QLQ-C30) (Appendix 4).

The EORTC QLQ-C30 (*Aaronson et al, 1993*) is the mostcommonly used QoL instrument in advanced melanoma clinical studies.

It is a 30--item instrument that has gained wide acceptance in oncology clinical studies. TheEORTC QLQ--C30 comprises six functional scales (physical functioning, cognitive functioning, emotional functioning, social functioning and global quality of life) as well as nine symptomscales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items,responses for all items are 4 point categorical scales ranging from 0 (Not at all) to4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

General Health Status

General health status will be evaluated by means of the European Quality of Life 5-Dimensions (EQ-5D) (*Brooks, 1996*) (Appendix 5), that comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety), each consisting of 3 levels (no, some/moderate and extreme problems), and a 0-100 mm visual analog scale (VAS) where 0 = worst imaginable health state and 100 = best imaginable health state. The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.

Work Productivity and Activity Impairment

Impairment of work productivity and activity will be evaluated by means of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire (*Reilly et al, 1993*) (Appendix 6).

This questionnaire is a 6-item questionnaire yielding four different types of scores. TheWPAI:GH was created as a patient--reported quantitative assessment of the amount ofabsenteeism (work time missed), presenteeism (impairment at work /reduced onthejobeffectiveness), work productivity (overall work impairment/absenteeism plus presenteeism) anddaily activity impairment attributable to general health. WPAI outcomes are expressed asimpairment percentages, with higher numbers indicating greater impairment and lessproductivity, i.e. worse outcomes. The recall period in all WPAI validation studies is 7 days. Thegeneral literature on recall burden suggests that a longer recall period would not be suitable forthe type of information being elicited in the WPAI.

In theory, a shorter recall period wouldimprove accuracy of WPAI responses, but this has not been tested. Assessment of workproductivity will be conducted at each site (or remotely) with the appropriately translated andvalidated version of the WPAI.

3.5.8 Laboratory Assessments

Hematology and biochemistry will be done as part of regular safety assessments. Specifically:

- Hematology: Hemoglobin, WBC, ANC, platelet count
- Biochemistry: glucose, BUN, creatinine or creatinine-clearance, sodium, potassium, calcium, magnesium, choloride, amylase, lipase, TSH, free T4, free T3,bicarbonate (if routinely performed on venous blood samples), total bilirubin with fractionation into direct and indirect bilirubin (if total bilirubin is elevated), alkaline phosphatase, AST [SGOT], ALT [SGPT]) and LDH
- Serum Pregnancy Test in women of child-bearing potential (within 24 hours prior to first administration of study drug).

4. STUDY POPULATION

4.1 Inclusion Criteria

A subject is eligible for the study if all of the following criteria are met:

1) Patients of either sex aged ≥ 18 years;
2) Histologically confirmed stage III (unresectable) or stage IV melanoma with the BRAF V600 mutation. Patients with mucosal melanoma (but not those with ocular melanoma) are eligible for study participation;
3) Treatment naïve patients. As previous systemic treatmtne for melanoma only interferon is permitted (note that prior adjuvant melanoma therapy is permitted if completed at least 6 weeks prior to randomization, and all related adverse events have either returned to baseline or stabilized).
4) Measurable disease by computed tomography (CT) or Magnetic Resonance Imaging (MRI) per RECIST 1.1 criteria;
5) Presence of BRAF V600E or V600K mutation in tumor tissue prior to enrolment;
6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (appendix 7);
7) Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. An archive sample is mandatory at the screening visit; however, a fresh sample would be preferable;
8) Female subjects of childbearing potential must have a negative serum pregnancy test result at Baseline and must practice a reliable method of contraception for the total study duration plus 23 weeks (i.e. 30 days plus the time required for nivolumab to undergo five half lives) after the last dose of nivolumab and ipilimumab;
9) Men who are sexually active with women of childbearing potential must practice a reliable method of contraception for the total study duration plus 31 weeks (i.e. 80 days plus the time required for nivolumab to undergo five half lives) after the last dose of nivolumab and ipilimumab;
10) Adequate bone marrow haematological function: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L AND platelet count ≥ 100 x 10^9/L AND haemoglobin ≥ 9 g/dL;
11) Adequate liver function: total bilirubin ≤ 1.5 x upper limit of normal (ULN) AND aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 X ULN (< 5 x ULN if liver metastases);
12) Adequate renal function: serum creatinine ≤ 1.5 mg/dL OR creatinine clearance ≥ 60 mL/min in males and ≥ 50 mL/min in females (calculated according to Cockroft-Gault formula);
13) Serum calcium levels, international normalised ratio (INR) and partial thromboplastin time were within normal limits;
14) Life expectancy of at least 3 months;
15) Ability to understand study-related patient information and provision of written informed consent for participation in the study.

4.2 Exclusion Criteria

A subject is excluded from the study if any of the following criteria are met:

1) Active brain metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration;
2) Subjects with active, known or suspected autoimmune disease;
3) Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of treatment;
4) Prior treatment with an anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody;
5) Female subjects who are pregnant (positive pregnancy test), breast-feeding, or who are of childbearing potential and not practicing a reliable method of birth control;
6) Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the investigator's opinion makes it undesirable for the patient to participate in the study, or which would jeopardize compliance with the protocol, or would interfere with the results of the study;
7) Patients with a history of cardiovascular or interstitial lung disease and evidence or risk of retinal vein occlusion or central serous retinopathy (Past or present evidence of rethinophaty central serous retinopathy - CSR -, occlusion of retinal - RVOo retinal degenerative disease) or ophthalmopathy, which according to the ophthalmologic evaluation at baseline could be considered a risk factor for CSR / RVO (eg. cupping of the optic disc, visual field defect, intraocular pressure - (eg: central IOP - > 21 mmHg).;
8) History of Gilbert's syndrome;
9) Inability to regularly access centre facilities for logistical or other reasons;
10) History of poor co-operation, non-compliance with medical treatment, or unreliability;
11) Participation in any interventional drug or medical device study within 30 days prior to treatment start.
12) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection;
13) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS);

4.3 Study treatments

Treatments information is given in the following table (Table 7).

Treatment Arm	Number of Pts Planned	Type of Study Drug	Compound	Minimum dose and unit	Frequency	Administration route
Arm A	69	Investigational	LGX818	450 mg	Daily	PO
		Investigational	MEK162	90 mg	Daily	PO
		Investigational	Ipilimumab	3 mg/kg	q3 weeks for 4 cycles	IV
		Investigational	Nivolumab	1 mg/kg	q3 weeks for 4 cycles then q2 weeks	IV
Arm B	69	Investigational	LGX818	450 mg	Daily	PO
		Investigational	MEK162	90 mg	Daily	PO
		Investigational	Ipilimumab	3 mg/kg	q3 weeks for 4 cycles	IV
		Investigational	Nivolumab	1 mg/kg	q3 weeks for 4 cycles then q2 weeks	IV
Arm C	69	Investigational	LGX818	450 mg	Daily	PO
		Investigational	MEK162	90 mg	Daily	PO
		Investigational	Ipilimumab	3 mg/kg	q3 weeks for 4 cycles	IV
		Investigational	Nivolumab	1 mg/kg	q3 weeks for 4 cycles then q2 weeks	IV
TOTAL	207					

Table 7: Treatments used in the study

4.4 Concomitant Medication and Treatment

The patient must 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 or the Surgical and Medical Procedures eCRF.

Patients taking concomitant medications chronically should maintain the same dose and dose schedule throughout the study if medically feasible. On the days PK blood sampling is performed, the patient should continue their consistent use of other concomitant medication.

However, if a concomitant medication is used intermittently during the study, this medication should be avoided on these days, if medically feasible.

A single new lesion can be treated with surgery or radiotherapy, provided that all the other measurable lesions have not yet progressed.

Prohibited concomitant therapy

Anticancer therapies (including chemo- or biologic-therapy or radiation therapy, covering >30% of the red bone marrow reserve, and surgery) are prohibited while the patients are receiving study treatment. If such therapeutic measures are required for a patient then the patient must be discontinued from study treatment.

4.5 Drug Interaction

LGX818 is a reversible inhibitor of CYP2B6, CYP2C9, CYP3A4 and UGT1A1. It is also a time dependent inhibitor of CYP3A4. MEK162 is also a reversible inhibitor of CYP2B6.

Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2B6, CYP2C9, CYP3A4, and UGT1A1 or those substrates that have a narrow therapeutic index (NTI).

There is a potential for MEK162 and LGX818 to induce CYP3A4 at concentrations >10-50 uM, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least one form of non-hormonal contraception will be needed during the participation in this study. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with MEK162 and/or LGX818.

LGX818 has been identified to be primarily metabolized by CYP3A4 *in vitro*. It is advised that LGX818 should be taken with caution when co-administered with strong inhibitors of CYP3A4.

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.

In vitro data showed that both MEK162 and LGX818 are substrates of P-gp. MEK162 is also a substrate of breast cancer resistant protein (BCRP). Thus, the use of drugs that are known to inhibit or induce P-gp and BCRP should be used with caution. LGX818 is a BCRP inhibitor. It is also a potent inhibitorof the renal transporters OAT1, OAT3 and OCT2 and the hepatic transporters OATP1B1 and OATP1B3. Therefore the co-administration of drugs that are known to be sensitive or NTI substrate of BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 should be used with caution.

The solubility of MEK162 and LGX818 is pH dependent and a 10-fold decrease in solubility is observed between pH 1 and 2. Patients receiving concomitant treatments that could potentially modify the gastric pH (i.e. PPI) should be instructed to take them at least two hours after the administration of MEK162.

Drugs with a conditional, possible, or known risk to induce Torsade de Pointes (TdP) should be used with caution. Patients receiving such medications 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 comedications, 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 trial.

4.6 Criteria for Premature Withdrawal

Patients have the right to withdraw from the treatment or from the study at any time and irrespective of the reason. Patients who discontinue from the study will be asked to return to the clinic within 28 days of the last dose of IMP for the follow-up visit and to be contacted every 12 weeks until 24 months for long term survival follow-up.

If lost to follow-up, the Investigator should make every effort to contact the patient by telephone or by sending a registered letter to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the Investigator without their consent. The Investigator may withdraw patients from the study in the event of intercurrent illness, AEs, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is felt by the Investigator that it is in the best interest of the patient to be terminated from the *study*. Any administrative or other reasons for withdrawal must be documented and explained to the patient.

If the reason for removal of a patient from the study is an AE, the principal specific event will be recorded on the eCRF. The patient should be followed until the AE has resolved, if possible. All patients will be followed for safety for 28 days following the last dose of study medication and every 12 week until 24 months after last patient enrolled (long term follow-up visit).

Patients with PD and evidence of unoperable brain metastases without the involvement of other sites will not undergo the biopsy, and will continue treatment according protocol arm.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational drugs are LGX818 and MEK162 given in combination (Combo Target) and nivolumab 1 mg/kg solution intravenously combined with ipilimumab 3 mg/kg solution intravenously every 3 weeks for 4 doses then nivolumab 3 mg/kg solution intravenously every 2 weeks (Combo Immuno).

5.1 Combo Target

5.1.1 Recommended Dose

Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) will be given until PD in arm A, and will be given for 8 weeks and then following PD 1 after Combo Immuno until PD 2 in arm C.

LGX818 and MEK162 will be administered orally on a daily schedule as a fixed combination dose, and not by body weight or body surface area (Table 8).

Study treatments	Pharmaceutical form and route of administration	Single Dose	Frequency	Total Daily Dose
LGX818[a]	Capsules for oral use	450 mg	Once daily	450 mg
MEK162[b]	Tablets for oral use	45 mg	Twice daily	90mg

[a]LGX818 will be provided as 100 mg and 50 mg capsules
[b]MEK162 will be provided as 15 mg tablets

Table 8: Combo Target dose and treatment schedule

Patients will be supplied with a sufficient number of tablets and/or capsules for the number of doses to be taken prior to the next scheduled visit. In addition, patients will be provided a dosing diary and should document in this diary each prescribed dose, and whether it was taken or not.

If a patient vomits at any time after dosing, the dose of study drug should not be re-administered. Doses of MEK162 that are omitted for AEs or any other reason should not be made up later in the day, or at the end of the dosing period. Doses of LGX818 that are omitted for AEs or any other reason can be taken up to 12 hours prior to the next dose.

Patients must avoid consumption of grapefruit or grapefruit juice 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.

Complete dosing instructions will be provided to study patients and will include the minimum times between doses and instructions for missed doses. Patients will also be instructed not to chew, crush, or dissolve tablets and/or capsules of study drugs. The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). All dosages prescribed and dispensed to the patient and

all dose changes and all missed doses during the study must be recorded on the Dosage Administration Record eCRF.

Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at the next visit. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drugs for subsequent dosing.

5.1.2 Dose Modifications, Interruption and delays criteria for Combo Target

Patients will be monitored for adverse events at each visit with the NCI CTCAE version 4.03 used for all grading.

For patients who do not tolerate LGX818 and/or MEK162 initial dosing schedule, dose adjustment is permitted in order to allow the patient to continue on study drug (see Table 9). A dose reduction below 50 mg bid for LGX818 and below 15 mg od for MEK162 is not allowed. Dose interruptions of more than 28 consecutive days are not allowed.

Dose level	LGX818	MEK162
0 (starting dose)	450 mg od	45 mg bid
-1	300 mg od	30 mg bid
-2	200 mg od	15 mg bid
-3	100 mg od	-
-4	50 mg od	-

Dose reduction should be based on the highest AE grade

Table 9: Dose reduction for LGX818 and MEK162

Doses of MEK162 that are omitted for AEs or any other reason should not be made up later in the day, or at the end of the dosing period. Doses of LGX818 that are omitted for AEs or any other reason can be taken up to 12 hours prior to the next dose. For both LGX818 and MEK162, when the toxicity that resulted in a dose reduction improves to Grade 1 or less, the dose can be re-escalated at the investigators discretion provided there are no other concomitant toxicities.

If MEK162 is dose reduced due to left ventricular dysfunction, no dose re-escalation is allowed.

All dosing interruptions and changes must be recorded on the Dosage Administration Record eCRF.

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below (Table 10). All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03).

In general, doses should not be reduced or interrupted for Grade 1 toxicities, but treatment to control symptoms should be provided as appropriate. All AEs should be followed weekly or as clinically appropriate until stabilization or resolution.

If a patient on the Combo Target therapy discontinues treatment with MEK162, the patient may continue treatment with LGX818. However, due to the limited efficacy of MEK162 alone in the study population, if a patient on the Combo Target therapy discontinues treatment with LGX818, he/she must discontinue treatment with MEK162, complete the end of treatment visit and continue to be followed until disease progression.

Please refer to Table 10 for dose adjustment recommendations for LGX818 and/or MEK162 induced toxicities. Please refer to Appendix 1and Appendix 2 for additional supportive care guidelines for the management of LGX818/MEK162 and MEK162-induced skin toxicity and diarrhoea respectively.

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.
Gastrointestinal disorders	
Diarrhea	
Grade 1	Maintain dose level of LGX818 and MEK162, but initiate anti-diarrhea treatment (see Appendix 3).
Grade 2	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
Grade 3	Omit dose of LGX818 and MEK162 until resolved to Grade ≤ 1, then reduce dose of LGX818 and MEK162 by 1 dose level*.

Grade 4	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	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. 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	Maintain dose level of LGX818 and MEK162
Grade ≥ 3	Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment
Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level of LGX818 and MEK162
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose of LGX818 and MEK162 until resolved to ≤ Grade 1, then maintain dose level of LGX818 and MEK162
Grade ≥3 (> 3.0 x ULN)	Omit dose of LGX818 and MEK162 and discontinue patient from study treatment.
Investigations (Hepatic)	
Bilirubin	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level of LGX818 and MEK162
Grade 2 (> 1.5 – 3.0 x ULN)	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
Grade ≥ 3 (> 3.0 x ULN)	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	Maintain dose level of LGX818 and MEK162
Grade 2 or Grade 3	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
Grade 4	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	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.
AST or ALT > 5.0 x ULN and total blood bilirubin ≥Grade 2	Omit dose of LGX818 and MEK162 and discontinue patient from study drug treatment.
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. 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.

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 LGX8182 - 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
If CPK increase measure serum creatinine to assess for renal impairment. Rhabdomyolysis definition according this protocol: • Muscle symptoms (typically muscle pain, weakness in the literature; specific PTs to be defined per cited current MedDRA version for the CSPD) • CK >10X ULN (CTCAE Grade 4) or CK >10,000 IU/L • hospitalization/medical intervention with IV hydration	
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
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 leveld of LGX818 and MEK162
Grade 3	Omit 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]
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	Omit 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 3)
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
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
Edema	
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 ≤ 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	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
[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	

Table 10: Recommended dose modifications associated with treatment-related adverse events

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, cardiologist or dermatologist should be consulted as deemed necessary.

5.1.3 Formulation, Packaging and Labelling of Combo Target

Study drug packaging will bear a label with the identification required by local law, the protocol number, drug identification and dosage (Table 11).

Medication labels (LGX818, MEK162) will be in the local language and comply with the legal requirements of each country in which the study will be conducted. They will include storage conditions for the drugs, and a unique medication number

Study treatments	Packaging	Labelling (and dosing frequency)
MEK162	Tablets in bottles	Labelled as "MEK162" (BID) Study treatment packaging has a label containing a write-in space for the patient number which will be hand-written onto the label by the responsible site personnel. A unique medication number is printed on this label.
LGX818	Capsules in bottles	Labelled as "LGX818" (OD) Study treatment packaging has a label containing a write-in space for the patient number which will be hand-written onto the label by the responsible site personnel. A unique medication number is printed on each part of this label.

Table 11: Packaging and labelling

LGX818

LGX818 100 and 50 mg will be provided as capsules and packaged per strength into bottle.

Each bottle will be labelled at a minimum with a unique identifier (medication number), the lot number, contents (number of capsules), dosage strength and storage conditions and the name and address of the sponsor.

MEK162

MEK162 15 mg will be provided as film-coated tablets and packaged into high-density polyethylene bottles. Each bottle will be labelled at a minimum with a unique identifier (medication number), contents (number of tablets), dosage strength, storage conditions and the name and address of the sponsor.

5.2 Combo Immuno

5.2.1 Recommended Dose

Combo Immuno (nivolumab 1 mg/kg solution (IV) combined with ipilimumab 3 mg/kg solution (IV) every 3 weeks for 4 doses then nivolumab 3 mg/kg solution (IV) every 2 weeks) will be given until PD in arm B, and will be given following PD after Combo Target in arm A and C.

Nivolumab and ipilimumamb will be administered IV, as reported in Table 12.

Study treatments	Pharmaceutical form and route of administration	Single Dose	Frequency
Nivolumab	Solution for infusion	1 mg/kg	Every 3 weeks for 4 doses in combination with ipilimumab than every two weeks until PD as monotherapy
Ipilimumamb	Solution for infusion	3 mg/kg	Every 3 weeks for 4 doses in combination with nivolumab

Table 12: Combo Immuno dose and treatment schedule

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

The first dose is to be administered within 3 days following randomization. Nivolumab is to be administered first. The second infusion will always be the ipilimumab study drug, and will start no sooner than 30 minutes after completion of the nivolumab infusion. Separate infusion bags and filters for nivolumab and ipilimumab must be used for each infusion.

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See belowfor premedication recommendations following a nivolumab or ipilimumab related infusion reaction.

Nivolumab

Nivolumab is to be administered as a 60-minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Nivolumab vials must be stored at a temperature of 2° C to 8° C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab Investigator Brochure section for "Recommended Storage and Use Conditions" and/or pharmacy reference sheets.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Ipilimumab

Ipilimumab is to be administered as a 90-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-2-ethylhexyl-phthalate) or glass containers and is stable for 24 hours at 2-8 ºC or room temperature/room light (RT/RL). For ipilimumab storage instructions, refer to ipilimumab Investigator Brochure and/or pharmacy reference sheets.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

5.2.2 Dose Modifications, Interruptions and delays criteria for Combo Immuno

Dose delay criteria

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). All study drugs must be delayed until treatment can resume

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:

- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay

- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for AST, ALT, or total bilirubin:
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥3 toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Because of the potential for clinically meaningful nivolumab or ipilimumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity.

In order to standardize the management across the Combo Immuno therapy, for the overlapping adverse event management algorithms present in both the nivolumab and ipilimumab Investigator's Brochure (GI, hepatic, and endocrine algorithms), the recommendations are to follow the nivolumab Investigator's Brochure adverse event algorithms as opposed to the ipilimumab Investigator's Brochure algorithms. Therefore, the algorithms recommended for utilization of nivolumab and ipilimumab are included in Appendix 3.

Dose modifications criteria

Dose reductions or dose escalations are not permitted for both nivolumab and ipilimumab.

Criteria to resume treatment

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin

- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (see below) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhoea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time-point per protocol. However, if the treatment is delayed past the next scheduled time-point per protocol, the next scheduled time-point will be delayed until dosing resumes.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified below.

Discontinuation criteria

Treatment with nivolumab and ipilimumabshould be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug--related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhoea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhoea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    a) Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    b) Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:

    AST or ALT > 8 x ULN

    Total bilirubin > 5 x ULN

    Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

Treatment of Nivolumab- or Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported as a SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.03) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤24 hours).

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen);remain at bedside and monitor subject until resolution of symptoms.

Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressure or ventilator support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

5.2.3 Formulation, Packaging and Labelling of Combo Immuno

Nivolumab will be made available as cartons each containing 10 vials. Ipilimumab will be made available as cartons each containing 4 vials.

Study drug packaging will bear a label with the identification required by local law, the protocol number, drug identification and dosage.

Nivolumab and ipilimumab will be administered open label. Nivolumab and ipilimumab will be required to be labelled locally as per local SOPs and regulations.

Medication labels (nivolumab, ipilimumab) will be in the local language and comply with the legal requirements of each country in which the study will be conducted.

5.3 Accountability, assessment of compliance and destruction of the drugs

Combo Target

Accountability and patient compliance for Combo Target will be assessed by maintaining adequate "drug dispensing" and return records.

These records must contain the following information:

- Documentation of drug shipments received (date received, quantity and batch number)
- Disposition of unused study drug not dispensed to patient

A Drug Dispensing Log must be kept current and should contain the following information:

- Identification code of the patient to whom the study medication was dispensed
- Date(s), quantity and batch number of the study medication dispensed to the patient
- Date(s), quantity and batch number of the study medication returned by the patient

Patients' compliance will be assessed by maintaining adequate study drug dispensing records. Patients will be asked to return all used and unused drug supply containers (of both LGX818 and MEK162) at any visit as a measure of compliance. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol.

All supplies, including partially used or empty containers and copies of the dispensing and inventory logs, must be returned to the Monitor at the end of the study, unless alternate destruction has been authorized by the Sponsor, or required by local or institutional regulations.

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, the study drugs should be stored according to the instructions specified on the drug labels and Investigator's Brochure for LGX818 and MEK162. Study medication is to be stored in a secure locked area while under the responsibility of the Investigator. Receipt and dispensing of study medication must be recorded by an authorized person at the Investigator's site.

Records of drug formulation, batch number, and number of blisters/bottles dispensed must be recorded in the pharmacy study file.

Combo Immuno

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, the study drugs should be stored according to the instructions specified on the drug labels and Investigator's Brochure for nivolumab and ipilimumab. Study medication is to be stored in a secure locked area while under the responsibility of the Investigator. Receipt and dispensing of study medication must be recorded by an authorized person at the Investigator's site.

Nivolumab and ipilimumab such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to the study sponsor upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, updated, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6. STATISTICAL CONSIDERATIONS

6.1 Study Endpoints

OS is primary endpoint of the study. OS will be calculated from the date of randomization until the date of death from any cause. Any patient not know to have died at the time of data analysis will be censored at the time of the last recorded date on which the patient was know to be alive.

Secondary endpoints of the study will be:

- Total PFS, calculated from the date of randomization until the date of the second progression (i.e. the progression to second treatment); any progression or death will be considered as an event if patient cannot complete treatment sequence;
- Percentage of patients alive at 2 and 3 years;
- Best overall response rate (BORR), defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST version 1.1 criteria;
- Duration of response (DoR), calculated as the time from the date of first documented response (CR or PR) until the date of the first documented progression or death due to underlying cancer. If a patient with a CR or PR has no progression or death due to underlying cancer, the patient is censored at the date of last adequate tumor assessment;
- Biological markers (biomarkers ancillary study).

6.2 Sample Size and Analysis Populations

6.2.1 Sample size

This study is designed as a phase II, randomized trial with no formal comparative test. The sample size is discussed for the primary endpoint Overall Survival (OS).

For each arm a single-stage design as described by A'Hern (*A'Hern, 2001*) will be used.

We have assumed a median PFS of about 10 months for the combo target therapy (LGX818/MEK162) (*Mc Arthur et al, 2013*) and a similar value for the combo immunotherapy (ipilimumab/nivolumab) derived from the aggregate clinical activity rate of 65% (*Wolchock et al, 2013*) which, using an exponential distribution for PFS, could broadly give a median PFS of about 9.5 months. OS seems to be strictly correlated with total PFS.

The null hypothesis is a median OS time of 15 months (i.e. percentage of surviving patient of 33% at 24 months). The alternative hypothesis is a median OS time of 23 months (i.e. percentage of surviving of 48% at 24 months)

Using an exact 5% one-sided significance test at least 69 patients have to be randomized in each treatment arm when the power of the study is 80%.

For each arm the strategy will be further investigated if at least 30 patients, alive at 24 months, are observed.

Taking in account a 10% drop-out rate, a total of 230 patients will be enrolled to ensure a minimum of 207 randomized patients.

6.2.2 Analysis Populations

Baseline is defined as the last valid visit or day before the treatment start

The following populations are defined for this study.

All Enrolled Set

All screened subjects who have been enrolled.

Intention To Treat (ITT) set

All randomized patients will be considered for the Intention-To-Treat population (ITT)

Safety Set

All patients of the ITT population receiving at least one dose of the study medication.

6.2.3 Statistical analysis

Data handling

The Overall Survival (OS) will be calculated as the date of randomization until the date of death from any cause.Any patient not know to have died at the time of data analysis will be censored at the time of the last recorded date on which the patient was know to be alive.

Total Progression Free Survival (TPFS) will be calculated from the date of randomization until the date of the second progression (i.e. the progression to second treatment); any progression or death will be considered as an event if patient cannot complete treatment sequence.

Duration of response (DoR) will be calculated as the time from the date of first documented response (Cr5 o PR) until the date of the first documented progression or death due to underlying cancer. If a patient with CR o PR has no progression or death due to underlying cancer, the patient will be censored at the date of the last adeguate tumor assessment.

Statistical analysis

A comprehensive Statistical Analysis Plan (SAP) will be prepared before database lock.

Deviations from methods described in this paragraph might appear.

In case of such deviations the reason for the deviation will be stated in the statistical analysis plan.

Analysis of efficacy endpoints will be performed in the ITT population whereas the safety analysis will be performed in the Safety Population.

No comparative tests between the three arms will be perfomed and results will be presented aas descriptive statistic. Site related differences will be evaluated.

Continuous variables will be summarized by descriptive statistics (number of cases, mean, standard deviation, median, minimum, maximum, first and third quartile). Categorical variables will be summarized using counts of patients and percentages 95% confidence interval will be employed, unless otherwise specified.

The time-dependent endpoints will be analyzed according to the Kaplan-Maier method. Medians with 95% confidence intervals will be derived from the K-M curves and presenting time-dependent endpoints as K-M plot (with a 95% CI over time).

Cox's proportional hazard model will be used to assess the impact of know prognostic factors and treatment assigned.

The list of the covariates to be included in the Cox's model will be presented and clinically justified in the statistical analysis plan.

The ORR will be calculated as the percentage of ITT population patients who have a CRo o PR before any evidence of progression (as defined by RECIST).

A 95% confidence interval (CI) will be derived for the ORR using Wilson score intervals (CIs for a single proportion).

Percentage of patients alive at 2 and 3 years will be reported using Wilson score intervals.

Adverse event are those with start date beyond or equal to the informed consent date,

Analysis includes adverse events with starting date until 30 days after the last study drug dose intake.

All adverse event will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to MedDRA thesaurus version 18 or higher.

Adverse events will be reported on a per-patient basis within Preferred Term. This mean that even if a patient will be report the same event repeatedly (i.e. events mapped to the preferred term) the event will be counted only once.

In the latter case the event will be assigned the worst CTCAE severity and the stroingest relationship to the study drug. The earliest date will regard as start date of the event and the latest date will regard as stop date of the event. Adverse events will be assessed accorind to CTCAE version 4.03.

Appropriate summaries of these data will be presented.

Safety and tolerability will be assessed in terms of AEs, laboratory data, ECG data, vitals signs and weight, which will be collected for all patients. AEs (both in terms of MedDRA preferred terms and CTCAE grade), laboratory data, ECG data, vital signs and weight will be listes individually by patient and summarized by treatment received. ECG changes will be summarized for each treatment group.

Vital signs data will be listes for each patient and changes in vital signs will be summarized for each treatment group.

Previous and concomitant medications will be coded using the ATC dictionary, latest version.

Changes from baseline in EQ-5D and QLQ-C£0 total score will be summarized by means of descriptive statistical methods.

6.3 Study Duration

This is a multicenter study that will be conducted in 24 sites located in Europe. It is expected that 230 eligible patients will be enrolled in total for this phase II study by the participating centers to ensure a minimum of 207 evaluable patients.

Treatment duration will be until PD (2 years estimated). It is expected that the study will start (First Patient First Visit Date) on Febrary 2016, the recruitment will end (Last Patient First Visit) on September 2017, and the Study will end (Last Patient Last Visit) on. September 2020. The date of study end is dependent on the clinical course of the disease and may therefore occur earlier than indicated.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Warning 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's Brochure for all the IMPs. Additional safety information collected between Investigator's Brochure 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.

The recommendations to be followed for the management of toxicities and adverse events are detailed in Section 5.1.2 (Combo Target) and in Section 5.2.2 (Combo Immuno).

Adverse events of special interest for LGX818 and MEK162 are detailed in Section 7.5.2.

7.2 Adverse Events and Laboratory Abnormalities

7.2.1 Clinical Adverse Events (AEs)

According to the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject (patient) administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign [including an abnormal laboratory finding], symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs.

7.2.2 Intensity

Intensity of all AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events v4.03 (CTCAE v 4.03 most recent sub-version) on a five-point scale (Grade 1 to 5) and reported in detail on the CRF.

AEs not listed on the CTCAE should be graded as follows:

CTC Grade Equivalent To:

Definition

- Grade 1: Mild Discomfort noticed but no disruption of normal daily activity

- Grade 2: Moderate Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
- Grade 3: Severe Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall wellbeing or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk
- Grade 4: Life threatening/disabling. An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival
- Grade 5: AE resulting in death

7.2.3 Drug AE relationship

The causality relationship of study drug to the AE will be assessed by the Investigator as either: *Yes* or *No*

If there is a reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as Yes.

The following criteria should be considered in order to assess the relationship as Yes:

- Reasonable temporal association with drug administration
- It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on re-challenge

The following criteria should be considered in order to assess the relationship as No:

- It does not follow a reasonable temporal sequence from administration of the drug
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- It does not follow a known pattern of response to the suspected drug
- It does not reappear or worsen when the drug is re-administered

7.2.4 Serious Adverse Events

A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfils at least one of the following criteria:

- is fatal (results in death; NOTE: death is an outcome, not an event)

- is Life-Threatening (NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death if it had been more severe).
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is a cancer;
- is associated with an overdose;
- is another Important Medical Event (any important adverse events/reactions that is not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require medically significant or requires intervention to prevent one or other of the outcomes listed above).Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization). Potential drug induced liver injury (DILI) is also considered an important medical event.

Note: The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably. The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting.

Overdose

An overdose is a significant variation above the recommended/scheduled dosage for a product. In this current trial an overdose of the IMPs is any dose higher than the dose specified in the in Sections 5.1.1 and 5.2.1 of this protocol.

Planned Hospitalization

A hospitalization planned by the subject prior to signing the informed consent form (ICF) is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

7.2.5 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this case, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy. If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

7.3 Treatment and Follow-up of AEs (100 days post discontinuation of study drugs)

After 100 days from the last dose of study drugs continue to follow-up AEs as follows:

- For Related AEs, follow until one of the following occurs:
  - Resolved or improved to baseline
  - Relationship is reassessed as unrelated
  - Death
  - Start of new anti-cancer regimen
  - Investigator confirms that no further improvement can be expected
  - Clinical or safety data will no longer be collected, or final database closure
- For Unrelated severe or life-threatening AEs, follow until one of the following occurs:
  - Resolved or improved to baseline
  - Severity improved to Grade 2
  - Death
  - Start of new anti-cancer regimen
  - Investigator confirms that no further improvement can be expected

- Clinical or safety data will no longer be collected, or final database closure

Unrelated Grade 1 or Grade 2 AEs: follow-up until 100 days after last dose of study drugs and every 12 weeks until 24 months for long term follow-up. The final outcome of each AE must be recorded on the CRF.

7.4 Laboratory Test abnormalities

Laboratory test results will be recorded on the laboratory results form of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Any laboratory result abnormality fulfilling the criteria for an adverse event of special interest (AESI) or a SAE should be reported as such, in addition to being recorded as an AE in the CRF.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication, which falls outside the laboratory reference range and meets the clinical significance criteria.

7.4.1 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

7.5 Handling of Safety Parameters

7.5.1 Reporting of AEs

Information about all adverse events, whether volunteered by the patient, discovered by Investigator questioning, or detected through physical examination, laboratory test or other means, will be collected on the Adverse Event CRF page, documented in the patient's medical records, and followed as appropriate.

The NCI CTC-AE (Version 4.03) will be used to evaluate the clinical safety of the treatment in this study. Patients will be assessed for AEs at each clinical visit and as necessary throughout the study.

The following Adverse Events of special interest assessed as non-serious must be reported to Sponsor within one working day of the Investigator becoming aware of the event (expedited reporting):

- Palmar-plantar erythrodysaesthesia syndrome
- Rash and related events
- Squamous cell carcinoma (SCC), keratoacanthoma (KA) and any other suspicious skin lesions.
- Ocular/visual events
- Retinal vein occlusion
- Rash and related events
- Peripheral/generalized edema/anasarca
- Serum creatinkinase (CK) elevation
- Cardiac failure related events
- Hepatic events.

LGX818

As a result of signals observed from previous LGX818 studies, several AEs requiring a close follow-up were identified. For each category, selected AEs similar in nature, will be identified and grouped:

- Palmar-plantar erythrodysaesthesia syndrome
- Rash and related events
- Squamous cell carcinoma (SCC), keratoacanthoma (KA) and any other suspicious skin lesions.

MEK162

As a result of signals observed from previous MEK162 studies, several AEs requiring a close follow-up were identified. For each category, selected AEs similar in nature, will be identified and grouped:

- Ocular/visual events
- Retinal vein occlusion
- Rash and related events
- Peripheral/generalized edema/anasarca
- Serum creatin-kinase (CK) elevation
- Cardiac failure related events
- Hepatic events.

7.5.2 Reporting of SAEs (immediately reportable)

Any clinical AE, or abnormal laboratory test value assessed as serious(as defined above), AESI or pregnancy case, occurred during the course of this study from the enrolment visit (start of study screening procedures), including long term follow-up, must be reported to Sponsor and PV Manufacturer within *one* working day of the Investigator becoming aware of the event (expedited reporting). The following proviso applies:

During the screening period, after written informed consent has been signed only SAEs related to protocol procedures will be reported. The Investigator must complete the SAE formand forward it to the SAE Responsible person:

Emergency contact	**Dr. Paolo A. Ascierto** Istituto Nazionale dei Tumori, Fondazione "G. Pascale" U.O.C. Melanoma, Immunoterapia Oncologica e Terapie Innovative Via M. Semmola 80131 - Naples	Tel: +39 081 5903 236 Fax: +39 081 5903 841 Email paolo.ascierto@gmail.com
	Clinical Research Technology srl Project Management	Tel: +39 089.301545 Fax: +39 089.7724155 e-mail: pvg@cr-technology.com

In addition, report of Adverse Events will be done, according to current Italian law, to local Health Authorities.

From the first administration of IMPs, all SAEs must be reported. Related SAEs MUST be collected and reported regardless of the time elapsed from the last study drugs administration, even if the study has been closed. Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to Investigators at each site and associated IRB/IEC when the following conditions occur:

- The event must be a SAE
- There must be a certain probability that the event is an adverse reaction from the administered drugs
- The adverse reaction must be unexpected, that is to say, not foreseen in the Investigator's Brochure of IMPs. When all patients at a particular site are off treatment as defined by the protocol:
  - only individual SUSAR reports originating in that particular trial will be forwarded to the site and associated IRB/IEC on an expedited basis
  - individual SUSARs considered to be a significant safety issue and/or which result in recommending a change to the ICF, will be reported in an expedited manner to all Investigators and IRBs/IECs

- SUSAR reports originating from other trials using the same IMP will be provided as six monthly SUSAR Reports to Investigators and IRBs/IECs where long-term follow-up studies are carried out, unless they are considered significant

Unrelated SAEs must be collected and reported during the study and for up to 100 days after the last dose of study medication and every 12 weeks until 24 months for long-term follow up.

This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting.

7.5.3 Pregnancy

Female patients must be instructed to stop taking IMP and immediately inform the Investigator if become pregnant during the study. The Investigator should report all pregnancies within 24 hours to the Sponsor, using the *Clinical Trial Pregnancy Reporting Form*. The Investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Pregnancies occurring up to 6 months after the completion of the study medication must also be reported to the Investigator. Pregnancies occurring in the partner of a male patient participating in the study should be reported to the Investigator and the Sponsor. The partner should be counselled, the risks of continuing the pregnancy discussed, as well as the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy.

8. DATA COLLECTION AND MANAGEMENT

8.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. 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.

8.2 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 enrolment, and to ensure that study treatment is being stored, dispensed, and accounted 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. The Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs.

8.3 Data collection

This study will use an Electronic Data Capture (EDC) system (eClinical platform provided by Clinical Research Technology). 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 eClinical platform provided by Clinical Research Technology, a fully validated secure web-enabled software that conforms to FDA 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 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.

8.4 Database management and quality control

The 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 is required to respond promptly to queries and to make any necessary changes to the data. Concomitant treatments 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. The occurrence of any protocol violations will be determined. After the data has been verified to be complete and accurate, the database will be declared locked. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Biostatistics and Data Management and the Sponsor.

9. ETHICAL CONSIDERATION

9.1 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 with the ethical principles laid down in the Declaration of Helsinki.

9.2 Responsibilities of the investigator and IEC

The protocol and the proposed informed consent form must be reviewed and approved by Independent Ethics Committee (IEC) of all participating centers before study start.

9.3 Informed consent procedures

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

9.4 Publication of study protocol and results

The key design elements of this protocol will be posted in the publicly accessible database clinicaltrials.gov. The Investigators assure that results of this study will be submitted for publication and reported in scientific meetings.

9.5 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 Fondazione Melanoma-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. For electronic CRFs an audit trail will be maintained by the system. 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 seven (7) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

9.6 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 enrolment log must be kept strictly confidential to enable patient identification at the site.

9.7 Audits and inspections

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

9.8 Financial disclosures

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

10. PROTOCOL ADHERENCE

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the Sponsor, 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 IEC it cannot be implemented.

10.1 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 IEC. Only amendments that are required for patient

safety may be implemented prior to IEC 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 IEC at the study site should be informed within 10 working days.

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12. APPENDIX

I. Recommended guidelines for the management of study drug (LGX818 and MEK162) induced skin toxicity

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In general, the following interventions are in addition to the rash dosing guidelines in Table 7of the protocol:

- Prophylaxis of skin toxicity to be initiated 24 hours prior to the first treatment with study drug or later as needed
- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back

Topical agents include non oily sunscreen (PABA free, SPF ≥ 30, UVA/UVB protection), topical steroids (preferably mometasone cream and topical erythromycin evening or topical pimocrolimus

Note: Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to the first dose, and more often as needed.

- Possibly oral doxycycline (100 mg daily) for the first 2-3 weeks of study drug administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

Mild rash (CTCAE Grade 1)

- Consider prophylactic rash treatment if not already started
- Topical or other topical corticosteroid (i.e. mometasone cream) and/or topical antibiotic (i.e. erythromycin 2%) are recommended.
- The patient should be reassessed within a maximum of 2 weeks or as per investigator opinion.

Moderate rash (CTCAE Grade 2)

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or pimecrolimus cream (1%) plus oral antibiotics such as:,lymecycline (408 mg OD), doxycycline (100 mg BID) or minocycline (50 to 100 mg OD).
- Although there has been no evidence of phototoxicity or photosensitivity in patients being treated with LGX818 or MEK162, doxycycline (or minocycline as secondline) should be used with thorough UV protection (i.e., avoidance of direct exposure to sunlight, use of sunscreen and sunglasses, etc.).
- Use of acitretin is not recommended

Severe rash (CTCAE Grade 3-4)

CTCAE Grade 3

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, i.e. 0.3 to 0.5 mg/kg)
- Use of acitretin is not recommended

CTCAE Grade 4

- Immediately discontinue the patient from study drug and treat the patient with oral and topical medications (see recommendation CTCAE Grade 3).

Symptomatic treatment:

It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment:

- For pruritic lesions, use cool compresses and oral antihistaminic agents
- For fissuring, use Monsel's solution, silver nitrate, or zinc oxide cream. If not sufficient use mild steroid ointments or combinations of steroids and antibiotics
- For desquamation, use emollients with mild pH 5/neutral (best containing urea 10%)
- For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and if no improvement is seen, refer to a dermatologist or surgeon
- For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

II. Recommended guidelines for the management of MEK162 induced diarrhoea

Proactively investigate for occurrence of diarrhoea and educate patients

a. Remind patients at each visit to contact the Investigator immediately upon the first sign of loose stool or symptoms of abdominal pain. Additionally, at each study visit, each patient should be asked regarding occurrence of diarrhoea or diarrhoea-related symptoms. If the patient has symptoms, the patient should be asked regarding the actions taken for these symptoms and re-instruct if indicated

b. The patients should be instructed on dietary modifications and on early warning signs of diarrhoea and potentially life-threatening illnesses (e.g. severe cramping might be a sign for severe diarrhoea, fever with diarrhoea might be a sign for infection, fever and dizziness on standing might be a sign for shock)

c. Patients should be educated about what to report to the Investigator (i.e., number of stools, stool composition, stool volume)

Anti-diarrhoea therapy

In order to effectively manage diarrhoea and mitigate the escalation in severity or duration of diarrhoea, patient education as outlined above as well as proper management of diarrhoea is important.

Management of diarrhoea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhoea. All concomitant therapies used for treatment of diarrhoea must be recorded on the Concomitant Medications eCRF. It is recommended that patients be provided loperamide tablets and are instructed on the use of loperamide at on the first day of MEK162 treatment. In addition to the MEK162 induced diarrhea dosing guidelines in Table 7 of the protocol, these instructions should be provided at each visit and the site should ensure that the patient understands the instructions

Explain the frequency of diarrhoea and its relationship to NCI CTCAE grading.

Determine if diarrhoea is complicated or uncomplicated.

Rule out other or concomitant causes.

These may include:

- Infection with Candida, Salmonella, Clostridium difficile, Campylobacter, Giardia, Entamoeba and Cryptosporidium species can lead to severe infections in immunosuppressed patients
- Medication-induced diarrhoea
- Malabsorption/lactose intolerance
- Faecal impaction, partial bowel obstruction

For uncomplicated Grade 1/2 diarrhoea

- Stop all lactose-containing products, alcohol and eat frequent small meals that include bananas, rice, applesauce or toast)
- Stop laxatives, bulk fiber and stool softeners
- Stop high-osmolar food supplements
- Drink 8 to 10 large glasses of clear liquids per day
- Consider administration of standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Discontinue loperamide after 12-hours diarrhoea-free (Grade 0) interval.
- If uncomplicated Grade 1 to 2 diarrhoea persists for more than 24 hours, escalate to high dose loperamide: 2 mg every 2 hours (max. of 16 mg/day) or after each unformed stool.

Note: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

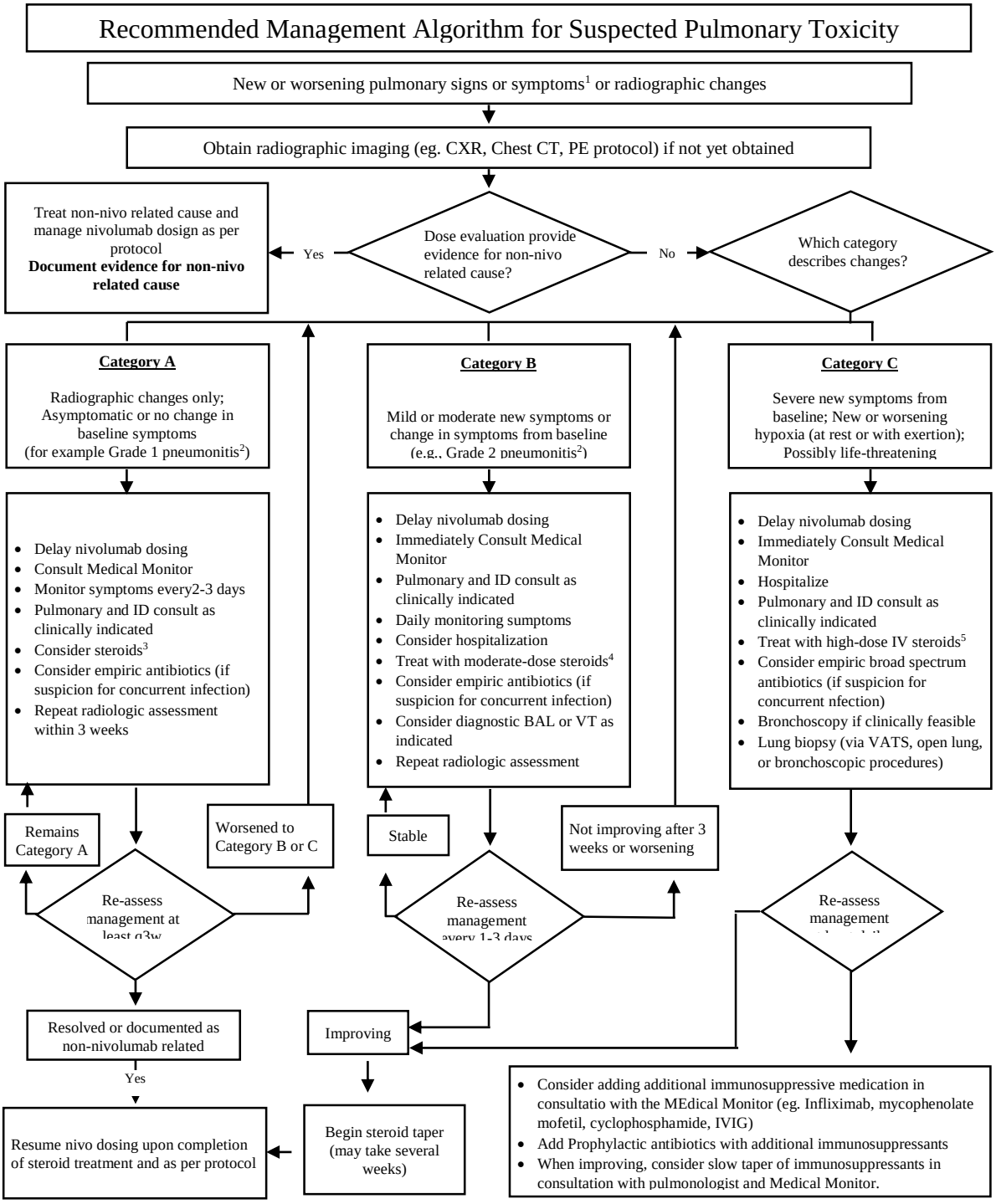
- If uncomplicated Grade 1 to 2 diarrhoea persists after 48 hours of treatment with loperamide, discontinue loperamide and begin a second-line agent which can be an opiate (opium tincture or paregoric), octreotide acetate or steroid (budesonide)

For complicated Grade 1/2 diarrhoea or any Grade 3 to 4 diarrhea

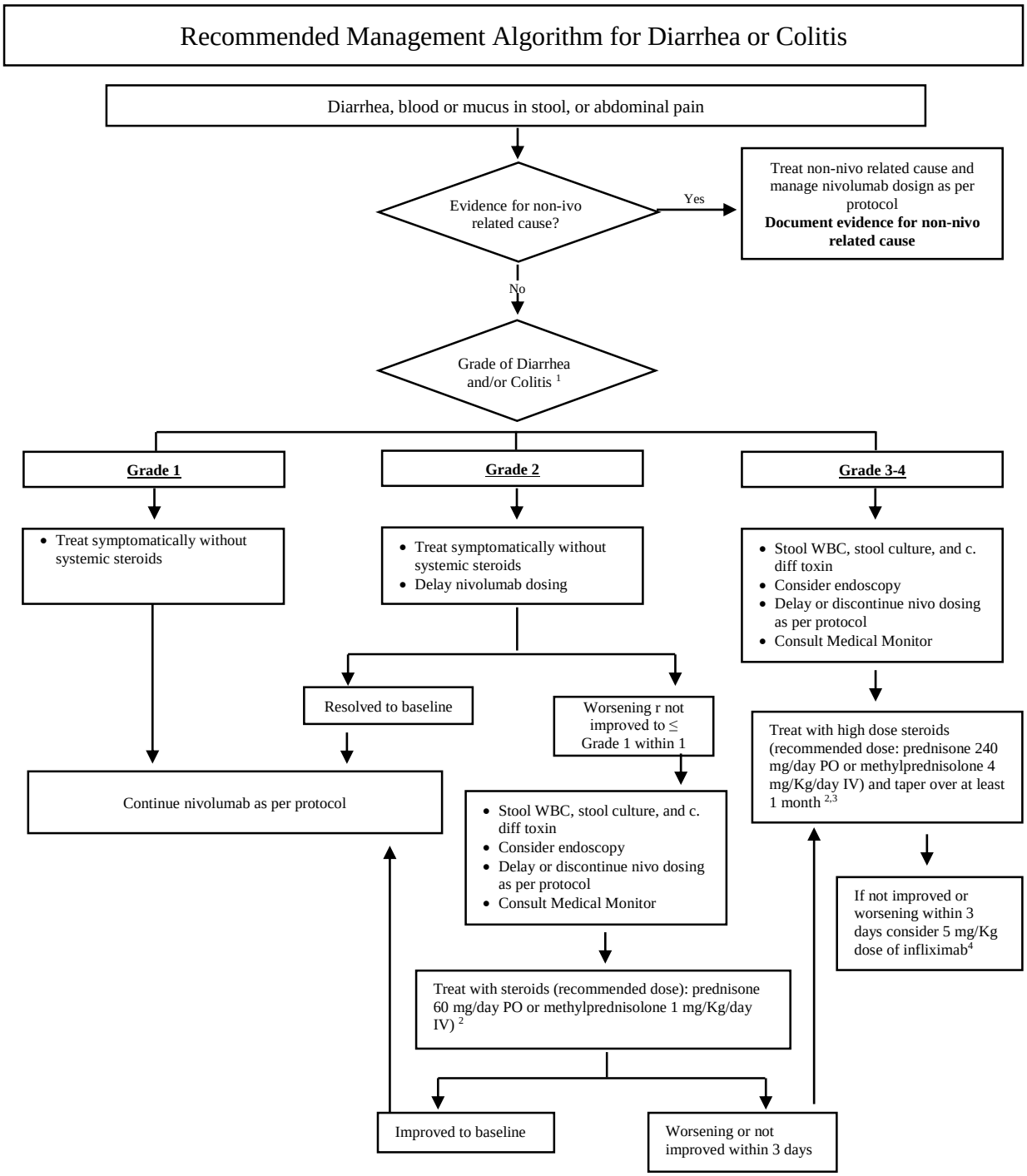
- The patient must call the investigator immediately
- If loperamide has not been initiated, initiate loperamide immediately. Initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Administer IV fluids and electrolytes as needed. In case of severe dehydration, replace loperamide by octreotide.
- Monitor/continue IV fluids and antibiotics as needed. Intervention should be continued until the patient is diarrhoea free for at least 24 hours.

Hospitalization may need to be considered.

III. Recommended algorithms for use of nivolumab and ipilimumab

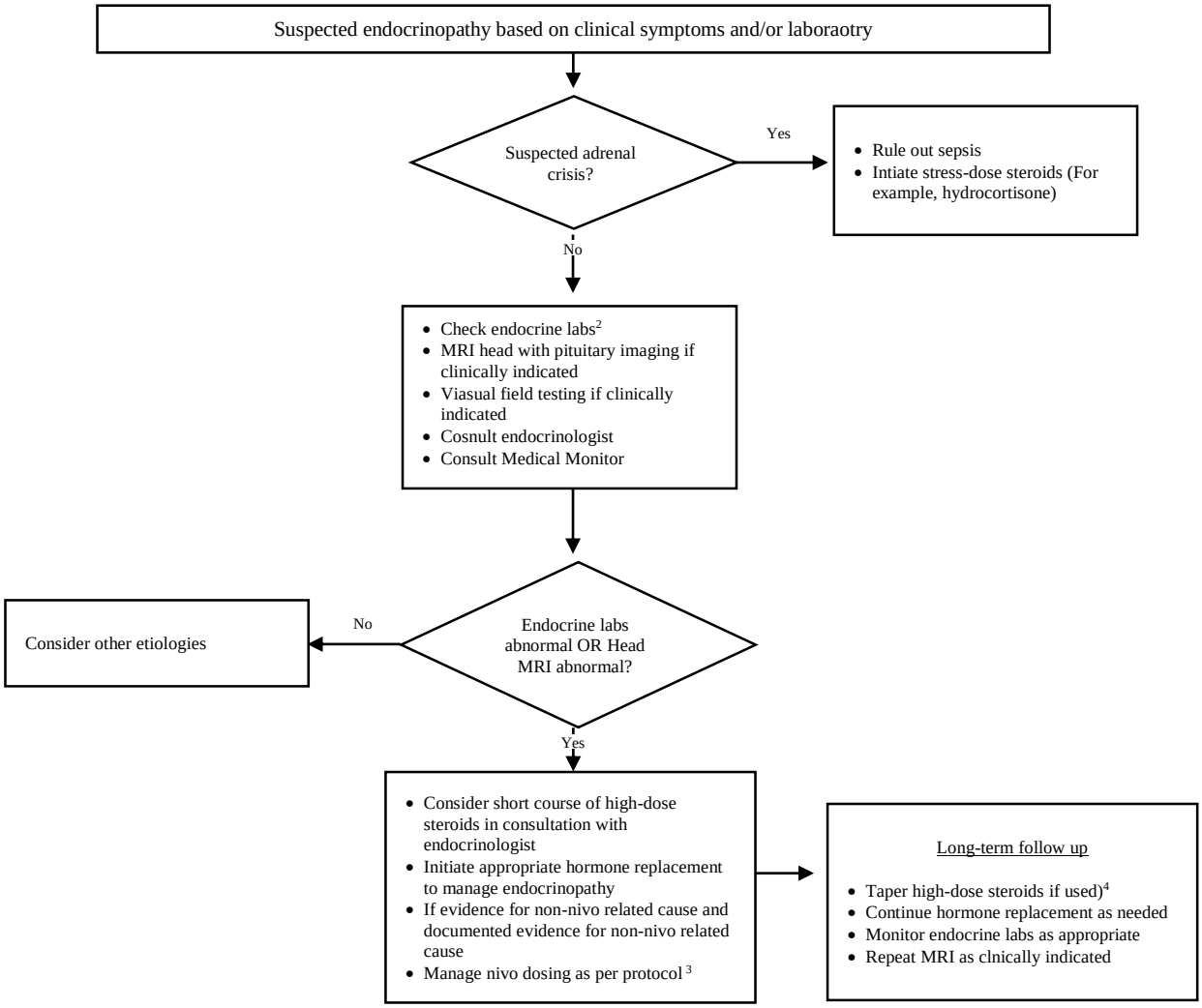


Footnotes
4. Signs and synptoms include dyspnea, cough, hypoxia and other respiratory compliants
5. Grading as per NCI CTCAE 4.03
6. Recommended initial costicosteroid regimen for category A: prednisone 60 mg/day PO or methylprednisone 1 mg/Kg/day IV
7. Recommended initial costicosteroid regimen for category B: prednisone 240 mg/day PO or methylprednisone 4 mg/Kg/day IV
8. Recommended initial costicosteroid regimen for category C: methylprednisone 1 g/Kg/day IV



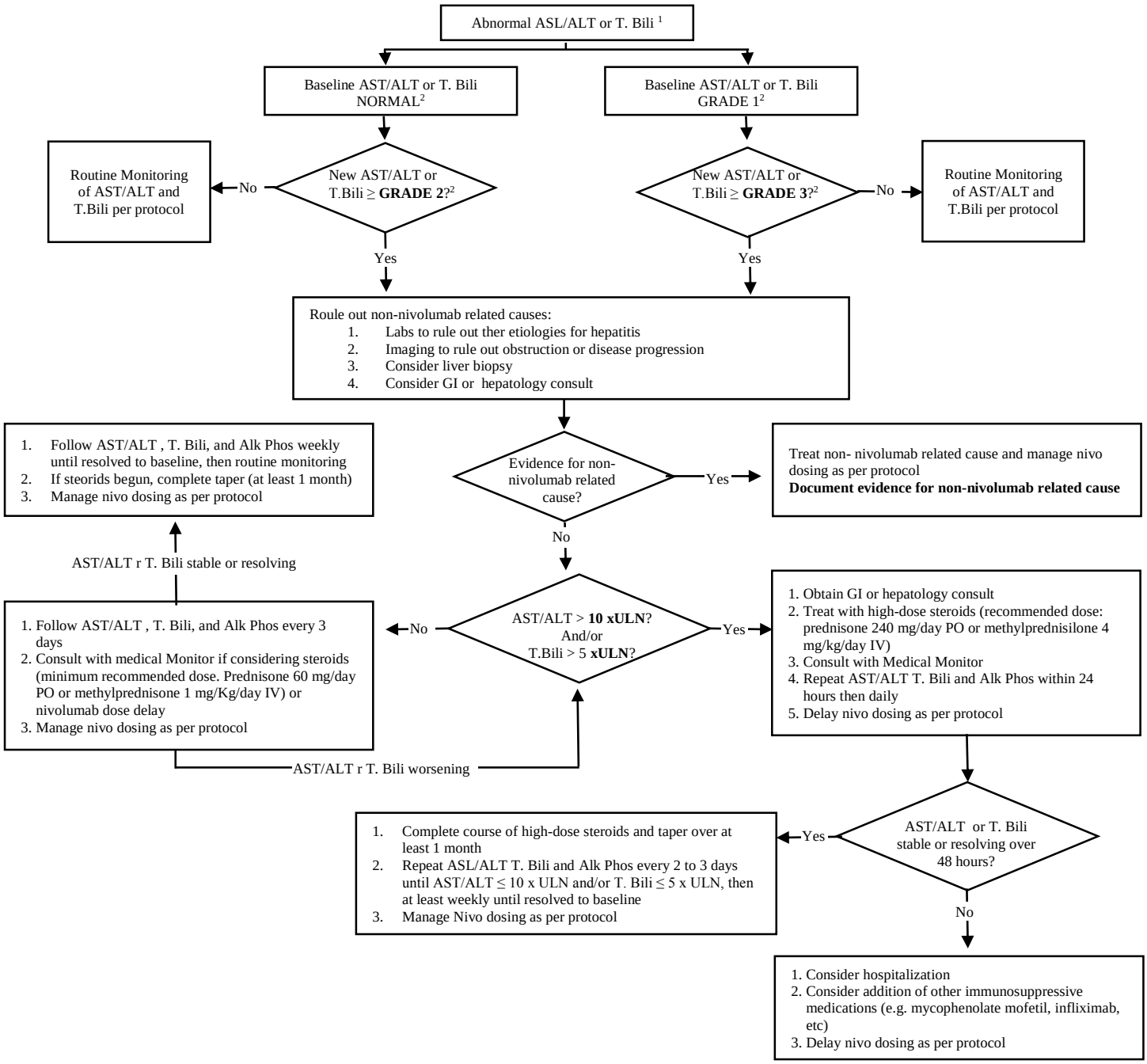
Footnotes
1. Grading as per NCI CTCAE version 4.03. If both diarrhea and colitis are present, manage as per toxicity with higher grade.
2. If infection work-up is positive, do not give steroids, stop following algorithm and treat specific infection.
3. If re-treatment with nivolumab is allowed as per protocol after completion of steroid taper, consult with Medical Monitor if considering re-treatment
4. Do not use infliximab if perforation or sepsis is present

Recommended Management Algorithm for Suspected Endocrinopathy



Footnotes
1. Cases have typically been identified through routine monitoring of laboratories or as part of a work-up for symptoms such as fatigue
2. It's important to draw labs at appropriate times; for example, certain labs should be drawn before giving steroids or at specific times of the day
3. Upon resolution or adequate treatment of endocrinopathy, patients may continue nivolumab dosing with appropriate hormone replacement unless limited by protocol
4. Patients may require chronic steroid replacement to maintain physiologic levels

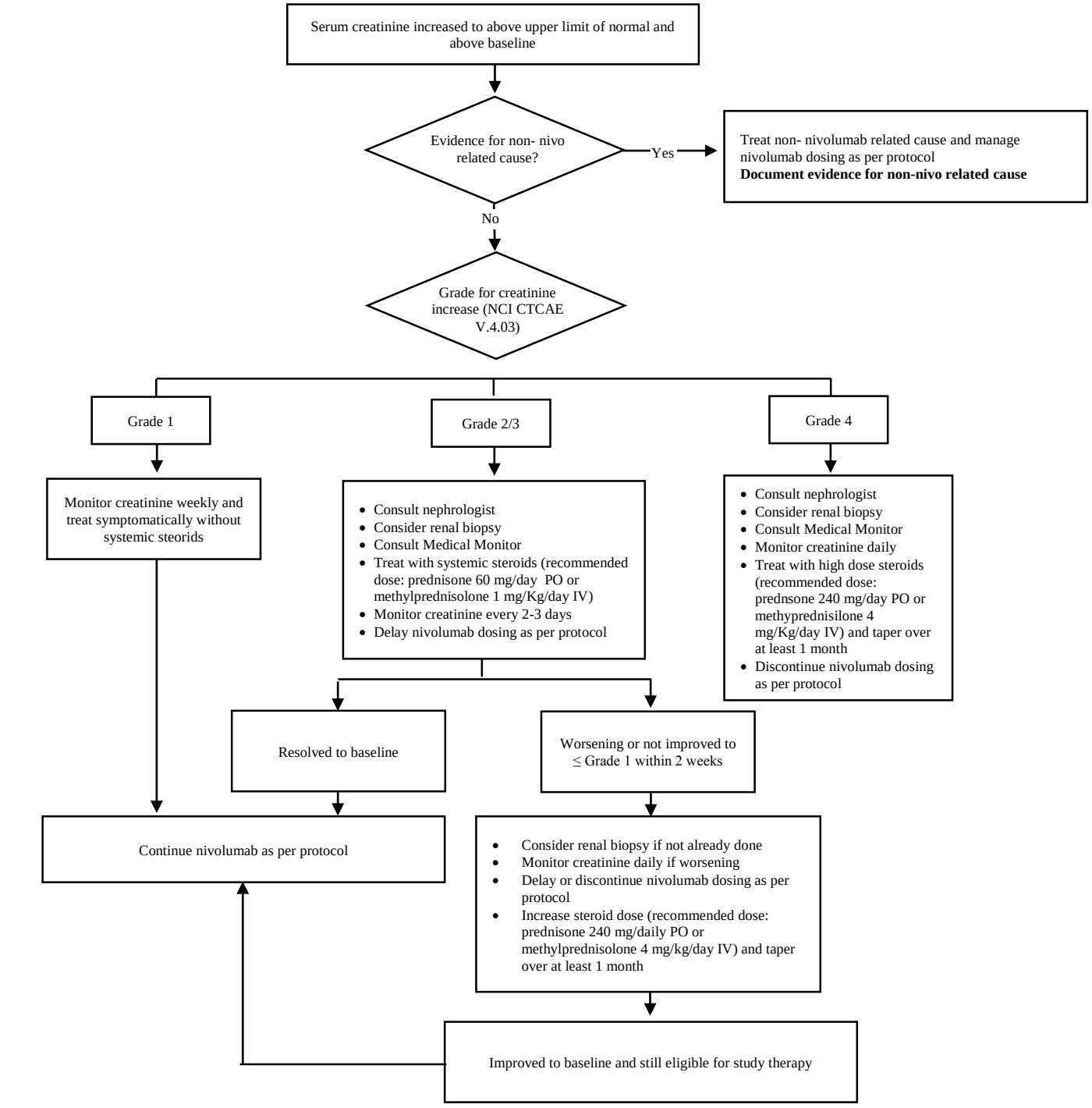
Recommended Management Algorithm for Suspected Hepatotoxicity



Footnotes

1. If elevations in both AST/ALT and T. Bili are present, the management of nivolumab dosing may be different than if only an isolated AST/ALT of T. Bili abnormality is present and may not be dependent on baseline values. Refer to the specific protocol if concurrent elevations occur
2. Grading as per NCI CTCAE versio 4.03

Recommended Management Algorithm for Nephrotoxicity



Skin toxicity Management Algorithm

Rule out non-inflammatory cause. If non.inflammatory cause, treat accordingly and continue ipilimumab

Severity of skin toxicity	Management	Follow-up
Grade 1-2	• Symptomatic therapy,e.g. antihistamine, topical steroids • Continue ipilimumab	**Symptoms resolve**: Continue ipilimuamb **Symptoms persist > 1-2 weeks or recur**: ○ Continue ipilimumab ○ Moderate to high dose steroids PO (e.g. prednisole 0.5 – 1 mg/Kg/day) ○ Once controlled, taper steroids over at least 1 month)
Grade 3-4	• Hold/delay ipilimumab (regardless of relationship) • Take photos of rash • Consider skin biopsy • Dermatology consult • High dose IV steroids (e.g. methylprednisolone 1-2 mg/kg/day)	**Symptoms resolve/ return to grade 1:** ○ Taper steroids over the least 1 month ○ Resume ipilimumab ○ Discontinue if grade 4 toxicity consider related

Patients on IV steroids may be switched to oral corticosteroid (e.g. prednisone) at an equivalent dose at start or tapering or earlier once sustained clinical improvement is observed. Lower bioavailability of oral costicosteroids should be taken into account when switching to the equivalent dose of PO costicosteroids.

Neurological toxicity Management Algorithm

Rule out non-inflammatory cause. If non.inflammatory cause, treat accordingly and continue ipilimumab.
Discontinue ipilimumab for any grade 3-4 motor neuropathy, regardless of relationship.

Severity of neurological toxicity	Management	Follow-up
Grade 1	Continue ipilimumab	Continue monitoring the patient. If symptoms worsen, treat as below
Grade 2	• Hold/ delay ipilimumab • Treat symptoms per local guidelines	Resume ipilimumab when resolved/ grade 1 If symptoms worsen, treat as below
Grade 3/4 sensory	• Discontinue ipilimumab if consider related • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g. 1-2 mg/kg/day methulprenisolone)	Symptoms resolve/return to grade 1: ○ Taper steroids over at least 1 month
Grade 3/4 motor	• Discontinue ipilimumab **<u>regardless of relationship</u>** • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g. 1-2 mg/kg/day methylprednisolone)	Symptoms resolve/return to grade 2: ○ Taper steroids over at least 1 month Symptoms do not resolve or progress; atypical presentation: ○ Consider IVIg or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to oral corticosteroid (e.g. prednisone) at an equivalent dose at start or tapering or earlier once sustained clinical improvement is observed. Lower bioavailability of oral costicosteroids should be taken into account when switching to the equivalent dose of PO costicosteroids.

IV. EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |__|__|__|__|

Your birthdate (Day, Month, Year): |__|__|__|__|__|__|__|__|

Today's date (Day, Month, Year): 31 |__|__|__|__|__|__|__|__|

		Not at All	A little	Quite e Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A little	Quite e Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4

11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25	Have you had difficulty remembering things?	1	2	3	4
26	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you:

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

V. EQ-5D

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐

I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

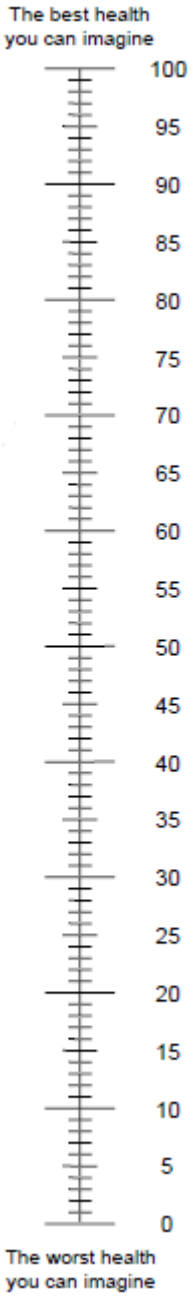
We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.
100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY ☐



VI. WPAI:GH

Work Productivity and Activity Impairment Questionnaire:
General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

VII. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead