Study Code: SECOMBIT
EudraCT Number: 2014-004842-92
Study sponsor: Fondazione Melanoma ONLUS
Investigational Products: LGX818/MEK162/Nivolumab/Ipilimumab
Study title:" 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*"*

Re: Summary of changes – Study protocol from v 1.0 dated 22 Oct 2015 to version 10.0 dated 03 May 2021.

Salerno, 03 May 2021

SECTIONS UPDATED –PROTOCOL VERSION 2.0

Section	**page**	**Description of change**	**Reason for change**
Synopsis Section 6.3	p. 15 p. 76	Milestones of the study postponed	Timeline adjusted according to regulatory submission timeline
Section 3.5.3	p. 40	HIV test added to screening procedures	Italian CA request

SECTIONS UPDATED –PROTOCOL VERSION 3.0

Section	**page**	**Description of change**	**Reason for change**
Synopsis	p. 8	Number of sites incresed from 20 to 30	Sponsor's decision in order to meet study timelines
Synopsis (Study plan)	p. 9	Strata were reduce from 4 to 3, matching LDH range values were fixed	Steering Committee request
Synopsis (Study plan)	p. 9	The following sentences have been added: Tumor assessments including measurable and non-measurable lesions (baseline brain CT or MRI, CT/MRI C/A/P, bone scan if clinically indicated).	Clarifications

Section	page	Description of change	Reason for change
		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	
Synopsis (Study treatment duration, dose and schedule) Section 3.4	p. 12,13 p. 39	The following sentences have been added: If the AE does not resolve or decrease to at least grade 1, during the second screening period (28 days), patient should be followed up for additional 28 days. All screening procedures must be repeated before starting the new combination therapy (tumor assessment, to exclude progression disease, included). If AE does not resolve or decrease to al least grade 1, during this additional period (until 56 days after PD1), patient will be permanently discontinued Patients in the ARM C, with a progression disease documented at the first tumor evaluation, will be discontinued from the study and will be treated as per institutional standard of care thereafter. 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. Hematology and biochemistry	Clarifications

Section	page	Description of change	Reason for change
		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. Test for HIV infection is mandatory at screening.	
Synopsis (Secondary Endpoints)	p. 13	A new secondary endpoint has been added (percentage of PFS after 3 years from randomization);	Steering Committee request
Synopsis Section 6.3	p. 15 p. 76	Timelines of the study postponed	Timeline adjusted according to regulatory submission timeline
Section 3.5.3	p. 41,42, 43, 44	Vital signs have been specified as follows: respiratory rate, pulse, blood pressure and temperature will be obtained in the same position, as appropriate prior to any blood collection. Two readings of supine blood pressure, in the same arm, separated by 2 min should be recorded in the Source Documents and the mean of the two consecutive readings, should be recorded in the eCRF throughout the study	Clarification
Section 3.5.3 Section 3.5.8 Section 7.5.3	p. 44 p 53 p. 88	A serum pregnancy test to be performed every 6 (± 1) weeks during the treatment period and at end of study treatment and follow-up visit up to 31 weeks after the last dose of nivolumab/ipilimumab	Clarification
Section 3.5.3	p. 45	Procedures related to Long term follow up visit (to be performed every 12 weeks until 24 months)	Clarification

Section	page	Description of change	Reason for change
		have been detailed	
Section 3.5.4 and 3.5.5	p. 48, 49	It has been clarified biological samples collection timeline	Clarification
Section 6.2.2	p. 78	The definition of the Per Protocol Population has been added	Addition
Section 7.5.2	p. 87	Emergency contact updated	Update
Several sections	Several pages	Deletions and retouches	Text Hamonization and minor corrections

SECTIONS UPDATED - PROTOCOL VERSION 4.0

Section	page	Description of change	Reason for change
Synopsis (Study plan)	p. 10	CT/MRI of brain as clinically indicated has been added.	Clinical rationale
Synopsis (inclusion criteria) Section 4.1	p. 10 p. 54	Incl #3 retouched to: Treatment naïve for metastatic disease patients. Previous adjuvant treatment, included checkpoint inhibitors anti CTLA-4, anti PD-1/PDL-1 is allowed. (if completed at least 6 weeks prior to randomization, and all related adverse events have either returned to baseline or stabilized). BRAF inhibitor treatment in adjuvant setting is not permitted	Clinical rationale
Section 2.4	p. 32	Final Risk/Benefit Statement section added	Addition
Section 3.5.0	p. 40	Subject Re-enrollment: This study permits the re-enrollment of patients that was not randomized within 28 from ICF signature, after	Clarification

Section	page	Description of change	Reason for change
		obtaining agreement from the medical monitor prior to re--enrolling a subject. If authorized to re-enrollment, the patient must be re-consented and the same subject-code can be used.	
Section 3.5.3 Section 3.5.8	p. 41, 42, 43, 44, 45, 46 p.53	Protocol Procedured aligned with the schedule of assessments	Adjustments and clarifications
Section 5.1.2 Section 5.2.2	p. 69 p. 74	The following sentences have been added: Patients who discontinued permanently the LGX818/MEK162 treatment can be followed up until progression disease and remain in the SECOMBIT study unless in the judgment of the Investigator, presents a substantial clinical risk to the subject with the study treatments. Patients who discontinued permanently the nivolumab/ipilimumab treatment can be followed up until progression disease and remain in the SECOMBIT study unless in the judgment of the Investigator, presents a substantial clinical risk to the subject with the study treatments.	Clinical rationale
Section 10	p. 93	The section “Protocol adherence” has been reworded	Clarifications
Several sections	Several pages	Deletions and retouches	Text Hamonization and minor corrections

SECTIONS UPDATED - PROTOCOL VERSION 5.0

The main reason for this protocol amendment was to update the safety risk section, better describe protocol procedures and correct typing errors.

Section	page	Description of change	Reason for change
Synopsis Number of participant centers	p. 3	Study Coordinator has been substituted with Global Chief Investigator.	Clarification
Synopsis Inclusion criterium #3 Protocol	p. 10 p. 60	The inclusion criterium has been amended to exclude patients with stage IV of disease.	Clinical rational
Synopsis Inclusion criterium #8 Protocol	p. 11 p. 60	The inclusion criterium has been modified to state that female subjects of childbearing potential must practice not one reliable, but two highly effective methods of contraception and that additional pregnancy testing must be performed every 6 weeks during the treatment Combo-Immuno and every 4 weeks during the treatment Combo-Target, as well as at the end of the systemic exposure.	Clinical rational
Synopsis Exclusion criterium #4 Protocol	p. 11 p. 61	The exclusion criterium has been amended to exclude patients only with stage III (unresecteble) or stage IV melanoma.	Clinical rational
Synopsis Exclusion criterium #7 Protocol	p. 12 p. 61	The exclusion criterium has been amended to exclude patients only with uncontrolled cardiovascular disease.	Clinical rational

Section	page	Description of change	Reason for change
Synopsis New exclusion criterium #8 Protocol	p. 12 p. 61	The exclusion criterion number 8 has been added to exclude patients with previous or concurrent malignant, except: adequately treated basal cell or squamous cell skin cancer; in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to study entry; or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to study entry.	New exclusion criteria
Synopsis Biomarkers ancillary study endpoints Protocol 3.2 Endpoints of the study - Biological markers (Biomarkers ancillary translational study)	p. 14 p. 39	The following sentence has been deleted: Immunotherapy SNP Panel will be also assessed at baseline	Clinical rational
Synopsis Duration of the study	p.15	Reference of the study dates has been amended to global and the Global Recruitment end has been postponed to December.	Timelines update
Schedule Assessment Arm A/Arm B/Arm C	p. 19-23	The Schedule Assessment has been harmonized with minor corrections.	Text Hamonization and minor corrections
Protocol 2.2.4 Nivolumab	p. 29	Sentence: ‘In a recent study’ has been amended to ‘In a previous study’.	Text harmonization
	p.30	The following information has been added: In the phase III trial (Robert et al.),418 previously untreated	Addition

Section	page	Description of change	Reason for change
		patiens who had metastatic melanoma without a BRAF mutation were randomized to receive nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks and dacarbazine-matched placebo every 3 weeks) or dacarbazine (at a dose of 1000 mg per square meter of body-surface area every 3 weeks and nivolumab-matched placebo every 2 weeks). The primary end point was overall survival. At 1 year, the overall rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (hazard ratio for death, 0.42; 99.79% CI, 0.25 to 0.73; P<0.001). The median progression-free survival was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group (hazard ratio for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P<0.001). The objective response rate was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; P<0.001). The survival benefit with nivolumab versus dacarbazine was observed across prespecified subgroups, including subgroups defined by status regarding the programmed death ligand 1 (PD-L1). Common adverse events associated with nivolumab included fatigue, pruritus, and nausea. Drugrelated adverse events of grade 3 or 4 occurred in 11.7% of the patients treated withnivolumab and 17.6%	

Section	page	Description of change	Reason for change
		of those treated with dacarbazine.	
2.2.6 Nivolumab and Ipilimumab combination	p. 32	The following information has been added: Recently updated data about the comination have been published (Wolchok et al, 2017). At a minimum follow-up of 36 months, the median overall survival had not been reached in the nivolumab-plus-ipilimumab group and was 37.6 months in the nivolumab group, as compared with 19.9 months in the ipilimumab group (hazard ratio for death with nivolumab plus ipilimumab vs. ipilimumab, 0.55 [P [P<0.001];hazard ratio for death with nivolumab vs. ipilimumab, 0.65 [P<0.001]). The overall survival rate at 3 years was 58% in the nivolumab-plus-ipilimumab group and 52% in the nivolumab group, as compared with 34% in the ipilimumab group. The safety profile was unchanged from the initial report. Treatment-related adverse events of grade 3 or 4 occurred in 59% of the patients in the nivolumab-plus-ipilimumab group, in 21% of those in the nivolumab group, and in 28% of those in the ipilimumab group.	Addition
2.3 Study rationale	p. 33-34	The following information has been added: Taking into account the recent updated data of Check-Mate 067 (Wolchok et al. N Engl J Med. 2017) In the two nivolumab-containing groups, the median overall survival was not reached among patients with BRAF mutations, and the rate of overall survival at 3 years was 68% in the nivolumab-plus-ipilimumab group and 56% in the	Addition

Section	page	Description of change	Reason for change
		nivolumab group. In a descriptive analysis, the hazard ratio for death with nivolumab plus ipilimumab versus nivolumab was 0.69 (95% CI, 0.44 to 1.07). Among patients without BRAF mutations, the median overall survival was reached in all three treatment groups. Additional analyses were performed to investigate efficacy according to the tumor PD-L1 expression level. Descriptive comparisons between the two nivolumab-containing groups suggest that as the data become more mature, better survival outcomes may be obtained with combination therapy than with monotherapy in patients with a lower tumor PD-L1 expression level. However, overall survival was similar between the nivolumab-plus-ipilimumab group and the nivolumab group among patients with a tumor PD-L1 expression level of 1% or more or a level of 5% or more. The overall response rate was higher in the nivolumab-plus-ipilimumab group than in the nivolumab group at each tumor PD-L1 expression level tested. Moreover in the light of the recent published data of Check-Mate 067 the combination therapy resulted in a higher rate of objective response than nivolumab alone regardless of the tumor PD-L1 expression level. Data from a phase 1b study, CA209-038, showed that tumor PD-L1 expression is up-regulated to a greater extent with combination treatment than with nivolumab alone, concomitant with a greater increase in	

Section	page	Description of change	Reason for change
		interferon-γ, CXCL9,and CXCL10 expression in the tumor microenvironment. The ROC-curve analyses did not identify a threshold of tumor PD-L1 expression for the discrimination of a difference in overall survival, which suggests that the tumor PD-L1 expression level alone may not be a definitive predictive biomarker of outcomes in patients with advanced melanoma, thus the tumor PD-L1 testing is not required.	
2.4 Final Risk/Benefit Statement	p. 35-36	The following information has been added: All hepatic adverse events were asymptomatic and reversible with either temporary discontinuation of the study drugs or administration of glucocorticoids. The risks of administration of a combination of ipilimumab and nivolumab are known to be potential clinically meaningful drug-related AEs, which may require early recognition and prompt intervention. Management algorithms have therefore been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity (Appendix III). Recommendations are to follow the nivolumab Investigator's Brochure adverse event algorithms. Dosing delay or discontinuation may then be implemented based on individual safety and tolerability (Section 5.2.2). Ongoing clinical studies suggest that the combination of LGX818	New section

Section	page	Description of change	Reason for change
		with MEK162 may in fact have an improved safety profile compared to the respective single agent therapies. However, known risks of this combination comprise MEK inhibitor-associated retinal syndromes and other toxic effects on the skin (e.g. rash) and gastro-intestinal system (e.g. nausea). Again, management algorithms are in place (Appendices I and II) to enable timely intervention if required. Dosing modifications, interruptions and delays can then be implemented based on individual safety and tolerability (Section 5.1.2). … Updated data were reported on targeted therapies, confirming the excellent results previously reported (Larkin J e t al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 371:1867–1876 2014; Long GV et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 371:1877–1888 2014) An update on the CoBRIM trial of combined BRAF inhibitor (vemurafenib) plus MEK inhibitor (cobimetinib) in patients with BRAFV600 mutation-positive tumors confirmed its superior impact on progression-free survival (PFS) compared to vemurafenib monotherapy [12.3 vs 7.2 months; hazard ratio (HR) 0.58 (0.46–0.72)]. An update on overall survival (OS) from the Combi-D study of combined dabrafenib plus trametinib in	

Section	page	Description of change	Reason for change
		patients with BRAF V600E/K metastatic melanoma was also reported (Long GV et al. 2015). Patients treated with the combination of dabrafenib and trametinib achieved a median OS of 25.1 months with 51% of patients still alive at 2 years, these findings confirmed results reported from the phase I–II study in 2014 (Flaherty et al. 2014) Finally, data from a phase Ib/II open-label study of patients with BRAFV600-mutant cutaneous melanoma treated with the newer combination of encorafenib plus binimetinib showed an overall response rate (ORR) of 74.5% and a disease control rate (DCR) of 96.4%. Of interest, in the cohort receiving a dosage regimen of encorafenib 400/450 mg and binimetinib 45 mg, the ORR was 77.5% and the DCR was 100%. e combination was also well tolerated, with no grade 3–4 pyrexia or skin tox- icity events reported (Sullivan RJ et al. 2015).	
3.5.3 Clinical Assessments and Procedures Screening		The information about pregnancy test performace has been amendended. The test should be performed during the treatment, Combo-Immuno and every 4 (± 1) weeks (within 24 hours prior to administration of study drug both serum or urine are accepted) during the treatment Combo-Target.	Text Hamonization and minor corrections
3.5.4 Biomarker study - Tumor biopsies	p.51	The following sections have been added: Note: Baseline tumor biopsies can be archival if is collected	New section

Section	page	Description of change	Reason for change
	p. 52	after prior systemic therapy; otherwise a fresh biopsy will be collected. Sample handling The ancillary study requires blood sample collection at baseline, on-treatment (within first 4 weeks after first dose), and upon progression when feasible. To assess the immunological biomarkers, in all arms the following peripheral blood samples must be collected: A. 10 ml of non-anticoagulated whole blood for collection of serum (2 tubes x 5 ml tubes with red/yellow stopper); B. 9 ml of whole blood in heparin for collection of plasma (2 x 4.5 ml tubes with green stopper); C. 50 ml of whole blood in EDTA tubes for isolation of PBMC (5 x 10 ml tubes with lilac stopper); D. 5 ml in serum tubes (1 tube x 5 ml with stopper); The samples will be processed locally and then shipped in a central laboratory. The details of sample processing will be provided separately to each site in a study sample manual.	
4.2.1 Women of	p. 62	The following section has been added: A woman is considered to	New Section

Section	page	Description of change	Reason for change
Childbearing Potential		be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone–releasing intrauterine devices, and copper intrauterine devices. Hormonal contraceptive methods must be supplemented by a barrier method. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below: With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of study treatment. Men must refrain from donating sperm during this same period. With	

Section	page	Description of change	Reason for change
		pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of study treatment to avoid exposing the embryo. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception	
4.6 Criteria for Premature Withdrawal	p. 65	The following paragraphs have been added: In addition, the Investigator may discontinue a participant, without their consent, from the trial at any time if the Investigator considers it necessary for any reason including: • Pregnancy • Ineligibility (either arising during the trial or retrospectively having been overlooked at screening) • Significant protocol deviation • Significant non-compliance with treatment regimen or trial requirements • An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures • Any other condition which requires discontinuation of the trial medication or results in inability to continue to comply	New Section

Section	page	Description of change	Reason for change
	p. 65 p. 65	with trial procedures • Withdrawal of Consent • Loss to follow up Patients who discontinue from a study treatment due to an Adverse event will be follow until the Progression disease according to the protocol (CT SCAN every 8 weeks from day 1). A safety follow up within 28 days of the last dose is required. The patient can switched at other ARM after the progression disease. Any administrative or other reasons for withdrawal must be documented and explained to the patient.	
		The following paragraph has been deleted: 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.	Minor correction

Section	page	Description of change	Reason for change
4.7 Definition of End of Trial	p. 66	The following sentence has been added: The end of trial is the date of the last visit of the last participant	New Section
5.1.2 Dose Modifications, Interruption and delays criteria for Combo Target	p. 68	The following sentence has been added: In case of adverse events or other reasons, the patient restarts the treatment from the current day (day corresponding to the current treatment cycle day) and not from the last day.	New Section
5.4 Treatment after the End of the Study	p. 85	The following sentence has been added: Study drugs will not be available to subjects after the study has concluded. However, if further treatment is required, local standard of care will apply.	New Section
7.5.3 Pregnancy	p. 97-98	The following section has been added: Investigators will counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators will advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. As stated in the inclusion criteria, at a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below: Highly effective methods of	New Section

Section	page	Description of change	Reason for change
		contraception have a failure rate of <1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows: 1. Progestogen only hormonal contraception associated with inhibition of ovulation. 2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena. 3. Nonhormonal IUDs, such as ParaGard. 4. Bilateral tubal occlusion. 5. Vasectomised partner with documented azoospermia 90 days after procedure. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success. 6. Intrauterine hormone-releasing system (IUS).	

Section	page	Description of change	Reason for change
		7. Complete abstinence: a. Complete abstinence is defined as the complete avoidance of heterosexual intercourse. (refer to Glossary of Terms). b. Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days). c. It is not necessary to use any other method of contraception when complete abstinence is elected. d. Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 3.5.3. e. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. f. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Less effective methods of contraception: 1. Diaphragm with spermicide 2. Cervical cap with spermicide 3. Vaginal sponge with spermicide	

Section	page	Description of change	Reason for change
		4. Male or female condom with or without spermicide* 5. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action. *A male and a female condom must not be used together. Unacceptable methods of contraception: 1. Periodic abstinence (calendar, symptothermal, post-ovulation methods) 2. Withdrawal (coitus interruptus) 3. Spermicide only 4. Lactation amenorrhea method (LAM)	

SECTIONS UPDATED - PROTOCOL VERSION 6.0

Section	page	Description of change	Reason for change
Synopsis Exclusion criteria #15 Section 4.2	p. 12 p. 62	The exclusion criteria in the protocol have been modified to state that patients who receive live vaccines within the previous 30 days are excluded.	Request from MHRA in UK
section 4.5	p. 65	Drug Interaction has been amended to indicate that use of live vaccines is prohibited during the study and for three months after last dose of PD-1 blocker (nivolumab).	Request from MHRA in UK
Synopsis Exclusion criterium #16 Section 4.2	p. 12 p. 62	The exclusion criteria in the protocol have been modified to explicitly exclude patients with a history of severe or life-threatening skin adverse events or reactions.	Request from MHRA in UK

Section	page	Description of change	Reason for change
Section 7.5.2	p. 95	Reporting of SAEs (immediately reportable) has been amended in accordance with the regulation by replacing "one working day" with "24 hours".	Request from MHRA in UK
Section 8.5	p. 100	The study does have a DMC and the protocol has been amended to clarify the functions of the DMC () and its membership and their areas of expertise.	Request from MHRA in UK
Synopsis Exclusion criterium #13 Section 4.2	p. 12 p. 62	The exclusion criterion number 13 has been amended to include a positive result for HIV testing.	Request from MHRA in UK

SECTIONS UPDATED - PROTOCOL VERSION 7.0

Section	page	Description of change	Reason for change
Synopsis Inclusion criterium #8-9 Section 4.1	p. 11 p. 60	Inclusion criteria #8 and #9 have been changed according to Array's current standard contraception language	Request from ANSM in France
Synopsis Inclusion criterium # 16-17 Section 4.1	p. 11 p. 61	The inclusion criteria #16 an #17 have been added – (Array's standard cardiac inclusion criterion recommendations) to include patient with adequate cardiac function.	Request from ANSM in France
Section 5.1.2	p. 73	An additional dose modification language has been incorporated in the protocol, as a procedure in case of QT/QTc > 500 msec	Request from ANSM in France

SECTIONS UPDATED - PROTOCOL VERSION 8.0

Section	page	Description of change	Reason for change
Several sections	p. 9-13-15-	Time-point at 2 years has	Study Statistician

Section	page	Description of change	Reason for change
	37-38-39-88-91	been deleted	decision based on CEC request of clarification in Austria
Statistical methods	p. 14 - 89	A sentence to specify that the total PFS will be considered the main secondary criteria (together with the other secondary endpoints) to select the best strategy has been added.	Study Statistician decision based on CEC request of clarification in Austria
Section 3.5.4	p. 51	The allocation of biopsies to the main study or to the biomarker study has been clarified.	Sponsor's decision based on CEC request of clarification in Austria
Section 3.5.4	p. 51	The procedure tissue sample collection has been better described, adding more information on which conditions general anesthesia me be done.	CEC request of clarification in Austria
Section 3.5.4	p. 52	baseline 2 time-point for a mandatory peripheral blood samples collection has been added	Correction.
Section 5.1.2 – table of Recommended Dose Modifications for LGX818/MEK162 combination	p. 74	Creatine phosphokinase (CPK) G3 and G 4– change from 14 to 28 the time limit for MEK162 dose resuming or permanent discontinuation	Sponsor's decision based on Columbus study data
Section 6.2.1	p. 89	Percentage of surviving at 24 months derivation has been explained.	Study Statistician decision based on CEC request of clarification in Austria
Section 6.2.1	p. 89	The conditions for further investigations have been more detailed.	Study Statistician decision based on CEC request of clarification in Austria
Section 6.2.3	p. 90	A sentence has been added to specify for each endpoint whether one or two-sided analysis is used.	Study Statistician decision based on CEC request of clarification in Austria
Throughout the document	Several pages	The Wording *Biomarker study* has been reported in every section the study on	Wording harmonization

Section	page	Description of change	Reason for change
		biomarkers was mentioned (the wording *ancillary* and *translational* has been removed)	

SECTIONS UPDATED - PROTOCOL VERSION 9.0

Section	page	Description of change	Reason for change
Synopsis	p. 16	The following information regarding Duration of the Study have been updated: 'Global Recruitment end' and 'Global Study end' have been 6 months postponed.	Basing on the enrollment rate, there was a prolongation of the recruitment phase.
Section 5.1.1-5.1.3	p.70 p.80	The information regarding supply of LGX818 has been amended. LGX818 will be provided as 75 and 50 mg capsules.	Array Biopharma's decision of changing the supply of LGX818, by replacing 100 mg capsules with 75mg ones.
Section 5.1.3	p.80	The following sentence has been added: LGX818 50 mg will be provided in small quantities to support dose reductions (dose level -2, -3, -4).	Array Biopharma's decision about the use of 50 mg capsules of LGX818.
Section 5.2.1	p.81	In relation to Combo Immuno dose and treatment schedule, the following sentence has been added: Subjects may be dosed no less than 12 days from the previous dose.	Sponsor decision to outline this point
Synopsis, Tables 1-3, Sections: 3.3,	p.10 p. 20-25 p. 42-50 p. 58	Information regarding the schedule of assessments have been added.	Sponsor decision to outline this point

3.4 - 3.5.4 3.5.6			
Section 4.6	p. 68	Information regarding discontinuation of study treatment have been added.	Sponsor decision to outline this point
Section 6.3	p. 93	The following information regarding Duration of the Study have been updated: 'Global Recruitment end' and 'Global Study end' have been 6 months postponed.	Basing on the enrollment rate there was a prolongation of recruitment phase.
Section 7.2.5	p. 97	Information regarding the management of the event 'Death due to progression of disease' have been added.	Sponsor decision to outline this point
Synopsis, Table 1-3, Sections: 3.3, 3.4 3.5.3, 4.6, 7.3, 7.5.2	p.10, 13,21, 23,25,41,44, 51,68,98, 102	The Follow up period has been increased from 24 to 36 months	Sponsor decision to monitor patients survival until 3 years from the end of study treatment

SECTIONS UPDATED - PROTOCOL VERSION 10.0

Section	page	Description of change	Reason for change
Synopsis (Study Plan and Study Treatent duration, dose and schedule) Schedule of assessments Section 3.4 Section 3.5.3 Section 4.6 Section 7.7 Section 7.3 Section 7.5.2	p. 10, 13 p 21,23,25 p 44 p. 51 p. 68 p. 69 p. 99 p 103	The Follow up period has been increased from 36 to 60 months from randomization	Sponsor decision to monitor patients survival until 5 years from randomization of last patient
Synopsis (Study Treatent duration, dose and schedule) Schedule of assessments Section 3 Section 3.4 Section 4.3 Section 5 Section 5.2.1	p.13 p 21,23,25 p. 38 p.43 p. 65 p. 70 p. 81	The following doses and schedules of Nivolumab have been added: 240 mg every 2 weeks or 480 mg every 4 weeks	Dose and schedule of Nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks have been approved by CA
Synopsis (Study Treatent duration, dose and schedule) Section 3.4 Section 4.6 Section 5.2.2	p. 13 p. 43 p. 68 p. 85	The following sentence has been added: To reduce the risk of long-term toxicity, no more than 2 years of ipilimumab/nivolumab dosing will be administered to study patients	Evidence-based sponsor's decision (CheckMate 067 and KEYNOTE-001 KEYNOTE-006, CheckMate 153)
Synopsis (Duration of the Study) Section 6.3	p. 16 p. 94	Study duration was postponed to May 2024. Patients still on treatment in May 2024 will be treated according to clinical practice	Change due to FU prolongation