KURZPROTOKOLL
COLUMBUS

Öffentlicher Titel	Phase III Studie zur Behandlung des Melanoms mit LGX818 mit oder ohne MEK162 im Vergleich zu Vemurafenib
Wissenschaftl. Titel	A Phase III randomized, 3-arm, partially blinded, placebo controlled, multicenter, study of the Combination of LGX818 plus MEK162 compared with vemurafenib, and of LGX818 compared with vemurafenib for the treatment of patients with unresectable stage IIIB, IIIC or Stage IV melanoma with BRAF V600 mutation
Kurztitel	COLUMBUS
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, Pharma-Studie, dreiarmig, einfach verblindet
Studienphase	Phase III
Erkrankung	Haut: Hautkrebs: Schwarzer Hautkrebs (Malignes Melanom) - Zweitlinie oder höher
Ziele	- The primary objectives are to determine whether treatment with LGX818 plus MEK162 prolongs PFS compared with vemurafenib, and/or whether treatment with LGX818 prolongs PFS compared with vemurafenib in patients with BRAF V600 mutant unresectable or metastatic melanoma.
Einschlusskriterien	- Signed written informed consent; - Male or female patient, age >= 18 years; - Histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma AJCC Stage IIIB, IIIC or IV; - Presence of BRAF V600E or V600K mutation in tumor tissue prior to screening, as determined by a central laboratory; - Naïve untreated patient for unresectable locally advanced or metastatic melanoma; - Evidence of at least one measurable lesion as detected by radiological or photographic methods according to Novartis guideline - ECOG performance status of 0 or 1; - Adequate bone marrow, organ function and laboratory parameters: a) Absolute neutrophil count (ANC) >= 1.5 x 10^9/L; b) Hemoglobin (Hgb) >= 10 g/dL without transfusions; c) Platelets (PLT) >= 100 x 10^9/L without transfusions; d) AST and/or ALT <= 2.5 × upper limit of normal (ULN); e) patient with liver metastases <= 5 ×ULN; f) Total bilirubin <= 2 × ULN; g) Creatinine <= 1.5 mg/dL, or calculated creatinine clearance (determined as per Cockcroft-Gault) >= 50mL/min; - Adequate cardiac function: a) left ventricular ejection fraction (LVEF) >= 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram; b) QTc interval <= 480 ms; - Able to take oral medications; - Patient is deemed by the Investigator to have the initiative and means to be compliant with the protocol (treatment and follow-up); - Negative serum -HCG test (female patient of childbearing potential only) performed locally within 72 hours prior to first dose.
Ausschlusskriterien	- Any active central nervous system (CNS) lesion (i.e., those with radiographically unstable, symptomatic lesions). However, patient treated with stereotactic radiotherapy or surgery are eligible if patient remained without evidence of CNS disease progression >= 3 months. Patients must be off corticosteroid therapy for >= 3 weeks. - Non-cutaneous melanoma; - History of leptomeningeal metastases; - History or current evidence of central serous retinopathy (CSR) or retinal vein occlusion (RVO) or predisposing factors to RVO or CSR (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled diabetes mellitus, history of hyperviscosity or hypercoagulability syndromes);

- History of retinal degenerative disease;
- History of allogeneic bone marrow transplantation or organ transplantation;
- History of Gilbert's syndrome;
- Previous or concurrent malignancy with the following exceptions: a) adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing is required prior to study entry); b) in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to the study; c) or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to study entry; d) Prior therapy with a BRAF inhibitor (including but not limited to vemurafenib, dabrafenib, LGX818, and XL281/BMS-908662) and/or a MEK inhibitor (including but not limited to trametinib, AZD6244, MEK162, GDC-0973 and RDEA119);
- Any previous anti-cancer treatment, extensive radiotherapy or investigational agent for locally advanced unresectable or metastatic melanoma; Prior systemic treatment in the adjuvant setting (including ipilimumab) is allowed;
- Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following: a) History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) <6 months prior to screening; b) Symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality <6 months prior to screening except atrial fibrillation and paroxysmal supraventricular tachycardia;
- Uncontrolled arterial hypertension despite medical treatment;
- Known positive serology for HIV(Human immunodeficiency virus), active hepatitis B, and/or active hepatitis C infection;
- Patients who have neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);
- Patients who are planning on embarking on a new strenuous exercise regimen after first dose of study treatment. NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided while on MEK162 treatment;
- Impairment of gastrointestinal function or gastrointestinal disease (e.g., ulcerative disease, ncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection);
- Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/ inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.;
- Patients who have undergone major surgery <= 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure;
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test;

- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study and for 8 weeks after study drug discontinuation. Highly effective contraception methods include: a) Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception; b) Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment; c) Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient; d) combination of any of the two following (a+b or a+c or b+c): i) Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception; ii) Placement of an intrauterine device (IUD) or intrauterine system (IUS); iii) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository In case of use of oral contraception, women should have been stable on the same pill before taking study treatment.
- Sexually active males unless they use a condom during intercourse while taking the drug and for 8 weeks after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid;
- Medical, psychiatric, cognitive or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study.

Alter	18 Jahre und älter
Gütesiegel	DQS; IQ Net (ISO9001-2008)
Sponsor	Novartis Pharma
Förderer	Novartis Pharma
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT01909453 EudraCT 2013-001176-38
Therapie	Drug: LGX818 Drug: MEK162 Drug: Vemurafenib