Département d'oncologie
Plateformes du DO
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Indication	Mélanome avancé non opérable ou métastatique avec mutation du gène NRAS
Title	**The NEMO trial (NRAS melanoma and MEK inhibitor): A randomized Phase III, open label, multicenter, two-arm study comparing the efficacy of MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma**
Protocol ID	**Novartis NEMO**
Phase	**Phase III**
Sponsor	Novartis
Local Principal Investigator	Prof. O. Michielin
Primary Objective	To determine whether treatment with MEK162 prolongs PFS as compared to dacarbazine in patients with advanced unresectable, or metastatic NRAS mutation-positive cutaneous melanoma who are previously untreated or who have progressed on or after prior first-line immunotherapy for metastatic disease.
Inclusion/exclusion criteria	**Key Inclusion Criteria** 1. Signed written informed consent; 2. Male or female patient, age ≥ 18 years; 3. Histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma AJCC Stage IIIC or IV; 4. Presence of NRAS Q61 mutation in tumor tissue prior to randomization, as determined by a Novartis designated central laboratory; 5. Naïve untreated patients or patients who have progressed on or after prior first-line immunotherapy for metastatic melanoma; **Note:** Prior adjuvant therapy is permitted, except the administration of MEK inhibitors 6. Evidence of at least one measurable lesion as documented by radiological or photographic methods according to Novartis guideline version 3.1 based on RECIST version 1.1; **Note:** A previously irradiated lesion is eligible to be considered as a measurable lesion provided that there is objective evidence of progression of the lesion since discontinuation of therapy and prior to starting study drug. 7. ECOG performance status of 0-1 (Table 7-3); 8. Adequate bone marrow, organ function and laboratory parameters: • Absolute neutrophil count (ANC) ≥ 1.5 x 109/L, • Hemoglobin (Hgb) ≥ 10 g/dL without transfusions, • Platelets (PLT) ≥ 100 x 109/L without transfusions,

	• AST and/or ALT ≤ 2.5 × upper limit of normal (ULN); patients with liver metastases ≤ 5 ×ULN, • Total bilirubin ≤ 2 × ULN, • Creatinine ≤ 1.5 mg/dL; 9. Adequate cardiac function: • left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram, • QTc interval ≤ 480 ms; 10. Able to take oral medications; 11. Patient is deemed by the Investigator to have the initiative and means to be compliant with the protocol (treatment and follow-up); 12. Negative serum β-HCG test (female patient of childbearing potential only) performed locally within 72 hours prior to first dose. **Key Exclusion Criteria** 1. 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 the patient remained without evidence of CNS disease progression ≥ 4 sweeks. Patients must be off corticosteroid therapy for ≥ 3 weeks. 2. Non-cutaneous melanoma; 3. History of leptomeningeal metastases; 4. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); 5. History of allogeneic bone marrow transplantation or organ transplantation; 6. History of Gilbert's syndrome; 7. Previous or concurrent malignancy with the following exceptions: • adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing is required prior to study entry), • in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to the study, • a primary malignancy which has been completely resected and in complete remission for ≥5 years; 8. Prior therapy with a MEK- inhibitor; 9. Patients who have received more than one line of immunotherapy for metastatic melanoma; 10. Patients with washout period < 6 weeks from the last dose of ipilimumab or other immunotherapy;

11. Any previous chemotherapy for unresectable locally advanced or metastatic melanoma;

12. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:

- History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) <6 months prior to screening,
- 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;

13. Uncontrolled arterial hypertension despite medical treatment;

14. Known positive serology for HIV, active hepatitis B, and/or active hepatitis C infection

15. Patients who have neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);

16. 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;

17. Impairment of gastrointestinal function or gastrointestinal disease (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection);

18. 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.;

19. Patients who have undergone major surgery or radiotherapy ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure;

20. 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;

21. 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 30 days after study drug discontinuation. Highly effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- 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 • Male sterilization (at least 6 months prior to screening). For female patient on the study, the vasectomized male partner should be the sole partner for that patient • Combination of any of the two following (a+b or a+c or b+c) a. 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 b. Placement of an intrauterine device (IUD) or intrauterine system (IUS) c. 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. **Note:** Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. 22. Sexually active males unless they use a condom during intercourse while taking the drug and for 30 days 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; Note: for patients randomized to dacarbazine, please refer to the information in the local prescribing information for additional guidance. 23. 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.