

**BACKGROUND**

- Mutations in BRAF (40%) and NRAS (15%) within the mitogen-activated protein kinase (MAPK) signaling pathway account for a majority of the known genetic mutations in cutaneous melanoma.
- A prognostic factor in melanoma, NRAS mutations are associated with increased proliferation, thickness, central nervous system and lymph node involvement, and shorter overall survival (OS) compared with other subtypes.
- There are no approved therapies that specifically target NRAS-mutant melanoma.
- Binimetinib (MEK162) is a potent, highly selective allosteric inhibitor of MEK1/2.
- In preclinical studies, binimetinib demonstrated broad antiproliferative activity in tumors with or without NRAS, KRAS, and BRAF mutations, with an acceptable safety profile.
- Binimetinib showed potent inhibition of cell proliferation in NRAS-mutant cell line SK-MEL-2.

**STUDY OBJECTIVES**

**Primary Objective**
- To determine whether treatment with binimetinib prolongs progression-free survival (PFS) compared with dacarbazine in patients with advanced, untreated or metastatic NRAS-mutant melanoma who were previously untreated or have progressed on or after prior immunotherapy for metastatic disease.

**Key Secondary Objective**
- To compare OS between binimetinib and dacarbazine arms.

**Secondary Objectives**
- To evaluate binimetinib compared with dacarbazine with respect to:
  - Overall response rate
  - Time to objective response
  - Duration of objective response
  - Disease control rate
  - Safety
  - Pharmacokinetics
  - Quality of life using the EORTC QLQ-C30 and EQ-5D-5L questionnaires
  - Time to deterioration of ECOG performance status
  - To determine concordance between the registrational clinical trial assay and companion diagnostic assay (to be submitted for postmarket approval) for determination of NRAS Q61 mutation.

**EXEMPLARY QUESTIONS**

- To evaluate potential associations of binimetinib mode of action with effectiveness or resistance to:
  - Pharmacodynamics biomarkers (e.g., ERK, pERK, p27, DUSP6, cyclinD1)
  - Predictive biomarkers of benefit (i.e., correlation of efficacy endpoints with molecular status)
- Potential binimetinib resistance mechanisms (i.e., molecular status before and after treatment)

**STUDY DESIGN**

- NEMO is a randomized, open-label, multicenter, 2-arm phase 3 trial. (Figure 2)
- Approximately 393 patients with advanced untreated or metastatic NRAS-mutant melanoma will be randomized into the study.
- Patients will be randomized 2:1 to receive binimetinib 45 mg orally twice daily (bid) or dacarbazine 1000 mg/m2 intravenously every 3 weeks (q3w) in 21-day treatment cycles.

**Efficacy**
- Tumor response will be assessed centrally and locally based on RECIST v1.1, using imaging assessments at screening, weeks 6, 12, 18, and 24.

**Safety**
- Survival will be monitored in all patients who progress, start a new antineoplastic therapy, or withdraw consent from tumor assessments every 12 weeks until death, loss to follow-up, or withdrawal of consent for survival.

**STUDY ASSESSMENTS**

- **Primary Objective:** To determine whether treatment with binimetinib prolongs PFS compared with dacarbazine in patients with advanced NRAS-mutant melanoma.
- **Secondary Objectives:** To compare OS between binimetinib and dacarbazine arms.

**STATISTICAL METHODS**

- **Primary analysis (260 events):** To compare the distribution of PFS per central review between the 2 treatment arms using a stratified log-rank test at 1-sided 2.5% cumulative level of significance.
- **Ad interim analysis:** Of 300 events: To assess the efficacy and allow study to be stopped if futile; futility criteria based on Bayesian criteria.
- **Key secondary endpoint:** OS.
- **OS will be tested a maximum of 2 times, using the same method above:**
  - If PFS is found to be significant at final PFS analysis, OS will be tested
  - If OS is not significant at final PFS analysis, it will be tested a second time when 224 deaths have occurred.

**TARGET RECRUITMENT**

- 393 patients will be randomized into NEMO.
- Worldwide recruitment is ongoing in 27 countries across North America, South America, Europe, Asia-Pacific, and Africa (Figure 3).

**REFERENCES**


This study was sponsored by Novartis Pharmaceuticals Corporation. Binimetinib (also known as MEK162) is licensed from Array BioPharma Inc.