Management of MEK Inhibitor (MEKi) Toxicities of Binimetinib (BINI) in the NEMO Trial

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INTRODUCTION

- Activating mutations in the mitogen-activated protein kinase (MAPK) pathway, which regulates cellular proliferation, survival, and differentiation, are common in melanoma.[1]
- MAPK pathway inhibitors, including BRAF and MEK inhibitors, alone or in combination, have been approved for the treatment of *BRAF*-mutant metastatic melanoma.[2-5]
- MEK inhibitors have known class toxicities, including dermatologic, gastrointestinal, and ocular adverse effects.[6-8]
- Despite the availability of immunotherapy[9-11] and MAPK pathway inhibitors, there is substantial unmet medical need for new therapeutic opportunities in metastatic *NRAS*-mutant disease.
- The NEMO study (ClinicalTrials.gov, NCT01763164; EudraCT, 2012-003593-51) is a randomized, open-label, multicenter, phase 3 study evaluating the MEK1/2 inhibitor binimetinib vs dacarbazine in patients with advanced *NRAS*-mutant melanoma.[12]
  - The study met its primary endpoint, progression-free survival (PFS). The hazard ratio for PFS for binimetinib vs dacarbazine was 0.62 (95% CI, 0.47–0.80; *P*<0.001), indicating a 38% reduction in risk for progression or death with binimetinib.

OBJECTIVE

- To examine adverse events (AEs) associated with binimetinib monotherapy and management approaches used during the NEMO study

METHODS

Study Design and Overview

- Enrolled patients had advanced unresectable or metastatic cutaneous or unknown primary *NRAS*-mutant melanoma and were previously untreated or had progressed on or after prior immunotherapy.
- A total of 402 patients were randomized 2:1 to receive binimetinib 45 mg orally twice daily (n=269) or dacarbazine 1000 mg/m^2 intravenously once every 3 weeks (n=133).[12]
  - Randomization was stratified by American Joint Committee on Cancer (AJCC) stage, Eastern Cooperative Oncology Group (ECOG) status, and prior immunotherapy for unresectable/metastatic disease.[12]
- Patients continued on study treatment until disease progression, intolerable toxicity, withdrawal of consent, death, physician decision, or early termination of treatment.

Safety Evaluations

- Safety was assessed in all patients who had ≥1 dose of study treatment and ≥1 postbaseline safety evaluation.
- Safety and tolerability were assessed by incidence and severity of AEs, changes in laboratory values, physical examination, vital signs, cardiac assessments, and ophthalmic evaluations.
  - Ophthalmic evaluations
    - Ophthalmic examinations (consisting of slit lamp testing, fundoscopy, visual acuity, and intraocular pressure measurements) were performed at each study visit for all patients receiving binimetinib and for those patients receiving dacarbazine who had baseline retinal abnormalities.
    - After adoption of protocol amendment 4 (initiated when 200 patients were randomized), ocular coherence tomography (OCT) was performed at screening for all patients, at each study visit for patients receiving binimetinib, and as indicated for patients receiving dacarbazine.
  - AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
- Presentation of AEs was descriptive except for time-to-event analyses, which were determined by Kaplan Meier analysis.

RESULTS

Patients and Binimetinib Exposure

- 402 patients were randomized in the NEMO study; 269 patients received binimetinib.
  - In the binimetinib subgroup
    - Median (range) age: 65 (18–90) years
    - Male sex: 62% (n=166)
    - ECOG performance status: 0, 72% (n=193); 1, 28% (n=76)
    - Prior immunotherapy stratum: 21% (n=57)
- All patients in the binimetinib arm received study drug and were included in the safety population.
- Binimetinib exposure
  - Median (range) duration of exposure: 12.6 (0–73) weeks.
  - Median (range) actual dose intensity: 75.4 (29–90) mg/d.

Adverse Events

- All-cause AEs were reported by 100% (all grades) and 68% (grade 3/4) of patients in the binimetinib arm, and by 91% (all grades) and 46% (grade 3/4) of patients in the dacarbazine arm. Details for select AEs are provided in **Table 1**.

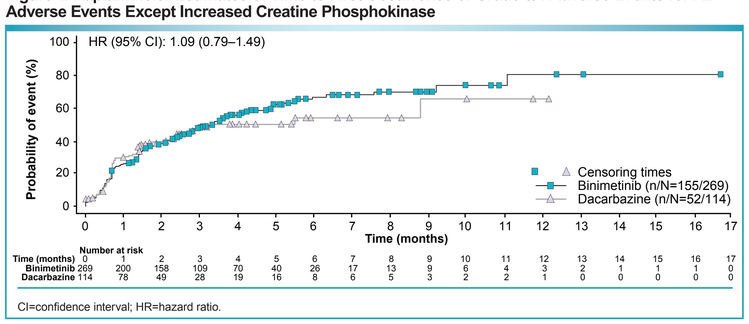
Table 1. Details of Selected Adverse Events in Patients Treated With Binimetinib

Adverse Event, Preferred Term	Incidence		Permanent Discontinuation (%)	Dose Modification (%)
	All Grades (%)	Grades 3/4 (%)		
Blood CPK increased	42	19	2	18
Diarrhea	40	1	<1	6
Rash	36	4	1	9
Peripheral edema	36	<1	<1	5
Dermatitis acneiform	35	3	1	7
Nausea	29	1	1	5
Fatigue	22	2	0	2
Vomiting	21	2	1	6
Hypertension	14	7	<1	4
Retinal detachment[a]	14	0	1	6
Ejection fraction decreased	11	4	4	6
Retinal vein occlusion[b]	2	1	2	NA

AE=adverse event; CPK=creatine phosphokinase; NA=not available.
[a]Events were reported as grade 1 (asymptomatic) in 7% of patients.
[b]Patients were permanently discontinued at onset.

- The most common AEs (≥20%, all grades) in the binimetinib group were blood creatine phosphokinase (CPK) elevations (42%), diarrhea (40%), rash (36%), peripheral edema (36%), dermatitis acneiform (35%), nausea (29%), fatigue (22%), and vomiting (21%).
  - CPK elevations were generally asymptomatic.
  - An analysis of AEs in the myopathy/rhabdomyolysis group performed within –15 to +30 days of worst CPK elevation showed that 22 patients (8%) had a grade 4 CPK elevation and 34 (13%) had a grade 3 CPK elevation. 6 out of 22 patients with a grade 4 CPK elevation and 10 out of 34 patients with a grade 3 CPK elevation had an AE across all grades including muscular weakness, musculoskeletal pain and myalgia.
- Median time to onset
  - Time to a grade 3/4 AE exclusive of CPK is shown in **Figure 1**.

Figure 1. Kaplan-Meier Estimates of Time to First Occurrence of Grade 3/4 Adverse Events for All Adverse Events Except Increased Creatine Phosphokinase



CI=confidence interval; HR=hazard ratio.

  - Median time to a grade 3/4 AE was 0.7 months for rash, 0.6 months for dermatitis acneiform, 2.5 months for skin infection, and 3.1 months for retinal vein occlusion (analysis not currently available for the remaining AEs listed in **Table 1**).
- AEs (all grades) led to dose interruption in 58% of patients and to dose reduction in 61% of patients in the binimetinib arm.
  - AEs most frequently responsible for dose modifications (interruptions or reductions) were increased blood CPK (18%), rash (9%), dermatitis acneiform (7%), ejection fraction decreased (6%), vomiting (6%), diarrhea (6%), and retinal detachment (6%).
- AEs (all grades) led to study drug discontinuation in 25% of patients in the binimetinib arm.
  - The most common AEs (≥1.5%) leading to study discontinuation were decreased ejection fraction (4%), increased blood CPK (2%), retinal vein occlusion (2%), and retinal detachment (1.5%).
  - The 6 patients with retinal vein occlusion had relevant antecedents of glaucoma (n=1) and hypertension (n=5).
- Median time to discontinuation
  - The probability of discontinuing treatment in the binimetinib arm because of an AE on or before 1, 2, and 3 months was 1.5%, 7.4%, and 14.9%, respectively.
  - In the dacarbazine arm, probability of discontinuing treatment because of an AE on or before 1, 2, and 3 months was 0.9%, 6.1%, and 6.1%, respectively.
- Recommendations and guidance on dose modifications (interruptions or reductions), discontinuations, and supportive care for specific binimetinib AEs that occurred during the NEMO study are summarized in **Tables 2–4**.

Table 2. Recommended Dose Reductions for Binimetinib

Dose reduction	30 mg orally BID
Subsequent modification	Permanently discontinue binimetinib if the patient is not able to tolerate 30 mg orally BID
Dose re-escalation	Do not re-escalate if the dose reduction is due to LVEF dysfunction or any grade 4 toxicity Patients with a dose reduction to 30 mg orally BID due to an AE may re-escalate to 45 mg orally BID if the AE that resulted in a dose reduction improved to baseline and remained stable for 14 days

AE=adverse event; BID=twice daily; LVEF=left ventricular ejection fraction.

Table 3. Recommended Dose Modifications for Binimetinib Based on Adverse Event Severity

Adverse Event	Recommendation
Cutaneous reaction	
Intolerable grade 2/3	Withhold binimetinib for ≤3 weeks • If improved to grade 0/1, resume at same dose level • If not improved, resume at lower dose level or permanently discontinue
Grade 4	Permanently discontinue binimetinib
Ocular events	
Symptomatic retinal pigment epithelial detachments	Withhold binimetinib for ≤3 weeks • If improved to grade 0/1, resume at same dose level • If not improved, resume at the lower dose level or permanently discontinue
Retinal vein occlusion	Permanently discontinue binimetinib
Cardiac events	
Asymptomatic, absolute decrease in LVEF from baseline and ≥10% and below the institutional LLN	Withhold binimetinib for ≤3 weeks: repeat LVEF Resume binimetinib at lower dose level if both of the following are present: • LVEF at or above the LLN • Absolute decrease from baseline is ≤10% If the LVEF does not recover within 3 weeks, permanently discontinue
Symptomatic congestive heart failure	Permanently discontinue binimetinib
VT	
Uncomplicated VT or PE	Withhold binimetinib for ≤3 weeks • If improved to grade 0/1, resume at lower dose. • If not improved, permanently discontinue.
Life threatening PE	Permanently discontinue binimetinib
Liver laboratory abnormalities and hepatotoxicity	
First occurrence grade 4	Withhold binimetinib for ≤4 weeks • If improved to grade 0/1, or grade ≤2 if liver metastasis, then resume at reduced dose • If not improved to grade 0/1 within 4 weeks, permanently discontinue
Recurrent grade 4	Permanently discontinue binimetinib
Rhabdomyolysis	
First occurrence of grade 4	Permanently discontinue binimetinib
CPK elevations	
Grade 4 CPK elevation Any CPK elevation and myalgia	Withhold binimetinib for ≤3 weeks • If improved to grade ≤3, resume at lower dose level • If not improved within 3 weeks, permanently discontinue
Hypertension	
Grade 3	Withhold binimetinib for ≤3 weeks • If improved to grade 0/1 or pretreatment/baseline level, resume at lower dose • If not improved, permanently discontinue
Grade 4	Permanently discontinue binimetinib
Interstitial lung disease/pneumonitis	
Grade 2	Withhold binimetinib for ≤3 weeks • If improved to grade 0/1, resume at lower dose • If not resolved within 3 weeks, permanently discontinue
Grade 3 or 4	Permanently discontinue binimetinib
Other	
Grade 2 (intolerable) adverse events	Withhold binimetinib for ≤3 weeks or until resolved to grade 0/1 then resume at lower dose
Grade 3	Withhold binimetinib for ≤3 weeks • If improved to grade 0/1 or pretreatment/baseline level, resume at lower dose • If not improved, permanently discontinue
Grade 4	Permanently discontinue binimetinib

CPK=creatine phosphokinase; LLN=lower limit of normal; LVEF=left ventricular ejection fraction. PE=pulmonary embolism; VT=venous thromboembolism.

Table 4. Approaches for Managing Binimetinib-Related Skin Toxicity and Diarrhea

Skin toxicity	• Monitor patients receiving binimetinib for skin toxicities and for secondary infections
	• Treat with topical corticosteroids with or without topical antibiotics, topical emollients, and oral antibiotics
	• Symptomatic treatment
	  • Pruritic lesions: cool compresses and oral antihistamines
	  • Fissuring: Monsel solution, silver nitrate, or zinc oxide cream; if not sufficient, use mild steroid ointments or combinations of steroids and antibiotics
	  • Desquamation: emollients with mild pH 5/neutral (best containing urea 10%)
	  • Paronychia: antiseptic bath and local potent corticosteroids, oral antibiotics; if no improvement refer to a dermatologist or surgeon
	  • Infected lesions: obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

Diarrhea	
Uncomplicated grade 1/2	• Consider administration of loperamide: initiate at 4 mg, then 2 mg every 4 hours (maximum, 16 mg/day) or after each unformed stool • Discontinue loperamide after 12-hour diarrhea-free (grade 0) interval • If uncomplicated grade 1/2 diarrhea persists >24 hours, escalate to high-dose loperamide: 2 mg every 2 hours (maximum, 16 mg/day) or after each unformed stool • If uncomplicated grade 1/2 diarrhea persists after 48 hours of loperamide treatment, discontinue loperamide and begin a second-line agent (opiate [opium tincture or paregoric], octreotide acetate, or steroid [budesonide]) • Note: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician
Complicated grade 1/2 or grade 3/4	• Patient must call investigator immediately • If loperamide has not been initiated, initiate immediately at 4 mg, then 2 mg every 4 hours (maximum, 16 mg/day) or after each unformed stool • Administer IV fluids and electrolytes as needed; if dehydration is severe, replace loperamide with octreotide • Monitor/continue IV fluids and antibiotics as needed; continue intervention until the patient is diarrhea free for ≥24 hours • Hospitalization may need to be considered

IV=intravenous.

CONCLUSIONS

- AEs observed in the NEMO study were consistent with the safety profile of currently marketed MEK inhibitors[2] and with those observed in earlier studies of binimetinib[13]; no new safety risks were identified.
- Retinal events are recognized as a class toxicity of MEK inhibitors[8]; the NEMO study included intensive monitoring with OCT to detect these events.
  - Earlier studies, which lacked frequent monitoring, may have underestimated the incidence of retinal events.[14]
- A time-to-event analysis of grade 3/4 AEs, excluding AEs of isolated grade 3/4 increased CPK, demonstrated that the probability of a grade 3/4 event was similar between binimetinib and dacarbazine arms through the first 3 months of treatment.
  - After 3 months, few patients remained in the dacarbazine treatment arm.
- Binimetinib AEs were manageable with dose modifications (interruptions or reductions), discontinuations, and supportive care.

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