Efficacy of Binimetinib in Patients With *NRAS*-Mutant Melanoma: Subgroup Analysis of the Phase 3 NEMO Study

Ana Arance,[1] Caroline Dutriaux,[2] Ralf Gutzmer,[3] Mario Mandala,[4] Claus Garbe,[5] Gabriella Liszkay,[6] Lev Demidov,[7] Viviana Bozon,[8] Victor Sandor,[8] Keith Flaherty,[9] Dirk Schadendorf[10]

[1]Hospital Clínic de Barcelona, Barcelona, Spain; [2]Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France; [3]Hannover Medical School, Hannover, Germany; [4]Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; [5]Eberhard Karls University, Tuebingen, Germany; [6]National Institute of Oncology, Budapest, Hungary; [7]N. N. Blokhin Russian Cancer Research Center, Moscow, Russia; [8]Array BioPharma Inc., Boulder, CO, USA; [9]Massachusetts General Hospital, Boston, MA, USA; [10]University Hospital Essen, Essen, Germany

INTRODUCTION

- Mutations that aberrantly activate the MAPK signaling pathway are common in melanoma.[1]
  - Activating *NRAS* and *BRAF* mutations are present in approximately 20% and 50% of patients with metastatic melanoma, respectively.[2]
- Although outcomes in patients with most melanoma subtypes have improved with the advent of immunotherapies,[3-5] the unmet need in patients with *NRAS*-mutant melanoma remains substantial.
- Certain melanoma disease characteristics are associated with poor prognosis, including advanced stage, poor performance status (PS), elevated lactate dehydrogenase (LDH), multiple organ involvement, and visceral disease.[6-8]
- In a phase 2 clinical trial, the oral MEK1/2 inhibitor binimetinib demonstrated clinical activity, with a response rate of 15% in patients with *NRAS*-mutant metastatic melanoma.[9]
- The NEMO study (ClinicalTrials.gov, NCT01763164; EudraCT, 2012-003593-51) is a randomized, open-label, multicenter phase 3 study of binimetinib vs dacarbazine in patients with advanced unresectable/metastatic cutaneous or unknown primary *NRAS*-mutant melanoma.[10]
  - **The NEMO study met its primary endpoint, progression-free survival (PFS).**
- This poster presents the results of an analysis of patient subgroups, a preplanned supportive analysis.

OBJECTIVE OF THE SUBGROUP ANALYSES

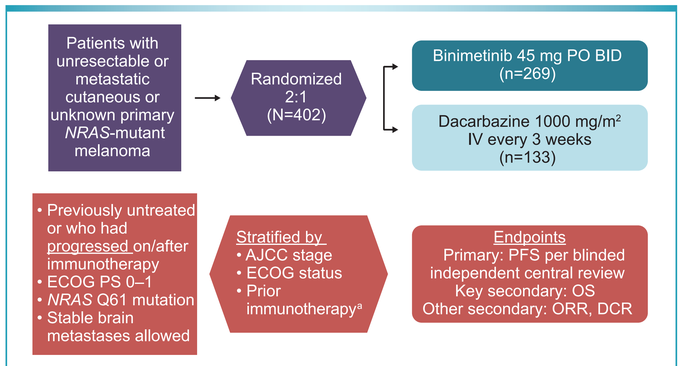
- To report PFS in subgroups of patients with poor prognostic characteristics and to evaluate factors prognostic for PFS

METHODS

Study Design and Overview

- Patients with advanced unresectable or metastatic cutaneous or unknown primary *NRAS*-mutant melanoma were randomized 2:1 to receive binimetinib (45 mg orally twice daily) or dacarbazine (1000 mg/m^2 intravenously once every 3 weeks; **Figure 1**).
  - Patients were previously untreated or had progressed on or after prior immunotherapy.
  - Patients were stratified by American Joint Committee on Cancer (AJCC) stage (IIIC, IVM1a, IVM1b vs IVM1c), Eastern Cooperative Oncology Group (ECOG) PS (0 vs 1), and prior immunotherapy for unresectable/metastatic disease (yes vs no).
- Patients continued on study treatment until disease progression, intolerable toxicity, withdrawal of consent, death, physician decision, or early termination of treatment.

Figure 1. NEMO Study Design



AJCC=American Joint Committee on Cancer; BID=twice daily; DCR=disease control rate; ECOG=Eastern Cooperative Oncology Group; IV=intravenous; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PO=by mouth; PS=performance status.
[a]Prior immunotherapy for unresectable/metastatic disease.

Tumor Assessments

- Tumor assessments (imaging per blinded independent central review according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) were performed at baseline, every 6 weeks until week 25, and then every 9 weeks. Additional evaluations were permitted for suspected disease progression.

Endpoints

- Stratified Cox regression analysis was used to estimate the hazard ratio (HR) for PFS, along with 95% CI, in the overall population (primary study endpoint).
- HRs for PFS and 95% CIs for prespecified subgroups were obtained from unstratified Cox proportional hazard models.
- Pre-specified prognostic factors for PFS were assessed using a multivariate Cox regression model.
  - Stratified by stratification factors for randomization (ie, AJCC stage, ECOG PS, and prior immunotherapy)
  - Covariates included treatment, LDH, gender, visceral disease (excluding lungs), baseline brain metastases, region, age, primary site of melanoma, and number of involved organs.
- Treatment effects were investigated within subgroups.

RESULTS

Patients

- A total of 402 patients were randomized to receive treatment in the NEMO study; 269 patients received binimetinib.
- In the binimetinib group, the median age of patients was 65 years and 62% were male **(Table 1)**.

Table 1. Baseline Patient Characteristics

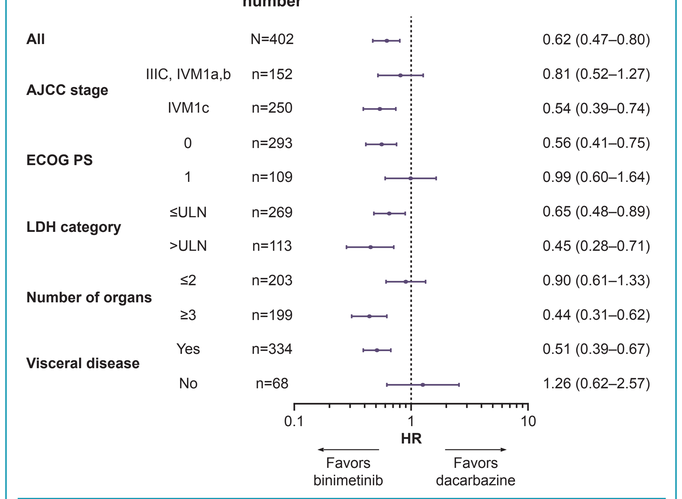
Characteristic	Binimetinib (n=269)	Dacarbazine (n=133)	Total (N=402)
Median (range) age, years	65 (18–90)	62 (27–89)	64 (18–90)
Male sex, n (%)	166 (61.7)	85 (63.9)	251 (62.4)
ECOG performance status, n (%)[a]			
0	193 (71.7)	96 (72.2)	289 (71.9)
1	76 (28.3)	36 (27.1)	112 (27.9)
Tumor stage at study entry, n (%)[b]			
IIIC	10 (3.7)	9 (6.8)	19 (4.7)
IVM1a	27 (10.0)	16 (12.0)	43 (10.7)
IVM1b	45 (16.7)	23 (17.3)	68 (16.9)
IVM1c with normal LDH level	109 (40.5)	50 (37.6)	159 (39.6)
IVM1c with elevated LDH level	78 (29.0)	35 (26.3)	113 (28.1)
Number of organs involved at baseline, n (%)			
1	64 (23.8)	28 (21.1)	92 (22.9)
2	73 (27.1)	38 (28.6)	111 (27.6)
3	59 (21.9)	25 (18.8)	84 (20.9)
>3	73 (27.1)	42 (31.6)	115 (28.6)
LDH level, n (%)[c]			
Normal	184 (68.4)	95 (71.4)	279 (69.4)
High	71 (26.4)	32 (24.1)	103 (25.6)
Missing	14 (5.2)	6 (4.5)	20 (5.0)

ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase.
[a]1 patient in the dacarbazine arm patient had a performance status of 2.
[b]Extent of melanoma according to the American Joint Committee on Cancer stage.
[c]Low and high categories of LDH defined by normal levels.

Progression-Free Survival

- In the overall population, the HR for PFS for binimetinib vs dacarbazine (0.62 [95% CI, 0.47–0.80]; *P*<0.001) indicated a 38% reduction in risk for progression or death with binimetinib.
  - The median PFS was 2.8 months (95% CI, 2.8–3.6) in the binimetinib arm and 1.5 months (95% CI, 1.5–1.7) in the dacarbazine arm.
- Point estimates for PFS favored binimetinib in most patient subgroups **(Figure 2)**.
  - The greatest differences in favor of binimetinib were observed in subgroups of patients with poorer prognostic disease characteristics of elevated LDH, ≥3 involved organs, visceral disease at baseline, and AJCC stage IVM1c.

Figure 2. Progression-Free Survival in All Patients and Subgroups by Prognostic Characteristics*

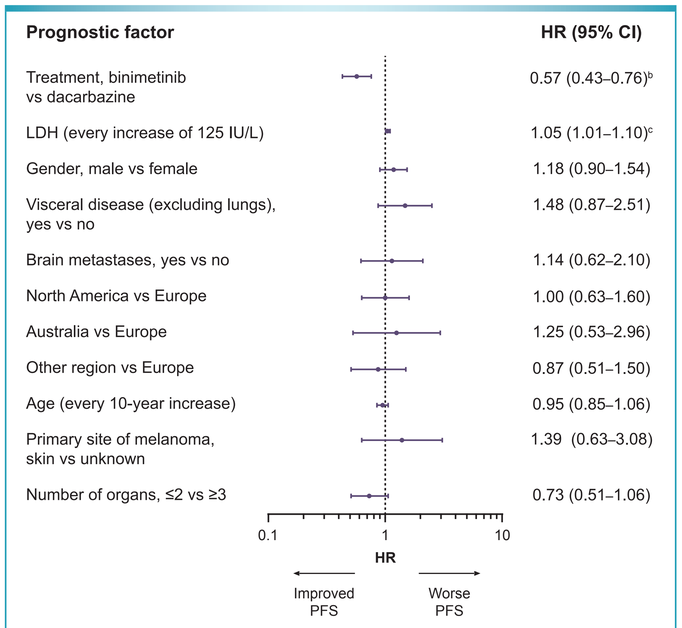


AJCC=American Joint Committee on Cancer; ECOG= Eastern Cooperative Oncology Group; HR=hazard ratio; LDH= lactate dehydrogenase; PS=performance status; ULN=upper limit of normal.
*The subgroup of patients with brain metastases not included because of low patient numbers.

- In a stratified multivariate Cox regression analysis of pre-specfied prognostic factors for PFS, 2 factors were significant **(Figure 3)**.
  - Treatment with binimetinib vs dacarbazine was associated with improved PFS (HR [95% CI], 0.57 [0.43–0.76]; *P*<0.001).
  - Increased LDH was associated with worsened PFS (HR [95% CI], 1.05 [1.01–1.10] for every 125 IU/L increase; *P*=0.020).

RESULTS (continued)

Figure 3. Stratified[a] Multivariate Cox Regression Model of Factors Associated With Progression-Free Survival



HR=hazard ratio; LDH=lactate dehydrogenase; PFS=progression-free survival.
[a]Stratified by American Joint Committee on Cancer tumor stage, prior immunotherapy, and Eastern Cooperative Oncology Group performance status.
[b]*P*<0.001.
[c]*P*=0.020.

CONCLUSIONS

- Treatment with binimetinib significantly prolonged PFS compared with dacarbazine in patients with *NRAS*-mutant melanoma.
- Subgroup analyses from the NEMO study suggest that binimetinib treatment provides clinical benefit in most patient subgroups, including patients with unfavorable prognostic characteristics.
- Among the factors assessed, treatment with binimetinib was the strongest prognostic factor, and was associated with improved PFS vs dacarbazine.

REFERENCES

1. Krauthammer M, et al. *Nat Genet.* 2015;47(9):996-1002.
2. Jakob JA, et al. *Cancer.* 2012;118(16):4014-4023.
3. Ribas A, et al. *Lancet Oncol.* 2015;16(8):908-918.
4. Robert C, et al. *N Engl J Med.* 2015;372(4):320-330.
5. Robert C, et al. *N Engl J Med.* 2011;364(26):2517-2526.
6. Balch CM, et al. *J Clin Oncol.* 2009;27(36):6199-6206.
7. Bedikian AY, et al. *Cancer Invest.* 2008;26(6):624-633.
8. Manola J, et al. *J Clin Oncol.* 2000;18(22):3782-3793.
9. Van Herpen C, et al. *Ann Oncol.* 2015;25(suppl 5):LBA35.
10. Dummer R, et al. *J Clin Oncol.* 2016;34(15 suppl):9500.

DISCLOSURES

AA has received honoraria/consulting fees from and been a member of a speakers bureau for Novartis, Roche, MSD, and BMS, and has received travel expenses from Roche and BMS. RG has received consulting fees from Roche, BMS, MSD, GSK, Novartis, Almirall, LEO, Amgen, and Pfizer; has received honoraria from Roche, BMS, MSD, GSK, Novartis, Almirall, Merck Serono, Amgen, and Boehringer Ingelheim; has received research funding from Roche, Novartis, Pfizer, and Johnson & Johnson; and has received expenses from BMS and Roche. MM has received honoraria from Novartis, GSK, BMS, MSD, and Roche; been a member of a speakers bureau for Novartis, GSK, Roche, and BMS; participated as an advisory board member for Novartis, Amgen, MSD, and BMS; and received research funding from Roche. CG has received honoraria and travel expenses from, served in a consulting/advisory role for, and been a speakers bureau member for Amgen, BMS, MSD, Novartis, Roche, and Philogen; and has received research funding for University Hospital Tübingen from BMS, Novartis, and Roche. VB is employed by Array BioPharma, Inc.; owns stock or has other ownership of Array BioPharma, Inc. and Takeda; and has patents with Takeda. VS is employed by and has a leadership role at Array BioPharma, Inc., and owns stock or has other ownership of Array BioPharma, Inc. and Incyte Corp. KF has received honoraria from and served in a consulting/advisory role for Novartis and Array BioPharma, Inc., and has received research funding from Novartis. DS has received honoraria and travel expenses from and served in a consulting/advisory role and speakers bureau member for Amgen, BMS, Novartis, Roche, and MSD; and has received research funding for University Hospital Essen from Amgen, BMS, Novartis, Roche, and MSD. CD, GL, and LD have nothing to declare.

Acknowledgments

The authors would like to thank the patients who participated in this study and their families. Editorial assistance was provided by Mariana Ovnic, PhD, of Complete Publication Solutions, LLC (North Wales, PA, USA), and was funded by Array BioPharma Inc. (Boulder, CO, USA).

This study was sponsored by Array BioPharma Inc., with funding support from Novartis Pharmaceuticals Corporation (Basel, Switzerland).

Available at: http://www.arraybiopharma.com/index.php/?cID=656

Scan this QR code with your reader to receive a PDF file of the poster.
To download a scan reader, go to www.i-nigma.mobi on your mobile device

Arance A, et al. Efficacy of Binimetinib in Patients With *NRAS*-Mutant Melanoma: Subgroup Analysis of the Phase 3 NEMO Study. Poster Presentation at the 13th International Congress of the Society for Melanoma Research; November 6–9, 2016; Boston, MA.