original reports

Initial Evidence for the Efficacy of Naporafenib in Combination With Trametinib in *NRAS*-Mutant Melanoma: Results From the Expansion Arm of a Phase Ib, Open-Label Study

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abstract

PURPOSE No approved targeted therapy for the treatment of patients with neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*)–mutant melanoma is currently available.

PATIENTS AND METHODS In this phase Ib escalation/expansion study (ClinicalTrials.gov identifier: NCT02974725), the safety, tolerability, and preliminary antitumor activity of naporafenib (LXH254), a BRAF/CRAF protein kinases inhibitor, were explored in combination with trametinib in patients with advanced/metastatic *KRAS*- or *BRAF*-mutant non–small-cell lung cancer (escalation arm) or *NRAS*-mutant melanoma (escalation and expansion arms).

RESULTS Thirty-six and 30 patients were enrolled in escalation and expansion, respectively. During escalation, six patients reported grade ≥3 dose-limiting toxicities, including dermatitis acneiform (n = 2), maculopapular rash (n = 2), increased lipase (n = 1), and Stevens-Johnson syndrome (n = 1). The recommended doses for expansion were naporafenib 200 mg twice a day plus trametinib 1 mg once daily and naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily. During expansion, all 30 patients experienced a treatment-related adverse event, the most common being rash (80%, n = 24), blood creatine phosphokinase increased, diarrhea, and nausea (30%, n = 9 each). In expansion, the objective response rate, median duration of response, and median progression-free survival were 46.7% (95% CI, 21.3 to 73.4; 7 of 15 patients), 3.75 (95% CI, 1.97 to not estimable [NE]) months, and 5.52 months, respectively, in patients treated with naporafenib 200 mg twice a day plus trametinib 1 mg once daily, and 13.3% (95% CI, 1.7 to 40.5; 2 of 15 patients), 3.75 (95% CI, 2.04 to NE) months, and 4.21 months, respectively, in patients treated with naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily.

CONCLUSION Naporafenib plus trametinib showed promising preliminary antitumor activity in patients with *NRAS*-mutant melanoma. Prophylactic strategies aimed to lower the incidence of skin-related events are under investigation.

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Alterations in the mitogen-activated protein kinase (MAPK [RAS/RAF/MEK/ERK]) signaling pathway often occur in cancer, including in melanoma.[1] Dual blockade proved to be efficacious in cells harboring a proto-oncogene *BRAF*^{V600} mutation, which displays sensitivity to BRAF and MEK inhibition.[2] However, no approved therapies that specifically target tumors with *NRAS* mutations are available, despite *NRAS* being mutated in 15%-20% of melanomas.[3] Compared with other subtypes, melanomas with *NRAS* mutations may be associated with a worse prognosis.[4,5]

Pharmacological inhibition of NRAS remains challenging because its GTPase activity has eluded the successful design of specific small-molecule antagonists. Use of MEK inhibitors in *NRAS*-mutant melanoma has previously been investigated. In a phase I study of trametinib that included seven patients with *NRAS*-mutant melanoma, stable disease (SD) was the best response achieved in two patients.[6] Studies with

CONTEXT

Key Objective

Immune checkpoint inhibitors are currently the standard-of-care treatment for patients with advanced/metastatic neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*)–mutant melanoma; however, on progression, no currently available therapy produces meaningful responses. Moreover, no targeted therapy is currently approved in this disease setting. We hypothesized that the combination of a pan-RAF inhibitor and a MEK inhibitor may provide meaningful clinical benefit in patients with *NRAS*-mutant advanced melanoma.

Knowledge Generated

We were able to demonstrate the preliminary antitumor activity and manageable safety profile of naporafenib, an ATP-competitive inhibitor of the BRAF and CRAF protein kinases, when administered in combination with trametinib, an inhibitor of the mitogen-activated protein kinases MEK1/2, in patients with *NRAS*-mutant melanoma who have progressed on prior standard treatment.

Relevance *(G.K. Schwartz)*

Combining inhibitors of both the BRAF/CRAF and MEK kinases shows particular promise in patients with *NRAS*-mutant melanoma and merits further evaluation.*

*Relevance section written by *JCO* Associate Editor Gary K. Schwartz, MD.

other MEK inhibitors also failed to provide satisfactory outcomes[7,8]; consequently, strategies of trametinib with novel agents were also pursued. A recent phase III study demonstrated some benefits of binimetinib compared with first-line dacarbazine in patients with advanced *NRAS*-mutant melanoma, with median progression-free survival (PFS) favoring binimetinib (2.8 months *v* 1.5 months [hazard ratio, 0.62], respectively).[9] However, discontinuation rate because of adverse events (AEs) suspected to be related to binimetinib was high (20% *v* 5% for binimetinib vs dacarbazine), and the benefit in PFS did not translate into improvements in overall survival.[9]

Naporafenib (LXH254) is an ATP–competitive inhibitor of the BRAF and v-raf-1 Murine Leukemia Viral Oncogene Homolog 1 (CRAF) protein kinases with sub-nM inhibitory concentration 50% values in biochemical assays, which demonstrated efficacy in a wide range of MAPK pathway–driven human cancer cell lines and in vivo tumor xenografts, including models harboring activating lesions in *BRAF* and *NRAS* oncogenes.[10] Collectively, the in vitro and in vivo data indicated that naporafenib may have antiproliferative activity in patients with tumors harboring activating mutations in the MAPK pathway. In in vivo preclinical studies, combination of naporafenib with the MEK1/2 kinase inhibitor trametinib resulted in significant antitumor effects in the MIA PaCa-2 model,[10] and led to improved depth and durability of response in the Calu-6 *KRAS*-mutant NSCLC and *NRAS*-mutant patient-derived melanoma tumor xenografts compared with naporafenib single-agent treatment (Novartis, data on file), which further supported the rationale to explore the effect of naporafenib in combination with trametinib in this patient population.

This phase Ib escalation/expansion study (ClinicalTrials.gov identifier: NCT02974725) investigated the safety, tolerability, and the preliminary antitumor activity of naporafenib in combination with the ERK1/2 kinase inhibitor LTT462, the cyclin-dependent kinase 4/6 inhibitor ribociclib, or trametinib in adult patients with advanced or metastatic *KRAS*- or *BRAF*-mutant NSCLC or *NRAS*-mutant melanoma. Here, we report the findings for patients treated with naporafenib plus trametinib in the escalation part of the study and the preliminary efficacy and safety results from the expansion arm in patients with *NRAS*-mutant melanoma treated at the recommended dose(s) for expansion (RDE).

PATIENTS AND METHODS

Study Patients

This study was conducted in patients age 18 years and older with confirmed advanced/metastatic *NRAS*-mutant cutaneous melanoma (dose escalation and dose expansion) and patients with locally advanced/metastatic *KRAS*- or *BRAF*-mutant NSCLC (dose escalation part only), who had progressed after standard of care or for whom no effective standard therapy was available. The presence of *NRAS*, *KRAS,* or *BRAF* mutation was determined by polymerase chain reaction or next-generation sequencing using tumor tissue before study treatment at a local or central laboratory. All patients had to have an Eastern Cooperative Oncology Group performance status ≤2 and at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[11] In expansion, prior treatment with any RAF, MEK1/2, and/or ERK1/2 inhibitor was not permitted. A full list of exclusion criteria is provided in the Data Supplement (online only).

TABLE 1. Baseline Characteristics of All Patients in Escalation and Expansion, Regardless of Tumor Type

	Patients Treated with Naporafenib Plus Trametinib	
Characteristic	**Escalation Arm (N = 36)**	**Expansion Arm (N = 30)**
Age, years		
Mean (SD)	61.9 (7.87)	64.5 (15.22)
Median (range)	63.5 (44-74)	69.0 (22-83)
18 to <65, No. (%)	19 (52.8)	8 (26.7)
65 to <85, No. (%)	17 (47.2)	22 (73.3)
Sex, male, No. (%)	23 (63.9)	15 (50.0)
Race, No. (%)		
White	33 (91.7)	24 (80.0)
Other/unknown[a]	3 (8.3)	6 (20.0)
ECOG PS, No. (%)		
0	14 (38.9)	19 (63.3)
1	21 (58.3)	10 (33.3)
2	1 (2.8)	1 (3.3)
Prior regimens, No. (%)		
0	0 (0)	1 (3.3)
1	7 (19.4)	10 (33.3)
2	10 (27.8)	9 (30.0)
≥3	19 (52.8)	10 (33.3)
Mutation status, No. (%)		
BRAF-mutant NSCLC	5 (13.9)	
KRAS-mutant NSCLC	25 (69.4)	
NRAS-mutant melanoma	6 (16.7)	30 (100.0)

Abbreviations: *BRAF*, B-Raf proto-oncogene; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *NRAS*, neuroblastoma RAS viral (v-ras) oncogene homolog; NSCLC, non–small-cell lung cancer; SD, standard deviation.

[a]Other race in the escalation part and unknown race in the expansion part.

The Protocol (online only) was approved by the institutional review boards of all participating institutions. Field monitors visited the site regularly to check the completeness of patient records, accuracy of entries, and adherence to the protocol. The study was conducted in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice as defined by the International Conference on Harmonisation. Patients gave written informed consent before any study-specific procedures.

Study Design, End Points, and Dose Administration

This was a multicenter, open-label, phase Ib study of naporafenib in combination with trametinib comprising a dose escalation part, which aimed to identify the RDE(s), followed by a dose expansion part to gather further safety and preliminary efficacy data at the identified RDE(s) (Data Supplement). The median follow-up was defined as the time from the start of the study to the last contact date or death.

The primary objective was to determine the safety and tolerability of naporafenib in combination with trametinib. Accordingly, the primary end point was the incidence and severity of AEs and serious AEs including changes in laboratory values, vital signs and electrocardiograms, incidence, and nature of dose-limiting toxicities (DLTs) during the first cycle of the dose escalation part only, dose interruptions, dose reductions, and dose intensity. AEs were coded using the Medical Dictionary for Regulatory Activities terminology version 4.03 and assessed for severity and relation to study drug. Dose interruptions were permitted, when necessary, but a patient had to receive at least 75% of the planned combination doses to meet the minimum exposure requirement to be evaluable for the dose-determining set. Mandatory prophylactic measures against skin rash were implemented in December 2020 when all patients in expansion had already started treatment. Before this, guidelines for supportive care of skin-related AEs were applicable to all patients and included recommended topical steroids and antibiotics from the first day of treatment.

Secondary end points for the assessment of the preliminary antitumor activity included objective response rate (ORR; proportion of patients with complete response [CR] or partial response [PR] per RECIST version 1.1), disease control rate (DCR; proportion of patients with CR, PR, or SD), duration of response (DOR), PFS per RECIST version 1.1, pharmacokinetic (PK) parameters, and changes from baseline of the pharmacodynamic (PD) marker dual-specificity phosphatase 6 (DUSP6) in tumor tissue.

In escalation, oral naporafenib in combination with oral trametinib were administered under fasted condition until the maximum tolerated dose (MTD) was reached or RDE was established. Five dose levels were explored: naporafenib 200 mg twice a day plus trametinib (1 mg or 0.5 mg) once daily , naporafenib 400 mg twice a day plus trametinib (1 mg or 0.5 mg) once daily, and naporafenib 400 mg twice a day plus trametinib 1 mg (once daily, 2 weeks on/2 weeks off). In escalation, cohort 1 was treated with naporafenib 200 mg twice a day plus trametinib 1 mg once daily, whereas cohorts 2a and 2b were treated with naporafenib 400 mg twice a day in combination with trametinib 0.5 mg and 1 mg once daily, respectively. Cohort 3 was treated with naporafenib 200 mg twice a day plus trametinib 0.5 mg once daily in parallel to backfilling cohorts 1 and 2a. Cohort 4 was treated with naporafenib 400 mg twice a day plus trametinib 1 mg once daily with a regimen of 2 weeks on/2 weeks off. The combination of naporafenib with trametinib 2 mg once daily was not explored because of the DLTs observed in cohorts 1 and 2b, as well as on the basis of the Bayesian logistic regression model (BLRM) and clinical review of data.

PK and PD Assessments

Drug plasma levels were determined using a validated liquid chromatography-tandem mass spectrometry assay. PK

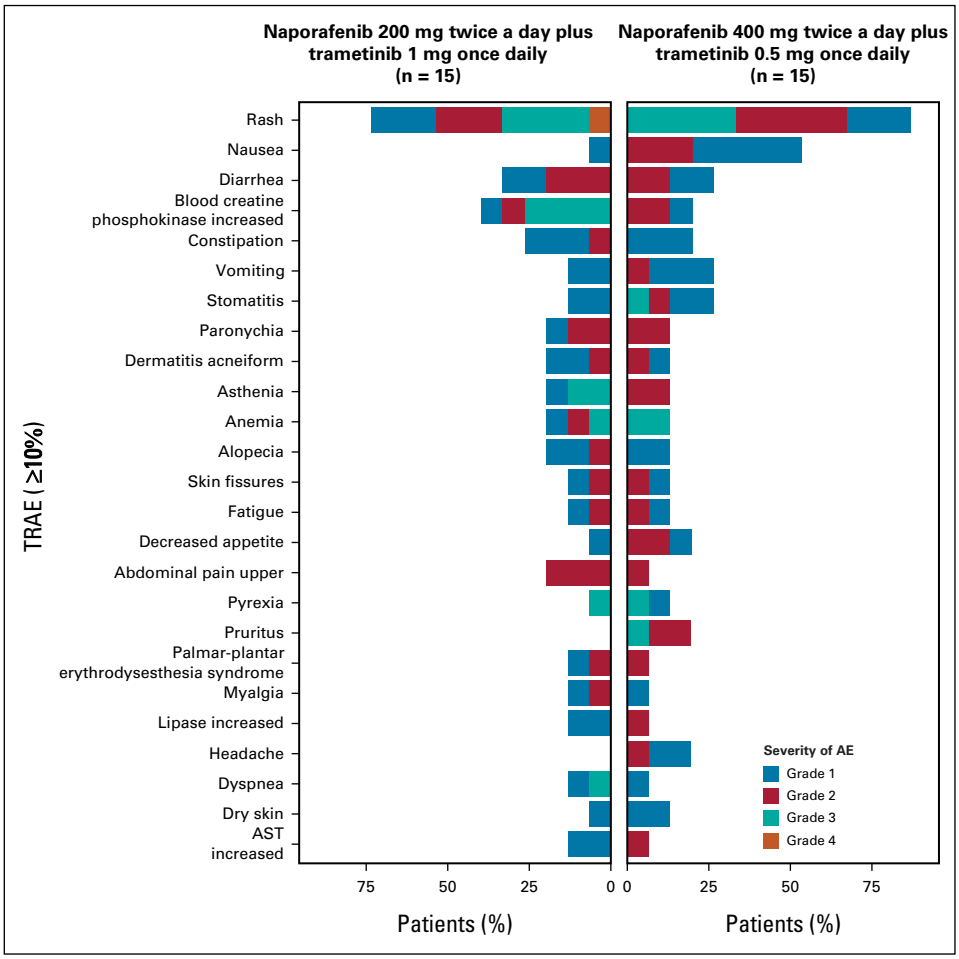

FIG 1. TRAEs (≥10% overall) in the expansion part of the study. A patient with multiple severity grades for an AE was only counted under the maximum grade. AE, adverse event; TRAEs, treatment-related AEs.

parameters were derived on the basis of noncompartmental methods using Phoenix WinNonlin version 8.0 or higher.

Fresh tumor biopsies for quantitative detection of mRNA levels for DUSP6 were collected before and during treatment for PD investigation, as previously described.[12] Threshold cycle (CT) values of DUSP6 mRNAs were normalized to the CT values of the internal control (GAPDH, PUM1, SDHA, and TUBB2A) for both baseline and postbaseline samples (ΔCT). Percent change in *DUSP6* expression was derived from the relative expression ratio (RER), which was calculated by raising 2.0 to an exponent computed by subtracting the ΔCT of the baseline sample from ΔCT of the postbaseline sample. RER was then transformed by subtracting 1.0, such that expression increases and decreases were indicated when % change was greater than or less than zero, respectively.

Genomic profiling of cell-free circulating tumor DNA (ctDNA) was done by next-generation sequencing of a panel of 579 cancer-relevant genes to a median depth of approximately 3,000×, as previously described.[13]

Sample Size

At least 18 patients for the combinations of naporafenib with trametinib were expected to be treated in dose escalation for the model to have reasonable operating characteristics relating to its MTD recommendation. In expansion, a sample size of 30 patients had ≥79% of probability of observing an AE with a true incidence rate of ≥5%.

Statistical Analysis

In escalation, naporafenib plus trametinib doses were explored on the basis of an adaptive BLRM with the escalation with overdose control (EWOC) and cycle one DLT data. The BLRM recommendations for the next cohort were based on the highest posterior probability of DLT rate being within the target toxicity interval (16%-33%), while satisfying the EWOC criterion that the probability of DLT rate in the overtoxicity interval (33%-100%) was <0.25. Dose escalation continued until a recommended dose, MTD, was determined for use in the expansion part. The MTD was defined as the highest dose combination that was unlikely

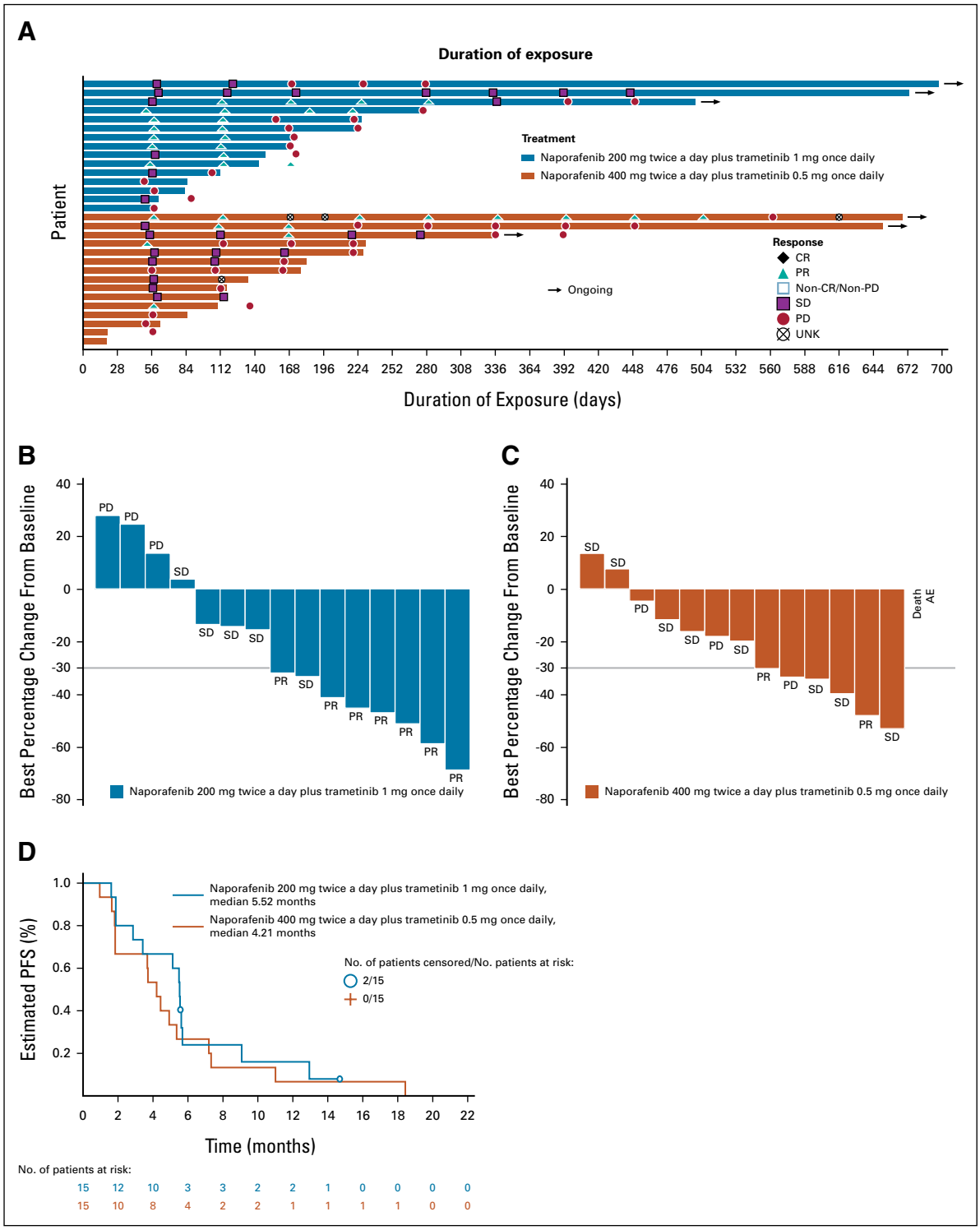

FIG 2. (A) Duration of exposure to naporafenib in combination with trametinib in patients with *NRAS*-mutant melanoma. (B-C) Change from baseline in the analysis set for response for patients with *NRAS*-mutant melanoma treated with (B) naporafenib 200 mg twice a day plus trametinib 1 mg once daily or (C) naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily. (D) Kaplan-Meier plot of PFS for patients treated in the expansion arm. CR, complete response; *NRAS*, neuroblastoma RAS viral (v-ras) oncogene homolog; PD, progression of disease; PFS, progression-free survival; PR, partial response; SD, stable disease; UNK, not known.

TABLE 2. Summary of BOR Based on Investigator Assessment in Patients With *NRAS*-Mutant Melanoma Treated at the RDE

Response	Naporafenib 200 mg Twice a Day Plus Trametinib 1 mg Once Daily, n = 15	Naporafenib 400 mg Twice a Day Plus Trametinib 0.5 mg Once Daily, n = 15	Overall, N = 30
BOR, No. (%)			
CR	0 (0)	0 (0)	0 (0)
PR	7 (46.7)	2 (13.3)	9 (30.0)
SD	5 (33.3)	8 (53.3)	13 (43.3)
PD	3 (20.0)	3 (20.0)	6 (20.0)
Unknown	0 (0)	2 (13.3)	2 (6.7)
Overall response, No. (%) [95% CI]	7 (46.7) [21.3 to 73.4]	2 (13.3) [1.7 to 40.5]	9 (30.0) [14.7 to 49.4]
DCR, No. (%) [95% CI]	12 (80.0) [51.9 to 95.7]	10 (66.7) [38.4 to 88.2]	22 (73.3) [54.1 to 87.7]

Abbreviations: BOR, best overall response; CR, complete response; DCR, disease control rate; *NRAS*, neuroblastoma RAS viral (v-ras) oncogene homolog; PD, progressive disease; PR, partial response; RDE, recommended dose for expansion; SD, stable disease.

(<25% of posterior probability) to cause DLTs in 33% or more of the treated patients in the first cycle of naporafenib and trametinib treatment during the escalation part of the study.

The expansion cohort included patients with *NRAS*-mutant melanoma treated at the RDE(s) until disease progression or withdrawal of consent. The full analysis set and safety set comprised all patients who received at least one dose of naporafenib or trametinib. PFS was described using the Kaplan-Meier method. 95% CI for ORR was calculated using the Clopper-Pearson method.

RESULTS

Baseline Characteristics and Disposition

Between March 6, 2018, and September 23, 2020, 36 patients and 30 patients were enrolled and treated in the escalation and expansion arms, respectively. Data cutoff date was December 9, 2021, and the median (range) duration of follow-up in expansion was 8.8 (1-21) months.

Baseline patient characteristics are presented in Table 1. All patients in escalation and 24 patients in expansion discontinued from the study because of PD (escalation, 61%; expansion, 60%), AE (escalation, 22%; expansion, 7%), death (escalation, 8%; expansion, 7%), patient decision (escalation, 6%; expansion, 7%), and physician decision (escalation, 3%; expansion, 0%).

RDE Determination

Six patients reported grade ≥3 DLTs during dose escalation. These included dermatitis acneiform (one patient each in the naporafenib 200 mg twice a day plus trametinib 1 mg once daily and in naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily group), maculopapular rash (one patient treated with naporafenib 200 mg twice a day plus trametinib 1 mg once daily and one patient treated with naporafenib 400 mg twice a day plus trametinib 1 mg once daily), increased lipase (one patient in the naporafenib 200 mg twice a day plus trametinib 1 mg once daily group), and Stevens-Johnson syndrome (one patient in the naporafenib 400 mg twice a day plus trametinib 1 mg once daily group).

Both naporafenib 200 mg twice a day plus trametinib 1 mg once daily and naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily satisfied the EWOC criterion and were chosen as RDEs.

Safety

During escalation, all 36 patients experienced ≥1 AE and eight patients (22%) discontinued because of an AE. Treatment-related AEs (TRAEs) occurred in 34 patients (94%), the most common being rash (44%, n = 16) and dermatitis acneiform (39%, n = 14; Data Supplement).

In expansion, all 30 patients experienced ≥1 AE, including rash (80%, n = 24), diarrhea (40%, n = 12), and anemia, blood creatine phosphokinase increased, and constipation (37%, n = 11 each). The most common AEs (≥10%) regardless of relationship to study treatment are shown in the Data Supplement. When looking at AEs with suspected relationship to study treatment, all 30 patients experienced a TRAE, the most common being rash (80%, n = 24) and blood creatine phosphokinase increased, diarrhea, and nausea (30%, n = 9 each; Fig 1). All skin-related treatment-related AEs are reported in the Data Supplement.

One fatal TRAE due to hypovolemic shock assessed to be related to thrombocytopenia with suspected hemorrhagic cause was reported in the naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily group. AEs requiring at least one dose interruption in expansion occurred in 23 patients (77%; Data Supplement). The most common grade 3 to 4 AEs (≥ 10%) leading to dose interruption and/or adjustment in the expansion phase were rash (23%, n = 7) and anemia (13%, n = 4). Twelve patients (80%) in the naporafenib 200 mg twice a day plus trametinib 1 mg once daily group and nine patients (60%) in the naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily group experienced at least one dose reduction (Data Supplement). Two patients (7%) in

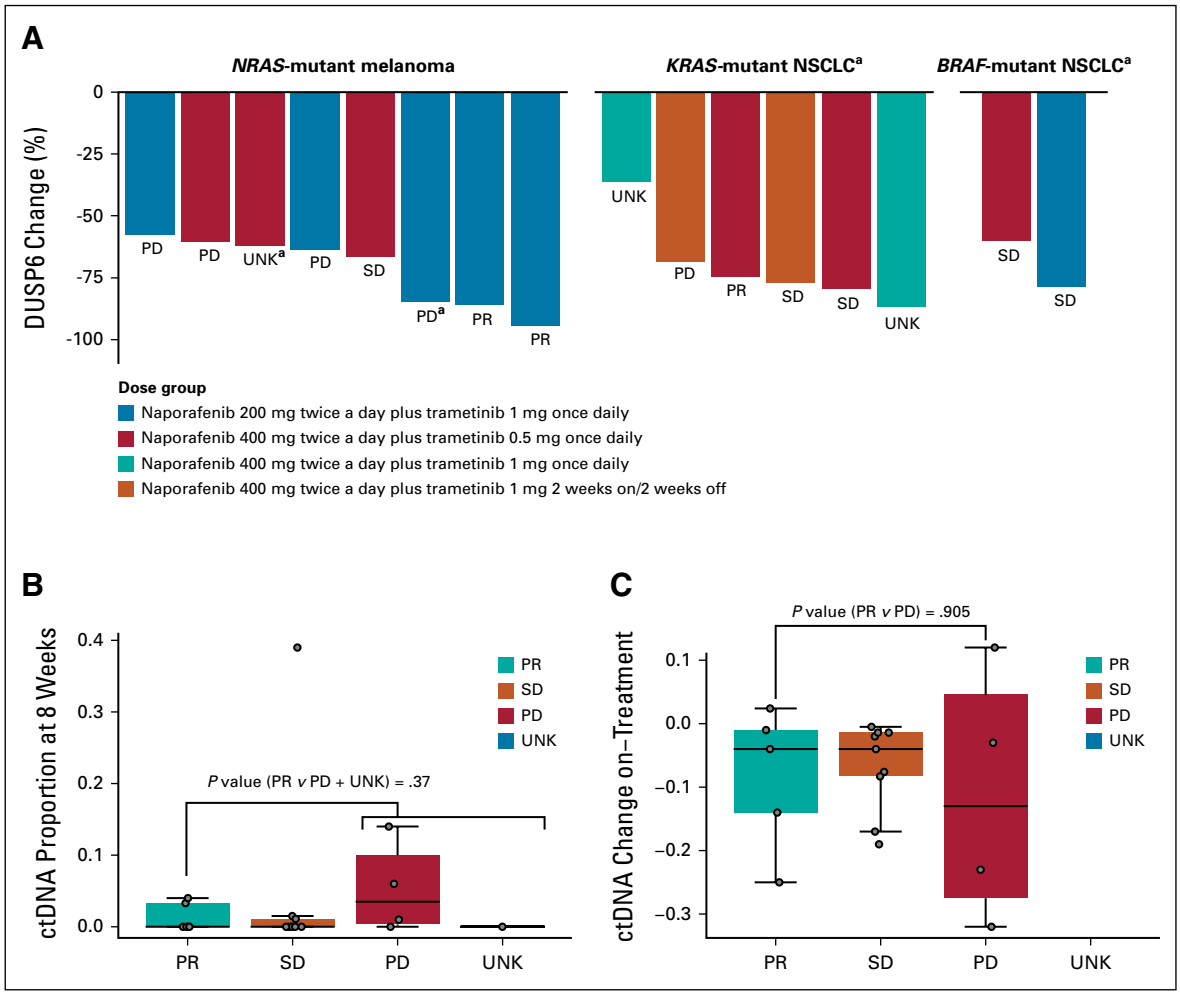

FIG 3. (A) Change in DUSP6 expression by mRNA in paired pretreatment vs on-treatment tumor samples. (B-C) Relationship between BOR and change in ctDNA between baseline and at 8 weeks in patients with detectable ctDNA at baseline and ctDNA level at 8 weeks. The dots represent the point values for each patient. The midline on the box plot is the median, the top and bottom of the box are the 75th and 25th percentiles, respectively, and the whiskers extend up to 1.5 times the interquartile range. BOR, best overall response; *BRAF*, B-Raf proto-oncogene; ctDNA, circulating tumor DNA; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *NRAS*, neuroblastoma RAS viral (v-ras) oncogene homolog; NSCLC, non–small-cell lung cancer; PD, progression of disease; PR, partial response; SD, stable disease; UNK, not known. [a]Patients in the escalation arm.

expansion discontinued study treatment because of an AE. AEs leading to discontinuation in expansion were hypovolemic shock, pyrexia, and Stevens-Johnson syndrome (3%, n = 1 each). Overall, two patients developed Stevens-Johnson syndrome, both considered related to the study drug, and their condition improved after permanently discontinuing both treatments and after steroid treatment.

Efficacy

In escalation, one patient with *KRAS*-mutant NSCLC who received naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily reported PR, 19 patients reported SD, and nine patients reported PD. Seven patients were not evaluable for disease response: three patients discontinued before the first evaluation (two patients because of an AE and one because of the patient's decision), and four patients did not have a valid assessment.

Of the 30 patients with *NRAS*-mutant melanoma enrolled in expansion, 15 patients (50%) were treated with naporafenib 200 mg twice a day plus trametinib 1 mg once daily, and the remaining 15 patients (50%) were treated with naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily. The median (range) duration of exposure was 159 (19-697) days (Fig 2A). The ORR was 46.7% (95% CI, 21.3 to 73.4; n = 7) in patients treated with naporafenib 200 mg twice a day plus trametinib 1 mg once daily and 13.3% (95% CI, 1.7 to 40.5; n = 2) in patients treated with naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily (Table 2). Overall, nine patients (30%) reported a PR, and 13 patients (43%) reported SD. No patients reported a CR (Figs 2B and 2C). The median (95% CI) DOR was 3.75 (1.97 to not estimable [NE]) months for patients treated with naporafenib 200 mg twice a day plus

trametinib 1 mg once daily, and 3.75 (2.04 to NE) for patients treated with naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily. The overall median (95% CI) PFS was 5.03 (3.42 to 5.62) months (5.52 months in patients treated with naporafenib 200 mg twice a day plus trametinib 1 mg once daily, and 4.21 months in patients treated with naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily; Fig 2D).

PKs and PDs

Across naporafenib twice a day dose escalation levels (200 mg and 400 mg), a dose-dependent increase in exposure was observed. PK parameters for naporafenib and trametinib are summarized in the Data Supplement. No significant changes were noted in the exposure of either naporafenib or trametinib when administered in combination regimens relative to the respective exposure when administered as single agents.

Biomarker analyses on tumor samples at baseline and on day 15 of cycle one at 4-8 hours after dose (n = 16) showed >50% of reduction in *DUSP6* expression (Fig 3A). Patients with PR (n = 3) regardless of tumor types had ≥75% of reduction in *DUSP6* expression.

Longitudinal ctDNA sequencing of a panel of 579 cancer-relevant genes was performed in 21 patients with *NRAS*-mutant melanoma; of these, 86% had detectable ctDNA levels at baseline, which subsequently dropped after 8 weeks of treatment in 89% of patients. The drop in ctDNA levels was not predictive of radiological response (Data Supplement). No association between ctDNA change and outcome was seen (Figs 3B and 3C).

DISCUSSION

In this study, the safety profile of naporafenib in combination with trametinib for the treatment of patients with *NRAS*-mutant melanoma was manageable, with most TRAEs being rash, increased blood creatine phosphokinase, diarrhea, nausea, and constipation. The incidence of TRAE was generally consistent across treatment groups in both the escalation and the expansion parts of the study. As previously observed in patients treated with naporafenib monotherapy (manuscript in preparation),[14] skin AEs suspected to be related to naporafenib treatment were common, and prophylactic strategies aimed to lower incidence of these events are under investigation. In terms of efficacy, 30% (n/N = 9/30) of patients experienced a PR, and most of the remaining patients reported SD (one patient for over 6 months) across the two recommended doses tested in expansion. The ORR, median PFS, and DCR were 47%, 5.52 months, and 80% at the naporafenib 200 mg twice a day plus trametinib 1 mg once daily, and 13%, 4.21 months, and 67% at the naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily dose, respectively. In NEMO, the ORR, PFS, and DCR were 15%, 2.8 months, and 58% in the binimetinib group and 7%, 1.5 months, and 25% in the dacarbazine group, respectively.[9] The ORR difference between the two treatment regimens observed in the present study may be due to the increased variance observed with small sample sizes rather than reflect a real difference in efficacy, as the two arms had a similar median PFS and DCR. A recent phase II study investigating the combination of naporafenib with trametinib in patients with *NRAS*-mutant melanoma reported favorable efficacy for both doses (ORR, 25% for naporafenib 200 mg twice a day plus trametinib 1 mg once daily and 29% for naporafenib 400 mg twice a day plus trametinib 0.5 mg once daily).[15] We also found that combination treatment of naporafenib with trametinib was associated with a substantial decrease in *DUSP6* expression in all analyzed tumor samples, which is indicative of MAPK inhibition, although no apparent correlation between reduction of *DUSP6* expression, dose exposure, and treatment response was noted.

In summary, the combination of naporafenib with trametinib in patients with heavily pretreated *NRAS*-mutant melanoma showed encouraging antitumor activity and a manageable safety profile with low discontinuation rates because of AEs, which warrants further evaluation in clinical studies.

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Novartis will not provide access to patient-level data if there is a reasonable likelihood that individual patients could be reidentified. Phase I studies, by their nature, present a high risk of patient reidentification; therefore, patient individual results for phase I studies cannot be shared. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions may preclude granting access under these provisions. Where codevelopment agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

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Initial Evidence for the Efficacy of Naporafenib in Combination With Trametinib in *NRAS*-Mutant Melanoma: Results From the Expansion Arm of a Phase Ib, Open-Label Study

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