Phase II Clinical Trial of Trametinib and Low-Dose Dabrafenib in Advanced, Previously Treated *BRAF*^{V600}/*NRAS*^{Q61} Wild-Type Melanoma (TraMel-WT)

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ABSTRACT

PURPOSE Patients with *BRAF*^{V600}/*NRAS*^{Q61} wild-type melanoma who progress after immune checkpoint inhibitors (ICIs) have a poor prognosis. MEK inhibition has shown activity in this patient population but is associated with treatment-limiting skin toxicity. Combining a BRAF inhibitor with a MEK inhibitor is associated with less skin toxicity.

METHODS This phase II trial investigated trametinib (2 mg once daily) in patients with advanced *BRAF*^{V600}/*NRAS*^{Q61} wild-type, ICI-refractory melanoma. In case of treatment-limiting skin toxicity, low-dose dabrafenib (50 mg twice daily) was added to trametinib. After a trial amendment, both drugs were combined upfront. The confirmed objective response rate (cORR) served as the primary end point.

RESULTS Twenty-four patients were included (50% male; median age 57 years; 92% Eastern Cooperative Oncology Group Performance Status 0-2; 75% stage IV-M1c/stage IV-M1d; median number of prior therapies: two [range, 1-5]). Three patients were enrolled before and 21 patients after the amendment, respectively. Seven confirmed and one unconfirmed partial responses (PRs) were observed (cORR, 29.2%). The median duration of response was 16.6 weeks (95% CI, 5.5 to 27.7). Stable disease (SD) was the best response in an additional five patients. Among the responding patients, genetic alterations causing mitogen-activated protein kinase (MAPK) pathway activation were documented in six patients. The disease control rate in patients with MAPK pathway–activating alterations was 64.3% (five confirmed PR, one unconfirmed PR, and three SD). The median progression-free survival was 13.3 weeks (95% CI, 3.5 to 23.1), and the median overall survival was 54.3 weeks (95% CI, 37.9 to 70.6). Adding low-dose dabrafenib to trametinib effectively mitigated or prevented treatment-limiting trametinib-related skin toxicity.

CONCLUSION The combination of trametinib plus low-dose dabrafenib demonstrated encouraging efficacy and effective mitigation of skin toxicity in patients with advanced, ICI-pretreated *BRAF*^{V600}/*NRAS*^{Q61} wild-type melanoma patients. MAPK pathway–activating alterations hold promise as a predictive biomarker.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

An unmet clinical need exists for the treatment of patients with advanced *BRAF*^{V600} wild-type melanoma who progress on treatment with immune checkpoint inhibitors (ICIs) that block the programmed cell death 1 (PD-1), cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and/or lymphocyte-associated antigen 3 receptors, as no subsequent therapy has shown to improve overall survival (OS).[1] Inhibition of MEK with binimetinib has shown activity in patients with advanced *NRAS*$^{Q61R/K/L}$-mutant melanoma (objective response rate [ORR] of 15% and a median progression-free survival [PFS] of 2.8 months) but did not improve the OS compared with dacarbazine in the phase III NEMO trial.[2] MEK inhibitor activity is also observed in patients with non-V600 *BRAF*–mutant melanoma, *NF1*-mutant tumors, and *GNAQ*/*GNA11*-mutant uveal melanoma.[3-9] In *BRAF*/*NRAS*/*NF1* wild-type (triple wild-type) melanoma cell lines, the MEK inhibitor

CONTEXT

Key Objective

Patients with advanced *BRAF*^{V600}/*NRAS*^{Q61} wild-type, immune checkpoint inhibitor (ICI) refractory melanoma have a poor prognosis. MEK inhibition has shown activity in this patient population but is associated with treatment-limiting cutaneous toxicity. Adding a BRAF inhibitor to a MEK inhibitor reduces the incidence of skin toxicity. In this phase II trial, we investigated trametinib plus low-dose dabrafenib in this patient population.

Knowledge Generated

Trametinib plus low-dose dabrafenib shows encouraging efficacy, with the highest antitumor activity being observed in melanoma harboring alternative activating mitogen-activated protein kinase (MAPK) pathway alterations. Adding low-dose dabrafenib to trametinib effectively mitigates and prevents trametinib-related skin toxicity.

Relevance

Trametinib plus low-dose dabrafenib can be an effective and better tolerated therapeutic option, as opposed to MEK inhibitor monotherapy, in patients with advanced *BRAF*^{V600}/*NRAS*^{Q61} wild-type, ICI-refractory melanoma, especially in the presence of genetic alterations known to activate the MAPK pathway. The absence of a *BRAF*^{V600} or *NRAS*^{Q61} mutation should prompt more comprehensive genomic profiling to detect these alterations and identify patients who could potentially benefit from trametinib plus low-dose dabrafenib.

trametinib blocks activation of the mitogen-activated protein kinase (MAPK) pathway and leads to cell death.[10] Finally, combined BRAF and MEK inhibition has synergistic efficacy in preclinical models with *NRAS* and class IIa *BRAF* mutations (which lead to mutant BRAF dimers that hyperactivate the MAPK pathway).[11,12]

MEK inhibitors are associated with a distinct toxicity profile, including cutaneous, cardiovascular, digestive, muscular, and ocular adverse events (AEs).[2,13] MEK inhibitor–related rash/acneiform dermatitis is frequent and can be severe (all-grade, 72% and grade 3-4, 7% in the NEMO trial) and negatively affects patient's quality of life.[14] Skin toxicity frequently leads to treatment interruptions, dose reductions, or, rarely, permanent treatment discontinuation.[2] Combining MEK with BRAF inhibitors (as approved for *BRAF*$^{V600E/K}$-mutant melanoma) leads to a substantially lower incidence of skin toxicity compared to MEK inhibitor monotherapy (eg, 28% all-grade skin toxicity for dabrafenib plus trametinib *v* 57% all-grade for trametinib monotherapy, at the same trametinib dosing).[13,15]

In the phase II TraMel-WT trial, we investigated the efficacy and safety of the MEK inhibitor trametinib (2 mg once daily orally) in patients with advanced *BRAF*^{V600} wild-type, *NRAS*$^{Q61R/K/L}$-mutant, *BRAF*^{V600} wild-type, or *NRAS*$^{Q61R/K/L}$ wild-type melanoma who have progressed after prior treatment with PD-1 and CTLA-4 ICI. In case of trametinib-related cutaneous toxicity, a low dose of the BRAF inhibitor dabrafenib (50 mg twice daily orally) was added to mitigate recurrent toxicity. We hypothesized that the addition of low-dose dabrafenib would lead to better tolerance of and consequently a potentially higher exposure to trametinib, without increasing the risk of dabrafenib-related AE. Results of the *NRAS*$^{Q61R/K/L}$-mutant stratum have recently been published showing that low-dose dabrafenib can effectively prevent or mitigate trametinib-related skin toxicity.[16]

In this article, we report the efficacy and safety results of the patients with advanced *BRAF*^{V600} wild-type, *NRAS*$^{Q61R/K/L}$ wild-type melanoma treated on this clinical trial.

METHODS

Study Design and Patient Population

This phase II clinical trial (ClinicalTrials.gov identifier: NCT04059224) was conducted at the Universitair Ziekenhuis Brussel (Brussels, Belgium) and included adult patients with advanced (unresectable or metastatic) *BRAF*^{V600} and *NRAS*$^{Q61R/K/L}$ wild-type melanoma who had confirmed progressive disease (PD) after (or who were ineligible for) treatment with PD-1 and/or CTLA-4 ICI. Eligible patients needed to have an Eastern Cooperative Oncology Group Performance Status of 0-2, adequate baseline organ function, and availability of archival or newly obtained melanoma tissue for confirmatory mutational testing. Major exclusion criteria were patients with uveal melanoma, prior treatment with MAPK pathway inhibitors, the presence of clinically active brain metastases, and uncontrolled cardiovascular and/or ocular diseases.

Procedures and Study Treatment

Screening procedures have been reported previously.[16] The *NRAS*$^{Q61R/K/L}$/*BRAF*^{V600} mutational status was confirmed on tumor tissue using the automated polymerase chain reaction (PCR)–based Idylla NRAS-BRAF Mutation Test (Biocartis,

Mechelen, Belgium) or by next-generation sequencing (NGS) following institutional standards (Appendix Table A1). Baseline and on-treatment plasma samples were collected for future exploratory circulating tumor DNA (ctDNA) analyses (see below).

Patients were treated with trametinib 2 mg once daily orally. Dabrafenib 50 mg twice daily orally (low-dose) was added to trametinib in case of trametinib-related cutaneous toxicity (grade 2 or more). Dabrafenib dosing could be increased in case of insufficient control of cutaneous toxicity to 100 or 150 mg twice daily. In June 2019, the trial was amended to administer low-dose dabrafenib upfront with trametinib, as early data in the $NRAS^{Q61R/K/L}$ mutant stratum suggested that all patients developed treatment-limiting skin toxicities to trametinib.[16]

Response assessments were performed every 8 weeks, and study therapy was continued until PD, unacceptable toxicity, or withdrawal of consent. Treatment beyond progression was allowed if deemed clinically meaningful. The database was locked on March 20, 2023. The study was conducted in accordance with both the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by the ethics committee of the Universitair Ziekenhuis Brussel. All participants provided written informed consent. The study was funded by Stichting tegen Kanker and Novartis.

End Points

The primary end point was the confirmed ORR (cORR), per RECIST version 1.1.[17] Secondary end points included the duration of response, PFS (time between treatment initiation and PD or death), and OS (time between treatment initiation and death) and to characterize the incidence and severity of AE (graded by the Common Terminology Criteria for Adverse Events version 4.03) of trametinib and dabrafenib. The investigation of the association of phosphorylated ERK (pERK) immunohistochemistry with response and the analysis of ctDNA on baseline plasma samples served as exploratory end points.

ctDNA Analysis

The Idylla ctNRAS-BRAF Assay (Biocartis, Mechelen, Belgium) was used to investigate the $BRAF^{V600}$/$NRAS^{Q61}$ mutational status on ctDNA (mutation detected *v* undetected) on a baseline plasma sample. The method of analysis has been reported previously.[18]

pERK Immunohistochemistry

Unstained paraffin sections of 4 μm of the formalin-fixed paraffin-embedded tumor biopsies were pretreated with Target Retrieval Solution (10×—Citrate buffer—pH 6.0 at 97°C). This was followed by incubation with a primary antibody: pERK Rabbit monoclonal antibody Clone D13.14.4E from Cell Signaling Technology. The primary antibody was detected by a secondary antibody (labeled polymer): Dako EnVision + System-HRP Labeled Polymer Anti-rabbit (Dako—K4003). pERK was reported as a H-score.

Statistical Analysis

The sample size in this trial was calculated according to a Simon two-stage optimal design (Appendix Fig A1). The null hypothesis that the true ORR was 10% would be tested against a one-sided alternative that the minimal ORR on the experimental therapy was 30%. In the first stage, 10 patients would be accrued. If there were one or less confirmed responses, the study would be stopped for futility. Otherwise, 19 additional patients would be accrued for a total of 29 patients in the second stage. The null hypothesis would be rejected if six or more responses were observed in these 29 patients. This design yielded a type I error rate of 0.05 and a power of 0.80.

Median PFS, OS, duration of response, and time on therapy were estimated using the Kaplan-Meier method (SPSS Statistics version 28, IBM, Armonk, NY).

RESULTS

Baseline Characteristics

Between January 2019 and September 2022, 25 patients were screened for eligibility, of whom 24 initiated study treatment: three patients were enrolled before the trial amendment (trametinib monotherapy upfront with addition of low-dose dabrafenib in case of trametinib-related skin toxicity) and 21 patients were enrolled after the trial amendment (combination of trametinib and low-dose dabrafenib up-front; Fig 1).

Baseline characteristics are summarized in Table 1. All patients had previously received treatment with at least one line of ICI. NGS of DNA extracted from tumor tissue was successfully performed in all but one patient (n = 23). Genetic alterations known to activate the MAPK pathway were detected in 13 patients (54.2%), with class II *BRAF*, *GNAQ*, *HRAS*, and *NF1* mutations being most common. The detailed results of tumor genomic DNA sequencing are summarized in Appendix Table A2.

Treatment Disposition

Three patients initiated trametinib 2 mg once daily (before the trial amendment) with a median duration of therapy of 8.0 weeks (range, 3.6-108.3; Fig 1). Two patients added-on low-dose dabrafenib after the onset of trametinib-related, treatment-limiting skin toxicity (after a median of 3.8 weeks [range, 3.1-4.4]). The duration of low-dose dabrafenib treatment was 4.9 weeks and 103.9 weeks, respectively. One patient permanently interrupted trametinib monotherapy after 3.6 weeks because of recurrent treatment-related

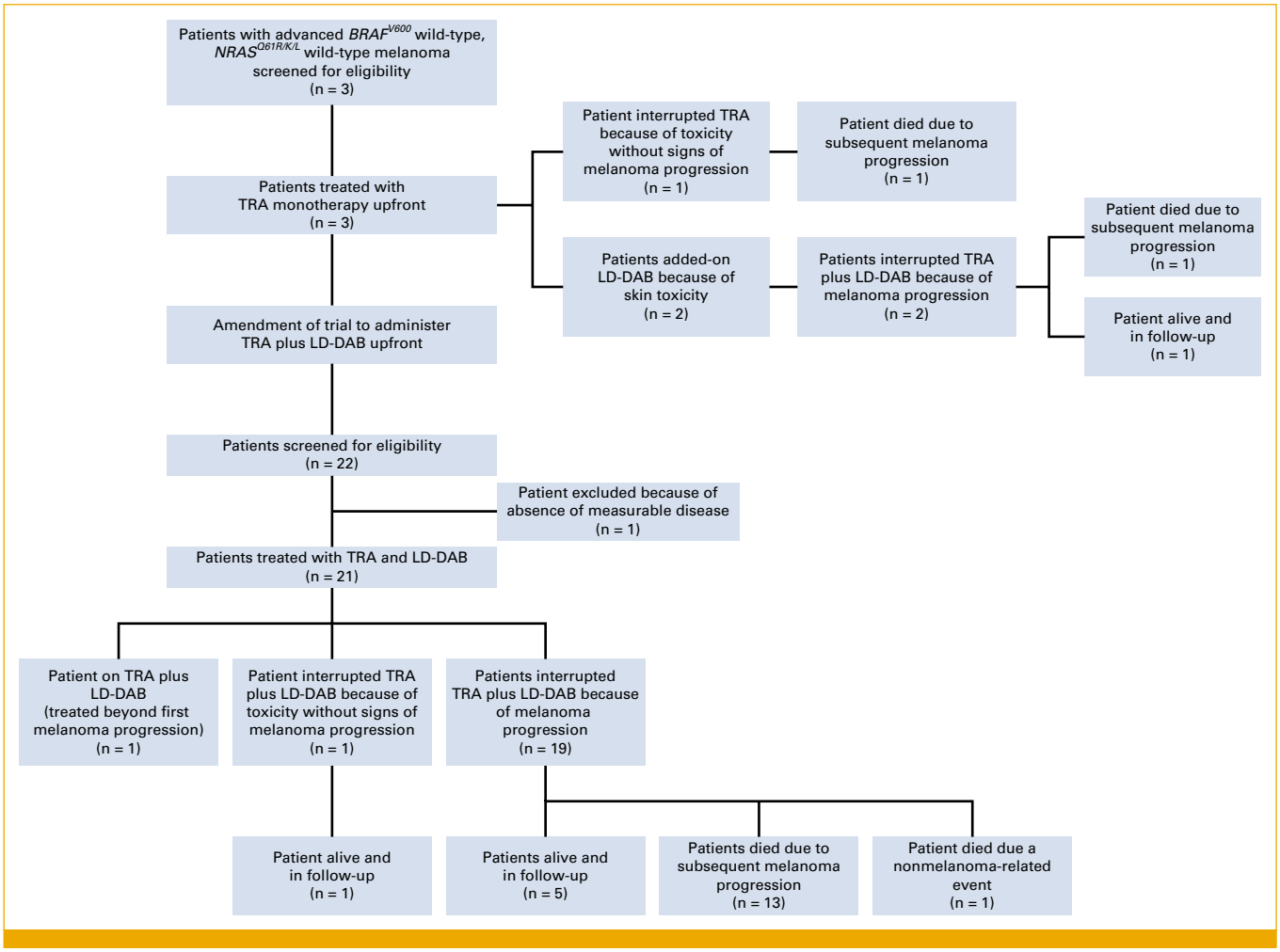

FIG 1. Study flow diagram. LD-DAB, low-dose dabrafenib; TRA, trametinib.

pneumonitis while the two other patients discontinued trametinib and low-dose dabrafenib because of PD. Interruptions of trametinib monotherapy (because of skin toxicity) were necessary in two patients, and temporary interruption of trametinib plus low-dose dabrafenib was necessary in one patient because of low-grade AE. No dose reductions were needed.

Twenty-one patients initiated trametinib and low-dose dabrafenib upfront (after the trial amendment). At the time of database lock, one patient was still on study treatment (beyond first progression after being treated with stereotactic radiotherapy for oligoprogressive disease), one patient discontinued treatment because of toxicity (refractory central serous retinopathy and uveitis) in the absence of tumor progression, and 19 patients had discontinued study treatment because of PD (Fig 1). The median duration of treatment was 16.1 weeks (95% CI, 0.8 to 31.5; range, 3.0-80.4). Treatment interruptions and dose reductions because of AEs were necessary in 13 and 10 patients, respectively (trametinib dose reduction in nine patients and dabrafenib dose reduction in eight patients).

Efficacy

At the time of database lock (March 20, 2023), the median duration of follow-up was 50.9 weeks (range, 3.0-200.0; Fig 2). All patients but one were evaluable for assessment of the tumor response (one patient died early from PD before the first planned tumor response assessment). The cORR was 29.2% (seven confirmed partial responses [PRs]; Table 2). One patient had a PR at first imaging but progressed at the subsequent evaluation. The median time to first response was 8.0 weeks (range, 7.4-27.7); the median duration of response was 16.6 weeks (95% CI, 5.5 to 27.7). The evolution of the sum of diameters of target lesions is depicted in Figure 3.

Five of eight patients with a PR were found to have MAPK pathway–activating alterations (two class II *BRAF* point mutations [L597S and G469A]; one class II *BRAF* in-frame deletion [N486_P490del]; one *GNAQ* point mutation [L96S]; one *MEK1* in-frame deletion [Q58_E62del]; Appendix Table A2 and Fig A2). One patient with a PR lasting 77 weeks and in whom baseline gene sequencing was not successful because

TABLE 1. Baseline Characteristics

Characteristic	N = 24
Sex, No. (%)	
Male	12 (50.0)
Female	12 (50.0)
Age, median (range)	57 (38-80)
ECOG PS, No. (%)	
0	6 (25.0)
1	16 (66.7)
2	2 (8.3)
Melanoma subtype, No. (%)	
Superficial spreading	8 (33.3)
Unknown primary lesion	5 (20.8)
Acral lentiginous	4 (16.7)
Nodular	4 (16.7)
Mucosal	2 (8.3)
Blue nevus melanoma	1 (4.2)
AJCC stage, No. (%)	
IIIB	1 (4.2)
IIID	1 (4.2)
IV-M1a	2 (8.3)
IV-M1b	2 (8.3)
IV-M1c	11 (45.8)
IV-M1d	7 (29.2)
No. of affected organs, median (range)	3 (1-8)
Lactate dehydrogenase, No. (%)	
Normal	15 (62.5)
Elevated	9 (37.5)
MAPK pathway alteration, No. (%)	
Class II *BRAF* mutation	3 (12.5)
GNAQ mutation	2 (8.3)
HRAS mutation	2 (8.3)
NF1 mutation	2 (8.3)
GNAS mutation	1 (4.2)
PRKD1-BRAF fusion	1 (4.2)
MEK1 mutation	1 (4.2)
Non-Q61 *NRAS* mutation	1 (4.2)
Prior lines of therapy	
Median (range)	2 (1-5)
1, No. (%)	5 (20.8)
2, No. (%)	14 (58.3)
3, No. (%)	4 (16.7)
>3, No. (%)	1 (4.2)
Prior PD-1 ICI monotherapy, No. (%)	19 (79.2)
Prior CTLA-4 ICI monotherapy, No. (%)	10 (41.7)
Prior PD-1 + CTLA-4 ICI, No. (%)	12 (50.0)
Baseline *NRAS*^{Q61}-mutant ctDNA, No. (%)	
Detected	1 (4.2)[a]
Undetected	22 (91.7)
Unknown	1 (4.2)

Abbreviations: AJCC, American Joint Committee on Cancer; ctDNA, circulating tumor deoxyribonucleic acid; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; MAPK, mitogen-activated protein kinase.

[a]This *NRAS*^{Q61}-mutant ctDNA status was detected a posteriori and was not detected on tissue mutational testing before enrollment.

of insufficient tumor tissue was found to have a *GOLGA4-RAF1* fusion on a postprogression biopsy. A *GNAQ*^{Q209P}, *GNAS*^{R201H}, and an *NRAS*^{T50I} mutation was detected in three of five patients with stable disease (SD). The disease control rate (DCR) in patients with an identified MAPK pathway–activating genetic alteration (n = 14, including one patient with detection of a genetic alteration on a postprogression biopsy) was 64.3% (five confirmed PR, one unconfirmed PR, and three SD; Appendix Table A2). Eleven patients (including two patients with *HRAS* mutations, two patients with an *NF1* mutation, and one patient with a *PRKD1-BRAF* fusion) had PD as best response.

Twenty-three patients have progressed, and the median PFS was 13.3 weeks (95% CI, 3.5 to 23.1; Appendix Fig A3). Eleven patients were treated beyond first progression, of whom seven were treated with additional radiotherapy for oligometastatic progression. Sixteen patients have died, and the median OS was 54.3 weeks (95% CI, 37.9 to 70.6; Appendix Fig A4).

Safety

All patients experienced AEs (Table 3). Serious AEs were observed in 25.0% of patients. Increase in creatine phosphokinase, fatigue, anemia, and increase in aspartate aminotransferase were the most common AEs. Two patients who initiated trametinib monotherapy developed trametinib-related skin toxicity that was managed with a temporary treatment interruption, topical metronidazole, and oral minocycline. After addition of low-dose dabrafenib, no clinically relevant recurrences of skin toxicity were observed. Five patients who initiated trametinib and low-dose dabrafenib up-front developed low-grade acneiform rash that did not necessitate treatment interruption. One patient who had a history of immune-related pneumonitis developed a recurrent drug-induced pneumonitis that was successfully managed with high-dose intravenous corticosteroids, after which trametinib was permanently discontinued. Another patient with a history of severe immune-related uveitis, vitiligo, and hepatitis developed a grade 3 central serous retinopathy and grade 2 uveitis which was managed with high-dose intravenous corticosteroids and a dose reduction of trametinib and low-dose dabrafenib, but eventually necessitated a permanent discontinuation of study therapy. Finally, a third patient who developed arthritis related to prior nivolumab plus ipilimumab therapy developed a recurrence of arthritis after the first administration of trametinib and low-dose dabrafenib which was successfully managed with low-dose steroids.

ctDNA Analysis

Baseline plasma of 23 patients was analyzed for the presence of *BRAF*^{V600}/*NRAS*^{Q61}-mutant ctDNA (Table 1). *NRAS*^{Q61}-mutant ctDNA was detected (a posteriori) in one patient, despite confirmation of the *NRAS* wild-type

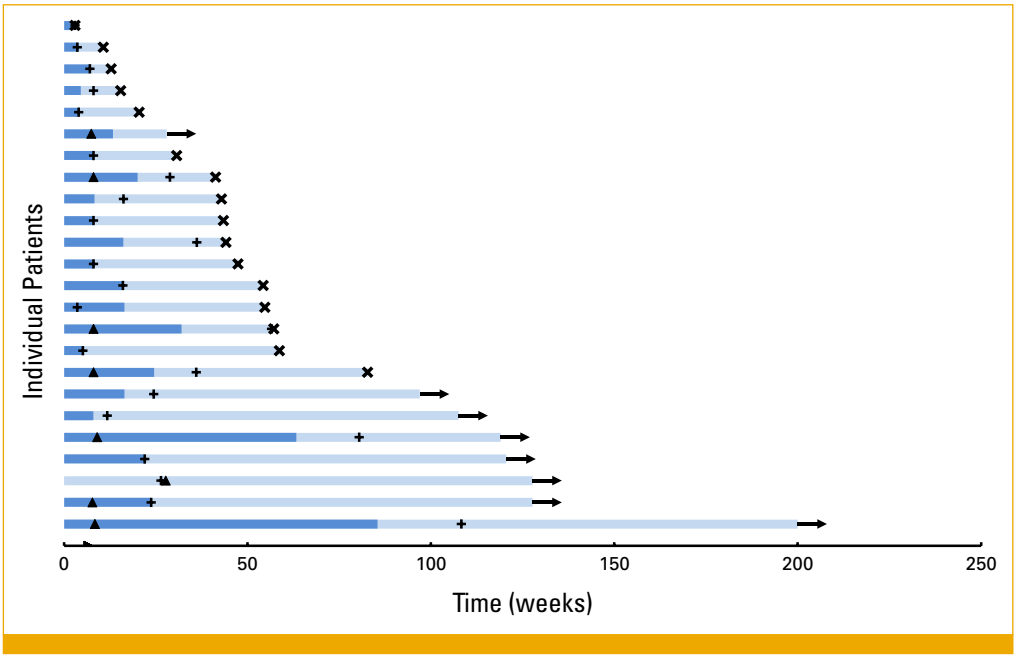

FIG 2. Swimmer plot. Arrow: alive; dark blue: progression-free survival; light blue: overall survival; +: treatment interruption; triangle: partial response; X: death.

status on tumor tissue before study treatment initiation. *BRAF*^{V600}/*NRAS*^{Q61}-mutant ctDNA was not detected in the remaining 22 patients.

pERK Immunohistochemistry and Association With Outcome

Immunohistochemical staining of pERK on a baseline or archival tumor sample could be performed in 18 patients, of whom five were noninformative because of the presence of high amounts of pigment (n = 2), intrinsic control negativity (n = 2), or insufficient availability of tumor tissue (n = 1; Appendix Table A3 and Fig A5). The median pERK H-score on the informative tumor samples was 20. Five of six patients with supramedian pERK H-scores had an identifiable MAPK pathway–activating alteration. Four patients with a confirmed PR, all with a MAPK pathway–activating alteration, were evaluable for baseline pERK. A supramedian H-score was observed in one of these four patients (*GOLFA4-RAF1* fusion). Of four patients with SD as best response, the H-score was above the median in one patient (without detection of an activating MAPK pathway alteration) while two patients (*GNAS*^{R201H} and *NRAS*^{T50I} mutation, respectively) had a H-score equal to the median. In the remaining five evaluable patients with PD as best response, a higher H-score was observed in four patients of whom all had an MAPK pathway–activating alteration.

TABLE 2. Best Objective Response in the 24 Evaluable Patients

Response	N = 24, No. (%)
Best objective response	
PR	8 (33.3)
Confirmed partial response	7 (29.2)
Unconfirmed partial response	1 (4.2)
Stable disease	5 (20.8)
Progressive disease	11 (45.8)[a]
Confirmed objective response rate	7 (29.2)

[a]This includes one patient who died early from progressive disease but did not undergo imaging.

DISCUSSION

Aiming to improve the efficacy and reducing skin toxicity of MEK inhibition, the phase II TraMel-WT trial investigated the efficacy and safety of trametinib plus low-dose dabrafenib in patients with advanced *BRAF*^{V600}/*NRAS*$^{Q61R/K/L}$ wild-type, ICI-refractory melanoma. The primary end point of this two-stage trial was met, as seven confirmed PR in 24 patients (cORR, 29.2%) were observed. This activity was observed in patients with advanced (more than half of patients had stage IV-M1c and stage IV-M1d melanoma) and extensively pretreated disease. Disease control was observed in 54.2% of patients, indicating similar efficacy as in comparable trials in ICI-refractory melanoma with the multitargeted kinase inhibitor lenvatinib and superior activity when compared with chemotherapy.[2,19] Although three patients had a response lasting more than 1 year, the relatively short median duration of response (16.6 weeks) suggests that acquired resistance develops in most patients, similar to what is observed with full-dose BRAF/MEK inhibition in advanced *BRAF*$^{V600E/K}$-mutant melanoma.[15]

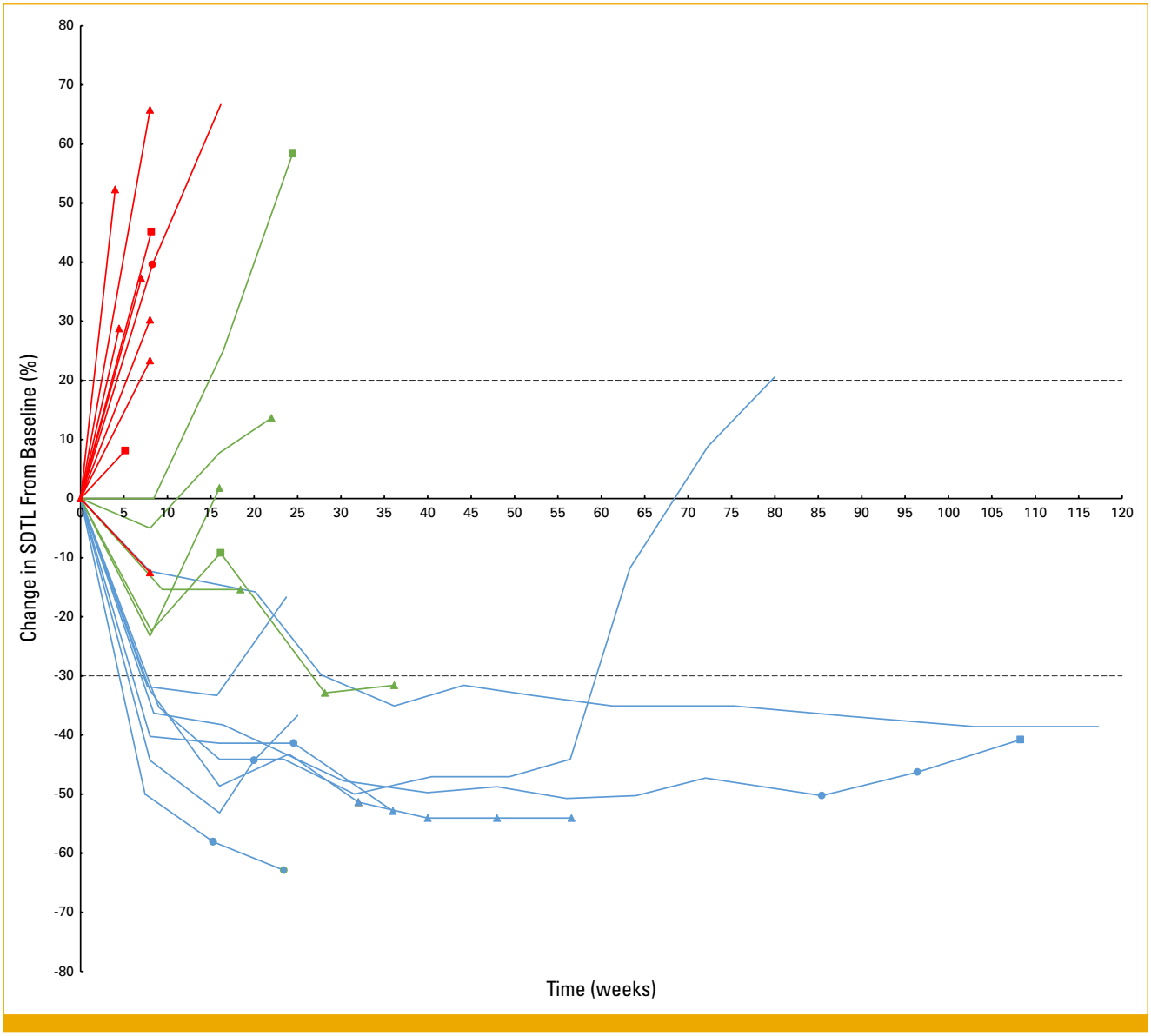

FIG 3. Evolution of the SDTL of 23 evaluable patients on study treatment or who have stopped study treatment without evidence of progressive disease. One patient died due to progressive disease before undergoing a first tumor evaluation. Blue line: partial response as best objective response; green line: stable disease as best objective response; red line: progressive disease as best objective response; sphere: new lesions; square: progression of nontarget lesions; triangle: progression of nontarget lesions and new lesions. SDTL, sum of diameters of target lesions.

With six of eight responding patients and three of five patients who achieved SD having mutations known to hyperactivate the MAPK pathway (three class II *BRAF* mutations, one *GOLGA4-RAF1* fusion, one *GNAQ* mutation, and one *MEK1* mutation and a *GNAQ*, *GNAS*, and a non-Q61 *NRAS* mutation, respectively), and the DCR in patients with an identified activating MAPK pathway alteration being 63.3%, this suggests trametinib and low-dose dabrafenib may be a highly effective treatment option for this subset of patients. However, not all mutations that activate the MAPK pathway are equally sensible to this combination, as five patients (two patients with *HRAS* mutations, two patients with *NF1* mutations, and one patient with a *PRKD1-BRAF* fusion) did not derive benefit, which is similar to what was observed in most patients included in the *NRAS*$^{Q61R/K/L}$-mutant stratum and in a phase II trial with trametinib monotherapy in non-V600 *BRAF*–mutant melanoma.[5,16] This suggests that these mutations may drive alternative oncogenic pathways or are less sensible to inhibition by trametinib (and dabrafenib). Furthermore, some genetic alterations (such as *NF1* mutations) can be subclonal or passenger mutations, rather than clonal driver mutations (in contrary to neurofibromatosis type 1 where *NF1* mutations act as the oncogenic driver).[6]

In two patients who achieved a PR (including one ongoing PR notwithstanding treatment discontinuation), no driver

TABLE 3. AEs in the *NRAS*$^{Q61R/K/L}$ Wild-Type Stratum

AEs	All Grade N = 24, No. (%)	Grade 3-4 N = 24, No. (%)
Any AE	24 (100)	12 (50.0)
Creatine phosphokinase increase	18 (75.0)	2 (8.3)
Fatigue	14 (58.3)	4 (16.7)
Anemia	12 (50.0)	0 (0)
AST increase	10 (41.7)	1 (4.2)
Lymphocyte count decreased	9 (37.5)	2 (8.3)
Acneiform rash	8 (33.3)	0 (0)
ALT increase	8 (33.3)	1 (4.2)
Lipase increase	8 (33.3)	0 (0)
Headache	7 (29.2)	1 (4.2)
Chills	6 (25.0)	0 (0)
AP increase	7 (29.2)	0 (0)
Platelet count decreased	6 (25.0)	0 (0)
Anorexia	5 (20.8)	0 (0)
Diarrhea	5 (20.8)	0 (0)
Edema limbs	5 (20.8)	0 (0)
Fever	5 (20.8)	0 (0)
Pain	5 (20.8)	1 (4.2)
Abdominal pain	4 (16.7)	1 (4.2)
Arterial hypertension	4 (16.7)	0 (0)
Hyponatremia	4 (16.7)	0 (0)
Muscle cramps	4 (16.7)	0 (0)
WBC decreased	4 (16.7)	0 (0)
Acute kidney injury	3 (12.5)	0 (0)
Dysgeusia	3 (12.5)	0 (0)
Hypoalbuminemia	3 (12.5)	0 (0)
Nausea	3 (12.5)	0 (0)
Vomiting	3 (12.5)	0 (0)
Arthralgia	2 (8.3)	0 (0)
Constipation	2 (8.3)	0 (0)
Dyspnea	2 (8.3)	0 (0)
Flu-like symptoms	2 (8.3)	0 (0)
GGT increase	2 (8.3)	0 (0)
Hypocalcemia	2 (8.3)	0 (0)
Hypotension	2 (8.3)	1 (4.2)
Myalgia	2 (8.3)	0 (0)
Palmar-plantar hyperesthesia syndrome	2 (8.3)	0 (0)
Paronychia	2 (8.3)	0 (0)
Psoriasiform rash	2 (8.3)	0 (0)
Central serous retinopathy	2 (8.3)	1 (4.2)
Skin infection	2 (8.3)	0 (0)
Thromboembolic event	2 (8.3)	0 (0)
Vitiligo	2 (8.3)	0 (0)
Arthritis	1 (4.2)	0 (0)
Ascites	1 (4.2)	0 (0)
Bloating	1 (4.2)	0 (0)
Blood bilirubin increase	1 (4.2)	0 (0)
Bone infection	1 (4.2)	0 (0)
Bronchial infection	1 (4.2)	0 (0)
Digestive hemorrhage	1 (4.2)	0 (0)
Eosinophilia	1 (4.2)	0 (0)
Epilepsy	1 (4.2)	0 (0)
Fracture	1 (4.2)	0 (0)
Lung infection	1 (4.2)	0 (0)
Neutrophil count decreased	1 (4.2)	0 (0)
Panniculitis	1 (4.2)	0 (0)
Paresthesia	1 (4.2)	0 (0)
Phlebitis	1 (4.2)	0 (0)
Pneumonitis	1 (4.2)	1 (4.2)
Paresthesia	1 (4.2)	0 (0)
Retinal pigment epithelial detachment	1 (4.2)	0 (0)
Skin fissures	1 (4.2)	0 (0)
Skin ulceration	1 (4.2)	0 (0)
Uveitis	1 (4.2)	0 (0)
Vaginal hemorrhage	1 (4.2)	0 (0)
Vasculitis	1 (4.2)	0 (0)
Vertigo	1 (4.2)	0 (0)
Serious AE	6 (25.0)	5 (20.8)
AEs leading to temporary treatment interruption	15 (62.5)	7 (29.2)
AEs leading to permanent treatment interruption	2 (8.3)	1 (4.2)
AEs leading to dose reduction	10 (41.7)	5 (20.8)

Abbreviations: AE, adverse event; AP, alkaline phosphatase; GGT, gamma-glutamyltransferase.

mutation was detected by PCR-based methods or an institutional somatic mutation panel assessed by NGS. Whole-genome, exome, or transcriptomic sequencing could be more appropriate to detect rare mutations, large deletions/insertions, copy number changes, or fusion genes involved in the MAPK pathway that could be targeted by MEK inhibitors. These more comprehensive investigations should be encouraged in patients without detected genomic alterations using standard methods to select patients likely to benefit most from trametinib and low-dose dabrafenib while these could also exclude patients from being exposed to futile therapy, in case of genomic alterations known to be not targetable by MEK inhibitors.

Although these genomic analyses are generally performed on tumor tissue, progress is also made in the field of liquid biopsy. In this study, plasma was investigated to exclude the presence of *BRAF*^{V600}/*NRAS*^{Q61}-mutant ctDNA. In one patient, an *NRAS*^{Q61} mutation was detected a posteriori on a baseline plasma sample while this mutation was not present on a panel NGS on tumor tissue, indicating a false-negative tissue result or development of a *NRAS*^{Q61}-mutant subclone.[20]

Evaluating pERK expression using immunohistochemistry on a baseline or archival tumor sample as a marker for MAPK pathway activation appears to be an imperfect surrogate marker for the presence of MAPK pathway–activating alterations, as high pERK expression was observed in only 50% (n = 5) of patients with identifiable MAPK pathway–activating alterations. Furthermore, high pERK expression did not seem to predict trametinib plus low-dose dabrafenib activity: low pERK expression was observed in most patients who responded to therapy with MEK/BRAF inhibitors while some patients who did not benefit from study therapy had increased expression of pERK.

No new safety signals were encountered with trametinib and low-dose dabrafenib, and all AEs were managed with available guidelines included in the Protocol. Interruptions due to AEs were relatively common (62.5%), confirming earlier data that tolerance to BRAF/MEK inhibitors is lower when patients were previously treated with PD-1 ICI.[21] Although the number of patients enrolled before amending the trial was lower than in the $NRAS^{Q61R/K/L}$-mutant stratum, we did encounter treatment-limiting trametinib-related skin toxicity in two of three patients which was managed by a treatment interruption, supportive therapy, and subsequent add-on of low-dose dabrafenib, which successfully prevented any clinically relevant recurrences.[16] In patients who initiated the combination up-front, no treatment-limiting skin toxicity was observed, suggesting that low-dose dabrafenib effectively mitigates trametinib-related cutaneous toxicity. The observation of chills and pyrexia indicated that dabrafenib, even at a third of its labeled dosing for $BRAF^{V600}$-mutant melanoma, is likely to cause these BRAF inhibitor–specific toxicities, although the incidence appears to be lower than when dabrafenib is administered at its full dose (58% experiencing pyrexia with dabrafenib and trametinib).[15] No secondary malignancies were observed in this trial, indicating adequate inhibition of paradoxical MAPK pathway activation by low-dose dabrafenib when administered in combination with full-dose trametinib in the $BRAF^{V600}$ wild-type cells.[22] While the size of our study cohort imposes limitations on the observation of low incidence, yet important treatment-related AEs, the large body of evidence indicating effective mitigation of dabrafenib-related secondary neoplasms when combined with full-dose trametinib in the $BRAF^{V600}$-mutant population is reassuring.[15] Three patients who had a history of immune-related toxicity had a clinical recurrence of these AEs which was managed with corticosteroids, and two patients had an increase in immune-related vitiligo. These cases illustrate the potential of BRAF/MEK inhibitors to reactivate prior immune-related toxicity. Similarly, BRAF/MEK inhibitors have shown to render the tumor microenvironment more immunoresponsive (which served as the basis to investigate BRAF/MEK inhibitors plus PD-1/PD-L1 ICI in $BRAF^{V600}$-mutant melanoma).[23,24] In parallel to reactivating tumor-infiltrating lymphocytes, these molecular-targeted therapies probably also reactivate lymphocytes involved in immune-related toxicities.

In conclusion, in this two-stage phase II clinical trial, trametinib plus low-dose dabrafenib was found to have promising antitumor activity and acceptable toxicity in patients with pretreated advanced $BRAF^{V600}$/$NRAS^{Q61/R/K/L}$ wild-type melanoma, especially in the presence of identifiable MAPK pathway–activating alterations.

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DATA SHARING STATEMENT

The data generated in this study are available on request from the corresponding author.

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Administrative support: Gil Awada, Bart Neyns
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Genes Included in the Universitair Ziekenhuis Brussel Panel Next-Generation Sequencing

Genes			
AKT1	*CYLD*	*KIT*	*PTPN11*
ALK	*DAXX*	*KMT2D*	*RAC1*
ANKRD26	*DCC*	*KRAS*	*RAD51B*
APC	*DELEC1*	*LZTR1*	*RAD54L*
AR	*DICER1*	*MAP2K1/2*	*RAF1*
ARAF	*DLC1*	*MET*	*RB1*
ARID1A	*DPYD*	*MLH1*	*RET*
ARID2	*EED*	*MRE11*	*RICTOR*
ATM	*EGFR*	*MSH2/6*	*RNF43*
ATR	*EIF1AX*	*MTOR*	*ROBO1/2*
ATRX	*ENG*	*MUTYH*	*ROS1*
AXIN1	*EPCAM*	*MYOD1*	*SMAD4*
B2M	*ERBB2/3/4*	*NF1/2*	*SMARCA4*
BAP1	*FAU*	*NOTCH1*	*SMARCB1*
BARD1	*FBXW7*	*NRAS*	*STK11*
BMPR1A	*FGFR1/2/3*	*NTRK1/2/3*	*SUZ12*
BRAF	*FOXO1*	*PBRM1*	*TENT5C*
BRCA1/2	*GNA11*	*PDGFRA*	*TERT*
CASP8	*GNAQ*	*PDGFRB*	*TGFBR2*
CDH1	*GNAS*	*PHOX2B*	*TP53*
CDK4	*HRAS*	*PIK3CA*	*TPMT*
CDK12	*IDH1/2*	*PIK3R1*	*TSC1/2*
CDKN2A	*IL7R*	*PMS1/2*	*UGT1A1*
CHEK1/2	*JAK2/3*	*POLD1*	*USP13*
CTNNB1	*KDM5C*	*POLE*	*VHL*
CUL4B	*KEAP1*	*PTEN*	

TABLE A2. Genomic Alterations Detected in Individual Patients and Best Response to Therapy

Patient	Method of Analysis	Detected Genomic Alterations	Best Response
2	Idylla qPCR + institutional panel NGS	*RB1* Q736*	SD
7	Idylla qPCR + institutional panel NGS	None	PD
9	Idylla qPCR	None +	PR
15	Idylla qPCR + institutional panel NGS	*HRAS* G13R	PD
21	Institutional panel NGS	*BRAF* L597S, *DPYD* HapB3, *TERT* C250T	PR
24	Idylla qPCR + institutional panel NGS	*BRAF* N486_P490del; *ATM* T460Nfs*27; *CTNNB1* G34E	PR
27	Institutional panel NGS	*GNAS* R201H; *BRCA2* Y3092C (VUS)	SD
28	Institutional panel NGS	*BRAF* G469A	PR
29	Idylla qPCR + institutional panel NGS	*GNAQ* L96S	PR
30	Idylla qPCR + institutional panel NGS	*POLE* R197T (VUS)	PR
31	Idylla qPCR + institutional panel NGS	None	PD
32	Institutional panel NGS	*GNAQ* Q209P	SD
33	Institutional panel NGS	None	PR
34	Institutional panel NGS	*HRAS* Q61R; *KMTD* Q2337H (VUS); *SMARCA4* S224L (VUS)	PD
36	Institutional panel NGS	None	PD
37	Idylla qPCR + institutional panel NGS	*TERT* A49V; *NTRK3* G67E (VUS)	SD
38	Idylla qPCR + institutional panel NGS	*NF1* K33Yfs*6	PD
39	Institutional panel NGS	*PRKD1-BRAF* fusion	PD
40	Institutional panel NGS	*NRAS* T50I; *TP53* R282W; *ALK* M1223L (VUS)	SD
41	Idylla qPCR + institutional panel NGS	*TERTp*; *TP53*; *NF1* R2429; *NF1* S574T; *SMAD4* Q311; *TERT* (VUS); *ALK* G464R (VUS); *AR* D840N (VUS); *ATR* S1764F (VUS); *CCND1* P287S (VUS); *CD798* S45L (VUS); *ERBB4* E1201L (VUS); *JAK3* P731S (VUS); *NTRK3* D565N (VUS); *PDGFRB* D1068N (VUS); *PTPN11* R399L (VUS); *RAD50* D767N; *RICTOR* H696T (VUS); *SMAD4* P91L (VUS)	PD
42	Comprehensive genomic profiling (TruSight Oncology 500, Illumina)	*ERCC5* S659Vfs*; *Myc* amplification; *NOTCH2-HAO2* fusion	PD
43	Comprehensive genomic profiling (Foundation One CDx, Foundation Medicine)	*SMARCB1* R201fs*3; *FANCA* D953E (VUS); *KDM6A* T584M (VUS); *MAF* Q137H (VUS); *MAP3K1* S939C (VUS); *PDCD1LG2/PD-L2* F236S (VUS); *SGK1* R300Q (VUS°); *SMARCA4* R1135Q (VUS)	PD
44	Institutional panel NGS	*mTOR* T220I (VUS)	PD
45	Comprehensive genomic profiling (TruSight Oncology 500, Illumina)	*MEK1* Q58_E62del; *RB1* ?; *LRP1B* W3334*; *LRP1B* I2644T (VUS); *LRP1B* D3049E (VUS); *ZNF217* E914_P915delinsDS (VUS); *GNAS* A436D (VUS); *TET1 P119Q* (VUS); *CD276* P185S (VUS); *LRP1B* E547Q (VUS); *PLCG2* N798S (VUS°); *SPTA1* S818F (VUS); *IL7R* G434D (VUS); *GRM3* G18K (VUS)	uPR

NOTE. + A *GOLGA4-RAF1* fusion was detected on a postprogression biopsy.
Abbreviations: NGS, next-generation sequencing; PD, progressive disease; PR, partial response; qPCR, quantitative polymerase chain reaction; SD, stable disease; uPR, unconfirmed partial response; VUS, variant of unknown significance.

TABLE A3. pERK H-Score in Eighteen Patients

Patient	MAPK Pathway–Activating Alteration	Best Response	pERK H-Score	Pattern	Metastasis Site	Remarks
31	No	PD	NE	NE	Brain	Insufficient tumor tissue
34	Yes (*HRAS* Q61R)	PD	250	Diffuse strong	Lymph node	
36	No	PD	0	Negative	Lymph node	Intrinsic control negative
38	Yes (*NF1* K33Yfs*6)	PD	80	Regional	Lymph node	
39	Yes (*PRKD1-BRAF* fusion)	PD	200	Diffuse strong	Skin	
41	Yes (*NF1* R2429; *NF1* S574T)	PD	120		Liver	
43	No	PD	20	Focal	Skin	
9	Yes[a] (*GOLGA4-RAF1* fusion)	PR	300	Diffuse strong	Lymph node	
21	Yes (*BRAF* L597S)	PR	10	Focal	Subcutis	
28	Yes (*BRAF* G469A)	PR	10	Focal/dispersed	Muscle	
29	Yes (*GNAQ* L96S)	PR	10	Dispersed	Skin	
30	No	PR	NE	NE	Subcutis	Strong pigment presence
33	No	PR	0	NE	Lymph node	Intrinsic control negative
2	No	SD	20	Focal	Lymph node	
27	Yes (*GNAS* R201H)	SD	20	Focal	Skin	
32	Yes (*GNAQ* Q209P)	SD	NE	NE	Liver	Strong pigment presence
37	No	SD	200	Diffuse strong	Lymph node	
40	Yes (*NRAS* T50I)	SD	20	Regional	Intestine	

Abbreviations: MAPK, mitogen-activated protein kinase; NE, not evaluable; PD, progressive disease; pERK, phosphorylated ERK; PR, partial response; SD, stable disease.
[a]Detected on a postprogression biopsy.

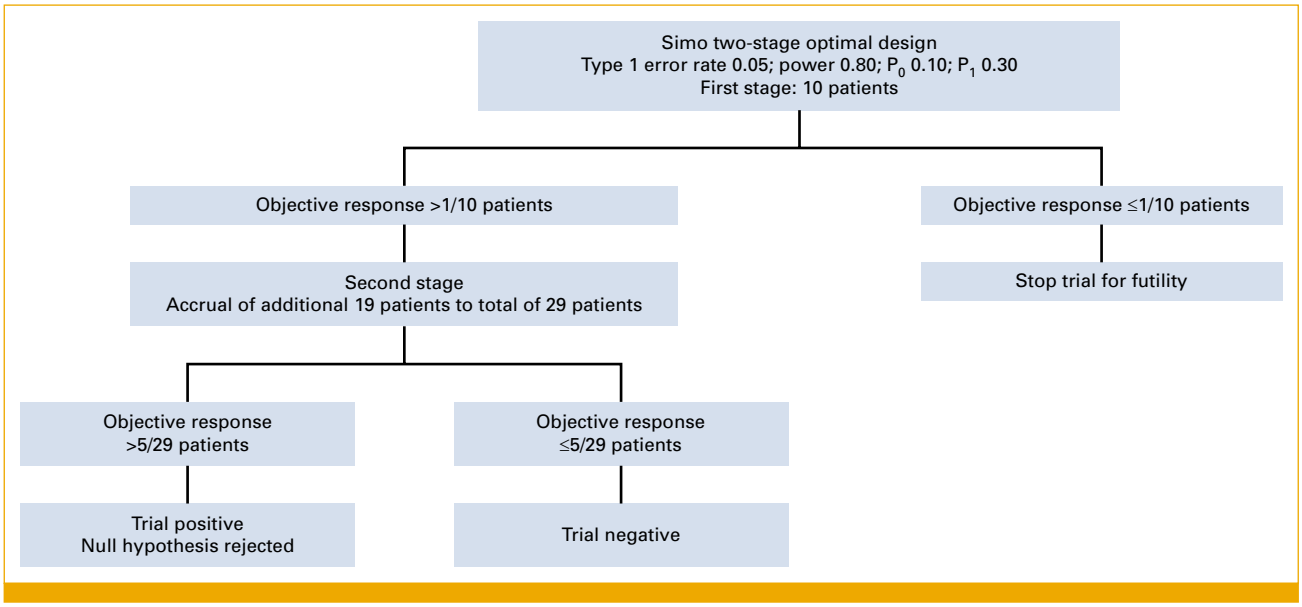

FIG A1. Statistical design TraMel-WT trial.

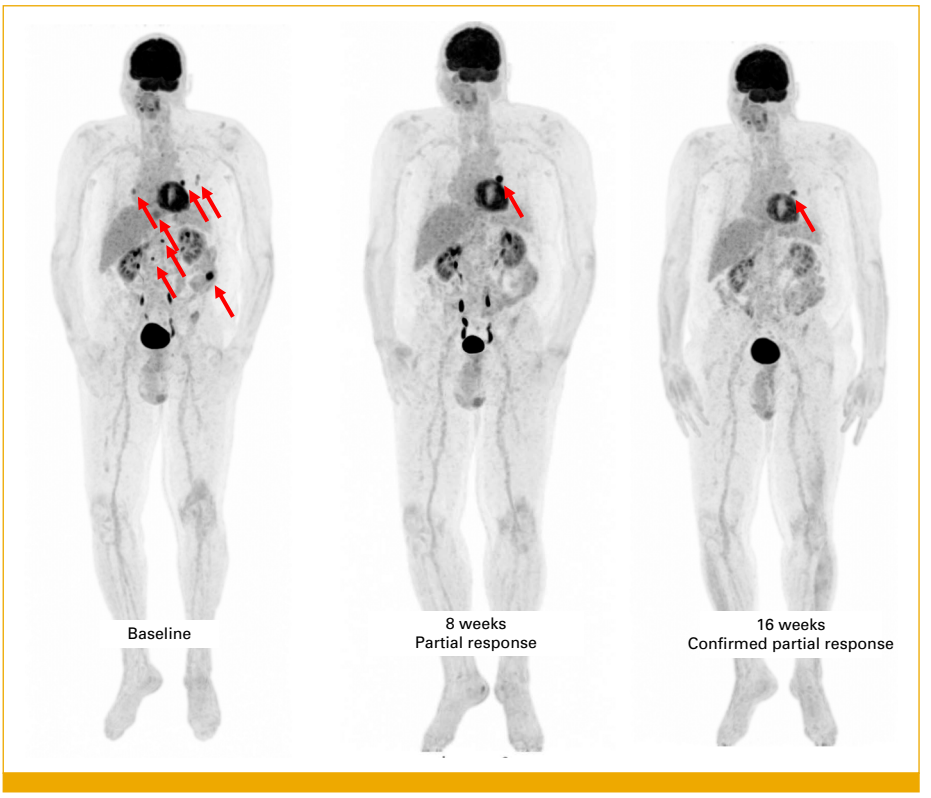

FIG A2. Illustrative case of a patient with a class II *BRAF*-mutant melanoma (in-frame deletion [N486_P490del]) showing a partial response at first evaluation that was confirmed at subsequent imaging.

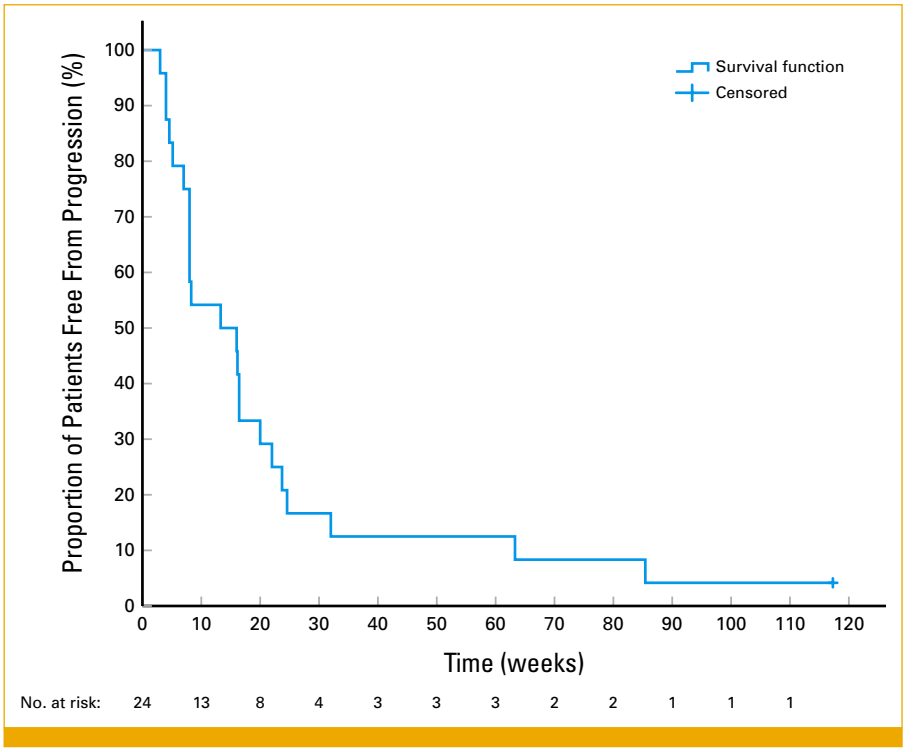

FIG A3. Progression-free survival curve.

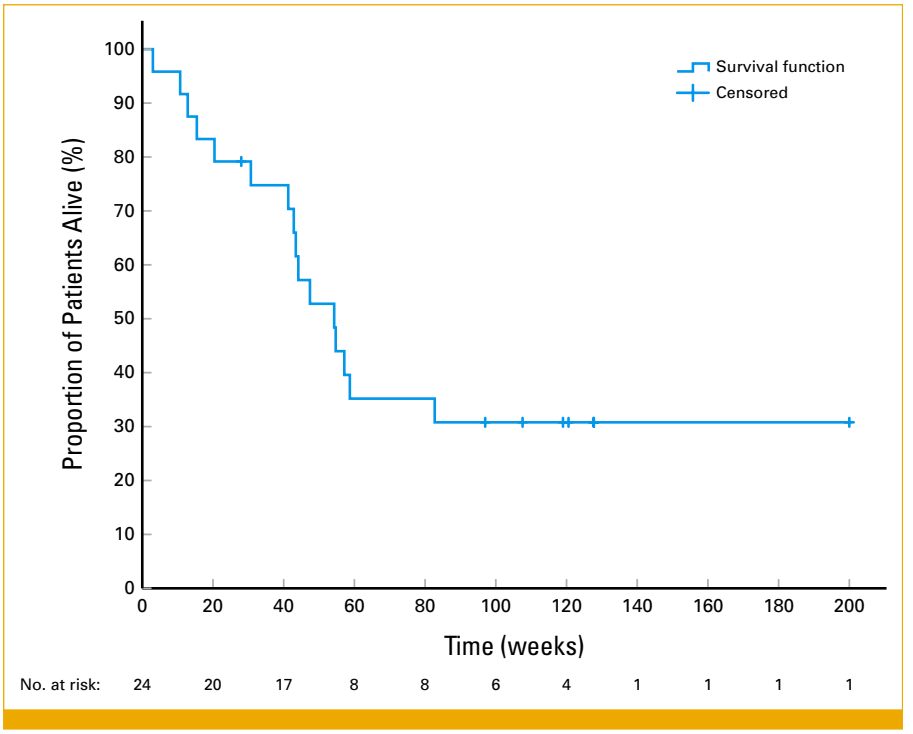

FIG A4. Overall survival curve.

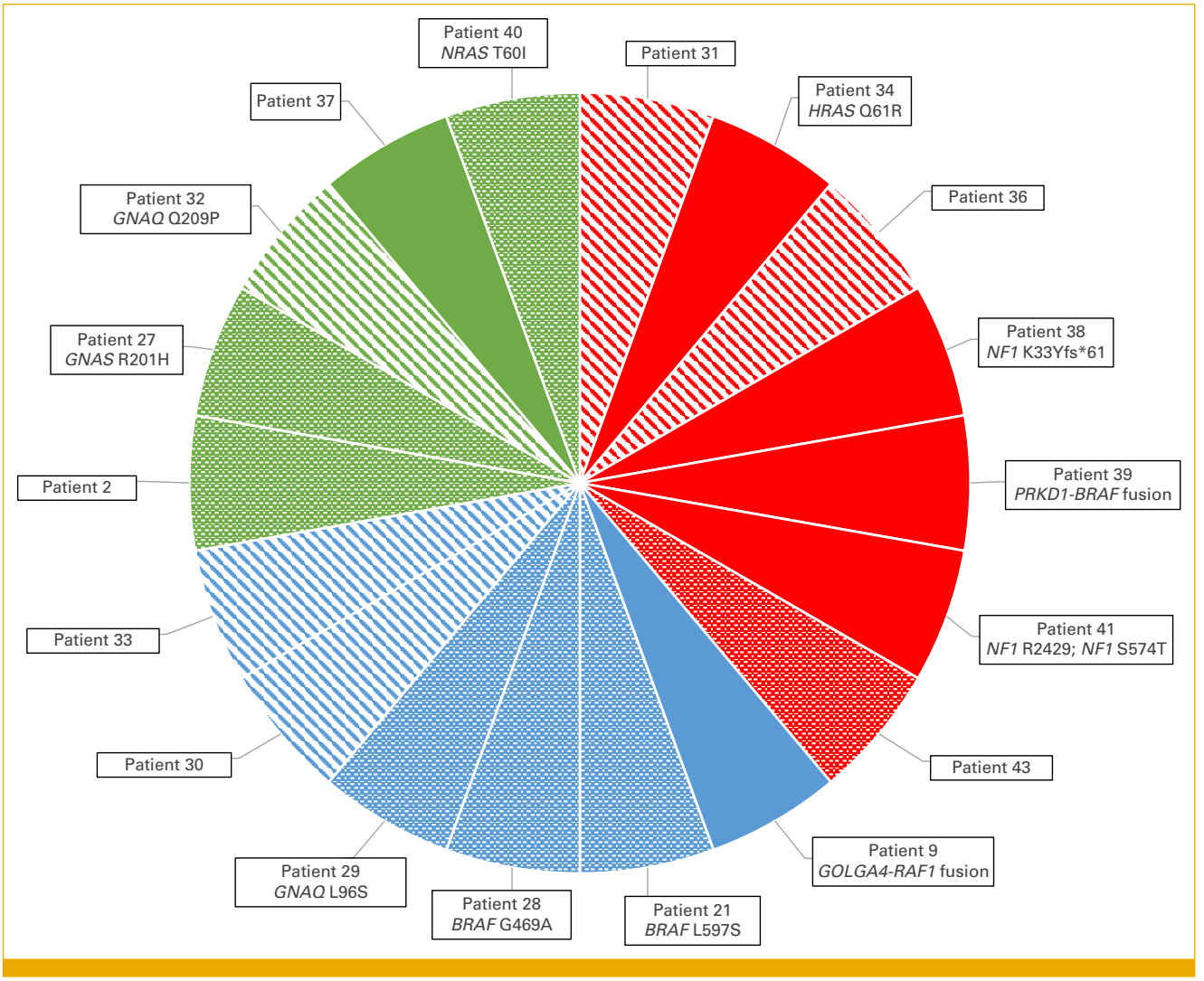

FIG A5. pERK H-score in 18 patients. Red indicates progressive disease as best response, green indicates stable disease as best response, and blue indicates partial response as best response. Barred elements denote nonevaluable pERK immunohistochemistry, matted colors denote an H-score equal or inferior to the median, and plain colors denote an H-score superior to the median. Mitogen-activated protein kinase pathway–activating alterations are shown in the boxes next to the chart. pERK, phosphorylated ERK.