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ORIGINAL ARTICLE

Efficacy and safety of regorafenib in patients with advanced pretreated melanoma: results of the RegoMel phase II clinical trial

I. Dirven[1]*, C. Bertels[1], Y. Moreels[1], J. I. Kessels[2], N. Vanlaer[1], A.-S. Vander Mijnsbrugge[1], M. Vounckx[1], I. Dirks[3,4], L. Raes[5], X. Geeraerts[6], L. Stevens[6], B. von Kemp[7], G. Fasolino[8], G. Awada[1], T. Janssen[9], B. Caljon[9], T. Lefevre[9], H. Everaert[5], A. Rogiers[1,10], J. Vandemeulebroucke[6,7,11], S. Tuyaerts[6] & B. Neyns[1]

[1]Department of Medical Oncology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Translational Oncology Research Center (TORC), Team Laboratory for Medical and Molecular Oncology (LMMO), Brussels; [2]Department of Dermatology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels; [3]Department of Electronics and Informatics (ETRO), Vrije Universiteit Brussel (VUB), Brussels; [4]Imec, Leuven; [5]Department of Nuclear Medicine, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels; [6]Team Laboratory for Medical and Molecular Oncology (LMMO), Translational Oncology Research Center (TORC), Vrije Universiteit Brussel (VUB), Brussels; [7]Department of Cardiology (Centrum Hart- en Vaatziekten, CHVZ), Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels; [8]Department of Ophthalmology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels; [9]Brussels Interuniversity Genomics High Throughput core (Brightcore), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels; [10]Department of Psychiatry, CHU Brugman, Brussels; [11]Department of Radiology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

Available online 9 April 2026

Background: Most patients with advanced melanoma progress despite standard-of-care treatments. Regorafenib (REGO), an oral multikinase inhibitor with RAF-dimer activity, demonstrated clinical activity in melanoma in retrospective case series and preclinical efficacy in overcoming resistance to BRAF/MEK inhibitors (BRAF/MEKi). This study prospectively evaluated REGO in heavily pretreated advanced melanoma patients.

Patients and methods: This single-center, phase II clinical trial (RegoMel, NCT05370807) assessed the objective response rate (ORR) upon continuous REGO dosing (40-120 mg daily) in 16 patients with advanced pretreated melanoma, regardless of the melanoma driver mutation. In *BRAF*^{V600}-mutant patients, BRAF/MEKi addition was permitted upon progression on REGO monotherapy. Based on early efficacy signs, a *KIT*-mutant expansion cohort was also recruited and analyzed. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety.

Results: There was one complete (*BRAF*^{V600}-mutant) and five partial responses [*KIT*- ($n = 3$), *BRAF*^{V600}-mutant ($n = 2$); ORR 37.5%; disease control rate (DCR) 56%]. Median duration of response was 37.4 weeks with median PFS (mPFS) and mOS of 12.1 weeks and 75.8 weeks, respectively. In the *KIT*-mutant expansion cohort ($N = 9$), ORR and DCR were 78% and 100%, respectively, and mPFS 43.4 weeks; mOS was not reached. Six *BRAF*^{V600}-mutant patients received REGO + BRAF/MEKi at first progression (ORR 33%, DCR 83%, mPFS 20.4 weeks, mOS 62.1 weeks). Grade 3 treatment-related adverse events (TRAEs) occurred in 59% of patients on REGO monotherapy and 50% on REGO + BRAF/MEKi. The most common TRAEs were hand-foot-skin reaction, hypertension, and diarrhea. All TRAEs were reversible.

Conclusion: This phase II clinical trial met its primary endpoint, demonstrating clinically meaningful antitumor activity and manageable toxicity with continuous daily REGO in advanced pretreated melanoma. The unprecedented high response rates in *KIT*-mutant melanoma and encouraging activity in *BRAF*^{V600}-mutant patients receiving REGO + BRAF/MEKi support further investigation of REGO-based regimens in these subpopulations of melanoma patients.

Key words: regorafenib, melanoma, BRAF/MEK inhibitors, *KIT*-mutation, prospective clinical trial, RAF dimer inhibitor

INTRODUCTION

An unmet clinical need exists in patients with advanced, unresectable melanoma who progress on treatment with immune checkpoint inhibitors (ICIs) and BRAF/MEK inhibitors (BRAF/MEKi), in *BRAF*^{V600}-mutant disease. For a fit subpopulation, adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) is an additional treatment option.[1] However, most patients will eventually progress.

*Correspondence to: Dr Iris Dirven, Department of Medical Oncology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Laarbeeklaan 101, 1090 Brussels, Belgium. Tel: +32-2-477-64-15
E-mail: iris.dirven@uzbrussel.be (I. Dirven).

In up to 90% of cutaneous melanomas, somatic mutations hyperactivate the mitogen-activated protein kinase (MAPK) pathway (RAS-RAF-MEK-ERK) promoting cell survival, proliferation, and metastasis.[2] The most prevalent class I *BRAF*$^{V600E/D/K}$ mutation (35%-50%) results in constitutive monomer *BRAF*-kinase activity. Other MAPK-activating alterations include *NRAS*^{Q61} and *NF-1* alterations. *KIT*- and *GNAQ/GNA11*-mutations are less frequent.

In *BRAF*^{V600}-mutant melanoma, class I or monomer-selective BRAF inhibitors (BRAFi) in combination with MEK inhibitors (MEKi); i.e. encorafenib/binimetinib (ENCO/BINI) and dabrafenib/trametinib (DAB/TRAM) initially yield high response rates, but over time adaptive resistance will emerge in most patients. One proposed mechanism involves the relief of ERK-induced negative feedback in the MAPK pathway following initial suppression of the ERK signal due to the class I BRAFi. Loss of this negative feedback relieves the brake on cell surface receptor tyrosine kinase signaling and allows for renewed RAS-dependent RAF-dimer formation and subsequent MAPK reactivation.[3] Preclinical studies suggest that addition of class II RAF-dimer inhibitors may overcome this resistance, including in *NRAS*-mutant melanoma with the combination of a RAF dimer and MEKi.[3-5]

Regorafenib (REGO) and sorafenib are currently the only Food and Drug Administration/European Medicines Agency-approved RAF-dimer inhibitors, with REGO being the most potent. In addition, REGO has effects against KIT, TIE2, VEGFR, PDGFR, RET, and CSF-1R.[6-8] It is approved for use in metastatic colorectal cancer, gastrointestinal stromal tumors (GISTs), and hepatocellular carcinoma. Recent preclinical findings highlight the potential of the combination of REGO with class I BRAFi and MEKi to overcome adaptive resistance to class I BRAFi.[3] Our group was the first to report clinical experience with REGO for advanced, pretreated melanoma demonstrating a manageable safety profile at continuous once daily (o.d.) dosing of 40-80 mg, as well as activity as a monotherapy, but with superior efficacy as a triple targeted therapy combination with BRAF/MEKi.[9] Furthermore, in heavily pretreated *BRAF*^{V600}-mutant melanoma patients with refractory brain metastases, REGO + BRAF/MEKi demonstrated promising antitumor activity [overall and intracranial objective response rate (ORR) of 11% and 29% and disease control rate (DCR) of 44% and 59%, respectively].[10]

In contrast to *BRAF*^{V600}-mutations, *KIT*-mutations are rare (1%-3% of melanomas), and are enriched in mucosal (MM) (15%-23%), acral lentiginous (AL) (10%-15%), and chronically sun-damaged skin melanomas (CSDSMs) (6%-25%), which respond poorly to ICIs.[11-13] While KIT inhibitors such as imatinib show activity, responses are often limited.[11,14]

Here, we report the results of the prospective phase II, single-center, two-stage, investigator-initiated clinical trial, RegoMel, evaluating REGO monotherapy in advanced pretreated melanoma. The efficacy of reintroducing BRAF/MEKi at the time of progression on REGO in *BRAF*^{V600}-mutant melanoma (REGO + BRAF/MEKi) and of REGO monotherapy in a *KIT*-mutant melanoma expansion cohort is also reported.

METHODS

Study design and patient population

This phase II trial (Clinicaltrials.gov ID: NCT05370807), conducted at Universitair Ziekenhuis Brussel (Brussels, Belgium), enrolled adult patients with advanced, unresectable melanoma progressing after standard-of-care treatment. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, adequate baseline organ function and measurable disease per RECISTv1.1. Major exclusion criteria included uveal melanoma and active brain metastases. The study protocol was approved by the Medical Ethics committee of UZ Brussel/VUB (EC number: EC-2022-150) and regulatory authorities. The study was conducted in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice as defined by the International Conference on Harmonization.

Procedures and study treatment

After providing written informed consent, patients were treated with continuous dosing of REGO 80 mg o.d., which was increased to 120 mg o.d. if tolerated. The primary endpoint, confirmed ORR per RECISTv1.1,[15] was evaluated every 6 weeks alternating computed tomography (CT) and [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography—computed tomography ([^{18}F]FDG—PET—CT) for the first 24 weeks, whereafter [^{18}F]FDG—PET—CT was repeated every 12 weeks. Treatment beyond progression was allowed if deemed clinically meaningful. In *BRAF*^{V600}-mutant patients, association of full dose (or the previously tolerated dose) of BRAF/MEKi was permitted upon first progression.

During the trial, adverse events were collected continuously. Patient-reported outcome measures were collected at baseline, week 9, and every 12 weeks thereafter to measure health-related quality of life [European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)], anxiety and depression [Hospital Anxiety and Depression Scale (HADS)], subjective cognitive complaints [Cognitive Failures Questionnaire (CFQ)] and fatigue [Fatigue Severity Scale (FSS)]. In addition, objective cognitive function was assessed through the Cognitive Basic Assessment (COGBAT®, Vienna Test System) at baseline and at 24 weeks. Other secondary endpoints included progression-free survival (PFS) and overall survival (OS). The analysis of circulating tumor DNA (ctDNA) and total metabolic tumor volume (TMTV) served as exploratory endpoints. The database was locked on 6 June 2025. A complete overview of the methods can be found in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2026.106941.

KIT-*mutant cohort*

Following a 100% ORR in the first three *KIT*-mutant patients and following the completion of recruitment in the initial trial cohort, an expansion cohort for patients with *KIT*-mutant melanoma was created. These patients received REGO and underwent response assessments according to the trial protocol. All patients signed written informed consent for data analysis (EC-2022-171).

Statistical analysis

The sample size in this trial was calculated according to a Simon's two-stage minimax design (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.106941). The null hypothesis that the true ORR in this population is 5% was tested against an alternative hypothesis that the minimal ORR on the experimental therapy was 25%. In the first stage, 12 patients were accrued. Upon one confirmed response, four additional patients were enrolled ($N = 16$). The null hypothesis could be rejected if three or more responses were observed (type I error rate 0.05, power of 0.80). Demographic information and categorical variables such as adverse events were summarized using frequency tables and proportions. For continuous variables, the median and standard deviation were calculated. Median PFS, OS, duration of response (DoR), and time on therapy were estimated using the Kaplan—Meier method (SPSS Statistics version 28, IBM, Armonk, USA; GraphPad Prism version 9.5.1 for Windows, GraphPad Software, Boston, MA). Additional statistical methods can be found in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2026.106941.

RESULTS

Baseline patient characteristics

From October 2022 to September 2023, 16 patients with American Joint Committee on Cancer (AJCC) stage IIIc ($n = 1$) or stage IV-M1a/c/d ($n = 1/12/2$) advanced pretreated melanoma were included in the trial. The median age was 61.5 years, and seven (44%) patients were female. Driver mutations were identified in *BRAF*^{V600} ($n = 7$), *KIT* ($n = 3$), *NF1* ($n = 3$), *NRAS*^{Q61} ($n = 2$), and *ATG7-RAF1* (fusion, $n = 1$). The median number of prior systemic treatment lines was three. All patients were pretreated with ICI. All patients with *BRAF*^{V600}-mutant melanoma previously progressed on BRAF/MEKi, three of them also on rechallenge with BRAF/MEKi, following at least 3 months interruption of these drugs. In addition to the three patients with *KIT*-mutant melanoma in the initial trial cohort, six additional *KIT*-mutant patients were identified, treated, and assessed according to the trial protocol (*KIT*-mutant expansion cohort). Among the total of nine *KIT*-mutant patients, eight had AJCC stage IV-M1c and one -M1d; the median age was 61.5 years. The primary melanoma subtypes were AL ($n = 4$), CSDSM ($n = 3$), and MM ($n = 2$). Driver *KIT*-mutations were documented in exon 11 ($n = 4$), 13 ($n = 4$), and 17 ($n = 1$). Three patients had progressed on imatinib. An overview of the baseline characteristics is included in Table 1 and an overview of the *KIT*-mutations is shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.106941.

Treatment disposition

REGO was administered orally, o.d., without planned interruptions. It was initiated at 80 mg in all 16 patients and increased to 120 mg in 8 patients. The median time on REGO was 12.1 weeks [95% confidence interval (CI) 6-18 weeks] and ongoing in two patients (Figure 1A). REGO was temporarily interrupted in 11 patients, mostly due to treatment-related adverse events (TRAEs). In one patient treatment was discontinued permanently due to recurrent pyrexia. Nine patients needed dose reductions. None of the patients could continue at 120 mg o.d. for >10 weeks due to intolerance ($n = 5$) or progression ($n = 3$).

BRAF^{V600}-mutant patients were allowed to combine REGO with BRAF/MEKi upon progression. Six *BRAF*^{V600}-mutant patients started combination treatment of REGO 40 mg o.d. with ENCO/BINI ($n = 3$) or DAB/TRAM ($n = 3$). The median time on this triple targeted therapy combination was 31.5 weeks (95% CI 0-69 weeks) (Figure 1B). The starting doses of ENCO/BINI ranged between 300 and 225 mg o.d. and 15 and 30 mg twice a day (b.i.d.), respectively, and were based on the patient's prior maximal tolerated dose. The starting doses of DAB/TRAM were 150 mg b.i.d. and 2 mg o.d., respectively. In all patients, a temporary treatment interruption of all three drugs was needed because of TRAEs; however, no permanent treatment interruptions were needed. In all patients, the dose of the MEKi was reduced as it was suspected to be the most important contributor to TRAEs, mostly diarrhea and acneiform rash.

In the *KIT*-mutant expansion cohort REGO was initiated at 80 mg o.d., except for three patients who started with REGO 40 mg o.d. due to cardiovascular comorbidities ($n = 2$) and low body weight ($n = 1$). The median time on REGO was 55.9 weeks (95% CI 36-75 weeks) and ongoing in four patients (Figure 1C). REGO was temporarily interrupted in six patients, mostly due to TRAEs.

Antitumor activity

All initial 16 patients were assessable for response. There were one complete response (CR; *BRAF*^{V600}-mutant patient) and five partial responses (PRs; two *BRAF*^{V600}-mutant and three *KIT*-mutant patients), yielding a confirmed overall response rate of 37.5%. The disease control rate (DCR) was 56%. The median duration of response was 37.4 weeks (95% CI 13-61 weeks) (Figures 1D, 2A and B). All but one patient progressed on REGO monotherapy; four patients were alive after median follow-up of 118 weeks (range 88-122 weeks). The median (m) PFS and mOS were 12.1 weeks (95% CI 3-20 weeks) and 75.8 weeks (95% CI 67-83 weeks), respectively (Figure 3A). Specifically, in the seven *BRAF*^{V600}-mutant patients, the DoR in the responding patients was 12, 18, and 69.4 weeks and ongoing in the complete

Table 1. Baseline patient characteristics

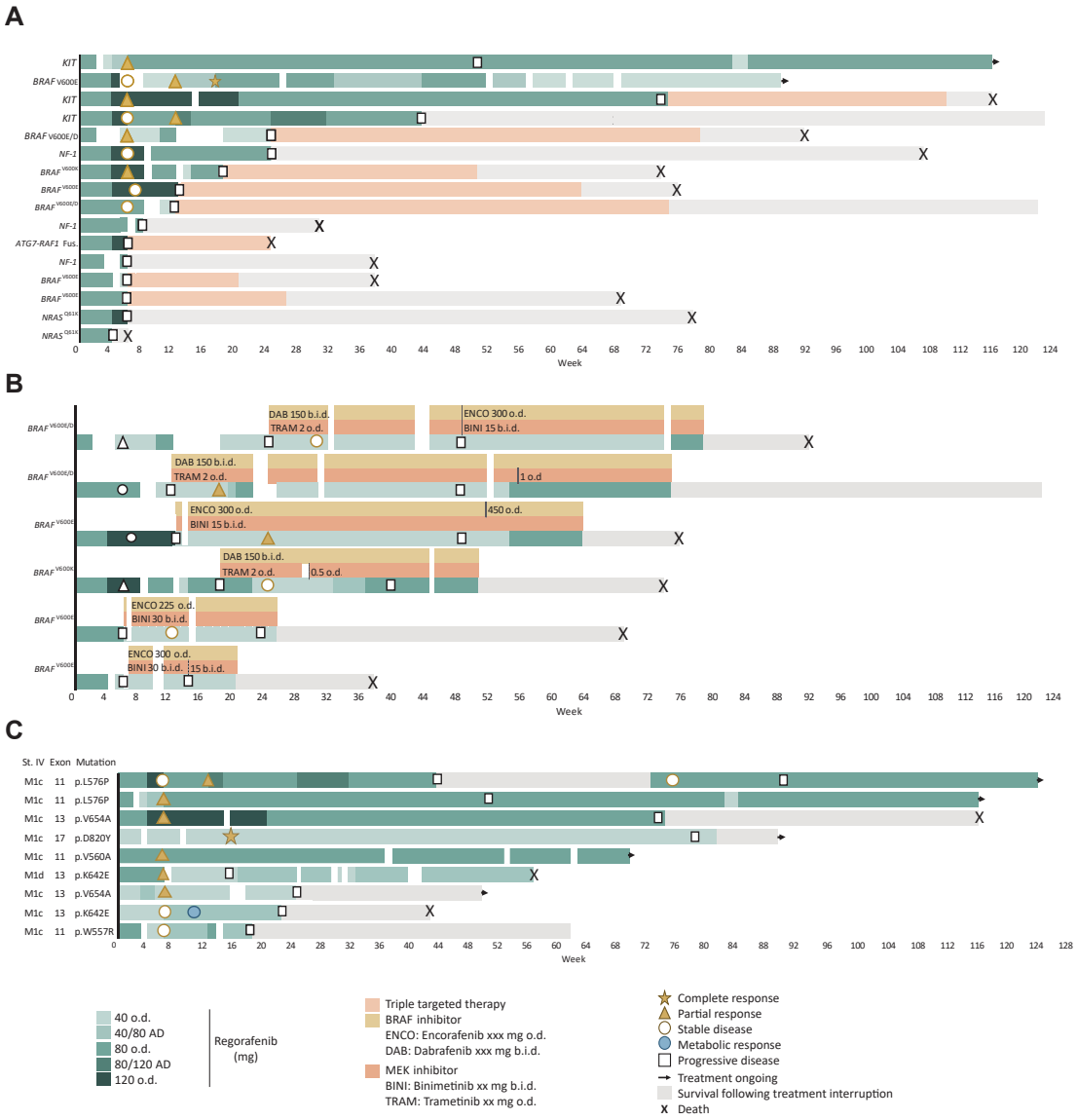
Baseline patient characteristics RegoMel cohort (*N* = 16)			
Age, years		Prior systemic therapy, *n* (%)	
Median (range)	61.5 (39-79)	Anti-PD-1 ICI	15 (94)
Sex, *n* (%)		Anti-CTLA-4 ICI	4 (25)
Male	9 (56)	Anti-PD-1 + anti-CTLA-4 ICI	12 (75)
Female	7 (44)	BRAF/MEKi	7 (44)
ECOG performance status score, *n* (%)		Rechallenge BRAF/MEKi[a]	3 (19)
0	10 (63)	Chemotherapy	4 (25)
1	6 (37)	Imatinib	1 (6)
Ethnicity, *n* (%)		High dose interferon	1 (6%)
Caucasian	16 (100)	T-VEC	1 (6)
Driver mutation, *n* (%)		Study treatment	2 (13)
BRAF$^{V600E/D/K}$	7 (44)	Prior lines of systemic therapy, *n* (%)	
KIT	3 (19)	2	4 (25)
NF1	3 (19)	3	7 (44)
NRAS$^{Q61K/L}$	2 (13)	4	4 (25)
ATG7-RAF1 fusion	1 (6)	10	1 (6)
AJCC stage		Baseline LDH, *n* (%)	
IIIc	1 (6)	≤ULN (250 U/l)	10 (63)
IV-M1a	1 (6)	>ULN	3 (19)
IV-M1c	12 (75)	>2 × ULN	3 (19)
IV-M1d	2 (13)		
Baseline patient characteristics *KIT*-mutant expansion cohort (*N* = 9)			
Age, years		AJCC stage	
Median (range)	61.5 (40-75)	IV-M1c	8 (89)
Sex, *n* (%)		IV-M1d	1 (11)
Male	6 (67)	Prior systemic therapy, *n* (%)	
Female	3 (33)	Anti-PD-1 ICI	8 (89)
ECOG performance status score, *n* (%)		Anti-PD-1 + anti-CTLA-4 ICI	8 (89)
0	6 (67)	Imatinib	3 (33)
1	3 (33)	Chemotherapy	1 (11)
Ethnicity, *n* (%)		Study treatment	2 (22)
Caucasian	9 (100)	Prior lines of systemic therapy, *n* (%)	
Primary melanoma, *n* (%)		0[b]	1 (11)
Acral	4 (44)	2	4 (44)
CSDSM	3 (33)	3	2 (22)
Mucosal	2 (22)	4	2 (22)
Exon *KIT*-mutation, *n* (%)		Baseline LDH, *n* (%)	
Exon 11	4 (44)	≤ULN (250 U/l)	6 (67)
Exon 13	4 (44)	>ULN	2 (33)
Exon 17	1 (11)	>2 × ULN	1 (11)

AJCC, American Joint Committee on Cancer; BRAF/MEKi, BRAF/MEK inhibitors; CSDSM, chronically sun-damaged skin melanoma; ICI, immune checkpoint inhibitor; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; ULN, upper limit of normal.
[a]Rechallenge defined as reinitiation of BRAF/MEKi after at least 3 months interruption of these drugs.
[b]One patient was unable to receive standard-of-care ICI as prior treatment due to an active auto-immune disease.

responder at time of analysis; mPFS was 12.3 weeks (95% CI 11-13 weeks).

In six *BRAF*^{V600}-mutant patients who received REGO + BRAF/MEKi, the ORR was 33% (two PR, confirmed) with duration of response of 24 and 30 weeks. One of these patients previously progressed on rechallenge BRAF/MEKi. The DCR was 83% (Figures 1D, 2C and D). All patients progressed and five died, resulting in an mPFS and mOS since the start of the triple targeted therapy of 20.4 weeks (95% CI 10-25 weeks) and 62.1 weeks (95% CI 53-71 weeks), respectively (Figure 3B). Five patients who were clinically benefiting from study treatment despite meeting the criteria for PD by RECISTv1.1 criteria continued triple targeted therapy beyond progression for an additional 3-30 weeks (representative case: Supplementary Figure S2A, available at https://doi.org/10.1016/j.esmoop.2026.106941).

In the *KIT*-mutant expansion cohort (including three among the first 16 patients), all nine patients were assessable for response. The confirmed ORR was 78% (one CR, six PR); DCR was 100% (Figures 1D, 2E and F). One patient with stable disease (SD) had a deep metabolic response on [^{18}F]FDG—PET—CT. The median duration of response was 37.9 weeks (95% CI 37-39 weeks) and was ongoing in one patient after 67 weeks. After a median follow-up of 79 weeks (range 42-123 weeks), eight patients had progressed and three had died, resulting in an mPFS of 43.4 weeks (95% CI 0-100 weeks); mOS was not reached (Figure 3C). Two patients continued REGO following progression (40 and 47 weeks). One patient experienced oligoprogression in the lung after 50 weeks of REGO, which was treated with stereotactic radiotherapy. In week 77, the patient developed a new solitary metastasis in the gallbladder, which was resected. After 115 weeks of treatment,



D

	REGO monotherapy	REGO + BRAF/MEKi (*BRAF*-mutant)	REGO monotherapy (*KIT*-mutant expansion cohort)
Best objective response, *n* (%)	***N* = 16**	***N* = 6**	***N* = 9**
Complete response	1 (6)	0	1 (11)
Partial response	5 (31)	2 (33)	6 (67)
Stable disease	3 (19)	3 (50)	2 (22)
Progressive disease	7 (44)	1 (17)	0
ORR (%)	37.5	33	78
DCR (%)	56	83	100
Median duration of response, weeks (95% CI)	37.4 (13-61)	24 + 30	37.9 (37-39)

Figure 1. Treatment disposition and efficacy. Treatment disposition, best objective response according to RECISTv1.1, and survival since treatment initiation in patients with advanced melanoma receiving REGO as monotherapy in the initial trial cohort (A); in *BRAF*^{V600}-mutant patients receiving REGO + BRAF/MEKi (i.e. triple targeted therapy) following progression on REGO monotherapy (B); and patients with advanced *KIT*-mutant melanoma receiving REGO monotherapy in the *KIT*-mutant expansion cohort (C). Overview of tumor response according to RECISTv1.1 (D).
AD, alternating days; b.i.d., twice daily; BINI, binimetinib; BRAF/MEKi, BRAF/MEK inhibitors; CI, confidence interval; DAB, dabrafenib; DCR, disease control rate; ENCO, encorafenib; o.d., once daily; ORR, overall response rate; REGO, regorafenib; TRAM, trametinib.

https://doi.org/10.1016/j.esmoop.2026.106941

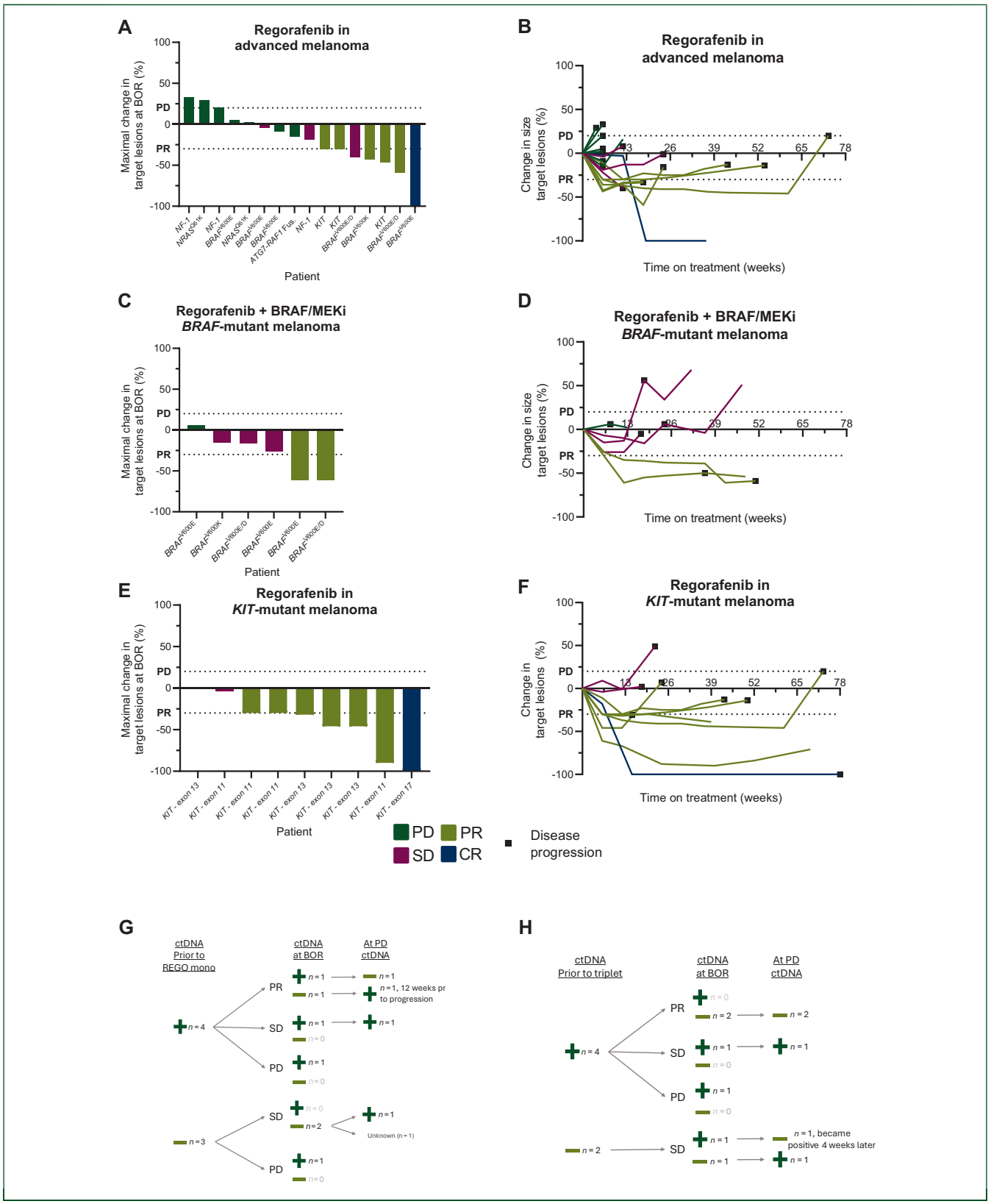


Figure 2. Responses according to RECISTv1.1 and ctDNA. (A) Maximal change in tumor size in patients with advanced melanoma receiving regorafenib (REGO) as monotherapy, (C) in $BRAF^{V600}$-mutant patients receiving REGO + BRAF/MEK inhibitors (BRAF/MEKi) (i.e. triple targeted therapy) following progression on REGO monotherapy, (E) and patients with advanced *KIT*-mutant melanoma receiving REGO monotherapy. The largest percentage change in the sum of target lesion diameters compared with baseline. (B) Change in sum of target lesions since baseline in patients with advanced melanoma receiving REGO as monotherapy, (D) in $BRAF^{V600}$-mutant patients receiving REGO + BRAF/MEKi (i.e. triple targeted therapy) following progression on REGO monotherapy, and (F) patients with advanced *KIT*-mutant melanoma receiving REGO monotherapy. The spider plots show the evolution over time from baseline of the percentage changes in the sum of target lesion diameters. The color in (A-F) depicts the best objective response: dark green = progressive disease (PD), Burgundy = stable disease (SD), light green = partial response (PR), and Blue = complete response (CR) according to RECISTv1.1. The horizontal lines depict a change in size of the target lesions of at least +20% (PD) and -30% (PR) compared

the patient is currently without evidence of disease and continues REGO 80 mg o.d. Of note, one patient received a rechallenge with REGO monotherapy to which there was a renewed complete metabolic response (Supplementary Figure S2B and C, available at https://doi.org/10.1016/j.esmoop.2026.106941).

Safety

All 22 patients receiving REGO monotherapy experienced at least one TRAE, most frequently hand-foot-skin reaction, fatigue, and hypertension. Thirteen patients (59%) experienced one or more reversible grade 3 TRAEs including arterial hypertension and maculopapular rash. Each of the six patients who combined REGO with BRAF/MEKi upon progression experienced at least one TRAE, most frequently diarrhea. Grade 3 TRAEs occurred in three patients (50%): diarrhea, decreased neutrophil count, and syncope. No grade 4 or 5 TRAEs occurred. Six patients receiving REGO monotherapy had a treatment-related serious adverse event (SAE) requiring hospitalization (acute kidney injury, pulmonary embolism, abdominal pain, fever, and jejunal ulcer). One patient receiving REGO with BRAF/MEKi had diarrhea with syncope as treatment-related SAE. All treatment-related SAEs resolved upon treatment interruption (Table 2).

Quality of life and neurocognitive functioning

For eight patients, a health-related quality of life (HRQoL) assessment was available at baseline and at 21 weeks. A statistically significant deterioration was observed in physical functioning ($Z = -1.973$, $P = 0.049$) and fatigue ($Z = -1.028$, $P = 0.043$). No significant differences were found in the other HRQoL outcomes, nor in emotional distress and cognitive complaints (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2026.106941).

For eight patients, baseline and follow-up assessment of objective neurocognitive functioning at 6 months were available. One patient was excluded from the neurocognitive functioning analysis due to low motivation during the evaluation. We found no statistically significant change between baseline and follow-up on composite objective neurocognitive functioning. When considering the individual neuropsychological tests, there was a statistically significant improvement in learning ability and inhibition. Only the improvement in learning ability was clinically relevant according to the Reliable Change Index (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2026.106941).

Biomarker analyses

In the *NRAS*- and *BRAF*^{V600}-mutant patients, ctDNA analysis of plasma samples obtained at baseline and response evaluations was carried out using the Idylla platform. Among *BRAF*^{V600}-mutant patients treated with REGO monotherapy, ctDNA was detectable at baseline in four of seven patients (57%). In one of two patients with a PR, ctDNA became undetectable and reappeared 12 weeks before radiographic progression. In two out of the three patients with undetectable ctDNA at baseline, ctDNA emerged at progression; ctDNA status was unknown at progression in the third (Figure 2G). Among the six patients receiving REGO + BRAF/MEKi, ctDNA was detectable at baseline in four (66%). In both patients with a PR, ctDNA became undetectable and remained so at progression. In the two with undetectable baseline ctDNA, it became detectable at SD and PD, respectively (Figure 2H). *NRAS*-mutant ctDNA was undetectable at all timepoints in both *NRAS*-mutant patients.

In the first three *KIT*-mutant patients, ctDNA was analyzed using digital droplet PCR. The mutant allele fraction (MAF) was calculated and used to quantify ctDNA at different timepoints. For the two patients with a *KIT* p.L576P mutation, the MAF at baseline was 0.39% and 0.04%. In the first patient the MAF decreased to 0% at week 30, coinciding with RECIST-PR and became detectable 12 weeks before and further increased at time of RECIST-PD. Following local treatment of oligoprogression, the MAF became undetectable and rose again to 0.20% at time of new oligoprogresssion (Supplementary Figure S2B, available at https://doi.org/10.1016/j.esmoop.2026.106941). In the other patient, the MAF also decreased and became equal to zero at RECIST-PR and increased 7 weeks before RECIST-PD (Supplementary Figure S2C, available at https://doi.org/10.1016/j.esmoop.2026.106941). For the patient with a *KIT* p.V654A mutation, ctDNA remained undetectable throughout.

Total metabolic tumor volume (TMTV) was explored as a quantitative imaging biomarker for tumor response, based on [^{18}F]FDG—PET—CT assessments at baseline and every 12 weeks thereafter. In nine patients receiving REGO monotherapy at least two scans were available. The median baseline TMTV ($n = 7$) was 24.2 ml (range 1.7-1542.1 ml). In four patients with a RECIST-PR, TMTV decreased to 0 ml (complete metabolic response) during treatment and rose again at progression; preceding RECIST progression by 12 weeks in one (Supplementary Figure S3A, available at https://doi.org/10.1016/j.esmoop.2026.106941). In all but one patient, TMTV evolution mirrored response or progression according to RECIST. The exception showed oligoprogression (one new lesion, i.e. RECIST progression) with a maintained metabolic response in other lesions (Supplementary Figure S3B, available at https://doi.org/10.1016/j.esmoop.2026.106941). In five assessable *BRAF*^{V600}-mutant patients treated with REGO + BRAF/MEKi, TMTV changes also corresponded with RECIST responses. Among three patients with RECIST-SD, the patient with a declining TMTV (i.e. metabolic response) experienced a longer PFS (24 weeks versus 17 weeks) (Supplementary Figure S3C and

with baseline. In (B), (D), and (F), the black square depicts time of disease progression according to RECISTv1.1. Evolution of *BRAF*^{V600}-mutant ctDNA according to RECISTv1.1 responses in patients treated with REGO monotherapy in the initial trial cohort (G) and in patients treated with regorafenib + BRAF/MEK inhibitors (i.e. triplet) in *BRAF*^{V600}-mutant patients (H).
BOR, best objective response; ctDNA, circulating tumor DNA.

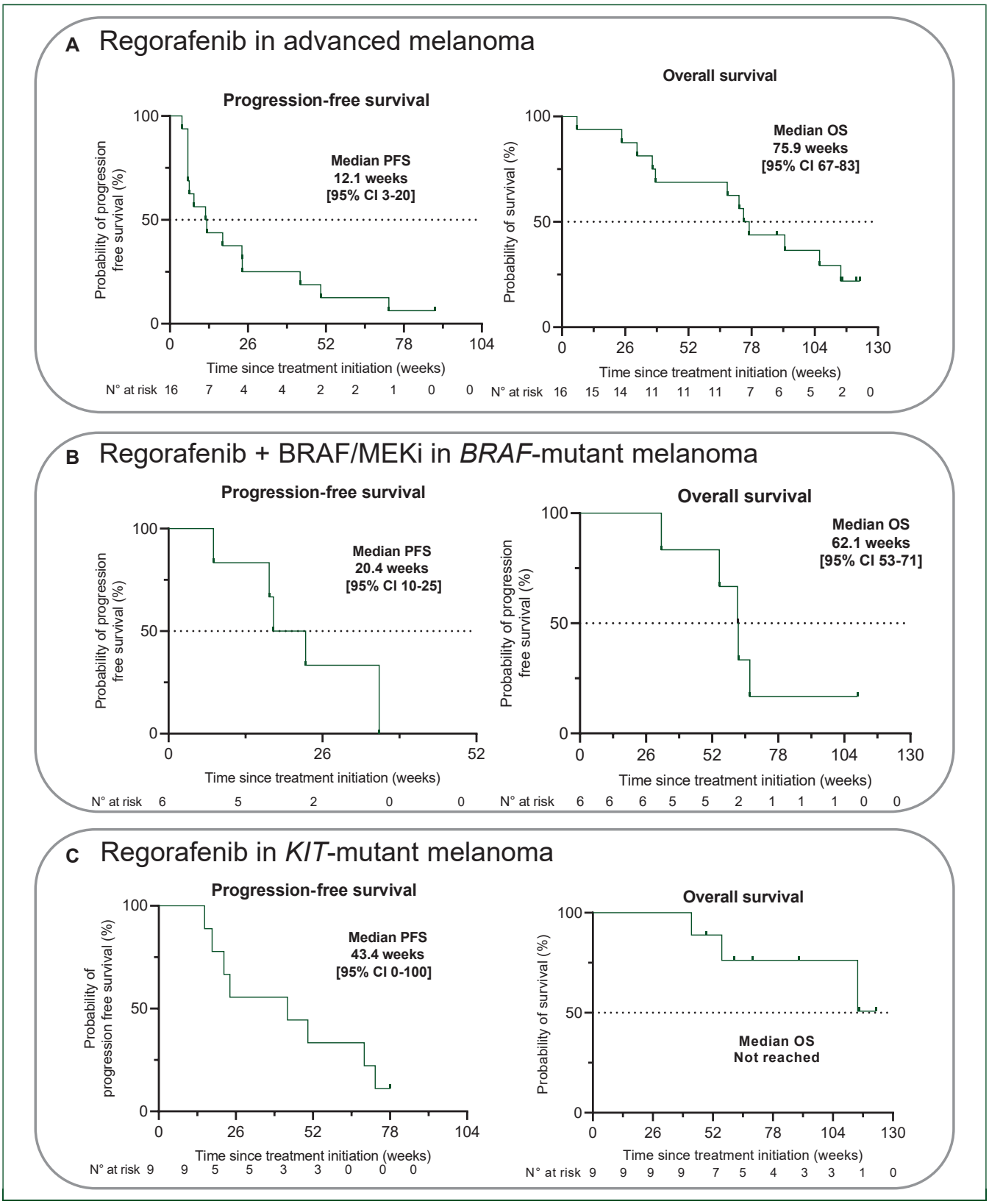


Figure 3. Progression free and overall survival. Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) in patients with advanced melanoma receiving regorafenib (REGO) as monotherapy (A); in *BRAF*^{V600}-mutant patients receiving REGO + BRAF/MEK inhibitors (BRAF/MEKi) (i.e. triple targeted therapy) following progression on REGO monotherapy (B), and patients with advanced *KIT*-mutant melanoma receiving REGO monotherapy (C). Censored patients are shown as a vertical mark.
CI, confidence interval; N°, number.

Table 2. Treatment-related adverse events (TRAEs) occurring in ≥25% of the patients or any grade 3

REGO monotherapy ($N = 22$)			REGO + BRAF/MEKi (*BRAF*-mutant, $N = 6$)		
	Any, *n* (%)	Grade 3, *n* (%)		Any, *n* (%)	Grade 3, *n* (%)
Any TRAE	22 (100)	13 (59)	Any TRAE	6 (100)	3 (50)
Hand-foot-skin reaction	14 (64)	1 (5)	Diarrhea	5 (83)	2 (33)
Hypertension	11 (50)	5 (23)	Neutrophil count decreased	2 (33)	1 (17)
Fatigue	11 (50)	—	CTRCD	2 (33)	—
Hoarseness	11 (50)	—	CPK increase	2 (33)	—
Diarrhea	9 (41)	—	AST/ALT increase	2 (33)	—
Hypophosphatemia	9 (41)	—	Hypophosphatemia	2 (33)	—
Oral dysesthesia	8 (36)	—	Nausea	2 (33)	—
Anorexia	7 (32)	—	Syncope	1 (17)	1 (17)
AST/ALT increase	7 (32)	—			
Alopecia	6 (27)	—			
Constipation	6 (27)	—			
Abdominal pain	4 (18)	1 (5)			
Lipase increased	4 (18)	1 (5)			
CTRCD	3 (14)	1 (5)			
Platelet count decreased	3 (14)	1 (5)			
Maculopapular rash	2 (9)	2 (9)			
Delayed wound healing	2 (9)	1 (5)			
Fever	2 (9)	1 (5)			
Acute renal injury	1 (5)	1 (5)			
Dyspnea	1 (5)	1 (5)			
Jejunal ulcer	1 (5)	1 (5)			
Pulmonary embolism	1 (5)	1 (5)			
TRAE leading to temporary interruption of					
REGO 120 mg o.d.	5 (23)	2 (9)	REGO + BRAFi + MEKi	6 (100)	3 (50)
REGO 80 mg o.d.	11 (50)	5 (23)	MEKi	1 (17)	—
REGO 40/80 mg AD	2 (9)	—			
REGO 40 mg o.d.	5 (23)	2 (9)			
TRAE leading to permanent interruption of					
REGO 80 mg o.d.	1 (5)	1 (5)			
TRAE leading to dose reduction of					
REGO 120 mg o.d.	5 (23)	2 (9)	MEKi	4 (67)	1 (17)
REGO 120/80 mg AD	1 (5)	—	BRAFi + MEKi	3 (50)	3 (50)
REGO 80 mg o.d.	8 (36)	4 (18)			
REGO 40/80 mg AD	3 (14)	—			
Serious adverse events					
Related	6 (27)	6 (27)	Related	1 (17)	1 (17)
Unrelated	4 (18)	4 (18)	Unrelated	1 (17)	1 (17)

Shown are treatment-related adverse events (TRAEs) occurring in ≥25% of patients or any grade 3 TRAE. Grading is according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

A full list of all TRAEs can be found in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2026.106941.

AD, alternating days; ALT, alanine transaminase; AST, aspartate transaminase; BRAFi, BRAF inhibitor; CPK, creatine phosphokinase; CTRCD, cancer therapy-related cardiac dysfunction; MEKi, MEK inhibitor; o.d., once daily; REGO, regorafenib.

D, representative case: Supplementary Figure S2A, available at https://doi.org/10.1016/j.esmoop.2026.106941).

DISCUSSION

This phase II, single-arm clinical trial met its primary efficacy endpoint demonstrating that REGO resulted in durable responses in advanced pretreated melanoma patients, with clinically meaningful improvements in PFS and OS. The best and longest responses were observed in *KIT*-mutant melanoma, largely outperforming previously reported ORR with other KIT inhibitors. Additionally, in $BRAF^{V600}$-mutant melanoma, continuation of REGO in combination with BRAF/MEKi showed a promising signal of clinical activity in patients who had previously progressed on BRAF/MEKi.

Currently, no life-prolonging treatments exist for patients who have progressed on dual ICIs, TIL therapy, and BRAF/MEKi. This represents a significant unmet need for ∼50% of advanced melanoma patients.[16,17] Based on these results, REGO may be an additional treatment option, especially in pretreated *KIT*-mutant melanoma. As a broad-spectrum KIT inhibitor, REGO demonstrated substantial clinical benefit, including in patients progressive on imatinib. REGO therefore seems to be more effective than other KIT inhibitors such as nilotinib, imatinib, and dasatinib, for which a systematic review reported a pooled ORR of 15% with mPFS of 2-6 months and mOS of 5-13 months.[11] In this study, the ORR is higher at 78%, with mPFS 43.4 weeks, or 10 months. The ORR in this study is also higher than the ORR of 30% in a phase II study by Kim et al. in Korean patients ($N = 23$) with pretreated *KIT*-mutant melanoma (mPFS 7.1 months, mOS 21.5 months).[14] The differences in efficacy could be attributed to genetic variations between Caucasian and Asian populations, as well as differences in dosing regimens (continuous daily 40-120 mg REGO versus 160 mg 21/28 days schedule with preplanned dose

interruptions). Previous studies in GIST have shown that continuous lower dosing of REGO results in reduced toxicity with comparable efficacy.[18,19] Furthermore, we have reported observations of rapid disease progression upon treatment interruption with targeted therapies.[10] Therefore, based on this study, continuous daily dosing at 40-80 mg REGO should be prioritized in future trials.

Beyond *KIT*-mutant melanoma, REGO in combination with BRAF/MEKi demonstrated activity in *BRAF*^{V600}-mutant melanoma patients who had previously progressed on BRAF/MEKi. BRAF/MEKi resistance remains a major challenge in melanoma treatment. Prior studies from our group showed that rechallenge with BRAF/MEKi after a treatment-free interval of 3 months led to renewed responses in ∼30% of patients.[20] However, following the DREAMseq trial, which established superior OS outcomes when BRAF/MEKi was sequenced after ICI progression rather than as an initial treatment, patients progressing on BRAF/MEKi as the final line of therapy are expected to become more common.[21] Therefore, strategies to overcome adaptive resistance to BRAF/MEKi are needed to broaden the therapeutic arsenal. Our findings confirm prior preclinical research, suggesting that adding a dimer-selective RAF inhibitor such as REGO to BRAF/MEKi may reinvigorate responses (ORR 33%, DCR 83%).[3] REGO monotherapy also yielded a high ORR of 43% and DCR of 71%. While the trial was not designed to compare REGO monotherapy with the triple combination in *BRAF*^{V600}-mutant melanoma, the responses and PFS seemed longer with the triple combination. Future cohorts of the RegoMel trial will explore whether the responses to the triple therapy observed in this cohort result from bona fide resistance reversal.

While there is a preclinical rationale supporting the potential efficacy of REGO as a dimer RAF inhibitor in *BRAF*- and *KIT*-wild-type melanoma, no clinical responses were observed in patients with, for example, *NRAS*- or *NF1*-mutant melanoma. This suggests that REGO monotherapy is insufficient to halt disease progression in these molecular subtypes, and that more comprehensive MAPK pathway inhibition—such as combination therapy with a MEKi—may be required.[4,5,22]

Continuous dosing of REGO did not result in unexpected adverse events. While grade 3 toxicities were observed in 63% of patients, they were all reversible upon treatment interruption. Continuous lower dosing appeared more tolerable compared with the approved dosing regimen (160 mg for 21/28 days), which has been associated with higher rates of severe toxicities in phase III clinical trials. For instance, in the CORRECT trial, grade ≥3 hypertension occurred in 36% of patients, whereas in our study, this was 19%.[23] Given that accumulating toxicities often necessitate dose modifications at standard dosing, lower continuous daily dosing warrants further investigation. With REGO + BRAF/MEKi, no unexpected adverse events were observed. The most common TRAE, diarrhea, was manageable with treatment interruptions and dose reductions of the MEKi. For future trials, optimizing MEKi dosing may further improve the tolerability of this triple combination.

There was no significant effect of the treatment on neurocognitive functioning. When evaluating HRQoL, a significant deterioration was found in physical functioning and fatigue. While fatigue is a well-defined TRAE of REGO, it is also important to note that the patients in this trial had advanced, pretreated melanoma and therefore were at high risk for further physical deterioration due to the natural course of their disease. More data in a larger group of patients and a comparator arm are needed to draw definite conclusions.

ctDNA and TMTV were explored as biomarkers for response and early progression detection. Quantitative assessment of ctDNA in the *KIT*-mutant patients coincided with RECIST assessment and even preceded RECIST progression in some patients. While previously qualitative *BRAF*- and *NRAS*-ctDNA analysis using the Idylla platform has been reported to be sensitive and specific to predict response or progression, this was not reproducible in this smaller cohort.[24,25] TMTV was a sensitive and specific quantitative imaging biomarker for tumor response that closely aligned with RECIST assessments and in one case also preceded RECIST progression. By evaluating the full extent of the disease, TMTV allows for a more comprehensive whole-body disease evaluation. For instance, TMTV provided added value in SD patients by distinguishing metabolic responders from nonresponders. TMTV has already been validated as a predictor of response to ICI in melanoma.[26] Given its automation potential and complementary clinical insights, integration of TMTV into clinical trials with targeted therapy and clinical practice warrants further exploration.

In conclusion, this prospective phase II clinical trial evaluating REGO monotherapy in advanced pretreated melanoma met its primary endpoint and demonstrated high antitumor activity, particularly in *KIT*-mutant melanoma patients and in combination with BRAF/MEKi for *BRAF*^{V600}-mutant melanoma. Its safety profile was manageable and continuous daily dosing at 40-80 mg may enhance tolerability, warranting further investigation. A phase II clinical trial evaluating REGO + BRAF/MEKi in *BRAF*^{V600}-mutant melanoma and a prospective phase II clinical trial in *KIT*-mutant melanoma have been initiated to confirm these findings.

ACKNOWLEDGEMENTS

We thank the patients who participated in the study, as well as their families and caregivers. We also thank the staff and investigators at the study site, in particular Evelien Vandeurzen for overseeing regulatory administration and data management and Katrien Van den Bossche for providing patient support in her role as onco-coach. We thank Kom op tegen Kanker for financial support and Bayer for providing drug support for the trial, in particular Caroline Lambrecht from Bayer, Belgium for her support.

FUNDING

Drug-only support was granted by Bayer (no grant number), the patent holder of REGO. The trial was supported by

a grant from Kom op tegen Kanker (not-for-profit organization).

DISCLOSURE

BN reports financial support provided by Kom op tegen Kanker. BN reports equipment, drugs, or supplies provided by Bayer. ID reports a relationship with Pierre Fabre that includes travel reimbursement. ID reports a relationship with Merck that includes travel reimbursement. GA reports a relationship with Novartis that includes travel reimbursement. All other authors have declared no conflicts of interest.

DATA SHARING

The dataset contains confidential patient information but can be made available with de-identified participant data to interested researchers upon request.

REFERENCES

1. Warner AB, Hamid O, Komanduri K, et al. Expert consensus guidelines on management and best practices for tumor-infiltrating lymphocyte cell therapy. *J Immunother Cancer*. 2024;12(2):e008735.
2. The Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. *Cell*. 2015;161(7):1681-1696.
3. Adamopoulos C, Ahmed TA, Tucker MR, et al. Exploiting allosteric properties of RAF and MEK inhibitors to target therapy-resistant tumors driven by oncogenic BRAF signaling. *Cancer Discov*. 2021;11(7):1716-1735.
4. Hong A, Piva M, Liu S, et al. Durable suppression of acquired MEK inhibitor resistance in cancer by sequestering MEK from ERK and promoting antitumor T-cell immunity. *Cancer Discov*. 2021;11(3):714-735.
5. Atefi M, Titz B, Avramis E, et al. Combination of pan-RAF and MEK inhibitors in NRAS mutant melanoma. *Mol Cancer*. 2015;14(1):27.
6. Schmieder R, Hoffmann J, Becker M, et al. Regorafenib (BAY 73-4506): antitumor and antimetastatic activities in preclinical models of colorectal cancer. *Int J Cancer*. 2014;135(6):1487-1496.
7. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer*. 2011;129(1):245-255.
8. Liu S, Du Y, Ma H, Ling Q, Zhu X, Tian J. Preclinical comparison of regorafenib and sorafenib efficacy for hepatocellular carcinoma using multimodality molecular imaging. *Cancer Lett*. 2019;453:74-83.
9. Vander Mijnsbrugge A-S, Cerckel J, Dirven I, et al. Regorafenib in patients with pretreated advanced melanoma: a single-center case series. *Melanoma Res*. 2024;34(4):366-375.
10. Dirven I, Pierre E, Vander Mijnsbrugge A-S, Vounckx M, Kessels JI, Neyns B. Regorafenib combined with BRAF/MEK inhibitors for the treatment of refractory melanoma brain metastases. *Cancers (Basel)*. 2024;16(23):4083.
11. Steeb T, Wessely A, Petzold A, et al. c-Kit inhibitors for unresectable or metastatic mucosal, acral or chronically sun-damaged melanoma: a systematic review and one-arm meta-analysis. *Eur J Cancer*. 2021;157:348-357.
12. McGillivray E, Ashouri K, Chatziioannou E, et al. Combined programmed cell death protein 1 and cytotoxic T-lymphocyte associated protein 4 blockade in an international cohort of patients with acral lentiginous melanoma. *Br J Dermatol*. 2025;192(2):316-326.
13. Pham JP, Kondo M, Hurwitz J, et al. Efficacy of immune checkpoint inhibitors in advanced mucosal melanoma: a systematic review and meta-analysis. *EJC Skin Cancer*. 2025;3:100756.
14. Kim KH, Lee HJ, Lee SJ, et al. A phase II study to evaluate the efficacy of regorafenib in C-KIT mutated metastatic malignant melanoma patients who have progressed on first-line treatment: a Multicenter Trial of Korean Cancer Study Group (UN-14—13). *Eur J Cancer*. 2022;174(suppl 1):S85-S86.
15. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
16. Belgium Cancer Registry. Cancer Fact Sheets 2022. Brussels: Belgian Cancer Registry. Available at https://kankerregister.org/sites/default/files/2024/Cancer_Fact_Sheet_All%20Cancers_2022.pdf; 2024. Accessed June 6, 2025.
17. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49.
18. Kim J-J, Ryu M-H, Yoo C, Beck MY, Ma JE, Kang Y-K. Phase II trial of continuous regorafenib dosing in patients with gastrointestinal stromal tumors after failure of imatinib and sunitinib. *Oncologist*. 2019;24(11):e1212-e1218.
19. Schvartsman G, Wagner MJ, Amini B, et al. Treatment patterns, efficacy and toxicity of regorafenib in gastrointestinal stromal tumour patients. *Sci Rep*. 2017;7(1):9519.
20. Schreuer M, Jansen Y, Planken S, et al. Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced BRAF(V600)-mutant melanoma: an open-label, single arm, dual-centre, phase 2 clinical trial. *Lancet Oncol*. 2017;18(4):464-472.
21. Atkins MB, Lee SJ, Chmielowski B, et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: the DREAMseq trial—ECOG-ACRIN EA6134. *J Clin Oncol*. 2023;41(2):186-197.
22. Whittaker SR, Cowley GS, Wagner S, Luo F, Root DE, Garraway LA. Combined pan-RAF and MEK inhibition overcomes multiple resistance mechanisms to selective RAF inhibitors. *Mol Cancer Ther*. 2015;14(12):2700-2711.
23. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.
24. Schreuer M, Meersseman G, Van Den Herrewegen S, et al. Quantitative assessment of BRAF V600 mutant circulating cell-free tumor DNA as a tool for therapeutic monitoring in metastatic melanoma patients treated with BRAF/MEK inhibitors. *J Transl Med*. 2016;14(1):95.
25. Seremet T, Planken S, Schreuer M, et al. Illustrative cases for monitoring by quantitative analysis of BRAF/NRAS ctDNA mutations in liquid biopsies of metastatic melanoma patients who gained clinical benefits from anti-PD1 antibody therapy. *Melanoma Res*. 2018;28(1):65-70.
26. Dirks I, Keyaerts M, Dirven I, Neyns B, Vandemeulebroucke J. Development and validation of a predictive model for metastatic melanoma patients treated with pembrolizumab based on automated analysis of whole-body [18F] FDG PET/CT imaging and clinical features. *Cancers (Basel)*. 2023;15(16):4083.