Regorafenib in Caucasian patients with advanced *KIT*-mutant melanoma: a dual center case series – Updated results

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Introduction

- Oncogenic *KIT*-mutations are found in ±3% of melanoma patients, most frequently in mucosal (15-21%), acro-lentiginous (11-23%), and melanoma on chronically sun-damaged skin (CSDS, 16-27%)[1]
- Only a minority of patients (14-30%) responds to treatment with small molecule c-KIT inhibitors (e.g., imatinib, sunitinib, nilotinib, dasatinib)[1]
- **Regorafenib** (REGO, Stivarga®) is an oral multikinase inhibitor (targeting KIT, TIE2,VEGFR, PDGFR, RET, RAF, CSF-1R)[2]
- REGO has shown **activity in pretreated melanoma**[3]
- REGO has shown activity (ORR 30%) in Korean pretreated *KIT*-mutant melanoma patients[4], but has never been studied in a Caucasian population with *KIT*-mutant melanoma.

Methods

- Dual center, retrospective case series in a Caucasian population
- Prospectively identified cohort of advanced *KIT*-mutant melanoma patients
  - Treated in the prospective REGOMEL phase 2 clinical trial (NCT05370807): n=3
  - Treated on a compassionate use basis: n=7
- Database lock on January 1st, 2025 - median follow-up: 52.9 weeks [range 27-101]
  - All patients evaluable for safety (CTCAE v5.0) and efficacy (RECIST v1.1)
- Responses were evaluated with CT and/or [18F]FDG-PET/CT
- Total metabolic tumor volume (TMTV) was calculated using [18F]FDG-PET/CT

Results

Baseline characteristics

Patient	Center	Stage IV	Primary melanoma	Mutation/exon	Prior treatment	LDH° (U/L)	ECOG PS
KIT001* (M, 63)	BEL	M1c	Acral	*KIT* p.(Val654Ala) (exon 13) *BRAF* Gly469Ala (class II)	Nivo; ipi/nivo	188	0
KIT002* (M, 40)	BEL	M1c	Mucosal	*KIT* p.(Leu576Pro) (exon 11)	Pembro; ipi/nivo; **imatinib**	275	1
KIT003* (F, 59)	BEL	M1c	Cutaneous	*KIT* p.(Leu576Pro) (exon 11)	Nivo; ipi/nivo	143	0
KIT004 (F, 61)	BEL	M1d	Acral	*KIT* p.(Lys642Glu) (exon 13)	Pembro; ipi/nivo; **imatinib**; dacarbazine	206	1
KIT005 (M, 75)	BEL	M1c	Acral	*KIT* p.(Asp820Tyr) (exon 17)	Pembro; ipi/nivo	166	0
KIT006 (M, 54)	BEL	M1c	Cutaneous	*KIT* p.(Val560Asp) (exon 11)	Pembro; ipi/nivo	2258	0
KIT007 (M, 65)	BEL	M1c	Cutaneous	*KIT* p. (Trp557Arg) (exon 11)	Nivo; ipi/nivo; **imatinib**; Amgen20210023	322	0
KIT008 (F, 46)	ITA	M1c	Mucosal	KIT c1724_1726delAAC (exon 11)	IL-2; imatinib, ipi; nivo	342	0
KIT009 (M, 84)	BEL	M1c	Mucosal	*KIT* p. (Lys642Glu) (exon 13)	None**	274	1
KIT010 (F, 40)	BEL	M1c	Acral	*KIT* p. (Val654Ala) (exon 13)	Pembro; ipi/nivo, IT ASO1b+ipi	142	0

* Included in REGOMEL clinical trial
** Not eligible for immune checkpoint blockade due to auto-immune disease
° LDH: upper limit of normal 250 U/L

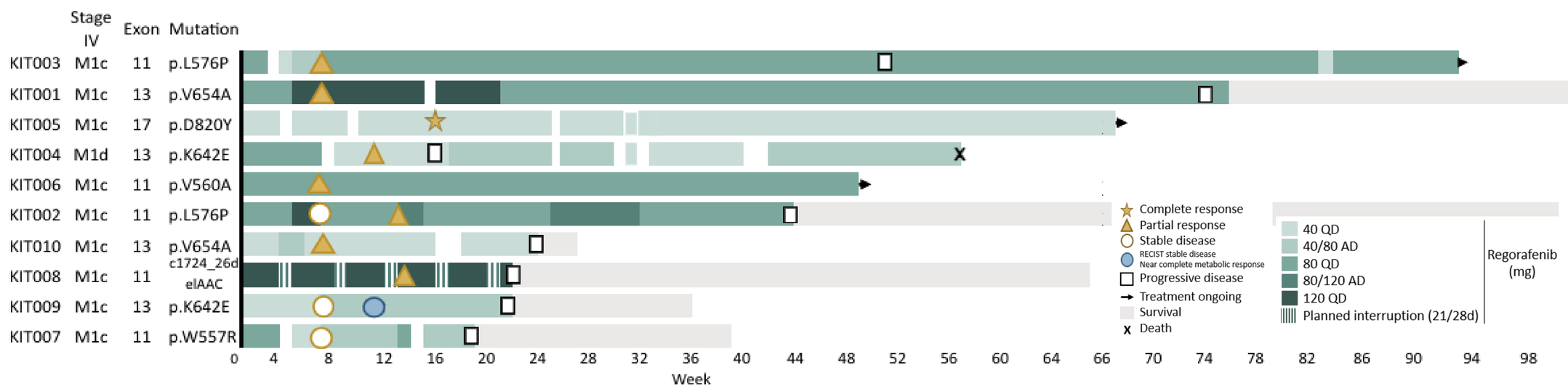
Treatment related adverse drug reactions

TRAE, n(%)	All grades	Grade 3°°
Any TRAE	10 (100%)	4 (40%)
Hoarseness	8 (80%)	
Hand-foot-skin reaction	7 (70%)	
Hypophosphatemia	6 (60%)	
Anorexia	6 (60%)	
Fatigue	5 (50%)	
Diarrhea	5 (50%)	
Hypertension	4 (40%)	2 (20%)
Muscle cramp	4 (40%)	
Oral dysesthesia	4 (40%)	
Abdominal pain	3 (30%)	
Alopecia	3 (30%)	
Lipase increase	2 (20%)	1 (10%)

TRAE, n(%)	All grades	Grade 3°°
Arthralgia	2 (20%)	
AST/ALT increase	2 (20%)	
Dry eye	2 (20%)	
Nail discoloration	2 (20%)	
Weight loss	2 (20%)	
Jejunal ulcer	1 (10%)	1 (10%)
Maculopapular rash	1 (10%)	1 (10%)
Dose reduction (due to TRAE)	5 (50%)	1 (10%)
Temporary REGO interruption (due to TRAE)	5 (50%)	2 (20%)
Permanent REGO discontinuation (due to TRAE)	0	0

°°No grade 4/5 TRAE

Outcome

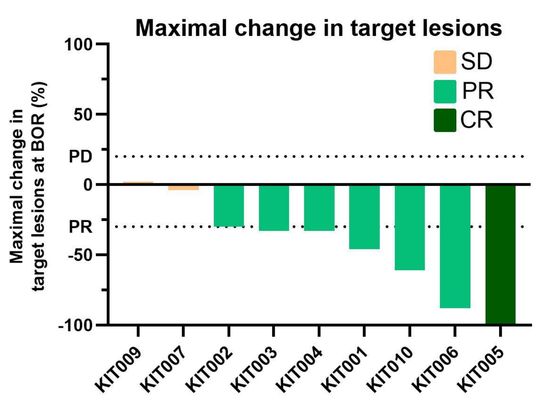


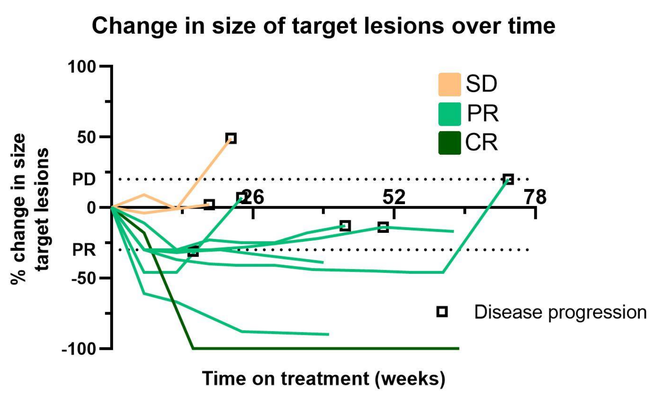
Treatment disposition
REGO 40-120 mg QD, continuous
REGO 120 21/28 days
Median time on REGO:
43.4 weeks [95% CI 0-87.5]
Ongoing in 3 patients (30%)

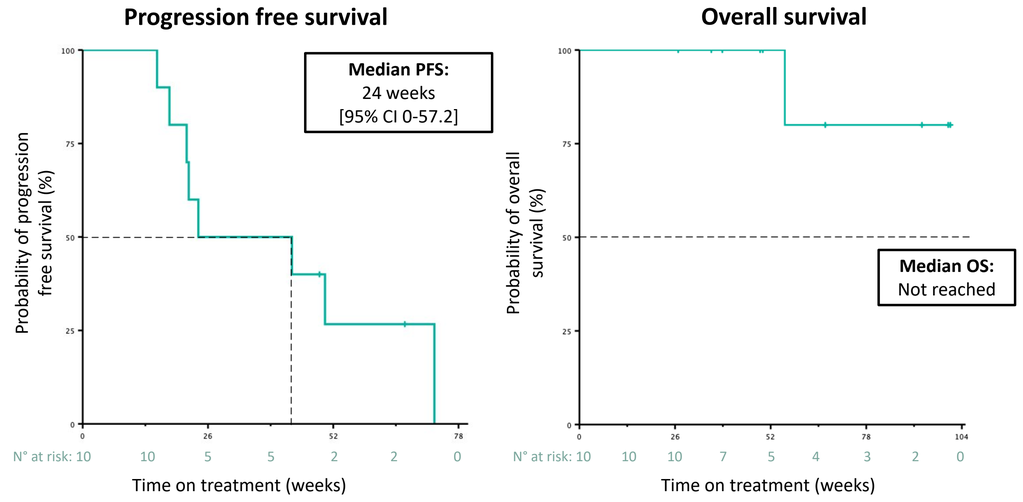
Response assessment
Complete response: n=1
Partial response: n=7
Stable disease: n=2
(incl. one metabolic response)

Objective response rate: 80%
Disease control rate: 100%

Duration of response:
37.4 weeks [CI 9.9-64.9 weeks]
Ongoing in 2 patients (20%)





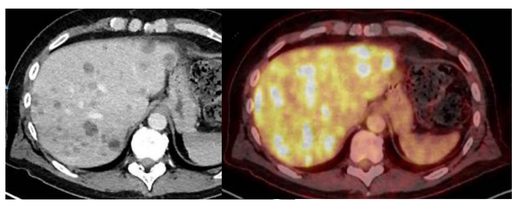


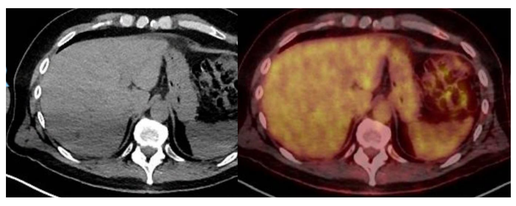
Case illustration KIT006: Male, 54y, Stage IV-M1c cutaneous *KIT*-mutant p.(Val560Asp), exon 11; progressive following pembrolizumab, ipilimumab/nivolumab; baseline LDH 2258 U/L

Baseline
Diffuse liver metastases

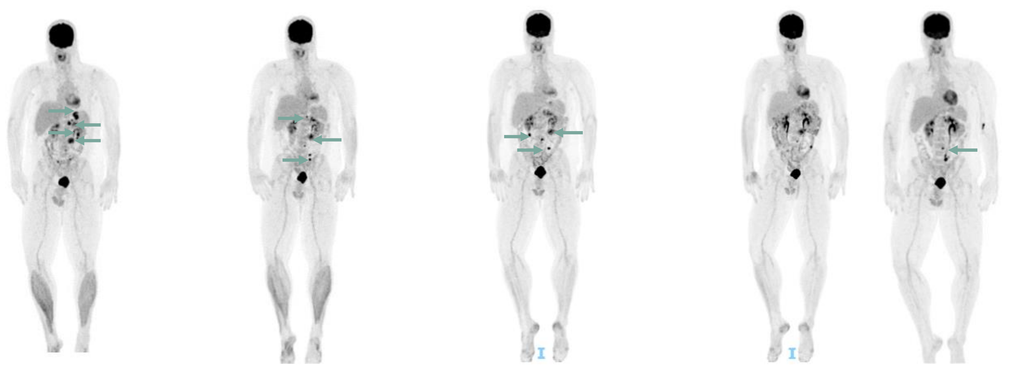
REGO 80 mg

24 weeks
Partial response
Complete (metabolic) response in liver





Case illustration KIT002: Male, 42y, Stage IV-M1c cutaneous *KIT*-mutant p.(Leu576Pro), exon 11; progressive following pembrolizumab, ipilimumab/nivolumab and imatinib; baseline LDH 275 U/L



Weeks	0	6	12	18	24	30	36	43
Response	Baseline	PR	PR	PR	PR	PR	PR	PD
% change target lesions		-30%	-30%	-23%	-25%	-25%	-18%	-13%
TMTV (mL)	36.58		9.75 (-73,35%)		32.94 (-9,95%)		0 (-100%)	14.78 (-59,60%)
Rego (mg)	0	80 QD	80/120 AD	80 QD	80/120 AD	80 QD	80 QD	STOP

CONCLUSION

Continuous uninterrupted once daily dosing of regorafenib (40-80 mg) demonstrates a **manageable safety profile.**
Regorafenib has unprecedented high anti-tumor activity in this Caucasian population of **advanced *KIT*-mutant melanoma** patients.
A prospective phase II trial has been submitted for regulatory approval.

References: 1. Steeb et al. Eur. J Cancer. 2021 2. Wilhelm et al. Int. J Cancer. 2011 3. Dirven et al. Cancers. 2024 4. Kim et al. Eur. J Cancer. 2023
Abbreviations: AD: alternate day BEL: Belgium; CSDS: chronically sun-damaged skin; cont,: continuous; ECOG PS: ECOG performance score; F: Female; HFrEF: heart failure with reduced ejection fraction; Ipi: ipilimumab; ITA: Italy; M: Male; Nivo: nivolumab; ORR: objective response rate; Pembro: pembrolizumab; PFS: progression free survival; QD: once daily; OS: overall survival; PFS: progression free survival; REGO: regorafenib; TRAE: treatment related adverse event

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