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Molecularly matched targeted therapy: a promising approach for refractory metastatic melanoma

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Abstract

Background: Only a fraction of patients with metastatic melanoma derive durable benefit from approved treatments. The clinical impact of personalized medicine strategies for melanoma, apart from *BRAF*, *NRAS*, or *CKIT* targeting, has rarely been reported.

Materials and Methods: By means of the Group of Cutaneous Oncology of the French Society of Dermatology, we retrospectively included all patients with advanced melanoma aged 18 years and older for whom molecular testing identified one or more actionable molecular alterations and who accordingly received molecularly matched therapy. We excluded patients with only *BRAF*, *NRAS*, or *CKIT* alterations and patients who received molecularly matched therapy for less than 15 days.

Results: We included 26 patients with a median follow-up of 8 months (1–54), a median age of 63 years (24–89), and a sex ratio of 2.7. These patients had been heavily pretreated, and 64% had elevated LDH levels. The disease control rate was 38%, with 4 cases of partial response (overall response rate: 15%) and 6 of stable disease for at least 6 months. The median duration of treatment was 3.1 months (0.9–13.5). Among patients with disease control, the median duration of control was 6.6 months (2.6–13.5) and 3 cases were ongoing at the end of the study. Patients with controlled disease had *GNA11*, *MAP2K1*, *FYCO1-RAF1*, *HRAS*, *ATM*, *CCND1*, *MDM2/CDK4*, and *CDKN2A/NRAS* alterations.

Conclusions: High-throughput sequencing followed by matched targeted therapy is a promising approach for patients with advanced melanoma refractory to approved treatments.

Key words: melanoma; precision medicine; targeted therapy; refractory melanoma; molecularly matched therapy; actionable molecular alteration.

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Implications for Practice

There is still an unmet medical need for most patients with metastatic melanoma since only a fraction benefit from approved treatments. The objective of this study was to evaluate the clinical benefit of personalized medicine strategies, excluding those targeting only *BRAF*, *NRAS*, or *CKIT* alterations, in advanced melanoma patients. In this heavily pretreated population, molecularly matched strategies achieved a 38% disease control rate. This study suggests that high-throughput sequencing followed by matched targeted therapy is a promising approach for patients with advanced melanoma refractory to approved treatments.

Introduction

The prognosis of patients with metastatic melanoma has dramatically improved in recent years with the introduction of 2 therapeutic strategies. BRAF and MEK inhibitors are small molecules that block the mitogen-activated protein kinase pathway, which is constitutively activated by recurrent *BRAF* V600 mutations in 45% of patients with melanoma.¹ In addition, monoclonal antibodies against the immune checkpoints cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and programmed death 1 (PD-1) can restore an efficient and durable antitumor immunity, even following treatment discontinuation.

In the metastatic setting, BRAF and MEK inhibitors have been shown to lead to a rapid and strong response, but the benefit is often limited by a high rate of secondary resistance, with a 5-year progression-free survival (PFS) of 19% for the dabrafenib plus trametinib combination.² The combination of ipilimumab and nivolumab (2 immune checkpoint blockade) reached a 36% 5-year PFS in one study.³ Therefore, only a fraction of patients derive durable benefit, and there is still an unmet medical need for most patients with metastatic melanoma.

Cancer precision medicine is an emerging strategy enabled by the increased accessibility to tumor genomic sequencing technologies. International and European pan-tumor recommendations have been published about next-generation sequencing (NGS)-based results interpretation in cancer.^{4,5} For melanoma, in addition to *BRAF*, *NRAS*, and *CKIT*, molecular testing is performed using melanoma-specific panels^{6,7} or nonmelanoma-specific large genomic panels, tissue DNA, or circulating tumor DNA. Whole-exome sequencing studies have demonstrated that among all cancers, melanoma has one of the highest rates of somatic mutations.⁸ Different large series using NGS custom melanoma-specific panels of 35-64 genes have revealed at least one alteration in 85%-87% of samples.^{6,9} The clinical impact of targeting actionable molecular alterations outside of *BRAF*, *NRAS*, and *CKIT*, has rarely been reported in melanoma, either in basket trials¹⁰ or small retrospective cohorts.^{6,11,12}

Our objective was to evaluate the clinical benefit of molecularly matched therapy following a molecular test identifying one or more actionable molecular alterations (and excluding only *BRAF*, *NRAS*, or *CKIT* alterations) in patients with advanced melanoma.

Materials and methods

Study design

MELtarget was a French national multicentric retrospective study conducted in France through the Group of Cutaneous Oncology of the French Society of Dermatology. This study was approved by the local IRB (PADS22-184). Informed consent was obtained from each surviving participant. For

deceased patients, the investigators checked whether the patients had expressed their opposition in writing during their lifetime.

We retrospectively included all metastatic or unresectable melanoma patients aged 18 years and older for whom a molecular test identified 1 or more actionable molecular alterations and who received molecularly matched therapy between 2018 and 2022. We excluded patients with only *BRAF*, *NRAS*, or *CKIT* alterations and patients who received molecularly matched therapy for less than 15 days.

The collected data included age, sex, primary melanoma characteristics, number and type of previous systemic treatments received, and prognostic factors at treatment initiation. We also collected molecular test results, including the type of sample used (tumor DNA or circulating tumor DNA), exact gene panel performed, type of alteration identified, variant allele frequency, and tumor mutational burden (TMB), when available. The following data were collected up to the end of the study: matched targeted therapy introduced, treatment plan, tumor board or molecular tumor board validation, tolerance according to CTCAE v5.0, treatment duration and dose adaptations, imaging results before and during treatment, reasons for treatment cessation, ensuing lines received, and status and date of latest follow-up.

Actionable molecular alterations

A gene alteration was defined as molecularly actionable if it had been defined as targetable by a tumor board or a molecular tumor board.

Accessibility of matched targeted therapies

Treatments approved for other indications were given using French exceptional access measures. Nonapproved therapeutics were accessed as follows: tipifarnib access was temporarily possible through an exceptional measure named "Accès Précoce" by the French national agency called ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé); for sirmaldin, patients were treated in the MEGAMOST phase 2 study, as promoted by the Centre Leon Berard, Lyon, France.

Response criteria

Response was evaluated using RECIST 1.1 criteria.¹³

Treatment duration was calculated from the date of molecularly matched therapy introduction to the date of treatment cessation.

Follow-up of patients was calculated from the date of molecularly matched therapy introduction to the date of death or loss to follow-up.

Progression-free survival (PFS) was defined as the time from the initiation of molecularly matched therapy introduction to disease progression or death from any cause.

Overall survival (OS) was defined as the time from the initiation of molecularly matched therapy introduction to death from any cause.

The disease control rate (DCR) was defined as the proportion of patients who achieved a partial response, complete response, or stable disease for at least 6 months.

The overall response rate (ORR) was defined as the proportion of patients who achieved a partial response or complete response.

Statistical analysis

Statistical analyses were performed using GraphPad Prism v9. Survival curves were generated using the Kaplan-Meier method to estimate the probability of survival.

The Mann-Whitney test was used to compare the TMB between patients with disease control and patients without disease control. A *P*-value <.05 was considered to indicate statistical significance, and *P* values were computed by default using 2-tailed tests.

Results

Our multicentric cohort was composed of 26 heavily pretreated patients with metastatic melanoma

We included 26 patients from 8 French oncodermatology centers with an 8-month (1-54) median follow-up. [Table 1](#) summarizes the clinical characteristics of the patients. The median age at inclusion was 63 years (24-89), with 19 men (73%) and 7 women (27%). The primary melanoma type was cutaneous for 18/26 patients (70%); 2 patients had primary uveal melanoma, 3 had mucosal melanomas, and 3 had melanomas of unknown origin. Only 12% of patients had the *BRAF*^{V600E} mutation, and 19% had *NRAS* mutation; no *CKIT* alterations were found. At treatment initiation, 27% of patients had Eastern Cooperative Oncology Group (ECOG)—Performances Status 2 or above, and lactate dehydrogenase (LDH) levels were above the upper limit in 64% of the patients ([Table 1](#)).

Most patients (24/26, 92%) received 2 or more previous lines of systemic treatment. Apart from patient 14 ([Figure 1](#); [Table 2](#)) who did not receive any previous line of treatment due to the severity of brain involvement and who required a salvage-targeted therapy strategy, all other patients had at least received a regimen based on anti-PD-(L)1 (only 1/25 received *atezolizumab*, an anti-PD-L1) and 73% an anti-CTLA4 treatment. All patients who carried the *BRAF*^{V600E} mutation had received a BRAF/MEK inhibitor combination, which failed. In addition, more than half of the patients had received at least one line of treatment with an investigational agent within a clinical trial, which failed ([Table 1](#)).

The MAP kinase pathway was the top targeted pathway, followed by the cell cycle pathway

Due to the different availability of molecular tests across centers, molecular testing was performed on tissue DNA for most patients (16/26) and on circulating tumor DNA for 7/26 patients; 3 patients had both ([Figure 2](#)). The median number of genes covered by the molecular test used to identify actionable molecular alterations was 324 (22-324), including 4 tests (15%) using a restricted and nondedicated panel of less than 40 genes.

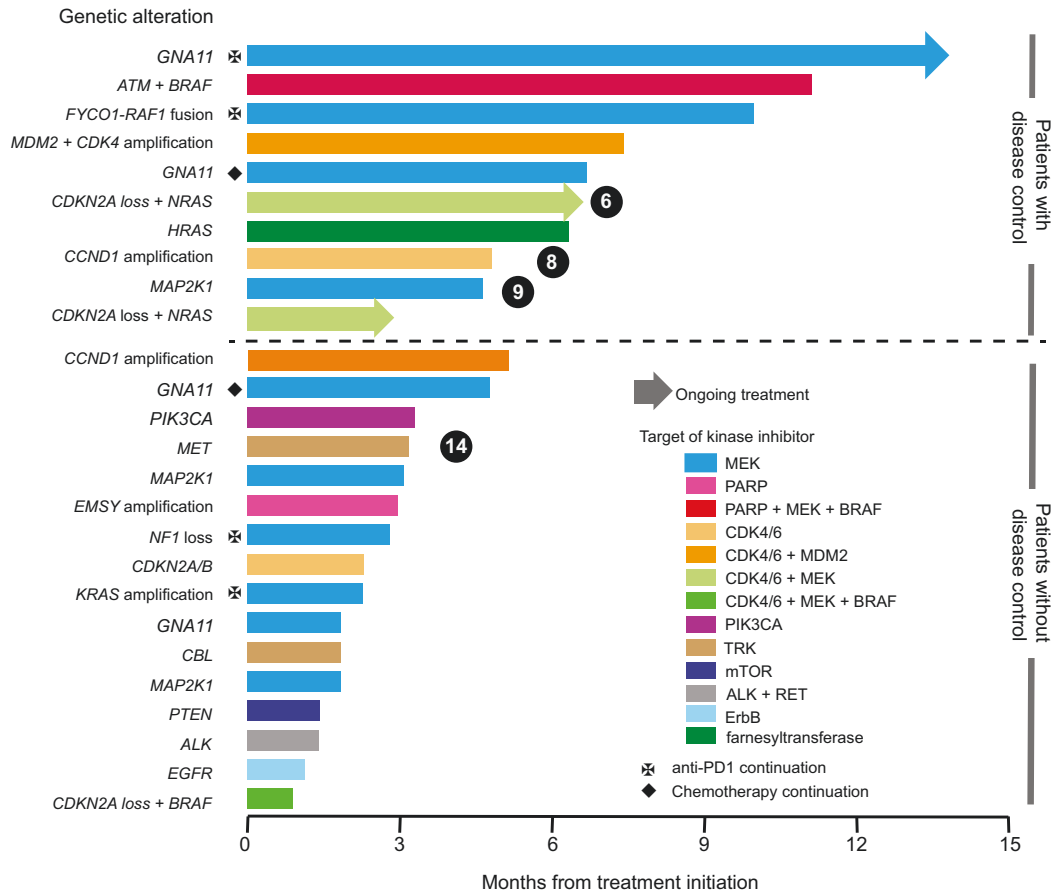
Table 1. Clinical characteristics of our cohort of patients with metastatic melanoma that received matched targeted therapy.

Variables	Number of patients (%)
Cohort	26 (100%)
Median age at inclusion (range)	63 (24-89)
Sex	
Male	19 (73%)
Women	7 (27%)
Primary melanoma type	
Cutaneous	18/26 (70%)
Uveal	2/26 (8%)
Mucosal	3/26 (11%)
Unknown	3/26 (11%)
Presence of a classical melanoma alteration	
<i>BRAF</i>	3/26 (12%)
<i>NRAS</i>	5/26 (19%)
<i>CKIT</i>	0/26 (0%)
Previous lines of systemic treatments received	
None	1 (4%)
1	1 (4%)
2	9 (34%)
≥3	15 (58%)
Previous line of treatment received including at least a regimen based on	
Anti-PD-(L)1	25/26 (96%)
Anti-CTLA4	20/26 (73%)
BRAF/MEK inhibitors	3/26 (12%)
Chemotherapy	8/26 (31%)
Developmental agents	14/26 (54%)
ECOG (PS) at inclusion	
0 or 1	18 (69%)
≥2	7 (27%)
Unknown	1 (4%)
Number of metastatic sites at inclusion	
<3	6/26 (23%)
≥3	20/26 (77%)
Metastatic specific localizations history	
Brain metastases	11/26 (42%)
Liver metastases	10/26 (38%)
LDH levels at treatment initiation	
Normal	9/25 (36%)
Abnormal	16/25 (64%)
<2N	11/15 (73%)
≥2N	5/15 (33%)
Unavailable	1/26 (4%)
Matched targeted therapy selected by a molecular tumor board	
Yes	23/26 (92%)

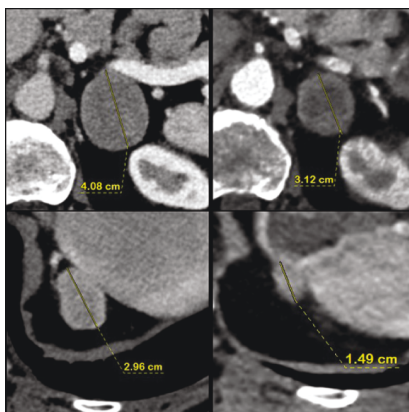
Abbreviations: LDH: lactate dehydrogenase, ECOG (PS): Eastern Cooperative Oncology Group (Performance Status).

Four patients (P2, P6, P10, and P26) had 2 concurrent targetable molecular alterations. Overall, 30 targetable alterations were detected: 17/30 (57%) affected the MAP kinase pathway, 6/30 (20%) affected the cell cycle pathway, 3/30 (10%) affected the receptor tyrosine

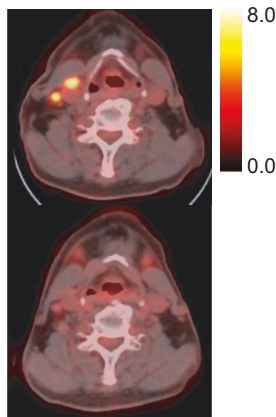
A



B



C



D

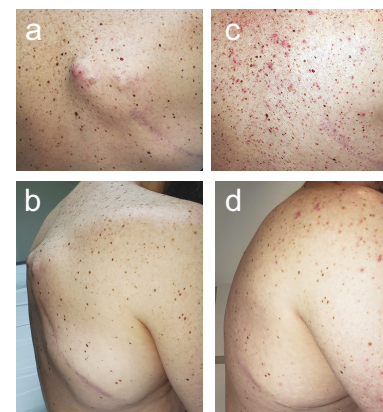


Figure 1. Matched targeted therapy outcomes. (A) Duration of matched targeted therapy received. In this swimmer plot, each bar represents 1 of the 26 patients with metastatic melanoma. The dotted line split patients with disease control (above) and patients without disease control (under). Among the 10 patients with disease control: 4 had a partial response (patients 6, 8, 9, and 10) and 6 had a stable disease of at least 6 months. (B) Radiological response of patient number 6 at baseline (on the left images) and at 3 months of treatment (on the right images) on adrenal (upper pictures) and retroperitoneal localizations (lower pictures). (C) Metabolic response of patient number 8 at baseline (upper picture) and at 3 months of treatment (lower picture). (D) Clinical response of patient number 9 on cutaneous and subcutaneous metastases at baseline (a and b) and at 1.5 months of treatment (c and d).

kinase pathway (RTK), 2/30 (6.5%) affected the PIK3CA pathway, and 2/30 (6.5%) affected the BRCA spectrum (Figure 2).

MAP kinase pathway alterations were targeted using trametinib for 10 patients with *GNA11* mutation ($n = 4$),

MAP2K1 mutation ($n = 3$), *NF1* loss ($n = 1$), *FYCO1-RAF1* fusion ($n = 1$), and *KRAS* amplification ($n = 1$), while tipifarnib was given for an *HRAS* mutation ($n = 1$) and sunitinib for a *CBL* mutation ($n = 1$). For cell cycle pathway alterations, abemaciclib was given for patients with a

Table 2. Detailed molecular alterations, molecular matched therapy introduced accordingly, and responses to treatment.

Patients	Genetic alterations	Variant allele frequency (%)	Treatment received	Best RECIST 1.1 response obtained	Treatment duration (months)
1	<i>GNA11</i> ^{Q209L}	E	Trametinib + pembrolizumab	SD	13.5
2	<i>ATM</i> (deletion exons 39-46); <i>BRAF</i> ^{V600E}	22; 75	Olaparib + dabrafenib + trametinib	SD	11.0
3	Fusion <i>FYCO1-RAF1</i>	E	Ttrametinib + nivolumab	SD	9.7
4	<i>CDK4-MDM2</i> amplification	NA	Siremadlin + ribociclib	SD	7.4
5	<i>GNA11</i> ^{R183C}	E	Trametinib + deticene	SD	6.7
6	<i>CDKN2A</i> loss; <i>NRAS</i> ^{Q61R}	NA; 8	Ribociclib + binimetinib	PR	6.4
7	<i>HRAS</i> ^{Q61R}	8	Tipifarnib	SD	6.3
8	<i>CCND1</i> amplification	NA	Palbociclib	PR	4.8
9	<i>MAP2K1</i> ^{E203K}	31	Trametinib	PR	4.6
10	<i>CDKN2A</i> loss; <i>NRAS</i> ^{Q61R}	NA; 37	Ribociclib + binimetinib	PR	2.6
11	<i>CCND1</i> amplification	NA	Siremadlin + ribociclib	SD	5.1
12	<i>GNA11</i> ^{Q209L}	E	Trametinib + fotemustine	PD	4.8
13	<i>PIK3CA</i> ^{E545K}	28	Alpelisib	PD	3.3
14	<i>MET</i> Exon 14	E	Cabozantinib	PD	3.1
15	<i>MAP2K1</i> 1103_K104del	48	Trametinib + dabrafenib (RD)	PD	3.1
16	<i>EMSY</i> amplification	NA	Olaparib	PD	3.0
17	<i>NF1</i> loss exon 1-8	NA	Trametinib + pembrolizumab	PD	2.8
18	<i>CDKN2A/B</i> -p16INK4a W15*	7	Abemaciclib	PD	2.3
19	<i>KRAS</i> amplification	NA	Trametinib + pembrolizumab	PD	2.3
20	<i>GNA11</i> ^{Q209L}	1	Trametinib	PD	1.8
21	<i>CBL</i> ^{R540} ; <i>CBL</i> ^{R559}	1; 1	Sunitib	PD	1.8
22	<i>MAP2K</i> E102_I103del	31	Trametinib + dabrafenib (RD)	PD	1.8
23	<i>PTEN</i> ^{G127}	31	Everolimus	PD	1.4
24	<i>ALK</i> ^{R1120W}	23	Alectinib	PD	1.4
25	<i>EGFR</i> ^{V765M}	E	Afatinib	PD	1.1
26	<i>CDKN2A</i> loss, <i>BRAF</i> ^{V600E}	NA; 75	Palbociclib + dabrafenib + trametinib	PD	1.0

Abbreviations: NA: not applicable, E: equivocal, PD: progressive disease, PR: partial response, SD: stable disease; dabrafenib RD: dabrafenib at reduced dosage to prevent skin adverse events.

CDKN2A/B mutation ($n = 1$), palbociclib for patients with a *CDKN2A* deletion ($n = 1$), a combination of ribociclib and binimetinib for patients with concurrent loss of *CDKN2A* and *NRAS* mutations ($n = 2$), and siremadlin and ribociclib for patients with *CCND1* amplification ($n = 1$) or *MDM2/CDK4* amplification ($n = 1$). *EGFR*, *ALK*, and *MET* mutations were targeted using afatinib ($n = 1$), alectinib ($n = 1$), and cabozantinib ($n = 1$), respectively. A *PIK3CA* mutation was targeted with alpelisib ($n = 1$) and a *PTEN* mutation was targeted with everolimus ($n = 1$). Finally, the BRCA spectrum (*ATM* deletion and *EMSY* amplification) was targeted with olaparib in 2 patients, in combination with dabrafenib and trametinib in one patient who had just experienced relapse after rechallenge with this therapy (Table 2).

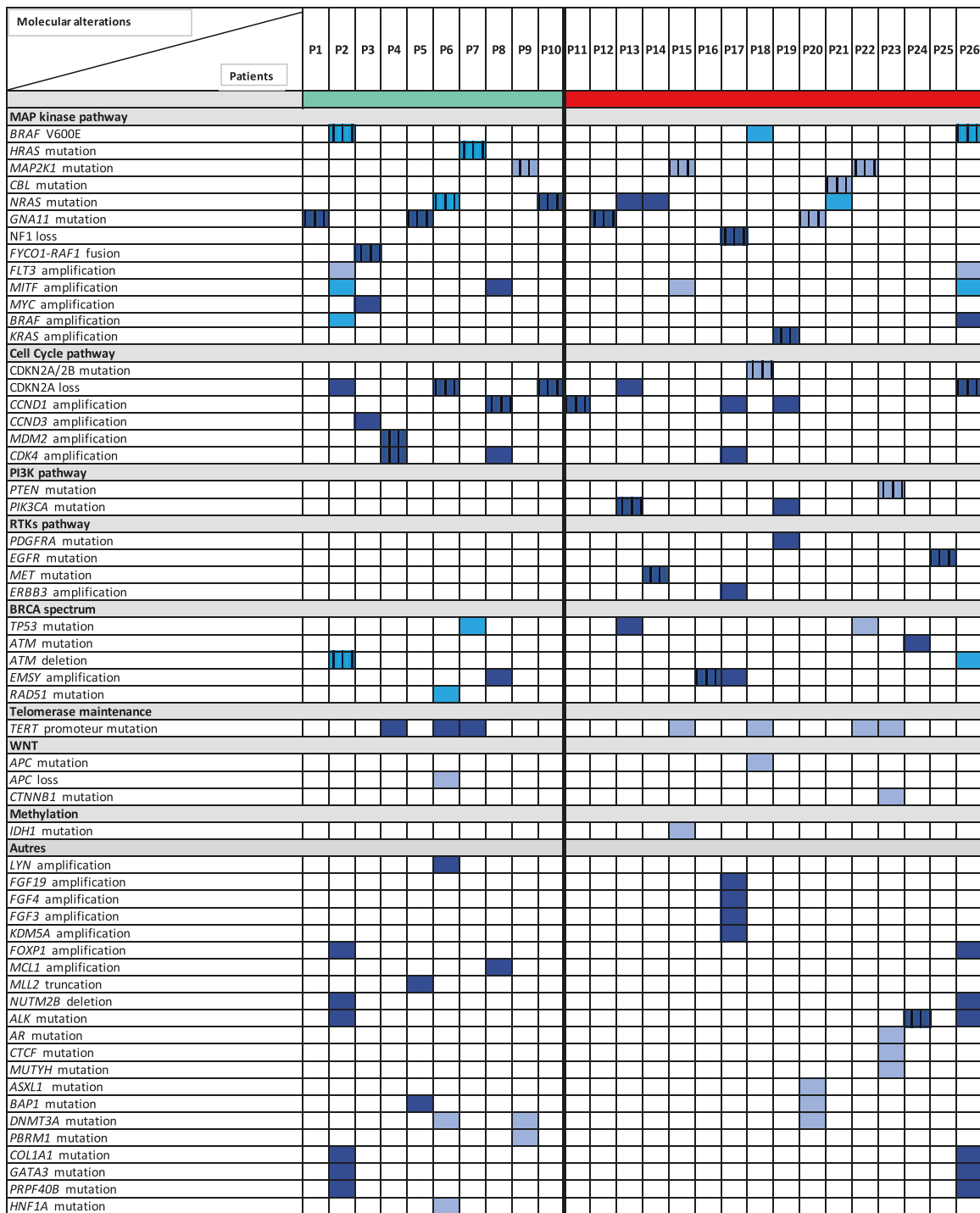
Sequencing-based matched targeted therapy was selected by a molecular tumor board for 23/26 patients (88%) and by a tumor board for all patients (100%). For 6 of the 26 patients (23%) from 1 center, the tumor board decided to add molecularly matched treatment while continuing the previous line of treatment as a strategy to overcome confirmed resistance to anti-PD-1 treatment ($n = 4$) or chemotherapy with dacarbazine ($n = 1$) or fotemustine ($n = 1$; Figure 1A).

This personalized strategy elicited a DCR of 38%

The DCR was 38%, with 4 cases of partial response and 6 of stable disease for at least 6 months. The median duration of treatment was 3.1 months (0.9-13.5). Among patients with disease control, the median duration of control was 6.6 months (2.6-13.5), and 3 cases were ongoing at the end of the study (Figure 1A). Images of the radiological, metabolic, and clinical responses of patients 6, 8, and 9 are presented in Figure 1B-1D. The median progression-free survival was 3.2 months and the median overall survival was 9.1 months (Supplementary Figure S1). Patients with controlled disease (patients 1-10) had *GNA11* ($n = 2$); *MAP2K1*, *FYCO1-RAF1*, *HRAS*, *ATM*, *CCND1*, and *MDM2/CDK4* or *CDKN2A/NRAS* ($n = 2$) alterations (Table 2).

Most patients reported mild adverse events related to their molecularly matched therapy

No side effects were reported for 5/26 patients (19%), and CTCAE grade 1 and 2 adverse events were reported for 11/26 patients (42%). They included cutaneous toxicity ($n = 10$), digestive tract toxicity ($n = 5$), and hematologic toxicity ($n = 3$), as well as drug-induced hepatitis



Legend:
 ■ targeted molecular alteration
 ■ molecular alteration found in tumor tissue
 ■ molecular alteration found in blood biopsy
 ■ molecular alteration found both in tissue and blood
 ■ Patients with disease control
 ■ Patients without disease control

Figure 2. Molecular coalterations among our patients with metastatic melanoma who received matched targeted therapy. Each column represents one patient (P).

for 1 patient and pulmonary toxicity for 1 patient. Three patients (12%) experienced severe grade 3 adverse events, namely, dropped head syndrome under trametinib,

pancytopenia under palbociclib, and drug-induced diabetes and cardiac left ventricular ejection fraction deterioration leading to treatment cessation under alpelisib.

Disease control was observed even in patients with poor prognosis

With caution due to the small number of patients included in our study, we observed disease control in 2 patients with an ECOG performance status greater than or equal to 2 and in 4 patients with elevated LDH levels, including 2 patients with LDH levels 2 times the upper reference limit (Supplementary Tables S1 and S2).

No significant differences were found between patients with disease control and patients without disease control regarding the existence of molecular coalterations and tumor mutational burden levels.

Most patients (81%) had 1 or more molecular coalterations in addition to those targeted by the molecularly matched therapy. Among the 5 patients for whom only 1 molecular alteration was identified and targeted, 4 did not derive any benefit (Figure 2).

Similarly, we wondered whether the tumor mutational burden (TMB) affects therapeutic response and observed no significant difference in the TMB between patients with disease control (mean = 7.1 mutations/Mb) and patients without disease control (mean = 14 mutations/Mb; $P = .3639$).

Discussion

In our multicentric and retrospective cohort, we observed an unexpected 38% DCR using a personalized medicine strategy to target tumor actionable molecular alterations in 26 heavily pretreated patients with unresectable metastatic melanoma.

The cohort characteristics were representative of patients refractory to available therapies except for the sex ratio in favor of men (2.7), which is usually balanced in melanoma, and for the low number of *BRAF*-mutant patients (12%), for whom we made the assumption that broad tumor sequencing is less common. Patients with poor prognosis included 2 with primary uveal melanoma and 3 with primary mucosal melanoma, both of which are known to be associated with poor outcomes.

The 38% DCRs and 15% ORRs indicate that 60% of the patients who benefited from the strategy had a stable outcome of at least 6 months.

This DCR is in line with the 30% clinical benefit lasting ≥ 6 months reported by Shoushtari et al,¹² who analyzed clinical and treatment data from 27 patients with rare targetable drivers who prospectively underwent sequencing in the Memorial Sloan Kettering MSK-Impact project and received genomically matched therapies. Most of the treatments received were mostly MEK and ERK inhibitors for *RAS* alterations and *BRAF* class II alterations and TRK inhibitors for *NTRK* fusions.

These numbers are also in line with those of a retrospective cohort of 33 patients treated with trametinib for pretreated *NRAS*-mutated melanoma which reported an 18% ORR and 49% DCR with a 6.8 months median duration of response.¹⁴ In the Shoushtari study and in our cohort of patients, the clinical outcomes of rare targetable drivers are of interest despite the small number of patients included and treated.

The durable disease control obtained with the combination of olaparib, dabrafenib, and trametinib in a patient with concurrent *ATM* deletion and the *BRAF*^{V600E} mutation is striking. The 11 months of stable disease achieved were unlikely due to dabrafenib and trametinib rechallenge since this patient had just experienced failure of a 3-month rechallenge with *BRAF*

and MEK inhibitors before olaparib introduction. A few recently published case reports also showed high response rates to olaparib in patients with homologous recombination deficiency. Interestingly, this was the case for mutations involving the DNA damage response pathway (DDR)^{15,16} or despite the absence of mutations in DDR genes.¹⁷

In addition, 2 remarkable partial responses were described for 2 patients with concurrent *CDKN2A* loss and the *NRAS*^{Q61R} mutation who received ribociclib combined with cobimetinib combination which is in line with a recently published phase Ib/II trial reporting a 32.5% response rate in this specific population.¹⁸

Finally, 1 of our 3 patients with *MAP2K1* (*MEK1*) mutation achieved a partial response to trametinib. One explanation is that *MEK1*^{E203K}, which was also successfully targeted in the Shoushtari et al cohort,¹² is sensitive to feedback inhibition of *RAF*, in contrast to insertion-deletion mutations in the *MAP2K1* inhibitory domain from amino acids 98-113.¹⁹

Despite these encouraging results, our study has numerous limitations due to its retrospective nature, the small number of patients included and the heterogeneity of available NGS panels and sequencing strategies between centers. Since personalized medicine is not a standard of care for patients with melanoma, despite the inclusion of patients through a national network of skin cancer specialists, the number of included patients was low. It was therefore impossible to obtain homogenous profiling strategies to assess broad tumor sequencing output in refractory metastatic melanoma. Finally, we chose to exclude patients treated for less than 15 days to avoid patients who did not receive treatment for a long enough time to be evaluated, even though some targeted therapies are able to provide rapid and strong responses.

In conclusion, personalized strategies are a promising approach for treating patients with refractory metastatic melanoma because of the importance of improving access to molecular testing, molecular tumor boards, and matched targeted therapies. In the future, prospective cohorts are needed to better define these strategy outcomes among upcoming metastatic melanoma strategies.

Author contributions

Emily Connell: collection of data, data analysis and interpretation, manuscript writing. Émilie Gerard: provision of study material or patients, final approval of manuscript. Bénédicte Oules: provision of study material or patients, final approval of manuscript. Florence Brunet-Possenti: provision of study material or patients, final approval of manuscript. Anouck Lamoureux: provision of study material or patients, final approval of manuscript. Hugo Bonnefille: provision of study material or patients, final approval of manuscript. Sorilla Mary-Prey: provision of study material or patients, final approval of manuscript. Ana Carrasquilla: provision of study material or patients, final approval of manuscript. Stéphane Mouret: provision of study material or patients, final approval of manuscript. Nora Kramkimel: provision of study material or patients, final approval of manuscript. Candice Lesage: provision of study material or patients, final approval of manuscript. Pierre-Emmanuel Stoebner: provision of study material or patients, final approval of manuscript. Axel Bartoli: provision of study material or patients, final approval of manuscript. Sandrine Monestier: data analysis and interpretation, final approval of manuscript. Florian

Correard: data analysis and interpretation, final approval of manuscript. Audrey Gros: provision of study material or patients, final approval of manuscript. Arnaud Jeanson: conception and design, data analysis and interpretation, final approval of manuscript. L'Houcine Ouafik: data analysis and interpretation, final approval of manuscript. Caroline Gaudy-Marqueste: conception and design, data analysis and interpretation, final approval of manuscript. Pascale Tomasini: conception and design, data analysis and interpretation, final approval of manuscript. Julie Charles: conception and design, provision of study material or patients, data analysis and interpretation, final approval of manuscript. Mona Amini-Adle: conception and design, provision of study material or patients, data analysis and interpretation, final approval of manuscript. Nausicaa Malissen: conception and design, provision of study material or patients, collection of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

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Conflicts of interest

E.C. has no conflict of interest. E.G. has received fees from MSD, BMS, Pierre Fabre, Sanofi (speaker honoraria, financial support for congress participation). B.O. declares having received meeting invitations from Novartis, Abbvie, and Bristol Myers Squibb. F.B.P. declares having received advisory fees from Bristol Myers Squibb, Merck and Novartis. A.L. has received fees from Novartis, BMS, MSD, Pierre Fabre, SANOFI (speaker honoraria, boards participation, or financial support for congress participation). H.B. has received fees from Novartis (financial support for congress participation). S.M.P. declares being investigator and having received meeting invitations from Bristol Myers Squibb, and MSD. A.C. has no conflict of interest. S.M. has no conflict of interest. N.K. has no conflict of interest. C.L. has received grants for boards or congresses from BMS, MSD, Novartis, Pierre Fabre Oncology, Sanofi. P.E.S. and A.B. have no conflict of interest. S.M. received advisory fee from BMS and Sanofi, payment for lectures or meeting invitations from Novartis, BMS, Sanofi, Pierre Fabre Oncology and MSD. FC reports personal fees from Novartis, BMS, MSD and Pierre Fabre outside the submitted work. A.G. has no conflict of interest. A.J. has no conflict of interest. L.O. declares having received advisory fees from AMGEN SAS, Janssen Cilag, Astrazeneca, GlaxoSmithKline, Lilly France, payment for lectures and meeting invitations from Myriads Genetics SAS, Janssen Cilag, Astrazeneca. C.G. has received honoraria from BMS France, Blue Print, MSD Oncology, Pierre Fabre, Consulting or advisory role for Pierre Fabre and travel and accommodations expenses for Pierre Fabre, BMS France and MSD Oncology. P.T. had a consulting or advisory role for Roche, AZ, BMS, Takeda, Amgen and travel and accommodations expenses for BMS and Amgen. J.C. has no conflict of interest. M.A.A. has received fees from BMS, Pierre Fabre, Sanofi (consultant and speaker honoraria, financial support for congress participation). N.M. declares having received advisory fees from Abbvie, Bristol Myers Squibb, Janssen Cilag and Novartis, payment for lectures and meeting invitations from Pierre Fabre

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material.

Supplementary material is available at *The Oncologist* online.

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