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Original Research

Biomarker-driven therapies for metastatic uveal melanoma: A prospective precision oncology feasibility study

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Abbreviations: UM, Uveal melanom; NGS, Next Generation Sequencing; TKI, Tyrosine Kinase Inhibitor; CPI, Checkpoint Inhibitor; TML, Tumor Mutational Load.

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KEYWORDS
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Precision oncology;
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High-throughput genomics

Abstract ***Background:*** Targeted therapies for metastatic uveal melanoma have shown limited benefit in biomarker-unselected populations. The Treat20 Plus study prospectively evaluated the feasibility of a precision oncology strategy in routine clinical practice.
Patients and methods: Fresh biopsies were analyzed by high-throughput genomics (whole-genome, whole-exome, and RNA sequencing). A multidisciplinary molecular and immunologic tumor board (MiTB) made individualized treatment recommendations based on identified molecular aberrations, patient situation, drug, and clinical trial availability. Therapy selection was at the discretion of the treating physician. The primary endpoint was the feasibility of the precision oncology clinical program.
Results: Molecular analyses were available for 39/45 patients (87%). The MiTB provided treatment recommendations for 40/45 patients (89%), of whom 27/45 (60%) received ≥1 matched therapy. First-line matched therapies included MEK inhibitors ($n = 15$), MET inhibitors ($n = 10$), sorafenib ($n = 1$), and nivolumab ($n = 1$). The best response to first-line matched therapy was partial response in one patient (nivolumab based on tumor mutational burden), mixed response in two patients, and stable disease in 12 patients for a clinical benefit of 56%. The matched therapy population had a median progression-free survival and overall survival of 3.3 and 13.9 months, respectively. The growth modulation index with matched therapy was >1.33 in 6/17 patients (35%) with prior systemic therapy, suggesting clinical benefit.
Conclusions: A precision oncology approach was feasible for patients with metastatic uveal melanoma, with 60% receiving a therapy matched to identify molecular aberrations. The clinical benefit after checkpoint inhibitors highlights the value of tumor mutational burden testing.

1. Introduction

Uveal melanoma is the most common intraocular malignant tumor, representing 80–90% of cancers of the eye. Twenty to fifty percent of patients will develop metastases correlated with stage, cytogenetic abnormalities [1,2], and gene expression profile [3]. In the metastatic setting, various chemotherapy regimens have demonstrated minimal antitumor response while checkpoint inhibitors have provided response rates of 12–18% without long-term survivorship [4]. Recently, tebentafusp, an immune-mobilizing monoclonal T-cell receptor targeting the tumor antigen gp100, was shown to significantly improve median overall survival (OS) compared with standard therapy in a randomized phase III trial, despite a low response rate of 9% [5].

Comprehensive studies of the genetic landscape of uveal melanoma have revealed four molecular subgroups that could have not only prognostic but also therapeutic implications [6,7]. By identifying novel therapeutic targets, these insights have raised new possibilities for treatment [8,9]. However, the few targeted therapies tested to date have shown minimal activity in studies not based on molecular tumor analysis [10], raising the possibility that better results could be obtained through a molecular-driven approach.

The clinical benefit of precision cancer medicine has been suggested by different studies across various malignancies including rare cancers that are usually underrepresented in clinical molecular research [11,12]. A precision oncology treatment strategy has not yet been evaluated in metastatic uveal melanoma. The Treat20 Plus study aimed to assess the feasibility of offering a comprehensive molecular analysis using high-throughput genomics to identify oncogenic drivers that could inform treatment recommendations by a multidisciplinary molecular and immunologic tumor board (MiTB).

2. Patients and methods

2.1. Patients

Eligible patients had histologically proven metastatic uveal melanoma, age ≥ 18 years, ECOG performance status 0–2, and adequate renal, liver, and bone marrow function. Prior intravenous chemotherapy, immunotherapy, or major surgery at least four weeks before inclusion were allowed. Patients with a history of cardiac disease or symptomatic brain metastases were excluded.

The Ethical Board of the Charité-Universitätsmedizin approved the study (EA4/063/13), which was registered at ClinicalTrials.gov (NCT05063058). The study was conducted according to the Good Clinical Practice Guidelines of the International Council for Harmonisation and the Declaration of Helsinki. Written informed consent was required for DNA/RNA sequencing analysis and to allow the MiTB to make treatment recommendations accordingly.

2.2. Molecular analysis

A fresh tissue biopsy was obtained from all patients. Molecular analyses utilized techniques comprised WES, low-coverage WGS, high-coverage WGS (in a subset of eight patients), and bulk rRNA-depleted total RNAseq. as previously published methodology [13]. The results were summarized in comprehensive, annotated reports covering the key molecular alterations, which were made available to the MiTB.

2.3. Multidisciplinary molecular and immunologic tumor board

A MiTB comprising clinicians, pathologists, molecular and tumor biologists, medical oncologists, and bioinformaticians developed individualized treatment recommendations by identifying and prioritizing predictive biomarkers [14]. (Suppl. Table S1, ESMO ESCAT levels of evidence shown in comparison) Recommendations were based on evidence levels attributed to each aberration and in the light of the patient situation, drug, and clinical trial availability (EudraCT: 2014-004437-22). The treating physician ultimately decided whether to treat the patient according to the MiTB proposal. During the study, medications were approved for off-label use through the German individual compassionate use program.

2.4. Statistical analysis

The primary endpoint of the study was to assess the feasibility of a using molecular testing to recommend the therapy for patients with metastatic uveal melanoma in a routine setting. Other endpoints included the proportion of patients that had valuable molecular testing and actionable genomic mutations, and that received a targeted therapy following the MiTB recommendations. Given that this was an observational feasibility study, power calculations were not performed, and the results should be considered exploratory and hypothesis-generating. The response rate was defined according to RECIST 1.1 criteria. The clinical benefit rate designated the addition of the rates of response and stable disease. Progression-free survival (PFS) was defined as the time from first treatment administration in the study to disease progression or death. OS was defined as the time from enrollment to death. Survival endpoints were analyzed using Cox regression with backward selection along with Kaplan–Meier estimates. Patients without an event were censored at the date of last follow-up. The log-rank test was used to compare survival curves. Univariate and multivariate Cox proportional hazards methods were used to model potential predictors of survival. The growth modulation index (GMI) was calculated as the ratio of PFS on the matched therapy to

Table 1
Patient characteristics.

Characteristic[a]	Matched patients (n = 27)	Unmatched patients (n = 18)	All patients (N = 45)
Sex			
Male	10 (37%)	9 (50%)	19 (42%)
Female	17 (63%)	9 (50%)	26 (58%)
Age, years	58 (17–80)	60 (24–80)	60 (17–80)
ECOG PS	0 (0–2)	0 (0–2)	0 (0–2)
Time to metastasis, years	3.7 (0.3–30)	3.2 (0–36)	3.7 (0–36)
Number of metastatic sites	5 (2–8)	2 (1–8)	4 (1–8)
Metastatic sites			
Liver	23 (85%)	18 (100%)	41 (91%)
Lung	20 (74%)	9 (50%)	29 (64%)
Skin/subcutaneous	14 (52%)	7 (39%)	21 (47%)
Lymph node	13 (48%)	8 (44%)	21 (47%)
Bone	12 (44%)	6 (30%)	18 (40%)
Peritoneum	11 (40%)	13 (72%)	14 (31%)
Adrenal gland	5 (18%)	1 (5%)	6 (13%)
Pancreas	5 (18%)	0	5 (11%)
LDH			
Normal	8 (30%)	9 (50%)	17 (38%)
Abnormal	19 (70%)	9 (50%)	28 (62%)
≥2 × ULN	6 (22%)	7 (39%)	13 (29%)
Previous therapies	1 (0–5)	0 (0–4)	1 (0–5)
Type of previous therapy			
Chemotherapy iv	11 (41%)	4 (22%)	15 (33%)
Checkpoint inhibitors	10 (37%)	4 (22%)	14 (31%)
Targeted therapy	2 (7%)	0	2 (4%)
Vaccine	2 (7%)	0	2 (4%)
Radio-embolization	4 (14%)	1 (5%)	5 (11%)
Chemo-embolization	7 (26%)	3 (17%)	10 (22%)

ECOG PS, Eastern Cooperative Oncology Group performance status; iv, intravenous; LDH, lactate dehydrogenase; ULN, upper limit of normal.
[a] Presented as n (%) or median (range).

time to progression on the most recent prior line of therapy on which the patient had progressed [15,16].

3. Results

3.1. Patient characteristics

Between March 2016 and November 2019, 45 patients were enrolled: 44 with metastatic uveal melanoma and one with a melanoma originating from a nevus of Ota. As summarized in Table 1, 26 patients were female, median age was 60 years (range: 17–80), and median ECOG was 0 (range: 0–2). The tumor burden was high, with a median of four metastatic sites (range: 1–8), and 62% of patients had an abnormal lactate dehydrogenase (LDH) level. The most common metastatic sites were the liver (91% of patients), lung (64%), skin (47%), lymph nodes (47%), and bone (40%). Two patients had small, asymptomatic brain metastases. Overall, 71% of patients had been previously treated. Clinical characteristics did not differ between patients that were treated according to MiTB recommendations (matched therapy group) versus those that were not (unmatched therapy group) (Table 1).

3.2. Molecular characteristics

Among the 45 patients, low tumor cell content precluded meaningful molecular analysis in six patients and, in two further patients, tumor purity of ~30% enabled only a partial analysis. Table 2 displays the results most relevant for MiTB treatment recommendations. In summary, the median tumor mutational burden was 30 somatic coding mutations (range: 12–459), with four patients having >100 mutations. Activating mutations in G protein subunits were observed in all patients. A loss-of-function mutation in *BAP1* was identified in 21 patients. *SF3B1* was mutated in 14 patients, one with a simultaneous *BAP1* mutation, while one patient had a mutation in *EIF1AX*. Thirty-three patients had *MYC* amplification. Other aberrations included overexpression of *MDM2* (n = 22), *MET* (n = 30), and *BCL2* (n = 31). Thirty-two patients had alterations in genes linked to cell cycle activation, including *CDKN2A* loss or downregulation (n = 21), copy-number gain of *CCND1-3* (n = 17) and *CDK6* (n = 4), and *CDK6* mutation (n = 1). Furthermore, tumors from 11 patients expressed the ALK^{ATI} transcript variant. Other targetable gene modifications included overexpression of *FGFR2/3* (n = 5), *ERBB3* (n = 7), or *KIT* (n = 4). Two patients with hypermutated tumors had a germline mutation in *MBD4*.

3.3. MiTB treatment recommendations

The median time from biopsy to results for the MiTB was 58 days (range: 16–144). A recommendation was made in all 39 patients with complete or partial molecular data (Fig. 1). Of the six patients lacking molecular results due to low tumor content, one received a recommendation for a MEK inhibitor based on presumed activating mutations in G protein subunits. The

Table 2
Key results of molecular analyses.

Characteristic[a]	Therapy/inhibitors	Evidence level	Matched patients (n = 26[b])	Unmatched patients (n = 13[b])	All patients (n = 39[b])
Number of mutations	Checkpoints	2a	31 (12–459)	30 (15–161)	30 (12–459)
GNAQ mutation	MEK	2a	12 (46%)	6 (46%)	18 (46%)
GNA11 mutation	MEK	2a	14 (54%)	7 (54%)	21 (54%)
BAP1 mutation	PARP/HDAC	3a	12 (46%)	9 (69%)	21 (54%)
BAP1 and *SF3B1* mutation		3a	0	1 (8%)	0
SF3B1 mutation	Checkpoints	4	10 (38%)	4 (31%)	14 (36%)
	SF3B1	3b			
EIF1AX mutation		–	1 (4%)	0	1 (3%)
No mutation identified			3 (12%)	1 (8%)	4 (10%)
Cell cycle activation (*CDKN2A*, *CCND1-3*, *CDK6* mutations)	CDK4/6	2b	22 (85%)	10 (77%)	32 (82%)
MYC gain	MYC	3b	21 (81%)	12 (92%)	33 (85%)
PTEN copy-number loss	mTOR	2b	3 (12%)	2 (15%)	5 (13%)
TP53 mutation/copy-number loss		–	3 (12%)	4 (31%)	7 (18%)
MET overexpression	MET	2b	20 (77%)	10 (77%)	30 (77%)
BCL2 overexpression	BCL2	3b	22 (85%)	9 (69%)	31 (79%)
MDM2 overexpression	MDM2	3b	16 (61%)	6 (46%)	22 (56%)
ALK^{ATI} expression	ALK	2b	8 (31%)	3 (23%)	11 (28%)
EGFR/*ERBB3* overexpression	EGFR	2b	2 (8%)	5 (38%)	7 (18%)
KIT overexpression	KIT	2c	2 (8%)	2 (15%)	4 (10%)
FGFR2-3 overexpression	FGFR	2b	4 (15%)	1 (8%)	5 (13%)
NF1 copy-number loss	MEK	2b	1 (4%)	1 (8%)	1 (3%)

[a] Presented as n (%) or median (range).
[b] Results were missing for one patient in the matched cohort and five patients in the unmatched cohort due to low tumor content in the sample.
Evidence levels according to reference 14.

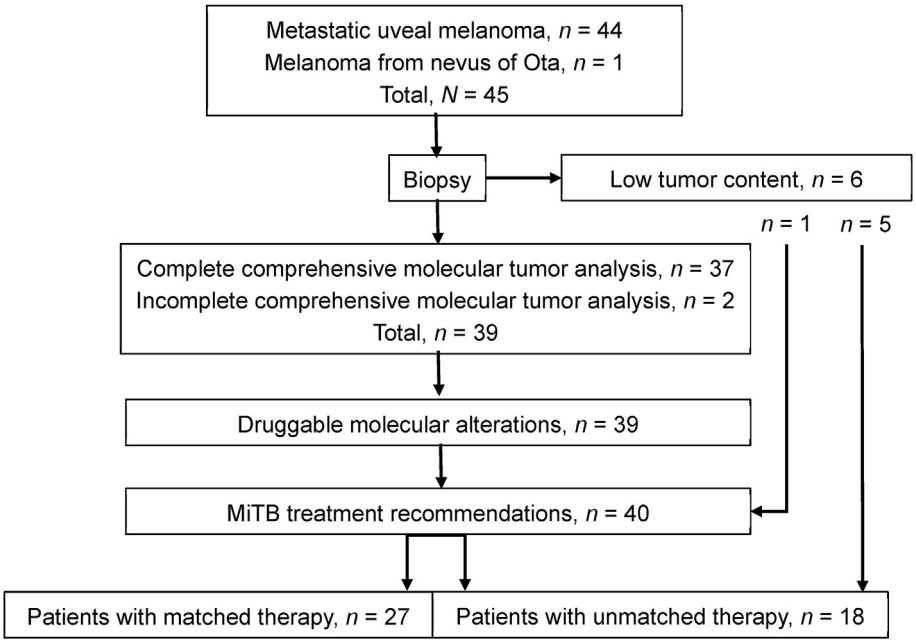

Fig. 1. CONSORT flow chart MiTB, molecular and immunologic tumor board.

median number of MiTB treatment recommendations per patient was two (range: 1–4). Recommended therapies included inhibitors of MEK (52%), MET (42%), CDK4/6 (3%), mTOR (2%), VEGFR (2%), PARP (1%), RAF (1%), BET (1%), or HDAC (1%).

A matched therapy recommended by the MiTB was administered in 27 patients (Table 3). Reasons for not administering matched therapy in the remaining 13 patients included rapid progression (n = 5), administration of intrahepatic therapies (n = 8), absence of recurrence after hemihepatectomy (n = 1), and death following complication after hemihepatectomy (n = 1).

3.4. Clinical outcome

Among the 27 patients, first-line matched therapy included MEK inhibitors in 15 patients (trametinib, $n = 13$; trametinib plus fotemustine, $n = 1$; selumetinib, $n = 1$), MET inhibitors in ten patients (crizotinib, $n = 6$; cabozantinib, $n = 4$), sorafenib, and the checkpoint inhibitor nivolumab in one patient each (Fig. 2; Table 3). Pembrolizumab was administered as second-line matched therapy in two patients, both of whom had a tumor mutational burden of >100 mutations. In five patients, a combination of a targeted therapy with fotemustine (n = 2), hydroxychloroquine (n = 1), trabectidine (n = 1), or sorafenib (n = 1) as second to fourth line was proposed to reverse the resistance to single targeted agent.

Of the 27 patients treated with a first-line matched therapy, a durable partial response was attained with nivolumab in one patient, with 459 somatic mutations and a *MBD4* mutation (Fig. 2). Stable disease was recorded in 12 patients and progression in 12 patients, while two patients achieved mixed response with partial remission of subcutaneous metastases and stabilization of the visceral ones. The clinical benefit rate was 56% with a duration of nine months (95% confidence interval [CI] 3–17). Of the three patients who received trametinib plus fotemustine in any treatment line, one attained a mixed response while two had progression. The patient treated with selumetinib plus paclitaxel in second line had stable disease. Progressive disease was recorded for the patients treated with trametinib in combination

Table 3
Treatments administered in the matched and unmatched cohorts.

Treatment type	First line	Second line	Third line	Fourth line	Fifth line
Matched patients ($n = 27$)					
Trametinib	13	4			
Crizotinib	6	1			
Cabozantinib	4				
Selumetinib	1				
Selumetinib/paclitaxel		1			
Trametinib/fotemustine	1		2		
Trametinib/hydroxychloroquine		1			
Trametinib/sorafenib				1	
Sorafenib	1				1
Palbociclib		1			
Olaparib/trabectedin			1		
Checkpoint inhibitors	1	2			
Unmatched patients ($n = 18$)					
Chemo-embolization	5	1	1		
Radio-embolization	3				
Chemosaturation		1			
Checkpoint inhibitors	1	1			
Tebentafusp	2				
Chemotherapy		1	1		
Hemihepatectomy	2				
Early progression	5				

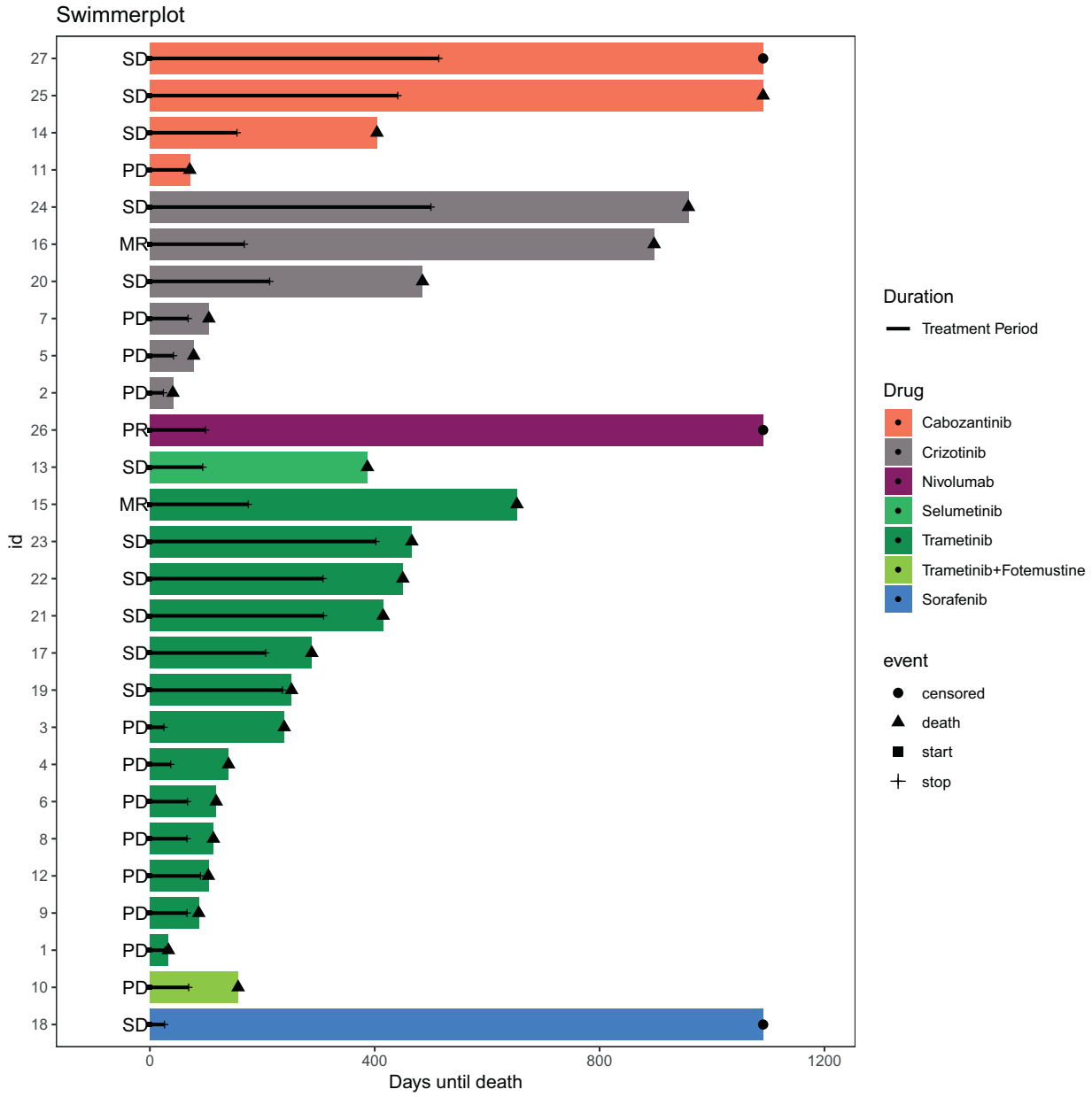

Fig. 2. Swimmer plot of first-line matched therapy MR, mixed response; PD, progressive disease; PR, partial response; SD, stable disease.

with either hydroxychloroquine (second line) or sorafenib (fourth line), and for the patient treated with olaparib plus trabectedin (third line).

After a median follow-up of 24.1 months, the median OS for all 45 patients was 12.5 months (95% CI 8.8–21.3, Fig. 3 A). OS did not differ significantly between the matched and unmatched cohorts (hazard ratio [HR] 0.82; 95% CI 0.4–1.57). In a univariate analysis of all patients, OS was significantly associated with LDH level, ECOG, *BCL2* overexpression, and *MYC* gain. In a multivariate analysis, LDH level and ECOG retained significance, while significant associations were also shown for *MET* overexpression (HR 0.33; 95% CI 0.12–0.95) and *BAP1* mutation (HR 3.14; 95% CI 1.10–8.92), with a borderline significant impact of *MYC* gain (HR 3.51; 95% CI 0.71–17.36) (Table 4). The median PFS for the matched therapy cohort was 3.3 months (95% CI 2.3–10.3) (Fig. 3B). In multivariate analyses, PFS was significantly associated with LDH level, alterations in cell cycle regulators, and *MYC* gain.

GMI, a measure of the clinical benefit in terms of tumor growth delay, was calculated in the subgroup of 17 patients who received chemotherapy or a checkpoint inhibitor before the matched therapy. Median GMI was 1.23 (range: 0.15–25) and six patients (35%) had a GMI >1.33, suggesting an advantage for the matched therapy in this subgroup. All six patients except one had a rapid progression (≤ 4 months) on previous chemotherapy

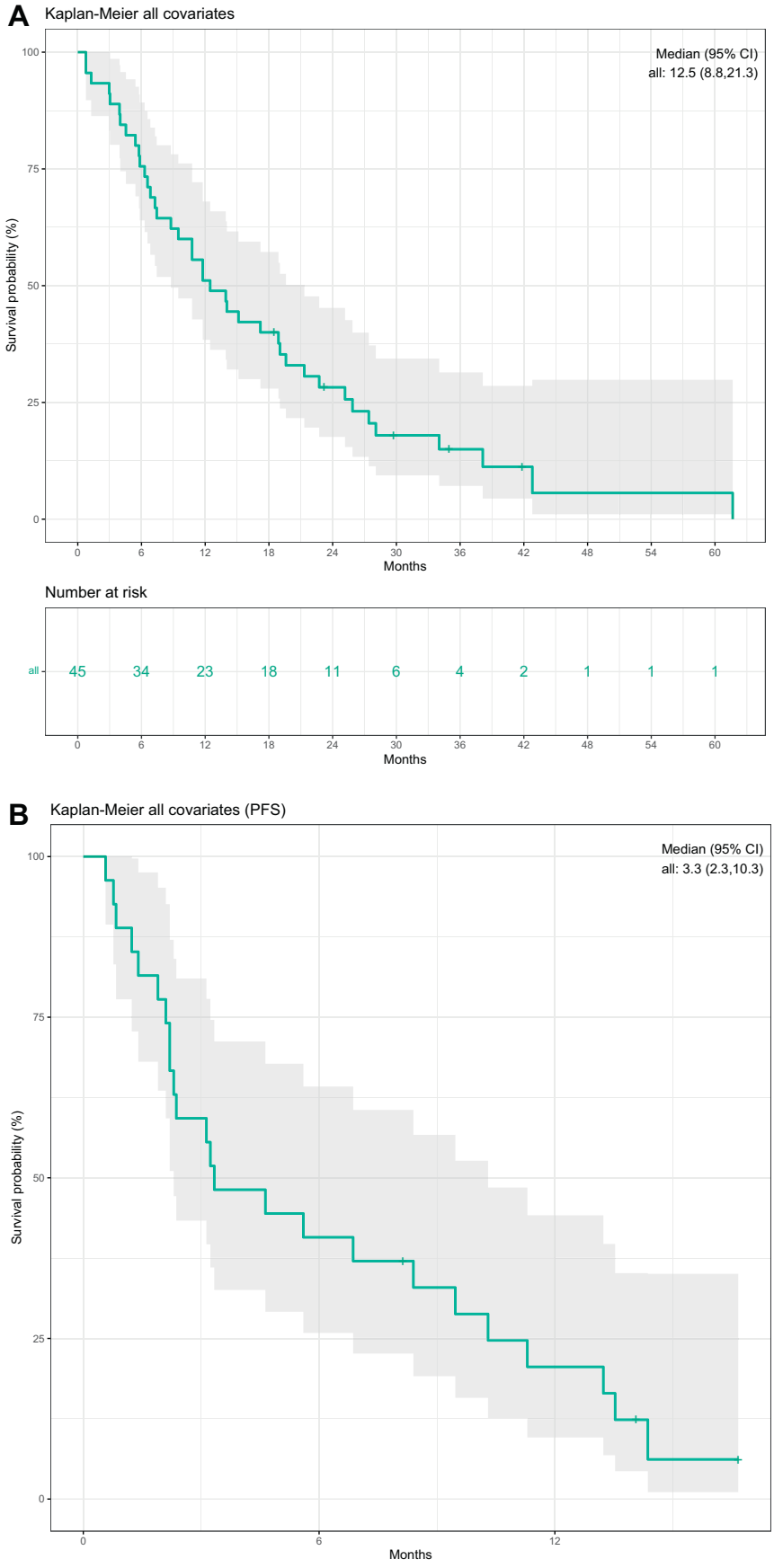

Fig. 3. A. OS for the whole population B. PFS in first line for patients receiving matched therapy Shaded area indicates the 95% CI. CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Table 4
Multivariate Cox regression analysis of OS for all patients using backward variable selection.

Factor	HR	*P*-value	Lower.95	Upper 0.95
BAP1 mutation	3.13	0.03	1.10	8.92
MYC gain	3.52	0.12	0.71	17.36
MET overexpression	0.34	0.004	0.12	0.95
ECOG PS	2.89	0.00	1.42	5.87
LDH	1.00	0.00	1.00	1.00

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; OS, overall survival.

(n = 3) or immunotherapy (n = 3). A GMI was >1.33 in 5/10 patients (50%) treated with trametinib and only 1/7 patients (14%) receiving a MET inhibitor.

4. Discussion

The outcome of metastatic uveal melanoma had not changed over the last 40 years [17], until the recent trial with the gp100-targeting immunotherapy tebentafusp limited to HLA-A0201 patients [5]. Treat20 Plus is the first prospective study of a biomarker-driven strategy for the treatment of metastatic uveal melanoma and demonstrates its feasibility in a routine clinical setting. With a median follow-up time of 24 months, 60% of patients were treated with a matched targeted therapy, with 22% and 7% receiving matched second- and third-line therapies, respectively. In large prospective studies of various types of hard-to-treat cancers, the feasibility of treatment matched according to somatic alterations was 13–20% [11,18]. In line with the present study, a patient-centered approach, considering the unique and complex genetic picture of each individual tumor, the proportion of patients treated with matched therapy was 62% [19].

Matched therapy was delivered within a clinical trial for two patients, while three patients received checkpoint inhibitors that are approved for the treatment of melanoma. The remaining patients were treated off-label with targeted therapies. MEK inhibitors were the most commonly prescribed monotherapy. It has been suggested that the antitumor activity of MEK inhibitors may be enhanced by combination with either chemotherapy [20] or other targeted therapies [21] or with hydroxychloroquine in preclinical models [22]. Considering the 42 matched therapies given across first to fifth lines, 57% of these included a MEK inhibitor, either as a single agent or in combination. The best response according to RECIST 1.1 criteria was disease stabilization for a median duration of 12 months, and two patients had a mixed response. Based on GMI evaluation in a subset of ten pretreated patients, the benefit could be demonstrated in five patients (50%). In phase II or III studies testing MEK inhibitors, the response rate remained low, at 3–14% [23,24]. Despite these low response rates, MEK inhibitors are recommended for use in the National Comprehensive Cancer Network guidelines [25]. Clinical trials are warranted to explore promising MEK inhibitor-containing combinations further [21].

MET overexpression was observed in 77% of patients, and MET/ALK inhibitors were administered in any line in 26% of patients, resulting in mixed response in one patient, stable disease in five patients, and progression in five patients. Only one patient had clinical benefit based on GMI of >1.33. Of note, crizotinib and cabozantinib did not demonstrate efficacy in trials in biomarker-unselected metastatic disease [26]. Tumors from both the patient with GMI >1.33 and the patient with a mixed response to a MET/ALK inhibitor also expressed the *ALK*ATI variant, which encodes a constitutively activated ALK receptor [27]. Two other *ALK*ATI-positive patients received crizotinib or cabozantinib without success. In cutaneous melanoma, *ALK*ATI has been proposed as a therapeutic target [28] and positive prognostic factor [29]. Although *ALK*ATI-positive patients appeared to have a more favorable outcome in the present study, the association was not significant in the univariate analysis.

Tumor mutational burden (TMB) has become a major factor in MiTB treatment recommendations [30]. Although uveal melanoma has a very low TMB that is more in the range of pediatric than adult tumors [7], four patients (9%) in the present study had a high TMB. Of these, two had a germline mutation in MBD4, a tumor suppressor gene involved in DNA repair. No other mutations were detected in mismatch repair or other DNA repair genes associated with immunotherapy response. In line with prior data [31,32], the two patients with MBD4 mutations responded to checkpoint inhibitors. One patient with high TMB had a prior response to checkpoint inhibition lasting 57 months, but developed a JAK1 mutation correlated with resistance at the time of enrollment [33]. A further patient with high TMB without MBD4 gene mutation had a transient partial response of a lung metastasis upon checkpoint inhibition before trial inclusion. Interestingly, this patient also had a SF3B1 mutation, which may predict response to checkpoint blockade [4,34].

Among all patients treated with matched therapies, median PFS was 3.3 months and median OS was 13.9 months, which did not differ significantly from 9.1 months in the unmatched cohort. These results are in line with those of other systemic therapies such as chemotherapy or checkpoint inhibitors [17].To evaluate the benefit of targeted therapies in this very heterogeneous population, we used the GMI as a complementary approach in a subgroup of patients previously treated with systemic therapy. GMI is now accepted by the European Medicines Agency as an endpoint for rare tumors and small studies [35]. Among the 17 previously

treated patients that were evaluated, 35% achieved a GMI of >1.33, which is consistent with other trials of targeted therapies [36].

The study used a comprehensive and integrative molecular analysis incorporating WES, WGS, and RNAseq, which allowed multiple druggable targets to be uncovered. However, at the clinical level, the recommendations for therapies were limited mainly to commercially available medications targeting a few alterations that could be approved for off-label use, with limited potential for combination therapies. In previous studies, the outcome of a precision oncology strategy in refractory tumors was linked to the targeting of multiple alterations (i.e., higher matching score) [19,37]. Preclinical models of uveal melanoma have shown greater activity of dual-targeting drug combinations compared with monotherapy [38–40].

The inhibition of autophagy by hydroxychloroquine has shown promise in other refractory tumors [41] and in preclinical uveal melanoma models [22]. Although the patient treated with a hydroxychloroquine combination in the present study had no clinical benefit, this strategy warrants further evaluation in a larger trial. More than 80% of tumors harbored *MYC* overexpression, which may sensitize to BET inhibition. The BET inhibitor JQ1 has shown positive results in a preclinical study [42], while the BET inhibitor mivebresib showed clinical activity in patients with uveal melanoma in a phase I study [43].

In conclusion, this study demonstrates the feasibility of a precision oncology approach for patients with metastatic uveal melanoma in routine clinical practice and highlights the benefit of tumor mutational burden testing. The greatest clinical benefit was obtained with checkpoint inhibitors in patients with a high tumor mutational burden. A subset of patients could also benefit from MEK inhibition, but further studies should focus on combination therapies that target multiple activating mutations.

Author contributions

Conception and design: **RS, MLY, UK**.

Development of methodology: **MS, TK, SB, RS, FK**.

Acquisition of data: **SL, CP, SO, GD, ML, DTR, KK, SB, CU, GP, AHJ**.

Analysis and interpretation of data: **SL, FK, MD, EDS, GD, DTR**.

Writing, review, and/or revision of the manuscript: **SL, FK, GD, DTR, MLY, UK**.

Study supervision: **SL, MLY, UK**.

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Conflict of interest statement

SL reports travel and advisory board support from Immunocore and Bayer.

CP reports speaker honoraria from Bristol-Myers Squibb, Novartis, Daiichi-Sankyo, EUSA Pharma and Sirtex Medical and advisory honoraria from EUSA Pharma.

MS is employee of Alacris Theranostics.

TK is employee of Alacris Theranostics.

SO reports consultancy fees from Astra Zeneca, Bristol-Myers Squibb, Janssen Biotech, Merck.

DTR reports Honoraria from Lilly, Bristol-Myers Squibb and Advisory Honoraria from Bayer and Alacris Theranostics.

KK reports advisory board and conference honoraria from Merck, Sanofi, Merck Sharp & Dohme, Glycotope, Roche, Novartis and Bristol-Myers Squibb.

CU reports consulting fees from Sanofi, grant for educational activities form Galderma, Beiresdorf and Almirall.

GP reports consulting fees and grant for educational activities from Amgen. Novartis, Sun Pharma.

Bristol-Myers Squibb, Merck Sharp & Dohme.

FK is co-founder of Aignostics GmbH and has received consulting support from Roche, Novartis, Bristol-Myers Squibb, Lilly, Agilent and Iomedico.

AJ reports Consultant fees from Novartis, Roche, Boehringer, Allergan, Bayer.

MLY is an employee and shareholder of Alacris Theranostics.

UK reports consulting fees for Merck Sharp & Dohme, travel support from Merck Serono, Pfizer, grant for educational activities from Merck Serono, Bristol-Myers Squibb, Pierre-Fabre.

FK, MD, ES, GD, ML, SB, RS have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.04.004.

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