



Treatment sequence with tebentafusp and immune checkpoint inhibitors in patients with metastatic uveal melanoma and metastatic *GNA11*/*GNAQ* mutant melanocytic tumors

Florentia Dimitriou^{a,b,*}, Marlana M. Orloff^c, Erica C. Koch Hein^{d,e,f}, Phil F. Cheng^g, Isaac F. Hughes^h, Ester Simeoneⁱ, Kamaneh Montazeri^j, Piyush Grover^{k,l}, Inderjit Mehmi^m, Camille L. Gerardⁿ, Caroline Gaudy-Marqueste^o, Jean-Jacques Grob^o, Olivier Michielin^g, Omid Hamid^m, Georgina V. Long^{k,l,p,q}, Ryan Sullivan^j, Ellen Kapiteijn^r, Douglas B. Johnson^s, Paolo A. Asciertoⁱ, Anthony M. Joshua^t, Richard D. Carvajal^h, Marcus O. Butler^{d,e}, Jessica C. Hassel^u, Reinhard Dummer^{a,b}

^a Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland

^b Faculty of Medicine, University of Zurich, Zurich, Switzerland

^c Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA

^d Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

^e Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Departments of Medicine and Immunology, University of Toronto, Toronto, Canada

^f Department of Hematology and Oncology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

^g Department of Oncology, Geneva University Hospital, Geneva, Switzerland

^h Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY, USA

ⁱ Istituto Nazionale Tumori IRCCS Fondazione G Pascale, Napoli, Italy

^j Massachusetts General Hospital, Harvard Medical School, Boston, USA

^k Melanoma Institute Australia, The University of Sydney, Sydney, New South Wales, Australia

^l Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

^m The Angeles Clinic and Research Institute, a Cedars Sinai Affiliate, Los Angeles, CA, USA

ⁿ Precision Oncology Center, Lausanne University Hospital (CHUV), Lausanne, Switzerland

^o Dermatology and Skin Cancer Department, Aix-Marseille University, Marseille, France

^p Department of Medical Oncology, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

^q Charles Perkins Centre, The University of Sydney, Camperdown, Australia

^r Department of Medical Oncology, Leiden University Medical Centre, Leiden, the Netherlands

^s Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA

^t Department of Medical Oncology, Kinghorn Cancer Centre, St Vincent's Hospital Sydney and Garvan Institute of Medical Research, Sydney, New South Wales, Australia

^u Heidelberg University, Medical Faculty Heidelberg, Department of Dermatology and National Center for Tumor Diseases (NCT), NCT Heidelberg, a partnership between DKFZ and University Hospital Heidelberg, Heidelberg, Germany

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ABSTRACT

Background: Metastatic uveal melanoma (mUM) is rare. Immune checkpoint inhibitors (ICIs) have shown modest efficacy in mUM. Tebentafusp prolonged overall survival (OS) in a phase 3 study. We aimed to investigate the efficacy and safety of the sequence of tebentafusp and ICIs.

Methods: Patients with HLA-A * 02:01 positive mUM, or metastatic *GNA11*/*GNAQ* mutant melanocytic tumors treated with tebentafusp followed by ICIs (group 1) or the inverse sequence (group 2) at any treatment line were retrospectively identified. The primary objective was OS rate at 2 years.

Results: 131 patients were included; 51 in group 1 and 80 in group 2. 30 % in group 1 % and 40 % in group 2 had normal baseline lactate dehydrogenase (LDH, $p = 0.05$). 94 % in group 1 % and 77 % in group 2 had multilobular liver disease ($p = 0.02$). Median OS was 22.4 months (95 % CI 19–24.8) in group 1 and 33.6 months (95 % CI 28.9–43) in group 2 ($p = 0.004$). Total median PFS was 12 months (95 % CI 10.7–18.8) in group 1 and 20.3

* Correspondence to: Department of Dermatology, University Hospital of Zurich, Raemistrasse 100, 8091 Zurich, Switzerland.

E-mail address: florentia.dimitriou@usz.ch (F. Dimitriou).

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months (95 % CI 17.2–27.3) in group 2 ($p = 0.04$). The frequency of cytokine release syndrome was higher in group 2 (15 % vs 27 %). Other clinical factors were associated with short total PFS in the multivariable analysis. **Conclusions:** Both treatment sequences are clinically feasible. A clinical benefit was noted in the sequential combination of ICIs followed by tebentafusp. This observation is limited by the retrospective nature of the study and merits further investigation in prospective clinical trials.

1. Introduction

Uveal melanoma (UM) is a rare melanoma subtype that accounts for up to 5 % of all melanomas [1]. Approximately 50 % of patients with UM develop metastatic disease, with the liver being the most frequent site of distant metastatic involvement [2]. Metastatic uveal melanoma (mUM) is associated with poor prognosis [3] and historical data indicate a median overall survival (OS) ranging from 6 to 12 months [4,5]. This poor prognosis is partially attributed to the lack of effective available treatments as well as to its distinct biology; in contrast to cutaneous melanoma (CM), nearly all cases of UM harbor oncogenic driver mutations in *GNA11* or *GNAQ* genes [6], whereas secondary oncogenic events in *BAP1*, *SF3B1* and *EIFAX1* are also mutually exclusive [7]. Furthermore, UM is less immunogenic, as it is characterized by the lowest tumor mutational burden (TMB) of all malignancies, and by a low expression of PD-L1 in the tumor microenvironment (TME) in both primary and metastatic sites [8–10].

Immune checkpoint inhibitors (ICIs) have shown limited treatment efficacy in mUM and the survival benefit that has been observed in CM has not been confirmed in mUM [11–14]. Studies with single-agent anti-PD1 [13], or ipilimumab [15] have shown that a small percentage of patients benefits from these treatments, and these results are limited by the number of patients included. In contrast to CM [16], treatment combination with ipilimumab/nivolumab resulted in a marginal effect on survival in two phase 2 clinical trials in mUM, with median progression-free survival (mPFS) ranging between 3 and 5.5 months and median overall survival (mOS) from 12.7 to 19.1 months [17,18]. Recently, tebentafusp, a first-in-class immune mobilizing T-cell receptor (TCR) bispecific fusion protein that targets a gp100 peptide presented by HLA-A* 02:01, and an anti-CD3 T-cell engaging domain, improved survival in patients with previously untreated mUM [19]. In the updated results from the phase 3 clinical trial with a minimum follow-up of 36 months, tebentafusp showed a sustained long-term benefit with mOS of 21.6 months compared to 16.9 months in the control group [HR of 0.68 (95 % CI 0.54–0.87)] [20]. Notably, tebentafusp has demonstrated a substantial clinical activity in previously treated patients as well, with 1-year OS rate of 62 % (95 % CI 53–70 %) and a mOS of 16.8 months (95 % CI 12.9–21.3), despite an overall response rate (ORR) of 5 % [21]. This decoupling of ORR and survival benefit was also observed in the phase 3 study, in which patients with progressive disease (PD) as best overall response (BOR) derived clinical benefit that extended beyond the radiological disease assessment and resulted in prolongation of the OS rates (mOS 15.3 vs 6.5 months, HR 0.43) [19]. These observations with tebentafusp treatment have been prompting efforts to identify novel biomarkers for clinical activity that correlate with the OS rates.

Translational studies further indicate that tebentafusp increases tumor T-cell trafficking, which may persist even after treatment cessation and can contribute to the treatment benefit that is derived beyond radiological progression [22,23]. This higher T-cell infiltration in the TME may result in an upregulation of immune checkpoints that could subsequently synergize with the tebentafusp treatment, thus sensitizing tumors that are ICI resistant. In fact, more than 70 % of the patients in the phase 3 study were treated beyond radiographic progression, and early data on tebentafusp in combination with durvalumab (anti-PD1) and/or tremelimumab (anti-CTLA4) in previously treated, advanced stage CM patients indicate a treatment efficacy with ORR of 14 % and 1-year OS rate of 76 % (95 % CI 70–81 %) [24]. Despite these data

suggesting an enhanced effect of tebentafusp with ICIs, the optimal combination or sequencing of these treatments is unknown. Moreover, the effect of subsequent systemic therapies on the OS rate in patients that have progressed to tebentafusp has not yet been reported.

In the present study, we aimed to investigate the efficacy and safety of the sequence of tebentafusp followed by ICIs and/vs the inverse sequence in patients with mUM. We further assess clinical factors that affect survival and have the potential to guide clinical decision making for patients with advanced UM. Importantly, this cohort also includes three cases of metastatic *GNA11*/*GNAQ* mutant melanocytic tumors that were treated with the above-mentioned sequence and are known to have strong morphological similarities to UM [25].

2. Methods

2.1. Study population

Patients with histologically confirmed mUM, or metastatic *GNA11*/*GNAQ* mutant melanocytic tumors, who were treated with immunotherapy, including ICIs (anti-PD1, anti-CTLA4 or combination anti-PD1/anti-CTLA4) and tebentafusp at 14 sites in Europe, USA, Canada and Australia. Included patients received tebentafusp followed by treatment switch to ICIs at disease progression (**group 1**) or the inverse sequence (**group 2**) at any treatment line. Eligible patients were HLA-A * 02:01 positive and had received at least one dose of systemic therapy with available radiological response assessment prior to treatment switch. Patients receiving tebentafusp were treated as part of a clinical trial (NCT03070392), or through an early access program (NCT04960891), or as standard-of-care. Patients with experimental treatment combinations other than tebentafusp, anti-CTLA4 and anti-PD-1 ± anti-CTLA4 were excluded. Prior systemic therapies in the adjuvant or advanced setting were included. No other inclusion or exclusion criteria were used in the patient selection. The study was approved by the local institutional ethics review boards.

2.2. Data collection, safety and response assessment

Clinical data were extracted from medical records. Patient demographics and baseline blood parameters [including lactate dehydrogenase (LDH), alanine transaminase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT)] at the time of commencing of tebentafusp and ICIs, respectively, and at treatment switch were retrospectively collected and analyzed. Disease characteristics, including Eastern Cooperative Oncology Group performance status (ECOG PS), sites and number of metastatic disease and liver-directed treatments were additionally collected. Tumor response was assessed at regular time intervals as per standard of care and according to each institution's protocols. Response was determined based on RECIST version 1.1 [26], according to the radiological response assessment, which was retrospectively abstracted from medical notes. Safety assessments were done continuously during treatment. Treatment-related adverse events (AEs) were collected and graded by the treating physician. The severity of AEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 [27]. Cytokine release syndrome (CRS) was evaluated and graded according to the 2019 recommendations of the American Society for Transplantation and Cellular Therapy (ASTCT) [28]. AEs of special interest included immune-related rash, hepatitis and colitis during

treatment with ICIs and rash, liver toxicity and CRS during treatment with tebentafusp.

2.3. Outcomes

The primary objective of the study was to investigate the OS rate at 2 years. Other objectives included investigation of total progression-free survival (tPFS), defined as the time from first-line treatment initiation to second-line treatment disease progression, BOR, ORR, disease control rate (DCR), and 3-year survival rates. ORR was defined as the proportion of patients with complete (CR) or partial response (PR). DCR was defined as the proportion of patients with CR, PR, and stable disease (SD). OS was defined as the time from treatment start to death or last follow-up.

2.4. Statistical analysis

Descriptive statistics are presented as percentages of total for categorical variables and as median for continuous and ordinal variables. Baseline characteristics were compared using the Wilcoxon rank-sum test for continuous variables and Fisher’s exact test was used for categorical variables when the expected count per cell was more than five. ORR was assessed as the proportion in each treatment group (group 1 and group 2). Survival curves were estimated using the Kaplan–Meier method with censoring on the last known date alive. The log-rank test was used to compare PFS and OS according to each treatment group. Univariable and multivariable analyses were used to evaluate the independent effect of selected clinical parameters on PFS and OS, controlling for potential cofounders. Cox regression was used to calculate hazard ratios (HRs) of covariates for OS and PFS. A *p* value < 0.05 was considered as statistically significant. All statistical analyses were done in R (version 4.3, Foundation, Vienna, Austria).

3. Results

3.1. Patient and treatment characteristics

A total of 131 HLA-A * 02:01 positive patients with mUM from 14 sites in eight countries were identified and included in the study; 51 patients with disease progression during treatment with tebentafusp were then switched to ICI-treatment (group 1) and 80 patients with disease progression during treatment with ICIs were then treated with tebentafusp (group 2). The baseline disease characteristics were similar for both groups; a significant difference was noted in the presence of unilobular or multilobular liver disease (*p* = 0.02). Besides, 15 (30 %) patients in group 1 and 32 (40 %) patients in group 2 had LDH < ULN at the baseline (*p* = 0.05). The baseline characteristics are summarized in Table 1. Mutational status was tested in 60/131 (46 %) patients in both groups. The most common mutations in group 1 were *GNAQ* (*n* = 12, 24 %), followed by *GNA11* (*n* = 9, 18 %). Of those tumors with available mutation information in group 2, 19/80 (24 %) had a *GNA11* mutation and 16/80 (20 %) had a *GNAQ* mutation. Seventy-nine patients (60 %), 30/51 (59 %) in group 1 and 49/80 (61 %) in group 2, were treatment naïve for their metastatic disease, while most of the remaining patients were treated with one or two prior systemic treatment lines. ICI treatment included combination anti-PD1/anti-CTLA4 in 41/51 (80 %) and 50/80 (63 %) patients of group 1 and group 2, respectively. Other treatment regimens were single-agent anti-PD1 (18 % in group 1 % and 26 % in group 2) and single-agent anti-CTLA4 (2 % in group 1 % and 11 % in group 2). At the time of the first treatment initiation, 34/51 (67 %) patients in group 1 and 62/80 (78 %) patients in group 2 were of ECOG PS 0. Twenty-two out of 51 (43 %) patients in group 1 and 13/80 (16 %) patients in group 2 had a baseline elevated LDH and most patients had stage IV M1a or M1b disease (76 % and 76 % for group 1 and group 2, respectively).

The median duration of tebentafusp treatment was 24 weeks (range

Table 1
Baseline characteristics at first treatment initiation.

Characteristic	Group 1 N = 51	Group 2 N = 80	<i>p</i> -value ^c
Sex			0.9
Female	25 (49 %)	39 (49 %)	
Male	26 (51 %)	41 (51 %)	
Age (years)			0.6
Median (range)	54 (18–80)	53 (16–74)	
ECOG performance status			0.9
0	34 (67 %)	62 (78 %)	
1–2	9 (18 %)	14 (18 %)	
Unknown	8 (16 %)	4 (5 %)	
Mutation status^a			0.6
<i>GNAQ</i> mutant	12 (24 %)	16 (20 %)	
<i>GNA11</i> mutant	9 (18 %)	19 (24 %)	
<i>SF3B1</i> mutant	2 (4 %)	4 (5 %)	
<i>BAP1</i> mutant	9 (18 %)	16 (20 %)	
Unknown	28 (55 %)	43 (54 %)	
ICI type			0.2
Anti-PD1/Anti-CTLA4	41 (80 %)	50 (63 %)	
Anti-PD1	9 (18 %)	21 (26 %)	
Anti-CTLA4	1 (2 %)	9 (11 %)	
Baseline LDH			0.05
Normal	15 (30 %)	32 (40 %)	
Elevated < 2.5 × ULN	16 (32 %)	11 (14 %)	
Elevated ≥ 2.5 × ULN	6 (12 %)	2 (3 %)	
Unknown	14 (27 %)	35 (44 %)	
Baseline GGT			0.4
Normal	6 (12 %)	19 (24 %)	
Elevated ≥ ULN	5 (10 %)	7 (9 %)	
Unknown	40 (78 %)	54 (68 %)	
Baseline ALP			0.07
Normal	28 (56 %)	39 (49 %)	
Elevated ≥ ULN	9 (18 %)	7 (9 %)	
Unknown	14 (27 %)	34 (43 %)	
Number of organs involved			0.4
1	29 (57 %)	53 (66 %)	
2–3	16 (31 %)	17 (21 %)	
≥ 4	6 (12 %)	10 (13 %)	
Site of metastatic disease			0.7
Hepatic only	28 (55 %)	49 (61 %)	
Extrahepatic only	3 (6 %)	6 (8 %)	
Both	20 (39 %)	25 (31 %)	
Liver disease			0.02
Unilobular	3 (6 %)	16 (22 %)	
Multilobular	45 (94 %)	57 (77 %)	
Unknown	-	1 (1 %)	
Extrahepatic disease^b			0.7
Lung metastases	12 (24 %)	16 (20 %)	
Bone metastases	10 (20 %)	13 (16 %)	
Brain metastases	2 (4 %)	5 (6 %)	
Soft tissue metastases	9 (18 %)	14 (18 %)	
Nodal metastases	5 (10 %)	7 (8 %)	
Size of the biggest liver metastasis			0.8
≤ 3 cm	23 (48 %)	32 (43 %)	
> 3 cm and ≤ 8 cm	8 (17 %)	10 (14 %)	
> 8 cm	3 (6 %)	2 (3 %)	
Unknown	14 (29 %)	30 (41 %)	
M1 metastatic stage (AJCC, 8th edition)			0.5
M1a (largest diameter, ≤ 3.0 cm)	28 (55 %)	48 (60 %)	
M1b (largest diameter, 3.1–8.0cm)	11 (21 %)	13 (16 %)	
M1c (largest diameter, ≥ 8.1 cm)	5 (10 %)	5 (6 %)	
M1 (distant metastases/no further information available)	7 (14 %)	14 (18 %)	
Prior lines of treatment			0.9
0	30 (59 %)	49 (61 %)	
1–2	18 (35 %)	27 (34 %)	
≥ 3	2 (4 %)	3 (4 %)	
Unknown	1 (2 %)	1 (1 %)	

Group 1: Includes patients treated with the treatment sequence of tebentafusp, followed by immune checkpoint inhibitor.

Group 2: Includes patients treated with the treatment sequence of immune checkpoint inhibitor, followed by tebentafusp.

Abbreviations: LDH, lactate dehydrogenase; GGT, gamma-glutamyl transpeptidase; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of

normal; ALP, alkaline phosphatase; AJCC, American Joint Committee on Cancer; ICI, immune checkpoint inhibitor.

^a More than one mutations were present in a proportion of patients.

^b Includes involvement of more than one metastatic organs in a proportion of patients.

^c Fisher's exact test; Wilcoxon rank sum test; Pearson's Chi-squared test.

1–201) in group 1 and 34 weeks (range 1–171) in group 2. The median duration of ICI treatment was 9 weeks (range 1–200) in group 1 and 9 weeks (range 1–420) in group 2. The primary reason for treatment discontinuation in group 1 was disease progression [ICI: 38/51 (75 %); tebentafusp: 46/51 (90 %)], followed by toxicity [ICI: 6/51 (12 %); tebentafusp: 3/51 (6 %)]. Similarly, primary reason for treatment discontinuation in group 2 was disease progression [ICI: 51/80 (63 %); tebentafusp: 58/80 (72 %)], followed by toxicity [ICI: 21/80 (26 %); tebentafusp: 2/80 (2 %)]. Baseline treatment characteristics at the time of the second treatment initiation are summarized in [Supplementary Table 1](#). The median time between the two treatments was 0.7 (0.7–8.1) months in group 1 and 4.4 (range 10–38) months in group 2. At the data cut-off date, 82/131 (63 %) patients were deceased; 34/51 (67 %) in group 1 and 48/80 (60 %) in group 2. Primary cause of death was melanoma progression in 80 out of 81 deceased patients.

3.2. Treatment efficacy

Median follow-up (mFU) was 45.4 months (range 26–NR) for group 1 and 43.8 months (range 34–63) in group 2. Response and survival rates are summarized in [Table 2](#). Median OS was 22.4 months (95 % CI 19–24.8) in group 1 and 33.6 months (95 % CI 28.9–43) in group 2 ($p = 0.004$) ([Fig. 1](#)), thus favoring the treatment sequence of ICI followed by tebentafusp. The percentage of patients who were surviving at 2 years among those treated with tebentafusp followed by ICI (group 1) was 33 %, and the respective percentage in those treated by ICIs followed by tebentafusp (group 2) was 70 %. Total mPFS was 12 months (95 % CI 10.7–18.8) in group 1 and 20.3 months (95 % CI 17.2–27.3) in group 2 ($p = 0.04$) ([Fig. 2](#)). The 1- and 2-year landmark tPFS rates were 50 % and 30 % in group 1 % and 81 % and 42 % in group 2, respectively. Median PFS for tebentafusp was 3.2 months (95 % CI 2.7–5.6) in group 1 and 4.9 months (95 % CI 3.6–10.1) in group 2 ($p = 0.084$) ([Supplementary](#)

[Fig. 1](#)). Median PFS for ICI was 2.7 months (95 % CI 2.2–3.1) in group 1 and 5.1 months (95 % CI 2.8–5.9) in group 2 ($p = 0.7$) ([Supplementary Fig. 2](#)). The percentage of patients treated with tebentafusp that had an objective response was 8 % in group 1 % and 8 % in group 2. In the ICI treatment, ORR was achieved in 12 % of patients in group 1 % and 8 % of patients in group 2. A greater percentage of patients achieved disease control; DCR for the tebentafusp treatment was 47 % in group 1 % and 51 % in group 2. DCR was higher for the ICI treatment in group 2, compared to group 1 (45 % vs 25 %, respectively).

Cox proportional hazard regression analysis with inverse proportional treatment weights using age, sex, baseline LDH and time between treatments was performed to adjust for confounding factors for the total PFS and OS rates. Adjusted total mPFS was 22.9 months (95 % CI 9.4–24.8) in group 1 and 34.7 months (95 % CI 23.1–41.6) in group 2 (HR 0.68, $p < 0.01$) ([Supplementary Fig. 3](#)). Similarly, adjusted OS was 13.4 months (95 % CI 7.6–24.7) in group 1 and 17.2 months (95 % CI 13.5–30) in group 2 (HR 0.70, $p = 0.04$) ([Supplementary Fig. 4](#)).

3.3. Treatment efficacy in metastatic GNA11/GNAQ mutant melanocytic tumors

Three patients from group 2 were diagnosed with metastatic GNA11/GNAQ mutant melanocytic tumors; two of these patients had an additional secondary oncogenic event of BAP1 inactivation. Primary disease involvement included the central nervous system (CNS) with leptomeningeal and brain metastases in two patients. The third patient presented with liver and soft tissue metastases from a cutaneous melanoma primary. Patient characteristics are summarized in [Supplementary Table 2](#). Indications for systemic treatment initiation was symptomatic CNS involvement and/or metastatic disease with radiologic progression. BOR at the first treatment with ICIs was PD for the two patients and SD for the third patient with brain involvement. BOR at the second treatment with tebentafusp was SD for the two patients and PD for the third patient. Total PFS was 14.1, 46 and 23 months for the three patients, respectively. At the time to the data cut-off, all patients were alive.

Table 2

Response and survival rates in group 1 and group 2.

	Group 1			Group 2		
	Total N = 51	Pre-PD (tebentafusp)	Post-PD (ICI)	Total N = 80	Pre-PD (ICI)	Post-PD (tebentafusp)
ORR, n/N %	NA	4 (8 %)	6 (12 %)	NA	6 (8 %)	6 (8 %)
DCR, n/N %	NA	24 (47 %)	13 (25 %)	NA	36 (45 %)	41 (51 %)
Best overall response (BOR)						
CR	NA	0	0	NA	2 (3 %)	0
PR	NA	4 (8 %)	6 (12 %)	NA	4 (5 %)	6 (8 %)
SD	NA	20 (39 %)	7 (14 %)	NA	30 (38 %)	35 (44 %)
PD	NA	25 (49 %)	31 (61 %)	NA	40 (50 %)	37 (46 %)
PFS						
Median, months (95 % CI)	12 (10.7–18.8)	3.2 (2.7–5.6)	2.7 (2.2–3.1)	20.3 (17.2–27.3)	5.1 (2.8–5.9)	4.9 (3.6–10.1)
1-year PFS rate	50 %	15 %	19 %	81 %	16 %	31 %
2-year PFS rate	30 %	4 %	10 %	42 %	5 %	10 %
3-year PFS rate	18 %	2 %	10 %	25 %	4 %	4 %
OS						
Median, months (95 % CI)	22.4 (19–24.8)	NA	NA	33.6 (28.9–43)	NA	NA
1-year OS rate	83 %	NA	NA	90 %	NA	NA
2-year OS rate	33 %	NA	NA	70 %	NA	NA
3-year OS rate	27 %	NA	NA	43 %	NA	NA
Treatment duration						
Median, weeks (range)	NA	24 (1–201)	9 (1–200)	NA	9 (1–420)	34 (1–171)
Follow-up						
Median, months (range)	45.4 (26–NR)	NA	NA	43.8 (34–63)	NA	NA

Group 1: Includes patients treated with the treatment sequence of tebentafusp, followed by immune checkpoint inhibitor.

Group 2: Includes patients treated with the treatment sequence of immune checkpoint inhibitor, followed by tebentafusp.

Abbreviations: ORR, overall response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NR, not reached.

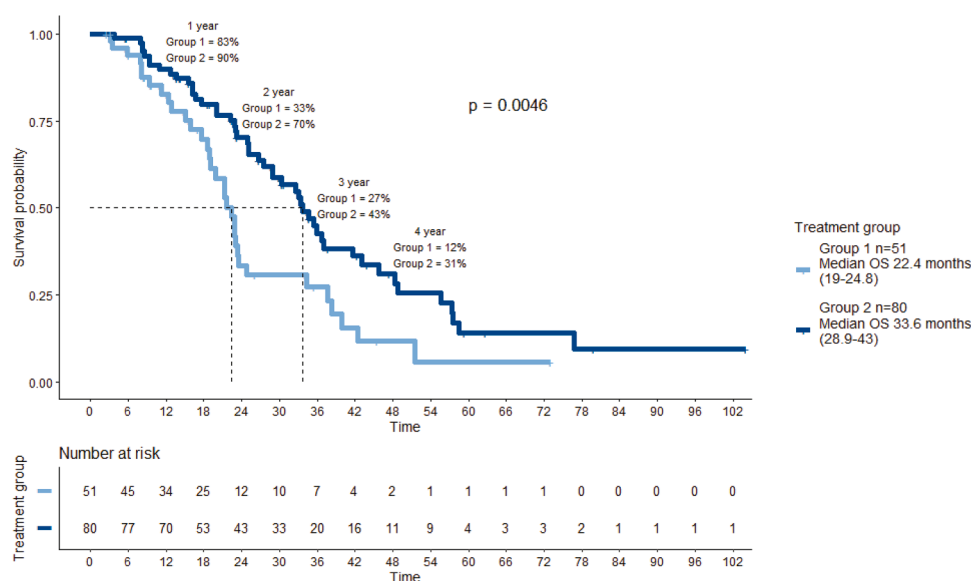


Fig. 1. Kaplan–Meier curve for overall survival (OS) in patients treated with tebentafusp followed by treatment switch to immune checkpoint inhibitors (ICIs) at disease progression (group 1) compared with the inverse sequence (group 2).

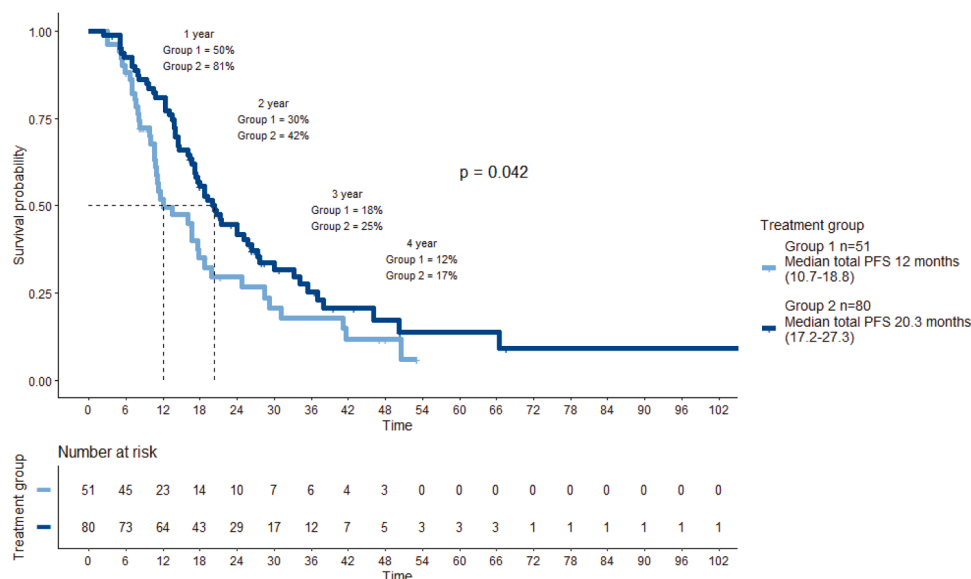


Fig. 2. Kaplan–Meier curve for total progression-free survival (tPFS), defined as the time from first-line treatment initiation to second-line treatment disease progression, in patients treated with tebentafusp followed by treatment switch to immune checkpoint inhibitors (ICIs) at disease progression (group 1) compared with the inverse sequence (group 2).

3.4. Treatment efficacy after disease progression

The dynamics of the BOR rates for the first and the second treatment are presented in [Supplementary Fig. 5](#). In patients with tebentafusp-refractory disease in group 1 (BOR, PD), subsequent treatment with ICI resulted in an ORR of 4 % and DCR of 10 %; in a significant proportion of patients, ICI did not result in a substantial clinical activity and BOR remained PD in 29 % of the patients. Similarly, in patients with ICI-refractory disease in group 2, tebentafusp treatment resulted in an ORR of 4 % and DCR of 21 %, whereas 26 % of the patients continued to have PD as BOR.

Notably, liver-directed treatment upon disease progression did not have an effect on the OS outcomes of the second treatment. In group 1, 15/51 (29 %) patients received liver-directed treatment after progression to tebentafusp and before the treatment initiation of ICIs

([Supplementary Table 1](#)). Liver-directed therapies included surgery (n = 1), radiotherapy (n = 6), chemoembolization (n = 4) or both surgery and radiotherapy (n = 4). Correspondingly, liver-directed therapy was administered in 28/80 (35 %) of patients in group 2 after disease progression to ICIs and prior to the treatment initiation of tebentafusp. In this group, liver-directed treatments included surgery (n = 2), radiotherapy (n = 10), surgery and radiotherapy (n = 1), chemoembolization (n = 4), immunoembolization (n = 5) and other (n = 6). In both treatment groups, mOS did not significantly differ in the subgroup of patients with liver-directed therapy compared to those without ([Supplementary Fig. 6 and 7](#)).

3.5. Safety and adverse events

In patients treated with combination ipilimumab and nivolumab,

completion of all four induction cycles occurred in 10/51 (20 %) of patients in group 1 and 21/80 (26 %) in group 2. Median number of infusions received for the induction and the maintenance part was 4 (range 1–16) in group 1 and 4 (range 1–50) in group 2. For all patients treated with ICIs, treatment-related adverse events (TRAEs) of any grade occurred in 51 % of patients in group 1 % and 66 % of patients in group 2 (Supplementary Table 3). Severe, grade ≥ 3 TRAEs occurred with a frequency of 14 % and 29 % for the two groups, respectively. The most frequent TRAEs were rash (group 1, 18 %; group 2, 15 %), hepatitis (group 1, 18 %; group 2, 19 %), colitis (group 1, 18 %; group 2, 26 %) and thyroiditis (group 1, 14 %; group 2, 20 %). Colitis was the most common grade ≥ 3 TRAEs in group 1 (6 %) and group 2 (14 %).

For the tebentafusp treatment, median number of infusions received was 20 (range 2–151) in group 1 and 21 (range 1–132) in group 2 (Supplementary Table 4). TRAEs of any grade occurred in 96 % and 88 % of the patients in group 1 and 2, respectively. The most common TRAEs of any grade were either cytokine mediated or skin related. Of note, the frequency of CRS was higher in group 2 (27 %), compared with group 1 (15 %). Other TRAEs included rash (group 1, 39 %; group 2, 43 %), liver toxicity (group 1, 9 %; group 2, 5 %) and fever (group 1, 5 %; group 2, 6 %). Severe, grade ≥ 3 TRAEs occurred with a frequency of 22 % and 15 % for the two groups, respectively. Liver toxicity (group 1, 10 %; group 2, 8 %) and rash (group 1, 8 %; group 2, 3 %) were the most common severe, grade ≥ 3 TRAEs.

3.6. Univariable and multivariable analysis for tPFS and OS rate

Univariable Cox regression analysis showed that treatment sequence of ICI followed by tebentafusp (HR 0.66 95 % CI 0.44 – 0.99, $p < 0.05$) was associated with long tPFS rate, whereas M1b or M1c disease stage (HR 1.72 95 % CI 1.08–2.75, $p = 0.02$) was associated with short tPFS rate (Supplementary Table 5). Similarly, treatment sequence of ICI followed by tebentafusp (HR 0.53 95 % CI 0.33–0.83, $p < 0.01$) was associated with long OS rate in the univariable Cox regression analysis, whereas M1b or M1c disease stage (HR 2.25 95 % CI 1.35–3.75, $p < 0.01$) and LDH $>ULN$ at baseline (HR 1.98 95 % CI 1.11–3.52, $p = 0.02$) were associated with short OS rate (Supplementary Table 6). Multivariable analysis demonstrated that LDH $> ULN$ at baseline (HR 37.16, 95 % CI 1.76 – 783.05, $p = 0.02$), number of organs involved ≥ 2 (HR 19.26, 95 % CI 1.62 – 229.5, $p = 0.01$) and one prior systemic treatment (HR 9.55, 95 % CI 1.44 – 63.52, $p = 0.02$) were significantly associated with short tPFS rate (Fig. 3). None of these factors was significantly associated with a short OS rate in the multivariable analysis

(Fig. 4).

4. Discussion

MUM is a rare melanoma subtype that is associated with dismal prognosis [29]. Although ICIs have changed the treatment landscape in advanced CM, ipilimumab in combination with nivolumab yielded a marginal improvement in the PFS and OS rates in two phase 2 clinical trials in mUM [17,18]. Tebentafusp is the first drug to significantly prolong OS compared to investigator’s choice in a randomized, phase 3 clinical trial in treatment-naïve, HLA-A * 02:01 positive patients with mUM. Results from translational studies, as well as early phase clinical trials, support a possible enhanced effect of tebentafusp when combined with ICIs. Nevertheless, the optimal combination or sequencing of ICIs and tebentafusp in mUM is not known. The results of this study indicate that both treatment sequences are clinically feasible. The treatment sequence of ICIs followed by treatment switch to tebentafusp at disease progression resulted in longer mOS compared to the inverse sequence, although there were notable differences in the baseline characteristics of the two groups which could impact the survival. The landmark 2-year OS rate was in favor to the treatment sequence of ICIs followed by tebentafusp, and this clinical benefit was also evident for other efficacy endpoints, including the mPFS and the tPFS rate. Nevertheless, this observation displays several limitations; there is a premise that a switch to ICIs after progression on tebentafusp is still clinically feasible and that tebentafusp is available as a treatment choice in pretreated patients. In fact, the median time between the two treatments was longer in group 2 than in group 1 (4.4 vs 0.7 months), which precludes patients with dismal disease characteristics from receiving tebentafusp and suggests differences in disease biology and better prognostic factors in these patients, as indicated in the baseline characteristics. Also, the latter was approved later and therefore available later than the treatment with ICIs in patients with mUM. Furthermore, it is acknowledged that the study included patients treated with tebentafusp and ICIs at any treatment line. In the multivariable analysis, one prior systemic treatment was associated with short tPFS rate, which was not significant for the OS rate. Nevertheless, it is acknowledged that previous treatments could influence the survival outcomes. These limitations, alongside the retrospective nature of the study and the difference in baseline characteristics, favoring group 2 (ICI first), suggest that although tebentafusp after treatment with ICIs might enhance antitumor activity, this observation merits further investigation in prospective clinical trials. A concurrent administration of tebentafusp and ICIs in mUM should be also

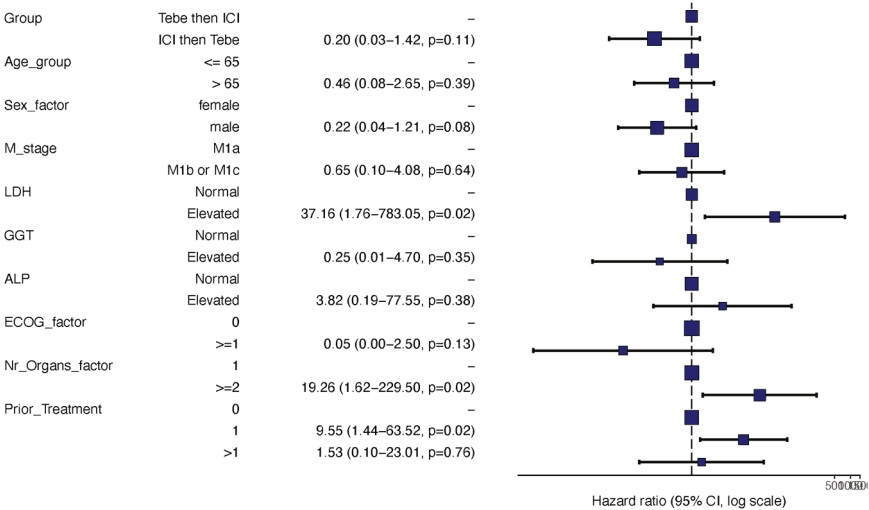


Fig. 3. Multivariable Cox regression analysis for the total progression-free survival (tPFS), defined as the time from first-line treatment initiation to second-line treatment disease progression for significant covariates combined.

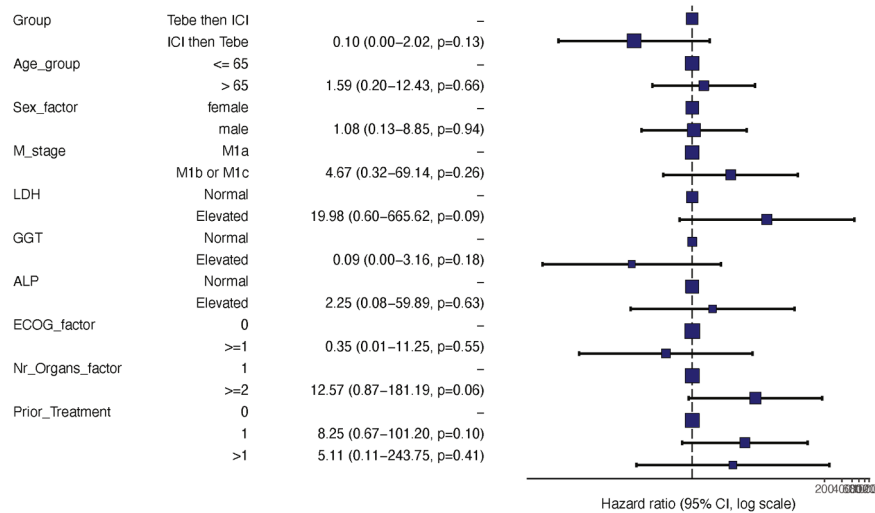


Fig. 4. Multivariable Cox regression analysis for the overall survival (OS) for significant covariates combined.

assessed. Lastly, both treatment agents displayed clinical activity in three cases of HLA-A * 02:01 positive, metastatic, *GNA11/GNAQ* mutant melanocytic tumors, a rare melanoma subtype, without standard-of-care treatment. Given their molecular similarity to UM, it is suggested that clinicians should consider off-label use of tebentafusp in these patients.

Tebentafusp is a first-in-class bispecific T-cell engager that redirects and activates polyclonal CD3+ T-cells to HLA-A * 02:01 positive UM tumor cells presenting a melanoma-associated antigen glycoprotein 100 (gp100)-derived peptide [30]. In contrast to other antibody-based therapies, it targets intracellular epitopes, from which the majority of the neoantigens are thought to be derived [31]. Notably, the activated T-cells in the TME might not be tumor-specific, but T-cell activation induces the release of pro-inflammatory cytokines that may lead to tumor cell lysis and “epitope spreading”, which further stimulates the T-cell activation [32]. Tumor tissue analyses indicate that tebentafusp increases CD3+, CD4+ and CD8+ lymphocyte infiltration and expression of the cell death marker cleaved caspase 3 during treatment [22]. Similar analysis of tumor tissue from the phase 2 and 3 studies demonstrates that tumors with high gp100 mRNA levels at the baseline, i.e. before treatment initiation, had increased CD3+ and CD8+ T-cell infiltration after treatment, but clinical outcomes on tebentafusp, including ctDNA reduction, tumor shrinkage and prolongation of the OS rate > 12 months, were observed across the range of gp100 expression levels [33]. Overall, these data suggest that despite the increase of the tumor infiltrating lymphocytes (TILs) observed during tebentafusp treatment, not all T-cells trafficked into the TME are tumor reactive.

In contrast, ICIs have a different mechanism of action, have demonstrated only a modest improvement in survival in patients with mUM, and treatment responses are often short-lived. The poor responses to ICIs have been confirmed in this retrospective study as well, with mPFS 2.7 months and 5.1 months in group 1 and 2, respectively. These findings specifically highlight a poor response rate to ICIs in patients progressing on tebentafusp. Although the phase 3, randomized study comparing tebentafusp to standard-of-care treatment in mUM did not include patients treated with ipilimumab in combination with nivolumab in the comparative arm, in a cross-trial data comparison between GEM-1402 and IMCgp100–202, tebentafusp demonstrated superior OS over ipilimumab in combination with nivolumab (HR 0.51, 95 % CI 0.32–0.79) [34]. Notably, in the phase 1 dose escalation study of tebentafusp, there was a subgroup of patients treated with ICIs following disease progression to tebentafusp, in which ICIs yielded a higher-than-expected anti-tumor efficacy [35]. This observation is further supported by tumor tissue analyses suggesting that tebentafusp results in modifications of the TME that sensitizes tumors to cytotoxic

CD8+ T-cells, which might indicate greater efficacy of the ICI-treatment, when administered after tebentafusp [22,36]. In the present retrospective study, the treatment sequence of tebentafusp followed by ICIs, resulted in an OS benefit that was comparable to the efficacy observed in the tebentafusp arm of the phase 3, randomized study. Specifically, in the phase 3 study, first-line treatment with tebentafusp improved mOS to 21.7 months, with 1-year OS rate of 73 % [19]. In the present study, the 1-year OS rate was 83 % and mOS was 22.4 months (range 19–24.8) in group 1. Nevertheless, the percentage of patients with dismal disease characteristics, such as LDH > ULN at baseline (44 % vs 36 %), was higher in the present study, compared to the phase 3 study. Additionally, 39 % of the patients had progressed to at least one prior systemic treatment. As such, a survival benefit from the subsequent treatment with ICIs cannot be entirely ruled out. A prospective study evaluating the efficacy of pembrolizumab and lenvatinib prior or following tebentafusp treatment is currently underway (NCT05282901), and the results of this study are expected to escort future study designs for the combination and sequence of systemic therapies.

In clinical practice, treatment combination of tebentafusp, durvalumab (anti-PD1) ± tremelimumab (anti-CTLA4) has been investigated in a phase 1 clinical trial in HLA-A * 02:01 positive patients with metastatic CM [24]. The study included patients with a median of 3 prior treatment lines, as well as 89 % of patients that had progressed to prior anti-PD(L)1 treatment. In the efficacy analysis of the study, combined treatment with tebentafusp and durvalumab ± tremelimumab yielded a clinical benefit with 1-year and 2-year OS rates of 76 % and 34 %, respectively. In the subgroup analysis, tumor shrinkage was noted in 49 % of patients with primary and 28 % with acquired resistance to anti-PD1, thus indicating that tebentafusp might sensitize tumors that are previously resistant to ICIs [37]. Of note, the safety profile of tebentafusp when combined to ICIs was similar to each agent alone. In the present retrospective study, the frequency of TRAEs attributed to tebentafusp did not increase post-ICI administration; nevertheless, the frequency of CRS was higher in patients treated with tebentafusp followed by ICIs, compared to the inverse sequence (27 % vs 15 %). This can be partially attributed to the mechanism of action of each agent, alongside their pharmacokinetic background, with the long half-life of ICIs, but the short half-life of tebentafusp (around 7.5 h, FDA, 2022). Similar TRAEs have been observed during treatment switch from ICIs to BRAF/MEK inhibitors in advanced, *BRAF*V600 mutant CM [38].

In line with previous studies, we further observed a discordance between the ORR and the OS rates for the tebentafusp treatment [19]. This decoupling effect is further underpinned by the observation that patients with radiologic PD per RECIST 1.1. assessment derive a survival

benefit that does not correlate with the radiological response. It is further observed that the OS benefit of tebentafusp seems to be driven by the prolonged SD; accordingly, in the present study, the median duration of treatment was longer when tebentafusp was administered post-ICI, rather than pre-ICI (34 vs 24 months). Liquid biopsy technologies, such as longitudinal assessment of ctDNA during treatment, have been shown to provide a more sensitive assessment than the standard imaging studies for the early indication of clinical benefit from the tebentafusp treatment [21]. Lastly, despite current recommendations for consideration of locoregional management of liver disease in mUM [39], liver-directed therapy did not yield a survival benefit when combined to the systemic treatment in the present study. This observation has several limitations, including the lack of data about the local treatment received, as well as the patient selection, and should be further evaluated in larger, prospective cohorts.

In conclusion, this study suggests that both treatment sequences are clinically feasible in patients with mUM. Further, both treatments displayed clinical activity in three cases of metastatic, *GNA11/GNAQ* mutant melanocytic tumors, and provide first evidence for further use in these rare tumors. A particular clinical benefit was noted in the sequential combination of ICIs followed by tebentafusp, when compared to the inverse sequence, but this analysis displayed limitations that should be considered. Collectively, these results, alongside translational and clinical data from early-phase clinical trials support a possibly enhanced antitumor activity of these treatment agents, which merits further investigation in appropriately powered, randomized, prospective studies. Given the poor efficacy of ICIs in mUM, as well as the current limitations in the use of tebentafusp, which is only restricted in HLA-A * 02:01 positive patients, biomarker analysis for treatment selection, and treatment sequence upon progression, as well as analysis of the factors that influence treatment response and resistance, are crucial to maximize treatment benefit and expand the available treatment options and combinations in this rare and aggressive tumor.

CRedit authorship contribution statement

Marcus O Butler: Writing – review & editing, Investigation, Data curation. **Jean-Jacques Grob:** Writing – review & editing, Investigation, Data curation. **Jessica C Hassel:** Writing – review & editing, Investigation, Data curation. **Reinhard Dummer:** Writing – review & editing, Investigation, Data curation. **Olivier Michielin:** Writing – review & editing, Investigation, Data curation. **Marlana M Orloff:** Writing – review & editing, Investigation, Data curation. **Caroline Gaudy-Marqueste:** Writing – review & editing, Investigation, Data curation. **Florentia Dimitriou:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kamaneh Montazeri:** Writing – review & editing, Investigation, Data curation. **Douglas B Johnson:** Writing – review & editing, Investigation, Data curation. **Piyush Grover:** Writing – review & editing, Investigation, Data curation. **Paolo A Ascierto:** Writing – review & editing, Investigation, Data curation. **Inderjit Mehmi:** Writing – review & editing, Investigation, Data curation. **Anthony M Joshua:** Writing – review & editing, Investigation, Data curation. **Camille Gerard:** Writing – review & editing, Investigation, Data curation. **Richard D Carvajal:** Writing – review & editing, Investigation, Data curation. **Omid Hamid:** Writing – review & editing, Investigation, Data curation. **Erica C Koch Hein:** Writing – review & editing, Investigation, Data curation. **Georgina V Long:** Writing – review & editing, Investigation, Data curation. **Phil F Cheng:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Isaac F Hughes:** Writing – review & editing, Investigation, Data curation. **Ryan Sullivan:** Writing – review & editing, Investigation, Data curation. **Ester Simeone:** Writing – review & editing, Investigation, Data curation. **Ellen Kapiteijn:** Writing – review & editing, Investigation, Data curation.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FD receives/received honoraria and travel support from Merck Sharp & Dohme, Bristol Myers Squibb, Pierre Fabre and Sun Pharma.

EKH reports: advisory role; Novartis, MSD; speaker's Bureau: Novartis, MSD; research Funding: funding paid to Dr. Koch Hein Institution for support of a melanoma registry in Chile; travel, accommodations, expenses: Pfizer, Novartis, Roche Pharma AG.

CGM receives/received honoraria for lectures/advisory board and travel support from Pierre Fabre, BMS, MSD.

GVL is consultant advisor for Agenus, Amgen, Array Biopharma, AstraZeneca, Bayer, BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Evaxion, Hexal AG (Sandoz Company), Highlight Therapeutics S.L., IOBiotech, Immunocore, Innovent Biologics USA, Merck Sharpe & Dohme, Novartis, PHMR Ltd, Pierre Fabre, Regeneron, Scancell, SkylineDX B.V.

O.M. has consulting/advisory roles for Bristol Myers Squibb, MSD, Roche, Novartis, Amgen, Pierre Fabre, and Neracare; has received research grants from Bristol Myers Squibb, MSD, and Amgen; is a consultant advisor or a paid speaker for Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Amgen, and Nektar; has received research funding from Bristol Myers Squibb and Pierre Fabre; and is the cofounder of a cell therapy company called Cellula.

DBJ has served on advisory boards or as a consultant for BMS, Catalyst Biopharma, Iovance, The Jackson Laboratory, Mallinckrodt, Merck, Mosaic ImmunoEngineering, Novartis, Oncosec, Pfizer, Targovax, and Teiko, and has received research funding from BMS and Incyte.

EK has consultancy/advisory relationships with Bristol Myers Squibb, Novartis, Pierre Fabre, Immunocore and Lilly, and received research grants from Bristol Myers Squibb, Delcath, Novartis and Pierre-Fabre. Not related to current work and paid to institute.

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RD declares financial interests from Novartis, Merck Sharp & Dohme (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, Alligator, T3 Pharma, MaxiVAX SA, Pfizer, Sincere and touchIME.

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Authors' contributions

Study concepts: FD, RD. Study design: FD, RD. Data acquisition: FD, MMO, EKH, IFH, ES, KM, PG, IM, CLG, CGM, DBJ, JH. Quality control of data and algorithms: FD. Data analysis and interpretation: FD. Statistical analysis: PFC, FD. Manuscript preparation: FD. Manuscript editing: FD, MMO, EKH, IFH, ES, KM, PG, IM, CLG, CGM, JJG, OM, OH, GVL, RS, EK, DBJ, PAA, AJ, RDC, MOB, JH, RD. All the authors revised the manuscript and approved the submission. All the authors had full access to all the data and the final responsibility to submit for publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2024.115161](https://doi.org/10.1016/j.ejca.2024.115161).

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