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ORIGINAL ARTICLE

Overall survival from tebentafusp versus nivolumab plus ipilimumab in first-line metastatic uveal melanoma: a propensity score-weighted analysis

J. M. Piulats[1,2,3]*, C. Watkins[4], M. Costa-García[2], L. del Carpio[1,2], S. Piperno-Neumann[5], P. Rutkowski[6], J. C. Hassel[7], E. Espinosa[8], L. de la Cruz-Merino[9], S. Ochsenreither[10], A. N. Shoushtari[11,12], M. Orloff[13], A. K. S. Salama[14], H. M. Goodall[15], J.-F. Baurain[16] & P. Nathan[17]

[1]Institut Català d'Oncologia, Barcelona; [2]Cancer Immunotherapy Group, OncoBell, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona; [3]Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain; [4]Clarostat Consulting Ltd, Cheshire, UK; [5]Institut Curie, Paris, France; [6]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [7]University Hospital Heidelberg, Heidelberg, Germany; [8]Hospital Universitario La Paz, CIBERONC, Madrid; [9]Oncology Department, Virgen Macarena University Hospital, Department of Medicine, School of Medicine, University of Seville, Seville, Spain; [10]Charité—Comprehensive Cancer Center, Berlin, Germany; [11]Memorial Sloan Kettering Cancer Center, New York; [12]Weill Cornell Medical College, New York; [13]Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia; [14]Duke University, Durham, USA; [15]Immunocore, Abingdon, UK; [16]Institut Roi Albert II Cliniques Universitaires St-Luc, UCLouvain, Brussels, Belgium; [17]Mount Vernon Cancer Centre, Northwood, UK

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Background: Tebentafusp demonstrated a superior overall survival (OS) benefit [hazard ratio (HR) 0.51] compared to investigator's choice (82% pembrolizumab) in a randomized, phase III trial (IMCgp100-202; $N = 378$) in untreated metastatic uveal melanoma (mUM). The 1-year OS rates for tebentafusp and pembrolizumab were 73% and 59%, respectively. In the single-arm GEM1402 ($N = 52$), the 1-year OS rate for nivolumab plus ipilimumab (N+I) in mUM was 52%. Due to limitations in conducting randomized trials in mUM, we compared OS on tebentafusp or pembrolizumab (IMCgp100-202) to N+I (GEM1402) in untreated mUM using propensity scoring methods.

Patients and methods: Analyses were adjusted using propensity score-based inverse probability of treatment weighting (IPTW), balancing age, sex, baseline lactate dehydrogenase (LDH), baseline alkaline phosphatase, disease location, Eastern Cooperative Oncology Group status, and time from primary diagnosis to metastasis. OS was assessed using IPT-weighted Kaplan—Meier and Cox proportional hazard models. Sensitivity analyses using alternative missing data and weights methods were conducted.

Results: The primary IPTW analysis included 240 of 252 patients randomized to tebentafusp from IMCgp100-202 and 45 of 52 N+I-treated patients from GEM-1402. Key baseline covariates, including LDH, were generally well balanced before weighting. The IPTW-adjusted OS favored tebentafusp, HR 0.52 [95% confidence interval (CI) 0.35-0.78]; 1-year OS was 73% for tebentafusp versus 50% for N+I. Sensitivity analyses showed consistent superior OS for tebentafusp with all IPTW HRs $\leq$0.61. IPTW analysis of pembrolizumab versus N+I showed no significant difference in OS (HR 0.72; 95% CI 0.50-1.06).

Conclusions: Tebentafusp was previously shown to provide an OS benefit compared to checkpoint inhibitors or chemotherapy in untreated mUM. Propensity score analysis demonstrated a similar OS benefit for tebentafusp compared with N+I. These data further support tebentafusp as the standard of care in previously untreated human leukocyte antigen (HLA)-A*02:01+ adult patients with mUM.

Key words: ipilimumab, metastatic uveal melanoma, nivolumab, overall survival, propensity score-weighted analysis, tebentafusp

INTRODUCTION

Uveal melanoma (UM) is a rare and highly malignant neoplasm affecting the vascular layers of the eye (iris, ciliary body, or choroid). It is the most frequent primary intraocular malignancy of the adult eye (~85%).[1] The incidence ranges from 5.3 to 10.9 cases per million and varies by geography, race, and age.[2] Despite improvements in the diagnosis and treatment of the primary tumor, up to 50% of

*Correspondence to: Dr Josep M. Piulats, Institut Català d'Oncologia, Avinguda Gran Via de l'Hospitalet 199-203, Hospitalet de Llobregat, Barcelona, 08908, Spain. Tel: +34-932-746-000

E-mail: jmpiulats@iconcologia.net (J. M. Piulats).

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patients with UM develop systemic metastases, predominantly to the liver (~90% of patients).[3] Once patients develop metastatic UM (mUM), the prognosis and outcomes are very poor, with an historic median overall survival (OS) of ≤1 year regardless of therapy.[4,5]

Until recently, treatment options for mUM were limited to participation in a clinical trial and therapies used to treat metastatic cutaneous melanoma (mCM), despite UM and CM being distinct disease entities in terms of biology, genetics, and clinical course.[6] Consequently, treatment options such as immune checkpoint inhibitors (ICIs) that have improved OS in mCM have not yielded equal survival benefits in mUM. Typical 1-year OS rates in mUM are in the range of 50% in the first-line setting when treated with ICI.[5,7]

Tebentafusp, a first-in-class T-cell receptor bispecific (gp100 × CD3) targeting gp100 peptide-human leukocyte antigen (HLA) complexes on the surface of melanoma cells, is the first and only therapy to demonstrate an OS benefit in mUM. In the primary analysis of the phase III randomized study (IMCgp100-202) investigating tebentafusp versus investigator's choice of therapy (dacarbazine, ipilimumab, or pembrolizumab) in previously untreated HLA-A*02:01+ mUM patients, the 1-year OS rate was 73% in the tebentafusp group compared with 59% in the control group [hazard ratio (HR) for death 0.51; 95% confidence interval (CI) 0.37-0.71; $P < 0.001$].[8] This OS benefit in favor of tebentafusp was maintained after a minimum follow-up of 3 years (HR 0.68; 95% CI 0.54-0.87).[9] The control arm of this trial did not include the choice of nivolumab plus ipilimumab as this combination was not prevalent in the global clinical setting for mUM at the time of trial design and because, unlike in mCM, this regimen has not demonstrated any additional benefit over ICI monotherapy in mUM. In a phase II open-label, multicenter, single-arm trial (GEM-1402) in previously untreated mUM patients, nivolumab plus ipilimumab resulted in a 1-year OS rate of 52%.[10] Despite never having demonstrated an OS benefit in mUM, nivolumab plus ipilimumab is used in selected patients with mUM based on the benefit demonstrated in mCM.[10]

The low prevalence of mUM limits the ability of researchers to carry out large randomized clinical trials. Given the lack of a randomized comparison, we sought to investigate the OS benefit of tebentafusp over nivolumab plus ipilimumab based on an indirect comparison to GEM-1402. Although comparisons of treatments across studies can be biased by differences in patient characteristics, this limitation can be addressed using propensity score modeling. Propensity score methods have been widely used in epidemiological settings for treatment comparisons involving nonrandomized observational data. This approach mimics the effect of randomization by creating a balance between groups of patients with respect to important baseline covariates, which allows for more valid statistical comparisons.[11] Propensity score methods can be used in any setting involving the comparison of nonrandomized groups provided there is access to patient-level data with adequate information on known important prognostic factors. Herein, we report a propensity score-weighted analysis using patient-level data from two mUM clinical trials to compare OS in patients treated with tebentafusp or pembrolizumab (IMCgp100-202) with OS in patients treated with the combination of nivolumab plus ipilimumab (GEM-1402).

PATIENTS AND METHODS

Study design and patient characteristics

Details regarding the study design and patient characteristics of the IMCgp100-202[8,9] and GEM-1402[10] trials have been reported previously. A brief description of each trial is provided below. This analysis is based on individual patient data from patients who received tebentafusp or pembrolizumab in IMCgp100-202 with a median duration of follow-up of 43.3 months (data cut-off 3 July 2023) and nivolumab plus ipilimumab in GEM-1402 with a median duration of follow-up of 35 months (data cut-off of August 2023).

IMCgp100-202: IMCgp100-202 (NCT03070392) was a multicenter, phase III, open-label trial that randomly assigned previously untreated patients with mUM in a 2 : 1 ratio to tebentafusp ($n = 252$) or investigator's choice ($n = 126$) of single-agent pembrolizumab ($n = 103$), ipilimumab ($n = 16$), or dacarbazine ($n = 7$); 82% of patients in the investigator's choice arm received pembrolizumab.[8] Patients received tebentafusp at a dose of 20 μg on day 1, 30 μg on day 8, and 68 μg weekly thereafter. Pembrolizumab, ipilimumab, and dacarbazine were administered at standard doses and regimens, as described previously.[8] Treatment (except ipilimumab) was continued until radiographic progression, unacceptable toxicity, investigator's decision, or withdrawal of consent by the patient. Seven patients in the tebentafusp arm and 15 in the investigator's choice arm (12 assigned to pembrolizumab) did not receive treatment. The primary endpoint was OS. The median duration of follow-up was 43.3 months.

GEM-1402: GEM-1402 (NCT02626962) was a multicenter, open-label, single-arm, phase II study conducted by the Spanish Multidisciplinary Melanoma Group (GEM) that evaluated the efficacy of nivolumab plus ipilimumab in treatment-naive patients with mUM.[10] Ipilimumab (3 mg/kg once every 3 weeks) and nivolumab (1 mg/kg once every 3 weeks) were administered during a maximum of four inductions, followed by nivolumab (3 mg/kg once every 2 weeks) until progressive disease, toxicity, or withdrawal. The primary endpoint was 1-year OS. The median duration of follow-up was 35 months.

Original data from both IMCgp100-202 and GEM-1402 were collected within an ethical framework. These clinical trials were carried out in accordance with the Declaration of Helsinki, had approval from respective institutional review boards, and had obtained informed consent from all patients.[8,10]

Propensity score analysis

The primary objective of this analysis was to compare, using propensity score-based methods, OS on tebentafusp (IMCgp100-202) to OS on nivolumab plus ipilimumab (GEM-1402) in mUM patients in the first-line setting. A secondary

objective was to compare OS on pembrolizumab (IMCgp100-202) to OS on nivolumab plus ipilimumab (GEM-1402) in the same manner.

The prospective analyses using retrospective data sources were carried out according to a pre-specified statistical analysis plan that described the propensity score-based methodology details and covariates to adjust for before commencing the analyses. The covariates considered for the propensity score model were age, sex, baseline lactate dehydrogenase [LDH; $\leq$ or $>$ upper limit of normal (ULN)], baseline alkaline phosphatase (ALP; $\leq$ or $>$ ULN), disease location (hepatic only, extrahepatic only, hepatic and extrahepatic), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 or $\geq$1), and time from primary diagnosis to metastasis. As there were only a small proportion of patients with extrahepatic disease only in IMCgp100-202 compared to GEM-1402, this may have impacted the effective sample size and/or caused modeling issues. Therefore, two alternative ways of defining the disease location covariate were also investigated: disease location pooled categories [hepatic only, any extrahepatic (pooled extrahepatic only plus hepatic and extrahepatic)] and largest metastatic liver lesion ($\leq$3 cm, $>$3 cm, no liver lesions).

To estimate the propensity scores, the covariates were used as main effects in a logistic regression model. Separate models were fitted for the comparison of tebentafusp versus nivolumab plus ipilimumab and the comparison of pembrolizumab versus nivolumab plus ipilimumab. This modeled the probability of a patient in the analysis population being treated with tebentafusp or pembrolizumab (i.e. being from IMCgp100-202 rather than GEM-1402) with the propensity score representing the probability of being treated with tebentafusp or pembrolizumab. The decision on the final set of covariates included in the primary propensity score-generating model was based on several factors such as model fit statistics, distribution of propensity scores/weights (minimizing extreme weights, etc.), and amount of missing data. Decisions were made without knowledge of the impact on the outcome of the survival analyses.

All planned covariates were included in the final propensity score model. The three-level disease location covariate (hepatic only, extrahepatic only, hepatic and extrahepatic) was used in the final model for the following reasons: there were no model-fitting issues with good balance between treatments after weighting with no extreme weights; it provided more information than two-level disease location pooled categories; it was more strongly associated with the patient being in IMCgp100-202 versus GEM-1402 than two-level (extrahepatic only is one of the more imbalanced factors between the studies); and it resulted in less missing data than the largest metastatic liver lesion and slightly better balance for other covariates (e.g. age). The propensity scores were converted to inverse probability of treatment weights (IPTW) with tebentafusp or pembrolizumab patients having a weighting of 1 (Figure 1). These IPTWs were then used in weighted survival analysis to adjust for differences in patient characteristics between treatments.

The primary endpoint for this analysis was OS, which was summarized via weighted Kaplan–Meier curves and associated medians (including 95% CIs) and 1-year estimates. An IPT-weighted HR and 95% CI was also produced from a weighted Cox regression model. Variance was calculated via robust sandwich estimation. For context, groups were also compared using an unadjusted Cox regression model and unweighted Kaplan–Meier curves to evaluate the impact and direction that the IPT weighting had on the naive unadjusted treatment effect.

The primary survival analysis was complete case (excluding patients with missing data for at least one relevant covariate) with average treatment effect of the treated (ATT) IPTWs (Figure 1). Sensitivity analyses used alternative missing data methods (multiple imputation) and weights [stabilized and unstabilized average treatment effect of the control (ATC), average treatment effect (ATE)] and a multivariate Cox regression analysis adjusted for the same effects as in the primary propensity score model.

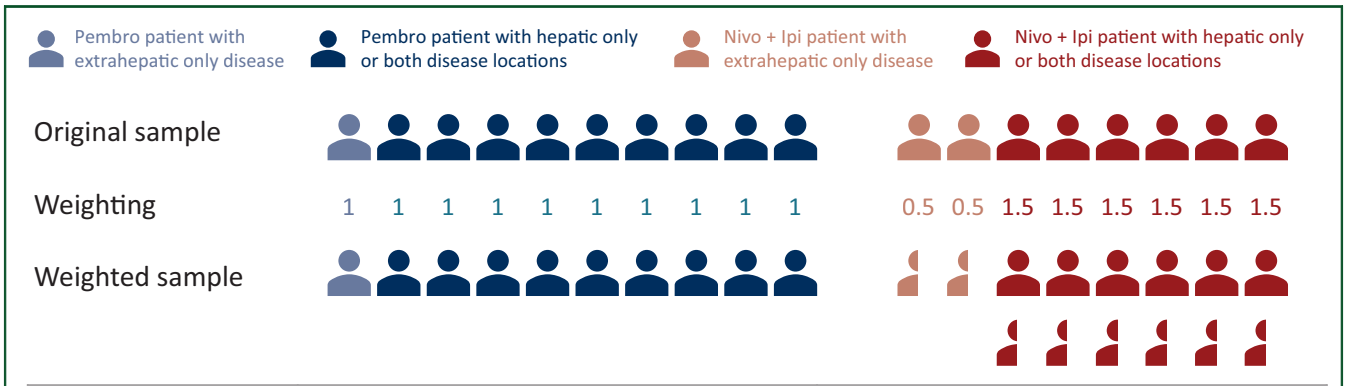
Additional analyses

Differences in the HLA haplotype of patients between the trials could not be adjusted for in the propensity score model. Survival analyses from an independent cohort of 40 patients with mUM treated at the Catalan Cancer Institute in Barcelona was conducted to determine whether HLA-A*02:01 held any prognostic value in patients with mUM. These are 40 prospective patients diagnosed with liver metastasis by liver biopsy. Patients were treated between February 2016 and January 2021; none of them had been treated with tebentafusp. Median age was 56 years (range 26-78 years), 22 (55%) were male, 32 (80%) had ECOG 0, and levels of LDH were normal in 21 (53%) patients. Median diameter of the largest liver lesion was 25 mm (range 12-85 mm) with patients having additional extrahepatic metastatic involvement. HLA typing of HLA-A, HLA-B, and HLA-C genes was obtained from RNAseq samples. Firstly, raw reads were mapped to the constructed HLA reference with razers3 algorithm. Then, haplotypes were predicted from aligned reads using the OptiType v1.3.1 software. Association between HLA haplotype, HLA-A*02:01 versus all other HLA types, and OS as the outcome was assessed using the Cox proportional hazard models. Categorical data were described as frequencies and percentages. Continuous variables were presented as medians and ranges. To compare differences between the two groups, Mann–Whitney *U* test was used for continuous variables, and the chi-square test was used for categorical variables. OS was calculated from date of diagnosis of metastatic disease to last control status. Survival curves were estimated using the Kaplan–Meier method and *P* value was determined by the log-rank test.

RESULTS

Qualitative comparison of eligibility criteria between studies

The eligibility criteria for each trial were very similar (Table 1) with the main distinction being the requirement for patients in the IMCgp100-202 trial to be positive for the



	Pembrolizumab		Nivolumab + Ipilimumab	
	Extrahepatic only	Hepatic only or both disease location	Extrahepatic only	Hepatic only or both disease locations
Original sample	1 (10%)	9 (90%)	2 (25%)	6 (75%)
Weighting	1	1	0.5	1.5
Weighted sample	1 (10%)	9 (90%)	1 (10%)	9 (90%)

Figure 1. Schematic of inverse probability of treatment (IPT) weighting. Simplified example to illustrate the average treatment effect of the treated (ATT) IPT weighting for a single confounder, disease location, for a small population.
Pembro, pembrolizumab; Nivo, nivolumab; Ipi, ipilimumab.

HLA-A*02:01 allele, which is present in ~40%-50% of Caucasians. Tebentafusp is specific for the gp100 peptide LEPGPVTA presented by the HLA-A*02:01 protein on the surface of melanoma cells. However, beyond differences in this requirement, patients in both trials were ≥18 years of age with histologically or cytologically confirmed mUM and no previous systemic therapy or liver-directed therapy for metastatic disease. At the time of enrollment, patients had to have ECOG performance score of ≤1 and measurable disease by RECIST v1.1 criteria.

Reasons for exclusion from both trials included active central nervous system metastases or active autoimmune disease, a history of active human immunodeficiency virus/hepatitis B virus/hepatitis C virus infection or other infection requiring systemic antibiotics, certain out-of-range laboratory values, and other prior malignancies within 2 years (or 3 years for GEM-1402). Due to tebentafusp's mechanism of action as a T-cell engager, patients with clinically significant cardiac disease, adrenal insufficiency, and a history of hypersensitivity reactions to other biologics were also specifically excluded from IMCgp100-202.

Tebentafusp versus nivolumab plus ipilimumab

Patients and weighting. In the primary complete case analysis, 12 of 252 patients assigned to the tebentafusp arm (4.8%) in IMCgp100-202 and 7 of 52 patients (13.5%) in GEM-1402 were excluded due to missing baseline covariates. A total of 240 patients who received tebentafusp and 45 patients who received nivolumab plus ipilimumab were included in the primary IPTW analysis. Key baseline covariates including LDH, ALP, and ECOG PS were generally well balanced across treatments; more patients in GEM-1402 had extrahepatic disease only (Table 2). After IPT weighting, all key baseline characteristics were well balanced.

In the propensity score model, the strongest covariate influencing the propensity for receiving tebentafusp versus nivolumab plus ipilimumab was disease location (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.11.013). There was reasonable overlap of propensity score distributions between treatment groups and no clear weight outliers or extreme weights.

Primary and sensitivity survival analyses. In the primary survival analysis (complete case with ATT IPT weights), the IPTW-adjusted OS favored tebentafusp over nivolumab plus ipilimumab (HR 0.52; 95% CI 0.35-0.78) (Figure 2A). The median OS and 1-year OS rate were 21.7 months and 73% for tebentafusp and 12.6 months and 50% for nivolumab plus ipilimumab, respectively.

Sensitivity analyses showed consistently superior OS for tebentafusp compared with nivolumab plus ipilimumab, with all IPTW HRs being ≤0.61 (Figure 2B).

Pembrolizumab versus nivolumab plus ipilimumab

Patients and weighting. In the primary complete case analysis, 8 of 103 patients (7.8%) assigned to receive pembrolizumab in IMCgp100-202 and 7 of 52 patients (13.5%) who received nivolumab plus ipilimumab in GEM1402 were excluded due to missing baseline covariates. A total of 95 patients who received pembrolizumab and 45 patients who received nivolumab plus ipilimumab were included in the primary IPTW analysis. Key baseline covariates including LDH, ALP, and ECOG PS were generally well balanced across treatments; more patients in GEM-1402 had extrahepatic disease only and an ECOG PS of 0 (Table 3). After IPT weighting, all key baseline characteristics were well balanced.

Table 1. Comparison of eligibility criteria for IMCgp100-202 and GEM-1402

Criteria[a]	IMCgp100-202	GEM-1402
Inclusion criteria		
HLA-A*02:01-positive by central assay	Y	N/A
≥18 years of age	Y	Y
Histologically or cytologically confirmed mUM	Y	Y
ECOG ≤1	Y	Y
Measurable disease by RECIST v1.1[b]	Y	Y
Exclusion criteria		
Prior systemic or liver-directed therapy for metastatic disease	Y	Y
Major surgery, radiotherapy, or use of hematopoietic colony-stimulating growth factors within 2 weeks of the first dose of study drug	Y	N
Active or symptomatic CNS metastases	Y	Y
Prior malignancy within 2 years (or 3 years for GEM-1402)	Y	Y
Active or recurrent autoimmune disease and receiving glucocorticoids/systemic immunosuppressive treatment	Y	Y
Clinically significant cardiac disease or impaired cardiac function	Y	N
History of adrenal insufficiency	Y	N
History of HIV infection; active hepatitis B virus or hepatitis C virus; or active infection requiring systemic antibiotic therapy	Y	Y[c]
- Non-oncology vaccine therapy for infectious disease prevention up to 1 month before/after Nivo + Ipi		Y
Out-of-range laboratory values for serum creatinine, total bilirubin, alanine aminotransferase, aspartate aminotransferase, absolute neutrophil count, absolute lymphocyte count, platelet count, or hemoglobin	Y	Y[c]
History of severe hypersensitivity reactions to other biologic drugs or monoclonal antibodies	Y	N
Prior history of treatment targeting T-cell costimulation or immune checkpoint pathway	N	Y
Concomitant therapy with any of the following: Interleukin-2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids, defined as >10 mg daily prednisone equivalents. Inhaled or topical steroids, and	Y	Y
- adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.	N	Y
Contraindication to all of the alternatives for investigator's choice	Y	N/A

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; mUM, metastatic uveal melanoma; N, no; N/A, not applicable; Y, yes.
[a]For a full list of inclusion/exclusion criteria, please refer to the trial protocols.
[b]Following protocol amendment 4 (31 March 2020), patients without measurable disease were eligible for enrollment in study IMCgp100-202.
[c]Included as opposite statements under inclusion criteria in GEM-1402.

In the propensity score model, the strongest covariate influencing the propensity for receiving pembrolizumab versus nivolumab plus ipilimumab was age (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.11.013). There was reasonable overlap of propensity score distributions between treatment groups and no clear weight outliers or extreme weights.

Primary and sensitivity survival analyses. In the primary IPTW analysis of pembrolizumab versus nivolumab plus ipilimumab, there was no significant difference in OS (HR 0.72; 95 CI 0.50-1.06) (Figure 3A). The median OS and 1-year OS rate were 16.9 months and 60% for pembrolizumab and 14.2 months and 52% for nivolumab plus ipilimumab, respectively. Sensitivity analyses showed consistent results (Figure 3B).

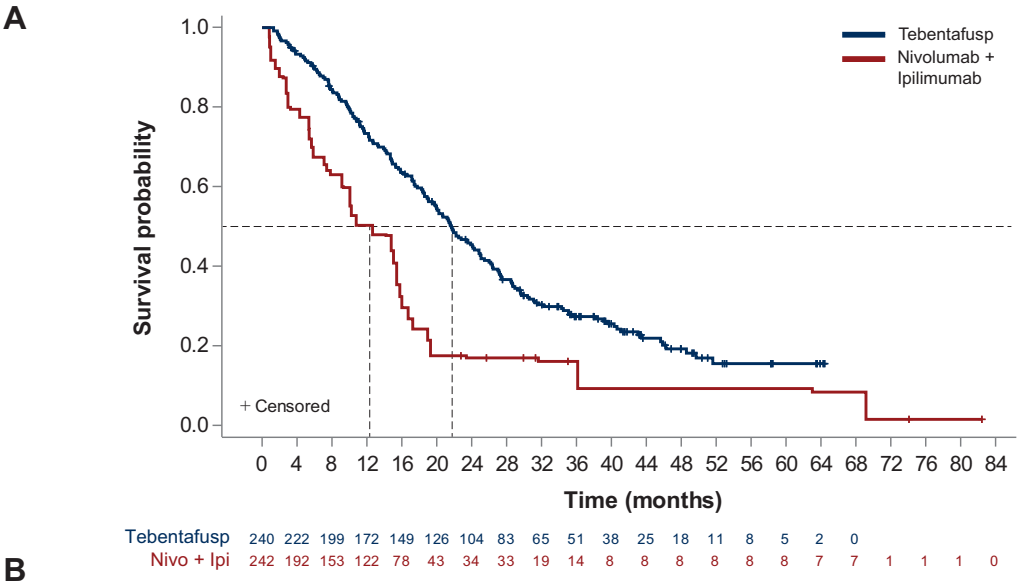
*HLA-A*02:01 is not prognostic in mUM*

All patients enrolled in the IMCgp100-202 trial were positive for the HLA-A*02:01 allele, while patients enrolled in GEM-1402 were not selected by HLA status. As differences in the HLA haplotype of patients between the trials could not be adjusted for in the propensity score model, an analysis from an independent cohort of 40 mUM patients treated at a single institution was conducted to determine whether HLA-A*02:01 held any prognostic value in patients with mUM. None of the patients included had been treated with tebentafusp. Based on

Table 2. Patient characteristics, observed and IPT weighted (ATT) by treatment (Tebe versus Nivo + Ipi)

Characteristic	Tebentafusp observed	Nivo + Ipi observed	Tebentafusp weighted	Nivo + Ipi weighted
N	240	45	240[a]	241.9[a]
Age (years) mean (SD)	61.2 (12.0)	59.3 (13.3)	61.2 (12.0)	61.7 (30.2)
Male sex	122 (50.8%)	23 (51.1%)	122 (50.8%)	112.6 (46.6%)
Baseline LDH > ULN	84 (35.0%)	19 (42.2%)	84 (35.0%)	81.8 (33.8%)
Baseline ALP > ULN	51 (21.3%)	7 (15.6%)	51 (21.3%)	50.6 (20.9%)
Disease location extrahepatic only	9 (3.8%)	10 (22.2%)	9 (3.8%)	8.5 (3.5%)
Disease location hepatic only	123 (51.3%)	20 (44.4%)	123 (51.3%)	124.0 (51.3%)
Disease location both	108 (45.0%)	15 (33.3%)	108 (45.0%)	109.4 (45.2%)
ECOG PS 0	191 (79.6%)	38 (84.4%)	191 (79.6%)	199.3 (82.4%)
Time from diagnosis to metastasis (years) mean (SD)	4.0 (4.4)	4.7 (4.6)	4.0 (4.4)	4.1 (9.6)

ALP, alkaline phosphatase; ATT, average treatment effect of the treated; ECOG, Eastern Cooperative Oncology Group; IPT, inverse probability of treatment; LDH, lactate dehydrogenase; PS, performance status; SD, standard deviation; Tebe, tebentafusp; ULN, upper limit of normal.
[a]Weighted *N* is the sum of the weights.



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Model	Tebe N	Nivo + Ipi N	HR (95% CI)
PS-based IPTW analyses			
Complete case, IPT ATT weights (primary)	240	242	0.53 (0.35-0.78)
Multiple imputation, IPT ATT weights	252	255	0.55 (0.38-0.79)
Complete case, IPT ATT stabilized weights	202	38	0.50 (0.32-0.76)
Complete case, IPT ATE weights	284	287	0.54 (0.37-0.79)
Complete case, IPT ATC weights	44	45	0.61 (0.41-0.92)
Other models			
Complete case, multivariate Cox analysis	240	45	0.41 (0.28-0.62)
Unadjusted analyses			
Unadjusted complete case	240	45	0.63 (0.44-0.90)
Unadjusted multiple imputation	252	52	0.66 (0.47-0.93)

Figure 2. IPT-weighted overall survival for tebentafusp versus nivolumab + ipilimumab. (A) IPT-weighted Kaplan–Meier curves of overall survival according to treatment assignment to tebentafusp versus nivolumab + ipilimumab for the primary analysis (complete case IPT ATT weights). (B) Forest plot of adjusted HRs and 95% CIs from weighted Cox proportional hazard model for the primary analysis and all sensitivity analyses compared to the unadjusted complete case and multiple imputation analyses.
ATC, average treatment effect of the control; ATE, average treatment effect; ATT, average treatment effect of the treated; CI, confidence interval; HR, hazard ratio; Ipi, ipilimumab; IPT, inverse probability of treatment; IPTW, inverse probability of treatment weighting; Nivo, nivolumab; PS, propensity score; Tebe, tebentafusp.

this analysis, the HLA-A*02:01 haplotype was found not to be associated with OS in mUM (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.11.013). There were no differences in other known prognostic factors between HLA-A*02:01 versus all other HLA types (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.11.013). These data suggest that not adjusting for HLA haplotype differences between the two trials would not have impacted the OS comparison.

DISCUSSION

Enrollment in clinical trials is limited by the low number of patients with rare diseases such as mUM. Propensity score-weighted analyses allow comparisons between treatments in the absence of a head-to-head randomized trial. This patient-level propensity score-weighted analysis, which was well balanced for key baseline covariates, demonstrated that tebentafusp resulted in significantly superior OS (HR 0.52; 95% CI 0.35-0.78) compared with nivolumab plus ipilimumab in patients with previously untreated mUM. Based on the IPTW analysis, the calculated 1-year OS rates of 73% for tebentafusp and 50% for nivolumab plus ipilimumab were very similar to those observed in each of the original trials (73% and 52%, respectively). Based on the IPTW analysis, there was no significant difference in OS (HR 0.72; 95% CI 0.50-1.06) between pembrolizumab and nivolumab plus ipilimumab. Therefore, this analysis suggests that the

Table 3. Patient characteristics, observed and IPT weighted (ATT) by treatment (Pembro versus Nivo + Ipi)

Characteristic	Pembrolizumab observed	Nivo + Ipi observed	Pembrolizumab weighted	Nivo + Ipi weighted
N	95	45	95[a]	97.7[a]
Age (years) mean (SD)	64.4 (10.1)	59.3 (13.3)	64.4 (10.1)	65.8 (18.4)
Male sex	46 (48.4%)	23 (51.1%)	46 (48.4%)	39.9 (40.9%)
Baseline LDH >ULN	37 (38.9%)	19 (42.2%)	37 (38.9%)	37.8 (38.7%)
Baseline ALP >ULN	19 (20.0%)	7 (15.6%)	19 (20.0%)	23.3 (23.9%)
Disease location extrahepatic only	8 (8.4%)	10 (22.2%)	8 (8.4%)	8.1 (8.3%)
Disease location hepatic only	44 (46.3%)	20 (44.4%)	44 (46.3%)	44.1 (45.1%)
Disease location both	43 (45.3%)	15 (33.3%)	43 (45.3%)	45.4 (46.5%)
ECOG PS 0	67 (70.5%)	38 (84.4%)	67 (70.5%)	69.2 (70.9%)
Time from diagnosis to metastasis (years) mean (SD)	3.8 (5.1)	4.7 (4.6)	3.8 (5.1)	5.0 (6.7)

ALP, alkaline phosphatase; ATT, average treatment effect of the treated; ECOG, Eastern Cooperative Oncology Group; Ipi, ipilimumab; IPT, inverse probability of treatment; LDH, lactate dehydrogenase; Nivo, nivolumab; Pembro, pembrolizumab; PS, performance status; SD, standard deviation; ULN, upper limit of normal.
[a]Weighted *N* is the sum of the weights.

combination of nivolumab plus ipilimumab is inferior to tebentafusp and may provide no clinically significant survival benefit over pembrolizumab in previously untreated mUM. This finding is further supported by a recent systematic review in which a population-level, match-adjusted indirect comparison (MAIC) of pooled patients treated with combination nivolumab plus ipilimumab ($N = 63$) versus tebentafusp ($N = 252$) showed a survival benefit in favor of tebentafusp.[12]

In previously untreated, unresectable advanced cutaneous melanoma, nivolumab plus ipilimumab demonstrated a significant OS benefit compared with ipilimumab monotherapy,[13,14] and has become a standard of care in this population. However, in mUM, nivolumab plus ipilimumab has not demonstrated any survival advantage over ICI monotherapy or chemotherapy in either prospective studies[10,15] or retrospective analyses of trial data[4,5] and real-world evidence.[16-18] Although the exact mechanisms underlying resistance to ICI therapy in mUM are unclear, potential reasons include low tumor mutational burden (TMB) and limited immunogenicity of UM, and low expression of programmed cell death protein 1 (PD1) and programmed death-ligand 1 (PDL1) suggesting a lack of effective antitumor tumor-infiltrating lymphocytes (TILs).[7,19]

The mechanism of action of tebentafusp, a T-cell receptor-based CD3 bispecific, represents a new approach to tumor immunotherapy which is distinct from ICI in that it does not require pre-existing tumor-specific immunity.[20,21] Tebentafusp redirects T cells, regardless of their intrinsic specificity, to kill gp100-expressing tumor cells by directly engaging with both gp100 peptide, presented by HLA-A*02:01 on the tumor cell surface, and CD3 on T cells.[22-24] This in turn can lead to cross-presentation of melanoma antigens and induction of new melanoma-specific immune responses.[22,25] As a result, tebentafusp stimulates a strong polyclonal antitumor immune response even in the absence of pre-existing activated TILs. Preliminary data indicate that tebentafusp-mediated cytotoxicity induces clinically relevant antigen spreading[25] but whether this results in durable tumor control by tumor-specific T cells remains an open question. By contrast, ICIs function by preventing the inactivation of existing tumor-reactive T cells and overcoming T-cell anergy in tumors, thus amplifying and sustaining T-cell effector function.[26] Consequently, ICIs work best in the context of a pre-existing antitumor immune response in immunogenic tumors with high TMB, and activity varies based on inhibitory ligand (e.g. PDL1) expression levels in the tumor microenvironment. Consequently, many patients do not respond or develop resistance to ICI therapy. By simultaneously engaging CD3 on TILs and target antigen on tumor cells, tebentafusp can bypass T-cell tolerance and stimulate a *de novo* antitumor immune response even in a 'cold' tumor.[22-24,27] This is particularly relevant given the typically low TMB of ~0.5 per megabase sequence of mUM[28] and low expression of PDL1.[7,29,30] Profiling of TILs in mCM and mUM has also shown a relatively lower quantity and growth of TILs in mUM.[30]

Using patient-level data from IMCgp100-202 and GEM-1402, our propensity score analysis demonstrates a clear OS benefit for tebentafusp compared to the combination of anti-PD1 with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and no significant difference in OS between anti-PD1 monotherapy compared to the combination of anti-PD1 with anti-CTLA4. Given the lack of any clear survival advantage in mUM associated with the combination of nivolumab plus ipilimumab and the increased toxicity associated with this regimen compared with anti-PD1 monotherapy or tebentafusp (23% versus 2%-5% treatment-related discontinuations and 2 versus 0 treatment-related deaths for combination immunotherapy in GEM-1402 and monotherapy in IMCgp100-202, respectively), we suggest only highly selected patients are considered for combination immunotherapy.

The IPT-weighted analysis used to adjust for differences in patient characteristics between the treatment groups showed slightly larger survival benefits for tebentafusp or pembrolizumab versus nivolumab plus ipilimumab than the unadjusted naive comparison, suggesting that patients in the GEM-1402 study had slightly better prognosis than those in the IMCgp100-202 study. This is consistent with the observed patient baseline characteristics, which were generally well balanced but with slightly more extrahepatic only disease and an ECOG PS of 0 in GEM-1402. However, after IPT weighting, all characteristics were well balanced.

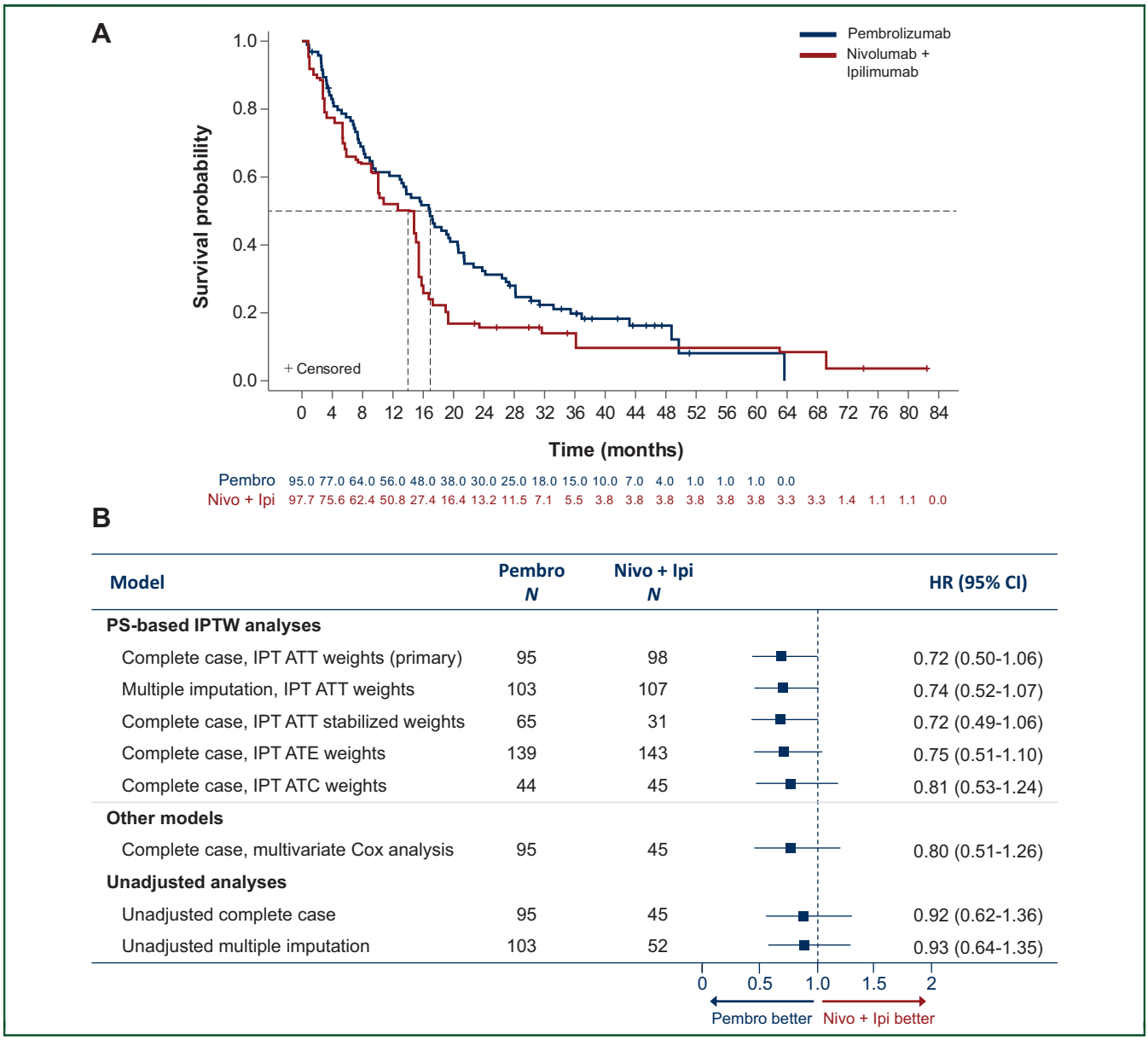

Figure 3. IPT-weighted overall survival for pembrolizumab versus nivolumab + ipilimumab. (A) IPT-weighted Kaplan–Meier curves of overall survival according to treatment assignment to pembrolizumab versus nivolumab + ipilimumab for the primary analysis (complete case IPT ATT weights). (B) Forest plot of adjusted hazard ratios and 95% confidence intervals (CIs) from weighted Cox proportional hazard model for the primary analysis and all sensitivity analyses compared to the unadjusted complete case and multiple imputation analyses.
ATC, average treatment effect of the control; ATE, average treatment effect; ATT, average treatment effect of the treated; HR, hazard ratio; Ipi, ipilimumab; IPT, inverse probability of treatment; IPTW, inverse probability of treatment weighting; Nivo, nivolumab; Pembro, pembrolizumab; PS, propensity score.

Sensitivity analyses indicated that these results are statistically robust to alternative weights, missing data mechanisms, and analysis methods. Results from this propensity score analysis are also consistent with those from a previously conducted MAIC comparing survival in the same studies[31] as well as a recent MAIC using a different cohort of patients treated with combination nivolumab plus ipilimumab.[12]

A key limitation of this analysis is the underlying assumption that there are no unmeasured confounders (i.e. variables not included in the model that are imbalanced between studies and that influence survival). No important unmeasured potential confounders were identified during clinical review, but as this is an untestable assumption, it remains a potential limitation of any such analysis. Patient characteristics between the trials were largely similar; however, tumor mutational analysis was not available for comparison. The HLA haplotype status of patients also differed between the two trials with all patients being HLA-A*02:01 in IMCgp100-202 versus an estimated ~40%-50% HLA-A*02:01-positive patients in GEM-1402. Although there is suggestive evidence for lack of impact of HLA-A*02:01 status for nivolumab plus ipilimumab on clinical outcomes in mUM in this analysis, there is not enough evidence to be conclusive. While geographic region also differed between the trials (i.e. only three overlapping trial sites), subgroup

analysis in IMCgp100-202 failed to detect differences in outcome solely based on region of study site.

In conclusion, tebentafusp is the only therapy to demonstrate a superior OS benefit in previously untreated HLA-A*02:01+ adult patients with mUM when compared with investigator's choice of predominantly pembrolizumab. Using a patient-level propensity score-weighted analysis, tebentafusp also demonstrated an OS benefit versus nivolumab plus ipilimumab. Furthermore, the data failed to demonstrate a clear difference in OS between the combination of an anti-PD1 and anti-CTLA4 compared to anti-PD1 monotherapy in previously untreated mUM patients. However, confirmation using longer follow-up analyses is warranted. These data also support the initial use of tebentafusp in previously untreated HLA-A*02:01+ patients with mUM as the first-line standard of care.

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