Clinical Trials in Metastatic Uveal Melanoma: Immunotherapy

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Keywords

Uveal melanoma · Immunotherapy · Immune checkpoint inhibitor · Vaccine · T cell

Abstract

Background: Uveal melanoma (UM) is a rare subtype of melanoma that generally has a poor prognosis once it has metastasized. Clinical trials evaluating immune checkpoint inhibitors (ICIs) in UM have demonstrated response rates lower than those seen in cutaneous melanoma. Despite lower efficacy demonstrated in initial ICI studies, there are a number of ongoing clinical trials investigating novel immunotherapy approaches in UM. **Summary:** This review aims to summarize important ongoing clinical trials investigating immunotherapeutic approaches in UM and previous trials that have evaluated a number of immunologic interventions. A thorough clinical trial investigation was conducted through clinicaltrials.gov using the disease search terms “uveal melanoma” and “ocular melanoma,” excluding non-immunotherapy-related trials. Here, we report on ICI, vaccine, adoptive T cells, and combination immunotherapy trials in UM. **Key Messages:** There is an increasing effort in the search for new, effective therapies for this difficult-to-treat

disease, with immunotherapeutic approaches being of particular interest. Increasing knowledge of UM biology and development of new biomarkers will direct future drug development and trial design.

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Introduction

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, with approximately 8,000 new cases worldwide per year [1]. The prognosis for patients with advanced UM remains bleak, with up to 50% developing metastatic disease, typically in the liver via the hematogenous route [1, 2]. Once metastatic, overall survival (OS) is limited, often reported as <12 months [2, 3].

Unfortunately, while poor outcomes are common for patients with UM, there is currently no globally recognized standard of care [4]. Institutions often adhere to individual algorithms for therapy based on their expertise and resources. In the absence of approved, disease-specific therapies, enrollment of UM patients on clinical trials has been critical [4]. Furthermore, there are ongoing

misperceptions about how UM differs from other melanoma subtypes, specifically the more common cutaneous melanoma (CM). Understanding the differences in biology and molecular characteristics of UM and CM is imperative for appropriate management and treatment selection.

This review will focus on the current status of immunotherapy treatment strategies and clinical trials for metastatic UM (MUM). Immunotherapies have been revolutionary in cancer treatment and hold promise as effective therapies for patients with UM and other difficult-to-treat tumor types. There is a rising number of immunotherapy clinical trials for patients with UM/MUM, including checkpoint inhibition, vaccines, and T-cell therapies. Please note that many of the therapies included in the clinical trials mentioned here are investigational agents, whose safety and efficacy may not have been established in larger and later-phase clinical trials.

Summary of Prior Studies and Ongoing Clinical Trials

Methods

Clinical trial information was downloaded from clinicaltrials.gov using the disease search terms “uveal melanoma” and “ocular melanoma” (July 24, 2020). Adjuvant trials and trials not including immunotherapies were excluded, and trials were combined from each search and grouped according to immunotherapy class: checkpoint inhibition, vaccines, adoptive T-cell therapy, and bispecific T-cell redirection. Trials were then ordered in terms of “status,” then “phase” and start date of the “trial period.” Tables 1–3 include trials that are “not yet recruiting,” “recruiting,” “active but not recruiting,” “enrolling by invitation,” and “suspended,” excluding trials that are “completed,” “withdrawn,” “terminated,” or “no longer available.” However, if any “completed,” “withdrawn,” “terminated,” or “no longer available” trials had data specifically for UM patients available, then these data were reported in the text summary.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that inhibit interactions between immune checkpoint proteins, such as programmed death-1 (PD-1)/PD-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4)/B7-1/B7-2, enabling T cells to recognize and attack cancer cells. ICIs, such as nivolumab, pembrolizumab (both PD-1 inhibitors), and ipilimumab (a CTLA-4 inhibitor), have positively transformed the

clinical management of CM patients, with monotherapy achieving response rates of approximately 10–45% [17], and combination therapy (most commonly ipilimumab with nivolumab) attaining response rates of 58% [18].

Conversely, responses to ICIs in MUM have been disappointing, possibly due to the lower mutagenicity, immunogenicity, and PD-L1 expression levels of UM compared with CM [2, 19, 20]. MUM responses to ICI monotherapy are around 0–7%, with short median progression-free survival (PFS) and OS values of about 2–3 months and up to approximately 1 year, respectively [20–24]. However, preliminary results from a terminated (due to slow accrual), phase II, single-arm, multicenter, 3-year, prospective study of pembrolizumab monotherapy (NCT02359851) were encouraging, although only in a total of 5 patients – all with MUM. One patient experienced complete response and 2 experienced stable disease; clinical benefit was associated with limited hepatic disease burden [25]. A larger, retrospective, phase IV trial, aiming to enroll 100 patients by invitation, will investigate the activity of nivolumab or pembrolizumab in MUM (NCT03964298), detailed later. ICI trials are presented in Table 1.

ICI combination therapy has yielded results inferior to those seen in CM [20]. Of three retrospective studies of combined PD-1 inhibitor and ipilimumab, one was limited to 15 patients and reported a 16.7% response rate and PFS of only 2.8 months [20, 22]. The two larger studies described similar results; one was in 64 patients across 16 centers and reported a 15.6% response rate, PFS of only 3 months, and an OS of 16.1 months [26], and the other was in 89 patients across 14 centers and reported an 11.6% response rate, PFS of 2.7 months, and OS of 15 months [27]. The ongoing GEM1402 phase II, single-arm, multicenter trial (NCT02626962), studying nivolumab/ipilimumab in 50 previously untreated patients with MUM, reported a 12% response rate and median PFS and OS of 3.3 and 12.7 months, respectively [5]. A single-arm, single-institution, expanded access program (CheckMate218 trial [NCT02186249]) assessed nivolumab/ipilimumab therapy in metastatic melanoma; in a small cohort of 6/64 patients (9%) with UM, none responded, and of 47/64 patients (73%) with CM, 28/44 (64%) responded [20, 28]. However, an ongoing phase II, single-arm, single-institution study investigating nivolumab/ipilimumab demonstrated more encouraging results in 30 treatment-naïve or previously treated patients with MUM (NCT01585194), with a response rate of 17% and median PFS and OS of 6 and 19.1 months, respectively [6].

Table 1. Clinical trials involving checkpoint inhibition [5–14]

NCT No. (reference)	Trial	Status	Phase	Sponsor/collaborators	Trial period
NCT04463368	Isolated hepatic perfusion in combination with ipilimumab + nivolumab in patients with UM metastases (SCANDIUM II)	Not yet recruiting	I	Sahlgrenska University Hospital, Sweden; Bristol-Myers Squibb	January 2021–June 2023
NCT02858869 ^a [8, 9]	Pembrolizumab + stereotactic radiosurgery for melanoma (including ocular) or NSCLC brain metastases	Recruiting	I	Emory University; Merck Sharp & Dohme Corp.	October 2016–October 2021
NCT03025256 ^a [11, 12]	IV and IT nivolumab in leptomeningeal disease, including MUM patients	Recruiting	I	MD Anderson Cancer Center; NCI	May 2018–December 2020
NCT03652077	INCAGN02390 in select advanced malignancies, including MUM	Recruiting	I	Incyte Corporation	August 2018–January 2021
NCT03922880	Nivolumab + ipilimumab + arginine deprivation (ADI-PEG 20) in MUM	Recruiting	I	Memorial Sloan Kettering Cancer Center	April 2019–April 2020
NCT02913417 [7]	SIR-Spheres [®] Yttrium90 + ipilimumab + nivolumab for MUM	Recruiting	I/II	David Minor, MD; California Pacific Medical Center; Jefferson Medical College of Thomas Jefferson University; University of Chicago; California Pacific Medical Center Research Institute	October 2016–June 2022
NCT04283890	PHP + immunotherapy (ipilimumab + nivolumab) in MUM (CHOPIN)	Recruiting	I/II	HW Kapiteijn, Leiden University Medical Center	December 2019–December 2024
NCT02831933 [14]	Radiation (SBRT) + gene therapy (ADV/HSV-tk) + valacyclovir before nivolumab for metastatic NSCLC + UM (ENSIGN)	Recruiting	II	Eric Bernicker, MD, The Methodist Hospital System	February 2017–June 2022
NCT03070392	Tebentafusp (IMCgp100) versus investigator choice (dacarbazine, ipilimumab, or pembrolizumab) in MUM	Recruiting	II	Immunocore Ltd.	October 2017–March 2023
NCT03472586	Ipilimumab + nivolumab + immunoembolization in MUM	Recruiting	II	Sidney Kimmel Cancer Center at Thomas Jefferson University; Bristol-Myers Squibb; Thomas Jefferson University	May 2018–January 2021
NCT03850691	IL-2 (aldesleukin) + nivolumab after radiation for MM (including ocular subtypes)	Recruiting	II	Masonic Cancer Center, University of Minnesota	May 2019–December 2025
NCT03964298	Nivolumab + pembrolizumab in MUM (imMUno)	Enrolling by invitation	IV	Institut Curie	November 2016–December 2019
NCT03068624 [10]	Autologous CD8+ SLC45A2-specific T lymphocytes + cyclophosphamide, IL-2 (aldesleukin) + ipilimumab in MUM	Active, not recruiting	I	MD Anderson Cancer Center; NCI	September 2017–September 2021
NCT01585194 [6]	Nivolumab + ipilimumab in MUM	Active, not recruiting	II	MD Anderson Cancer Center; NCI	November 2012–November 2019
NCT02626962 [5]	Nivolumab + ipilimumab in previously untreated MUM (GEM1402)	Active, not recruiting	II	Grupo Español Multidisciplinar de Melanoma; Bristol-Myers Squibb	April 2016–September 2020
NCT02697630 [13]	Pembrolizumab + entinostat to treat MUM (PEMDAC)	Active, not recruiting	II	Vastra Gotaland Region; Merck Sharp & Dohme Corp; Syndax Pharmaceuticals	February 2018–August 2023

ADI-PEG 20, pegylated arginine deiminase; ADV/HSV-tk, adenovirus-mediated expression of herpes simplex virus thymidine kinase; CD, cluster of differentiation; IL-2, interleukin-2; IT, intrathecal; IV, intravenous; MM, metastatic melanoma; MUM, metastatic uveal melanoma; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; PHP, percutaneous hepatic perfusion; SBRT, stereotactic body radiation therapy; SLC45A2, solute carrier family 45 member 2; UM, uveal melanoma. ^a Trials that have data published; however, UM patient data are not called out.

Table 2. Clinical trials involving vaccines

NCT No. (reference)	Trial	Status	Phase	Sponsor/collaborators	Trial period
NCT04335890	IKKb-matured, RNA-loaded dendritic cells for metastasized UM	Not yet recruiting	I	Hasumi International Research Foundation; Beatrice Schuler-Thurner, PhD, University Hospital Erlangen	May 2020–May 2025
UM, uveal melanoma.					

Table 3. Clinical trials involving T-cell therapies [10, 15, 16]

NCT No. (reference)	Trial	Status	Phase	Sponsor/collaborators	Trial period
NCT03635632	C7R-GD2.CART cells for patients with relapsed or refractory neuroblastoma and other GD2-positive cancers (GAIL-N)	Recruiting	I	Naylor College of Medicine; Center for Cell and Gene Therapy, Baylor College of Medicine; The Methodist Hospital System; Cancer Prevention Research Institute of Texas	April 2019–December 2037
NCT03070392	Tebentafusp (IMCgp100) versus investigator choice (dacarbazine, ipilimumab, or pembrolizumab) in MUM	Recruiting	II	Immunocore Ltd.	October 2017–March 2023
NCT03467516	Adoptive transfer TILs for MUM	Recruiting	II	Udai Kammula; University of Pittsburgh	May 2018–December 2021
NCT03068624 [10]	Autologous CD8+ SLC45A2-specific T lymphocytes + cyclophosphamide, IL-2 (aldesleukin) + ipilimumab in MUM	Active, not recruiting	I	MD Anderson Cancer Center; NCI	September 2017–September 2021
NCT02654821 [16]	TCR gene therapy (TCR-transduced T cells) in MM (including ocular melanoma)	Active, not recruiting	I/II	The Netherlands Cancer Institute	March 2012–January 2020
NCT02570308 [15]	Inpatient escalation dosing with tebentafusp (IMCgp100) in MUM patients	Active, not recruiting	I/II	Immunocore Ltd.	February 2016–January 2021
NCT02743611	BPX-701 (a genetically modified autologous T-cell product incorporating a HLA-A2-restricted PRAME-directed TCR and a rimiducid-inducible safety switch) in previously treated AML/MDS or MUM	Active, not recruiting	I/II	Bellicum Pharmaceuticals	April 2017–July 2020

AML, acute myeloid leukemia; CD, cluster of differentiation; HLA, human leukocyte antigen; IL-2, interleukin-2; MDS, myelodysplastic syndrome; MM, metastatic melanoma; MUM, metastatic uveal melanoma; NCI, National Cancer Institute; PRAME, preferentially expressed antigen in melanoma; SLC45A2, solute carrier family 45 member 2; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

The potential of durability of response with ICIs should also be considered. A recent report presented a case of complete metabolic response lasting 22 months post-treatment with ipilimumab and nivolumab [29]. The aforementioned retrospective analysis in 64 patients with MUM or unresectable UM treated with ipilimumab/PD-1 inhibitor reported a 15.6% response rate; however, median duration of response was a promising 25.5 months (range: 9–65) [26].

In predicting patient responses to ICIs, there is encouraging evidence that methyl-CpG binding domain

protein 4 (MBD4)-deficient tumors may be sensitive to checkpoint inhibitors, and therefore MBD4 is a potential predictor of ICI response for therapy in the future. Rodrigues et al. [30] reported that in a series of 102 patients with MUM, 2 (2%) were identified as having germline deleterious frameshift deletions of MBD4, of which one was an outlier patient with an exceptionally high sensitivity to pembrolizumab.

Although, to date, most immunotherapy trials in MUM have evaluated CTLA-4- and PD-1/PD-L1-based therapies, there is ongoing research into new ICI tumor

targets, such as T-cell immunoglobulin and mucin domain-3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3) to use for the development of monotherapies or add-on agents. TIM-3, an inhibitory receptor involved in immune tolerance, is expressed in many human cancers and infiltrating immune cells. INCAGN02390 is a novel, antagonistic antibody specific for TIM-3 that is being evaluated in a phase I, single-arm trial (NCT03652077) with an accrual goal of 41 patients with advanced malignancies, including MUM [31]. Though there are no current LAG-3 trials specific for the MUM population, there is a rationale for this target, and trials are likely forthcoming [32].

Clinical trials are also underway for ICIs combined with liver-directed therapy in an effort to enhance their anticancer toxicity. It is postulated that tumor death and antigen presentation, driven by liver-directed therapy, could augment a response to combination or subsequent immunotherapy. Interim results for NCT02913417, a phase I/II, single-arm, multicenter trial, have shown that treating MUM metastatic to the liver with radioembolization with yttrium90, followed by ipilimumab and nivolumab is a feasible treatment option. Of 13 patients, 10 received both yttrium90 and immunotherapy, and an overall response was recorded for 23% of patients (3/13), who remained stable for >5 months, and median PFS and OS values were reported as 6.2 and >11 months, respectively [7]. A phase II, single-arm, single-center trial will investigate ipilimumab and nivolumab with immunoembolization in 35 patients with MUM (NCT03472586). There are also two trials investigating ipilimumab/nivolumab combined with selective administration of chemotherapy (melphalan) to the liver via percutaneous hepatic perfusion in MUM: CHOPIN (NCT04283890), a phase I/II, randomized, three-arm, single-center study in an estimated 88 patients with MUM, and SCANDIUM II (NCT04463368), a phase I, randomized, multicenter study, in an estimated 18 patients with MUM.

Additionally, there are trials combining standard ICIs with alternative agents and other immunotherapy modalities. For example, PEMDAC (NCT02697630) is a phase II, single-arm, multicenter trial evaluating pembrolizumab in combination with the epigenetic therapy regulator entinostat, a benzamide histone deacetylase inhibitor, in 29 patients; 90% with MUM. Interim results showed that of 29 patients, 3 achieved a partial response to give an overall response of 10%, 9 patients (31%) had stable disease, and median OS was 11.5 months [33]. There are also two small phase I trials for advanced UM: one single-arm, single-institution study investigating nivolumab/ipilimumab combined with arginine deple-

tion using pegylated arginine deiminase (ADI-PEG 20) in 9 patients with MUM (NCT03922880) and a second, recently completed, single-arm, multicenter trial (VLA-024 CLEVER) that investigated ipilimumab with oncolytic virus CAVATAK® in 11 patients with MUM (NCT03408587). Furthermore, there are two other recruiting trials studying ICIs in combination with forms of radiotherapy (NCT02858869 and NCT03850691) and gene therapy (NCT02831933). There is also a phase I, single-arm, single-center study aiming to investigate ipilimumab combined with autologous tumor-infiltrating lymphocyte (TIL) transfer in 19 patients with MUM (NCT03068624, see 'Adoptive T-cell therapies' section), three completed trials of ICIs in combination with vaccine therapy that include patients with MUM (NCT00025181, NCT00032045, and NCT00084656), and a phase I/II trial that reported poor results for ipilimumab with interleukin-2 (IL-2) therapy in metastatic melanoma, including UM (NCT00058279) [34].

Another ICI trial of note is a recently completed phase II, two-arm, randomized, multicenter trial evaluating ipilimumab versus nab-paclitaxel and bevacizumab as first-line therapy in 24 patients with stage IV melanoma, including MUM, that cannot be surgically removed (NCT02158520); no data have yet been reported. Additional recruiting trials include a phase I, single-arm, single-center study evaluating intrathecal and intravenous delivery of nivolumab in an estimated 30 patients with leptomeningeal melanoma, including patients with MUM (NCT03025256), and a phase II, randomized, two-arm, multicenter study investigating dacarbazine, ipilimumab, or pembrolizumab versus the new bispecific T-cell receptor (TCR) redirection therapeutic, tebentafusp, in MUM (NCT03070392), discussed later.

Vaccines

Cancer vaccines are designed to stimulate the immune system to better recognize tumor-associated antigens on cancer cells and destroy them, and there has been a concerted effort to evaluate vaccines in UM. Dendritic cells can be used in vaccine-based therapies; these are antigen-presenting cells with the ability to activate naïve antigen-specific T cells to stimulate immune activity against tumors. There is a new phase I, single-arm, single-center trial, not yet recruiting, which will evaluate IKKb-matured, dendritic cells loaded with RNA coding for tumor mRNA, defined tumor-associated antigens and driver mutations, in the treatment of MUM (NCT04335890). This vaccine trial is presented in Table 2.

T-Cell-Based Approaches

It has been postulated that MUM may demonstrate innate resistance to currently available immunotherapies due to low mutational burden, as well as low PD-L1 expression and paucity of intratumoral T cells, especially in hepatic metastases [20, 35]. A recent study demonstrated that cytotoxic (cluster of differentiation 8-positive [CD8+]) TILs are mostly located peritumorally at the tumor/normal liver interface rather than within the tumors [20, 36]. Redirection of patient T cells into MUM tumors is another strategy being pursued to treat MUM. Adoptive T-cell therapies, such as TIL therapy and engineered TCR T cells, have been considered, as well as the novel ImmTAC® (immune-mobilizing monoclonal TCR against cancer) molecule, tebentafusp. T-cell-based approach trials are presented in Table 3.

Adoptive T-Cell Therapies

Adoptive T-cell therapies involve removing T cells from a cancer patient, isolating and expanding them *ex vivo*, and then reinfusing them back into the patient in an attempt to enhance their immune system to more efficiently attack the cancer. The T cells may be extracted from a harvested tumor or removed from peripheral circulation through apheresis. An example is TIL therapy, which has shown promise in treating MUM in a phase II, two-arm, single-center trial (NCT01814046). Twenty patients with MUM were treated with lympho-depleting conditioning chemotherapy, followed by infusion of autologous TILs with high-dose IL-2. An interim analysis demonstrated an overall response rate of 35% in terms of objective tumor regression. Remarkably, liver metastatic tumors completely regressed for 1 patient, with no signs of recurrence 21 months after therapy [37]. This trial was terminated in 2018 with no further data on OS or durability of response. A larger-scale, phase II, single-arm, single-center study is currently recruiting to evaluate a non-myeloablative, lympho-depleting preparative regimen consisting of fludarabine and cyclophosphamide, followed by infusion of autologous TILs and high-dose IL-2 in 59 patients with MUM (NCT03467516).

Autologous tumor antigen-specific T cells can be generated and expanded from peripheral blood, and patient T cells can also be modified so they are better able to target a particular cancer antigen. A phase I, single-arm, single-center trial is evaluating the side effects, best dose, and efficacy of autologous CD8+ SLC45A2 (a membrane-associated melanocyte differentiation antigen)-specific T lymphocytes, administered along with cyclophosphamide, IL-2, and ipilimumab, in 19 patients with MUM

(NCT03068624). Additionally, a small phase I/II, single-arm, single-center trial, including patients with ocular melanoma, is investigating treatment with non-myeloablative chemotherapy followed by adoptive transfer of autologous T cells modified with a TCR specific for melanoma-associated antigens recognized by T cells (NCT02654821). There is also an ongoing phase I/II, two-arm, multicenter trial exploring the safety and activity of preferentially expressed antigen in melanoma (PRAME)-TCR therapy, which includes a cohort of MUM patients (NCT02743611); autologous T cells (BPX-701) are modified to target the tumor marker PRAME and include a biological safety switch that is controllable with rimiducid. T-cell therapy has also been used to target GD2, a ganglioside expressed across the surface of neuroblastomas, melanoma cells, and other tumor types [38]. The GAIL-N trial is an early phase I, single-arm, single-center study aiming to recruit 64 participants, including MUM patients, to evaluate the largest safe dose, toxicity, and efficacy of autologous T lymphocytes expressing GD2-specific chimeric antigen and constitutively active IL-7 receptors (GD2-C7R and chimeric antigen receptor [CAR] T cells) to treat GD2-positive solid cancers (NCT03635632).

Bispecific TCR Redirection

Tebentafusp (IMCgp100) is a potential new therapy designed to treat MUM based on a unique ImmTAC TCR-based bispecific platform. Tebentafusp has a binding region developed to target intracellularly derived melanoma-associated gp100₂₈₀₋₂₈₈ peptide in complex with human leukocyte antigen (HLA)-A*02:01 on the surface of cancer cells. Gp100 is expressed more frequently (100 and 85%, respectively), uniformly, and at higher levels on UM cells compared with CM cells [39]. HLA-A*02:01 is present in approximately 50% of Caucasian patients [40]; HLA-A2*02:01 positivity is an inclusion criterion for patients in tebentafusp clinical trials. Once bound, in clinical studies, tebentafusp recruits a broad range of T cells (regardless of their specificity) into the tumor via its effector anti-CD3 single-chain variable fragment region, designed to mimic an immune synapse, and activates T-cell-mediated lysis [2, 15, 41, 42]; this mechanism is independent of tumor mutational burden.

Clinical activity of tebentafusp was first demonstrated in a phase I, two-arm, multicenter IMCgp100-01 trial evaluating dose, safety, and efficacy (NCT01211262) in both MUM and metastatic CM (MCM); the MUM cohort of 19 patients reported a response rate of 16%, with a 1-year OS rate of 65% for the overall population of both MCM and

Table 4. Summary table of key clinical study endpoint data currently available for UM patients in immunotherapy clinical trials [5–7, 15, 21, 22, 24, 26, 27, 33, 37, 43, 44]

	Type of study	UM patients, <i>n</i>	Overall response rate, %	Median PFS, months	Median OS, months
Immune checkpoint inhibition					
Monotherapy					
Clinical outcomes in MUM treated with PD-1 and PD-L1 antibodies[21]	Retrospective explorative analysis	56	3.6	2.6	7.7
Prognostic factors and outcomes in MUM treated with PD-1 or combined PD-1/CTLA-4 inhibition [22]	Retrospective explorative analysis	86	4.7	2.8–3.1	10–14
Nivolumab for patients with MUM previously untreated with ipilimumab: a single-institution retrospective study [24]	Retrospective explorative analysis	14	7.1	2.3	13.8
Combination therapy and with other agents					
Prognostic factors and outcomes in MUM treated with PD-1 or combined PD-1/CTLA-4 inhibition [22]	Retrospective explorative analysis	15	16.7	2.8	nr
Combined immune checkpoint blockade for MUM: a retrospective, multicenter study [26]	Retrospective explorative analysis	64	15.6	3.0	16.1
Ipilimumab + nivolumab for patients with MUM: a multicenter, retrospective study [27]	Retrospective explorative analysis	89	11.6	2.7	15
Nivolumab + ipilimumab in previously untreated MUM (GEM1402) (NCT02626962 [5])	Phase II clinical	50	12	3.3	12.7
Nivolumab + ipilimumab in MUM (NCT01585194 [6])	Phase II clinical	30	17	6.0	19.1
SIR-Spheres [®] Yttrium90 + ipilimumab + nivolumab for MUM (NCT02913417 [7])	Phase I/II clinical	13	23	6.2	>11
Efficacy study of pembrolizumab with entinostat to treat MUM (PEMDAC) (NCT02697630 [33])	Phase II clinical	29	10	nr	11.5
TILs					
Immunotherapy using TILs for metastatic ocular melanoma (NCT01814046 [37])	Phase II clinical	20	35 ^a	nr	nr
Bispecific TCR T-cell redirection – tebentafusp					
Tebentafusp (IMCgp100) in MM (NCT01211262 [43])	Phase I clinical	19	16	nr	nr
Inpatient escalation dosing with tebentafusp (IMCgp100) in MUM patients (NCT02570308 [15, 44])	Phase I clinical	19	18	5.6	Not reached after follow-up at 19.1

This table sets forth reported data only, including interim data. Due to the differing nature of each trial design and the lack of head-to-head studies, this table is not intended to present any comparison of treatment agents or effectiveness. The trials in this table are the more meaningful studies involving >10 patients. PFS, progression-free survival; OS, overall survival; MM, metastatic melanoma; MUM, metastatic uveal melanoma; nr, not reported; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; TIL, tumor-infiltrating lymphocytes; UM, uveal melanoma; CTLA-4, cytotoxic T-lymphocyte anti-gen-4; TCR, T-cell receptor. ^a In terms of objective tumor regression.

MUM patients, with similar survival reported for both MCM and MUM patients [43]. A subsequent phase I/II, two-arm, multicenter study (IMCgp100-102 [NCT02570308]), which only enrolled patients with MUM, demonstrated a response rate of 18%, a median PFS of 5.6 months, median OS not reached after follow-up at 19.1 months, and a 1-year OS rate of 74% based on 19 patients from the phase I portion of the study [2, 15, 44]; the phase II expansion in 130 previously treated patients is currently

ongoing, but no longer recruiting. Additionally, adverse events have generally been manageable and consistent with the hypothesized mechanism of action for tebentafusp, with most adverse events relating to on-target (gp100) off-tumor activity (such as rash, pruritus, or depigmentation), or cytokine-mediated events (such as pyrexia and hypotension) [2, 15, 43]. There is now a pivotal, randomized, two-arm, multicenter controlled study aiming to recruit >300 previously untreated MUM patients to compare

tebentafusp to dacarbazine, ipilimumab, or pembrolizumab monotherapy (IMCgp100-202 [NCT03070392]).

A summary of the key clinical study endpoint data currently available for UM patients in immunotherapy clinical trials, discussed in this review, is presented in Table 4. However, due to the differing nature of each trial design and the lack of head-to-head studies, this table is not intended to present any comparison of treatment agents or effectiveness.

Conclusion

The race to find an effective and safe immunotherapy to treat UM is underway. Checkpoint inhibition has been beneficial in managing CM and an option to treat UM. However, the low mutational burden and poor immunogenicity of UM tumors may underlie poor responses and resistance to ICIs alone [19, 20]. Trials investigating combination ICIs, multimodality approaches, novel inhibitors targeting newer checkpoints, vaccine approaches, and adoptive T-cell strategies are ongoing. Pretreatment, on-treatment, and on-progression biopsies have been incorporated into many of the trials discussed. Information gathered from studying these important samples will inform the field about biomarkers, predictors of response, and mechanisms of innate and acquired resistance. Subsequently, this will contribute to a greater understanding

of UM biology that may further direct future drug development and clinical trial design. Moreover, continued referral of UM patients for clinical trials is vital for moving the field forward.

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Conflict of Interest Statement

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Author Contributions

The sole author of this manuscript was Dr. Marlana Orloff, who was involved in all stages of manuscript development and approved the final version.

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