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Clinical Trials in Metastatic Uveal Melanoma: Current Status

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Abstract
Background: Uveal melanoma is a rare subtype of melanoma. Prognosis and survival rates for patients with metastatic uveal melanoma remain poor. No current FDA-approved standard of care therapy is available for patients with metastatic uveal melanoma. Thus, clinical trials are essential for the development of new therapies and to provide patients hope for improved survival and outcomes. ***Summary:*** In this article, we review clinical trials identified on the database https://clinicaltrials.gov that are open and enrolling patients with metastatic uveal melanoma as of November 26, 2019. This search produced 17 active trials involving liver-directed therapy, CNS-directed therapy, and systemic therapy with immunotherapy, targeted therapy, or oncolytic virus therapy. Here, we discuss liver and CNS-directed therapy as well as systemic targeted therapy and oncolytic virus therapy. Immunotherapy clinical trials are discussed in a companion review article by Dr. Marlana Orloff. ***Key Messages:*** Various novel therapeutic targets and immunomodulatory approaches are on the horizon for patients with metastatic uveal melanoma and may yield incremental therapeutic benefit. Selecting a clinical trial must be individualized and made jointly with the patient and his/her oncologist.

Introduction

Uveal melanoma is the most common intraocular tumor in adults. The overall incidence of uveal melanoma has remained stable from 1973 to 2013, with about 5 patients per million affected, which comprises 3% of all melanomas [1, 2]. For all stages, the 5-year overall survival (OS) remains about 80.9% [1]. While about 5% of patients present with metastatic disease, up to 50% develop metastatic disease with subsequently worse prognosis [3]. Of patients who develop metastatic disease, liver is the most common site (89%) [4]. Historically, median OS for metastatic uveal melanoma ranges from 3 to 12 months, with a 1-year OS of 20% [4, 5]. However, more recent data from clinical trial patients suggests a median progression-free survival (PFS) and OS of 3.3 months and 10.2 months, and 1-year OS of 43% [6]. Prognosis and survival rates for metastatic uveal melanoma remain poor, and there is currently no FDA approved therapy in the metastatic setting. Clinical trials are essential for the development of new therapies and to provide patients hope for improved survival and outcomes.

Methods

We conducted a search for active clinical trials available worldwide for metastatic uveal melanoma on November 26, 2019, through the clinical trial database available at https://clinicaltrials.gov. ClinicalTrials.gov is run by the National Library of Medicine

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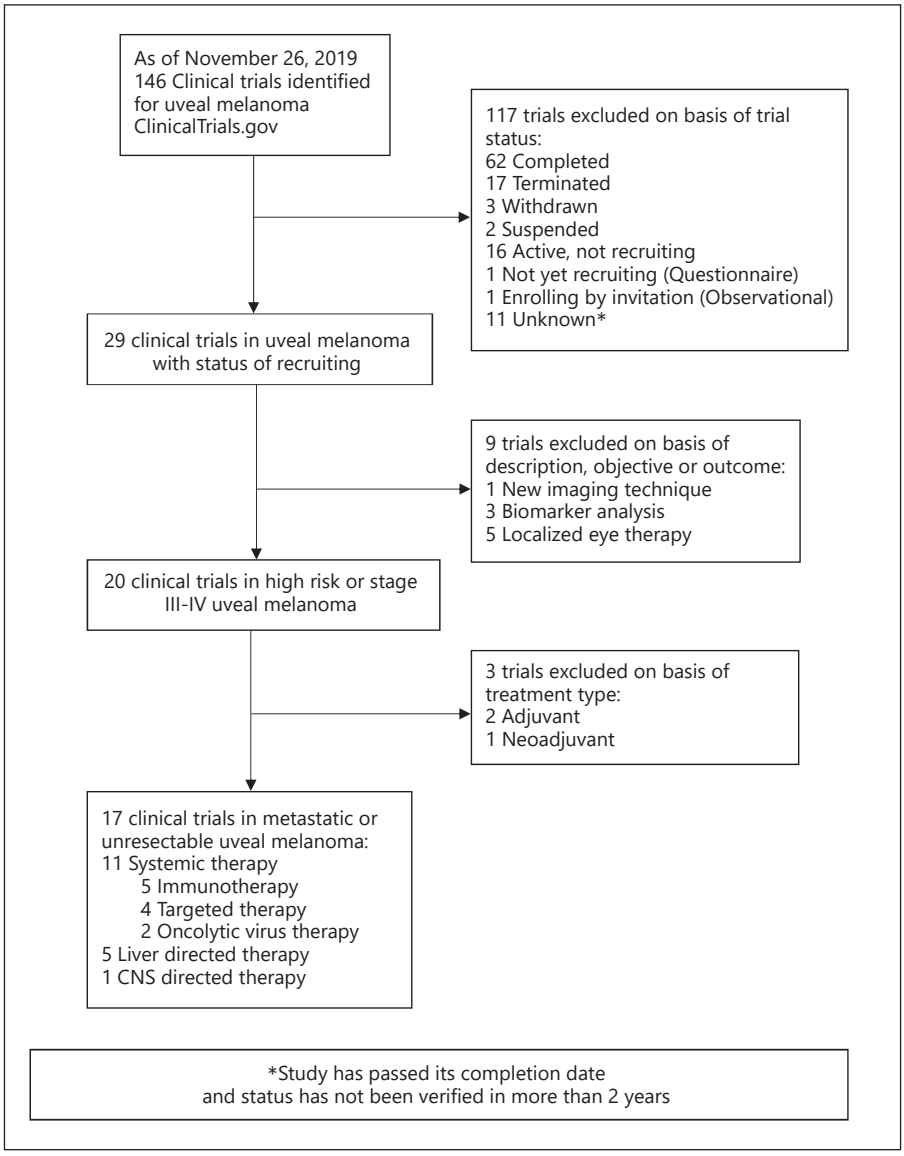

Fig. 1. Flow diagram of clinical trials for uveal melanoma.

at the National Institutes of Health, and is the largest clinical trials registry, currently holding registrations from over 818,000 trials from 209 countries. Our search produced 146 available trials for uveal melanoma (Fig. 1), with a significant proportion (80%, n = 117) of trials not accruing patients due to status of completed, terminated, withdrawn, suspended, active – not recruiting, or unknown status. Once removed, 29 currently recruiting trials remained. Of these trials, 12 were excluded: 4 nontherapeutic trials, 5 localized eye therapy trials, and 3 trials for neoadjuvant or adjuvant therapy for resectable disease. A final 17 trials were identified for treatment of metastatic uveal melanoma; including 5 trials utilizing liver-directed therapy, 1 trial with CNS-directed therapy, and 11 trials with systemic immunotherapy or targeted therapy used in combination or as single agent. Trials including immunological checkpoint inhibitors with liver-directed therapies are categorized as liver-directed therapy trials. Similarly, a trial including an immunological checkpoint inhibitor in combination with CNS-directed therapy is categorized as CNS-directed therapy trial. All clinical trials for metastatic uveal melanoma discussed in this review are summarized in Table 1.

Clinical Trials for Patients with Metastatic Uveal Melanoma

Systemic Therapy Clinical Trials

No current standard of care therapy exists for metastatic uveal melanoma. Response rates with checkpoint inhibitor therapy with single agent anti-CTLA4 (ipilimumab) or anti-PD1 (nivolumab) or combination anti-CTLA4/anti-PD1 inhibition have been disappointing,

Table 1. Clinical trials in metastatic uveal melanoma

NCT number	Trial	Status	Phase	Locations
NCT02768766	Intermittent selumetinib for uveal melanoma	recruiting	I	Columbia University Medical Center; Memorial Sloan Kettering Cancer Center; MD Anderson Cancer Center
NCT03947385	IDE196 in patients with solid tumors harboring GNAQ/11 mutations or PRKC fusions	recruiting	I/II	Columbia University Medical Center; Thomas Jefferson University; Sarah Cannon Research Institute/Tenessee Oncology; MD Anderson Cancer Center; Westmead Hospital (Sydney, Australia)
NCT03207347	Niraparib in BAP1 and other DNA damage response deficient neoplasms	recruiting	II	University of Florida
NCT04187833	Nivolumab in combination with talazoparib in melanoma and mutations in BRCA or BRCA-ness genes	active, not yet recruiting	II	Cleveland Clinic
NCT03297424	PLX2853 in advanced malignancies	recruiting	I/II	Honor Health (Arizona); Sylvester Comprehensive Cancer Center/University of Miami Miller School of Medicine; Columbia University; South Texas Accelerated Research Therapeutics; Virginia Cancer Specialist
NCT02831933	Radiation and gene therapy before nivolumab for metastatic non-small cell carcinoma and uveal melanoma	recruiting	II	Houston Methodist Hospital
NCT03865212	Modified virus VSV-IFNbetaTYRP1 in treating patients with stage III-IV melanoma	recruiting	I	Mayo Clinic in Florida; Mayo Clinic in Rochester
NCT02913417	Yttrium90, ipilimumab, & nivolumab for uveal melanoma with liver metastases	recruiting	I/II	California Pacific Medical Center; University of Chicago; Thomas Jefferson University
NCT03472586	Ipilimumab and nivolumab with immunoembolization in treating participants with metastatic uveal melanoma in the liver	recruiting	II	Thomas Jefferson University
NCT01785316	The Scandinavian randomized controlled trial of isolated hepatic perfusion for uveal melanoma liver metastases	recruiting	III	Sahlgrenska University Hospital (Sweden)
NCT00986661	A study to assess PV-10 chemoablation of cancer of the liver	recruiting	I	Sharp Memorial Hospital (San Diego, California); Florida Hospital Tampa; St. Luke's University Health Network (Bethlehem, Pennsylvania); Vanderbilt University Medical Center; MD Anderson Cancer Center
NCT02678572	Percutaneous hepatic perfusion in patients with hepatic-dominant ocular melanoma (FOCUS)	recruiting	III	Stanford University; Moffit Cancer Center; Emory University; University of Chicago; University of Maryland Cancer Center; Atlantic Melanoma Center at Morristonwn Medical Center (NJ); Roswell Park Cancer Institute; Duke University Medical Center; Ohio State University; St. Luke's University Hospital Cancer Center; Thomas Jefferson University; University of Tennesee; MD Anderson Cancer Center; sites in Austria, Belgium, France, Germany, Italy, Spain, Switzerland, UK
NCT03025256	Intravenous and intrathecal nivolumab in treating patients with leptomeningeal disease	recruiting	I	MD Anderson Cancer Center

with response rates of 3.6% with single agent, and 12–17% with combination therapy [7–9]. PFS and OS with immunotherapy are 2.8 months and 8.9 months, respectively. Similarly, PFS and OS with targeted (kinase) therapy are 2.8 months and 9.1 months [6]. Currently, 11 clinical trials with systemic therapy are available, specifically 5 trials with immunological checkpoint inhibitors, 4 trials with targeted therapy, and 2 trials with oncolytic virus therapy. The 5 trials with systemic immunotherapy are discussed separately in the companion review article by Marlana Orloff, MD. The remaining systemic therapy trials will be discussed in this review. Trials with agents targeting spe-

cific pathways alone or in combination with immunological checkpoint inhibitors are categorized as targeted therapy clinical trials. Similarly, trials with oncolytic viral therapies alone or in combination with immunological checkpoint inhibitors are categorized as oncolytic virus therapy trials. Details of the targeted therapy and oncolytic virus therapy trials are presented in Table 1.

Targeted Therapy Clinical Trials

The current landscape of systemic therapy for cutaneous melanoma is largely driven by immunotherapy. Although effective in treating patients with cutaneous melanoma, response rates have been disappointing in uveal melanoma. Different approaches, including targeted should also be explored in this field. Four clinical trials are currently available utilizing targeted therapy. A phase 1 trial of intermittent dosing of the mitogen-activated protein kinase kinase (MEK) enzyme inhibitor, selumetinib, in metastatic uveal melanoma patients who have not received prior MEK inhibitor therapy (NCT02768766), targets the mitogen-activated protein kinase (MAPK) pathway, regardless of tumor mutational status. Oncogenic mutations in *GNAQ* or *GNA11* are observed in more than 80% of primary uveal melanomas and activate signaling pathways primarily including the MAPK pathway, which leads to cell proliferation and survival [10, 11]. A prior randomized phase 2 trial compared selumetinib to chemotherapy in 101 metastatic uveal melanoma patients and found a modest benefit in PFS (15.9 vs. 7 weeks) and in objective response rate (14 vs. 0%) for those treated with selumetinib [12]. However, treatment-related adverse events were observed in 97% of patients treated with selumetinib. With this trial, an intermittent dosing schedule may achieve a better toxicity profile and response rate if higher doses of selumetinib can be achieved.

Mutations in *GNAQ* or *GNA11* also activate the protein kinase C pathway, which also leads to cell proliferation and survival and thus serves as another target for cancer-directed therapy. A current phase 1/2 basket trial is available to metastatic uveal melanoma patients and other solid tumors, which uses the drug IDE196 in patients harboring *GNAQ/11* mutations or protein kinase C fusions (NCT03947385). A recent phase 1 study of IDE196 in patients with metastatic uveal melanoma demonstrated encouraging clinical activity with 6/66 patients achieving a partial response and 45/66 with stable disease [13]. The toxicity profile was tolerable, with 25% of patients developing grade 3–4 adverse events, namely hypotension. While two dosing strategies were employed in this trial (once daily dosing and twice daily dosing), twice daily dosing was better tolerated and potentially exhibited longer duration of response. All patients (n = 38) in the daily dosing regimen discontinued treatment due to progressive disease, whereas 5 patients in the twice-daily dosing regimen (n = 30) remained on treatment for greater than 13 months. Of these 5 patients, 2 maintained a partial response and 3 had stable disease [13]. For this reason, the study design for IDE196 includes a dose escalation phase for twice daily dosing to determine the recommended phase 2 dose in patients with metastatic uveal melanoma, cutaneous melanoma, colorectal cancer, and other solid tumors.

Another target for clinical trials is double stranded DNA damage repair genes. Germline and somatic mutations in the double-stranded DNA damage repair gene *BAP1* have been found in patients with uveal melanoma. PARP1/2 enzymes are responsible for repairing single-stranded DNA breaks. Inhibition by a PARP inhibitor, along with a deficient DNA damage repair gene, ultimately leads to truncation of DNA replication, transcription, and cell death, also known as synthetic lethality [14]. Several trials in other tumor types, specifically breast, ovarian, and prostate cancers that target the *BRCA1/2* genes have successfully shown improved response rates and PFS with PARP inhibitor therapy [15–17]. A current clinical trial is evaluating niraparib in *BAP1* and other DNA damage response deficient neoplasms in metastatic uveal melanoma, mesothelioma, and renal cell carcinoma (NCT03207347). Similarly, another phase 2 trial that is active, but not yet recruiting patients, is using the combination of talazoparib (PARP inhibitor) and nivolumab (anti-PD-1 immunotherapy) in metastatic uveal or cutaneous melanoma patients that harbor a mutation in a DNA damage repair gene (NCT04187833). The DNA damage repair genes included in this study are *BRCA1/2* and *BRCA*ness genes, which are specifically responsible for homologous recombination repair of DNA. In cutaneous melanoma, the combination of PARP and PD-1 inhibition has shown to increase the immunogenicity of tumor cells by promoting T cell and natural killer cell infiltration, and increasing tumor expression of PD-L1 in vitro and in vivo [18–20].

Lastly, a phase 1/2 trial evaluates PLX2853 in advanced malignancies (NCT03297424). PLX2853 is an inhibitor of bromodomain-containing protein 4 (BRD4), a BET family member, an epigenetic regulator that is known to exert key roles involved in chromatin remodeling and transcriptional regulation. BRD4 is significantly upregulated in melanoma tissue; treatment with BRD4 or BET inhibitors have shown to impair melanoma cell prolifera-

tion and tumor growth in vitro and in vivo [21]. Similarly, BRD4 inhibition demonstrated cytotoxic activity in uveal melanoma cell lines and mouse xenograft models carrying *GNAQ/11* mutations [22].

Oncolytic Virus Therapy Clinical Trials

Oncolytic viruses are also an alternate approach in treating metastatic uveal melanoma patients.

Oncolytic virus therapy has been utilized in cutaneous melanoma with the development of talimogene laherparepvec (TVEC), approved by the FDA in October 2015. TVEC is currently being studied in combination to expand its use and synergize with other interventions, including immune checkpoint inhibitor therapy. However, oncolytic virus therapy has not yet been introduced in the field of uveal melanoma. Currently, two clinical trials are available for intratumoral injection of oncolytic virus therapy. One is a phase 2 trial for anti-PD-1 naïve patients to receive gene therapy with intralesional injection of adenovirus-mediated expression of herpes simplex virus thymidine kinase (ADV/HSV-tk) with valacyclovir and stereotactic body radiation therapy followed by nivolumab administration on day 17 (NCT02831933). This therapeutic combination builds on the concept of "suicide gene therapy," where a therapeutic gene-encoding enzyme (ADV/HSV-tk) is capable of transforming a nontoxic prodrug (valacyclovir) into a cell toxin that enhances the cytotoxic effect within cancer cells and protects the healthy cells [23]. Another clinical trial using a modified virus is a phase 1 study of VSV-IFNbetaTYRP1 in patients with metastatic uveal or cutaneous melanoma (NCT03865212). The vesicular stomatitis virus (VSV) is altered to include two extra genes: human interferon beta (hIFN-β), which may protect normal healthy cells from becoming infected with the virus, and TYRP1, which is expressed mainly in melanocytes and melanoma tumor cells. TYRP1 can trigger a strong immune response to kill the melanoma tumor cells. VSV has been shown to have a rapid replication rate within the tumor and to be cytotoxic in melanoma xenograft models. Targeting TYRP1 antigen has been shown to increase CD4 T cells and IL-17 in vitro and in vivo, resulting in increased immune cell infiltration into the tumor microenvironment [24–26].

Liver-Directed Therapy Clinical Trials

As up to 89% of patients with metastatic uveal melanoma develop metastatic disease to the liver, recent studies have suggested statistically significant improved progression-free survival (PFS) and OS with liver-directed therapy when compared to systemic therapy (median PFS 5.2 vs. 2.8 months; mOS 14.6 vs. 9.3 months) [6]. However, when controlling for key patient characteristics, the OS benefit for liver-directed therapies is no longer seen. Five studies are currently available for metastatic uveal melanoma patients with significant liver disease burden and limited extrahepatic disease, which include: a phase 1/2 study of combination immunotherapy with ipilimumab/nivolumab with SirSpheres Yttrium-90 internal hepatic radiation (NCT02913417); combination ipilimumab/nivolumab with immunoembolization (phase 2) to liver metastases (NCT03472586); phase 3 isolated hepatic perfusion study where high concentration chemotherapy is perfused through the liver with minimal systemic exposure (NCT01785316); a phase 1 study of intralesional injection of PV-10 (10% rose bengal disodium), which has an expansion cohort of patients that can receive immune checkpoint inhibitor therapy (NCT00986661); and a phase 3 study of percutaneous hepatic perfusion with melphalan (NCT02678572). This study (also known as the FOCUS trial) delivers melphalan 3 mg/kg using the Delcath Hepatic Delivery System via percutaneous catheterization of the femoral artery to access the hepatic artery to infuse the chemotherapeutic agent, and in the inferior caval vein to aspirate the chemosaturated blood returning through the hepatic veins, which is perfused through an extracorporeal filtration system, and then returned to systemic circulation. Patients can receive up to six treatments at 6-week intervals. In another phase 3 trial, percutaneous hepatic perfusion of melphalan was compared with best alternative care in 93 patients with melanoma liver metastases. Eighty-three patients in this study had uveal melanoma. Hepatic PFS was significantly prolonged with melphalan infusion (median 7.0 vs. 1.6 months); however, no difference was observed in OS (median 10.6 vs. 10.0 months) [27].

CNS-Directed Therapy Clinical Trial

While uveal melanoma does not typically metastasize to the central nervous system, several case reports and case series have demonstrated leptomeningeal involvement [28, 29]. Data from metastatic cutaneous melanoma patients with leptomeningeal disease has shown a median OS of only 1.8 months [30]. Limited treatment options are available for cutaneous and uveal melanoma patients with leptomeningeal disease with limited evidence of long-term clinical benefit from them [31]. A current phase 1 clinical trial available for uveal melanoma patients with leptomeningeal disease involves the administration of intrathecal nivolumab with intravenous nivolumab beginning in cycle 2 (NCT03025256).

Conclusions

The current landscape of clinical trials available for treatment of metastatic uveal melanoma is comprised of 17 active trials that encompass a range of modalities, including immunotherapy, targeted therapy, oncolytic virus therapy, as well as liver-directed therapy, and CNS-directed therapy. While informative, our review of available clinical trials has limitations. While our search criteria were broad in order to encompass all clinical trials available for metastatic uveal melanoma, trials were largely limited to "recruiting" status. Therefore, trials that opened or started recruiting after the search date of November 26, 2019, were not included in this review. As uveal melanoma is a rare disease, we would expect a few trials may have opened after the search was performed. As no current standard of care therapy exists for metastatic uveal melanoma, clinical trials are essential for developing new therapies and offering patients hope for improved outcomes. Various novel therapeutic targets and immunomodulatory approaches are on the horizon and may yield incremental therapeutic benefit. Selecting an appropriate clinical trial can be overwhelming and should be made with a patient's oncologist. Oncologists and their clinical trial team can discuss with patients the details of a trial, eligibility criteria, and expected toxicity. Additionally, oncologists can compare available clinical trials to standard of care therapy in the context of a patient's comorbidities, location, and burden of metastatic disease.

Conflict of Interest Statement

Tamara Sussman has no conflicts of interest to declare. Pauline Funchain receives consultant fees from Eisai and research funding from Pfizer. Arun Singh receives consulting fees from Eckert and Zeigler, and Isoaid; advisory board meeting with Immunocore; and stock options with Aura.

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Author Contributions

T.A.S. collected data, performed search, and wrote manuscript. A.S. designed concept and revised manuscript. P.F. revised manuscript. All authors approve the final version of the manuscript.

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