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Uveal Melanoma: From Diagnosis to Treatment and the Science in Between

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Abstract

Melanomas of the choroid, ciliary body, and iris of the eye are collectively known as uveal melanomas. These cancers represent 5% of all melanoma diagnoses in the U.S., an age-adjusted risk of 5 per million. These less frequent melanomas are dissimilar to their more common cutaneous melanoma relative, with differing risk factors, primary treatment, anatomical spread, molecular changes, and responses to systemic therapy. Once metastatic, therapy options are limited, and often extrapolated from cutaneous melanoma therapies despite routine exclusion of uveal melanoma from clinical trials. Clinical trials directed at uveal melanoma have been completed or are in progress and data from these well-designed investigations will help guide future directions in this orphan disease.

Keywords

uveal melanoma; review; science; diagnosis; treatment; choroidal melanoma; ocular melanoma; GNAQ; GNA11; BAP1

Background and Epidemiology

Uveal melanoma is the most common primary intraocular malignancy. The uveal tract is the pigmented layer of the globe encompassing the iris, ciliary body and choroid. The terms choroidal or ocular melanoma are alternative terms for this cancer as the majority of the uveal tract is choroidal, although the latter term should be avoided as it implies the inclusion of conjunctival and adnexal melanomas, which behave and are managed like cutaneous rather than uveal primaries. Approximately 1,500 new cases are diagnosed in the U.S. each year.[1] While the disease has no gender preference it is more common in middle-aged

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Caucasians with a median age of presentation of 58 years. Risk factors include presence of a choroidal nevus, which can be seen in up to 7–8% of the Caucasian population. Certain skin conditions such as dysplastic nevus syndrome and nevus of Ota are also associated with uveal melanoma.[2] Exposure to ultraviolet radiation has been theorized by some to increase the risk of neoplasia, but this has not definitively been proven. While certain somatic mutations are associated with neoplastic growth and distant metastasis (see below) the malignancy is not inherited in a traditional genetic fashion although individuals with germline *BAP1* mutations are thought to be at higher risk for uveal and cutaneous melanoma as well as mesothelioma and renal cancers.[3]

Clinical Presentation

Most patients present with painless loss or distortion of vision (metamorphopsia). Not infrequently, larger tumors will be associated with a serous (fluid) retinal detachment causing flashing or flickering of light (photopsia).[4] In some cases, the patient will be entirely asymptomatic, with the tumor identified on routine ophthalmic screening. When uveal melanoma affects the anterior segment of the eye, patients may notice discoloration of the iris or persistent injection of the episclera; chronic conjunctivitis may also be a referring diagnosis. Ciliary body tumors can cause increased and asymmetric astigmatism due to displacement of the intraocular lens. Rarely, a blind eye or one with a dense cataract may harbor an occult melanoma.[5]

Patients with suspicious pigmented lesions should be assessed by an ophthalmologist with clinical expertise in ocular tumors. Diagnostically small melanomas need to be differentiated from benign nevi. The clinical appearance and ophthalmoscopic features assist with this differential. The presence of subretinal fluid, orange pigment and documented growth on fundus photography are findings that support the diagnosis of melanoma.[6] Drusen and pigment epithelial changes are more suggestive of a benign lesion.

Fluorescein angiography can demonstrate an intrinsic secondary vasculature of the choroid; however ocular echography is the single most effective diagnostic tool available to the clinician. Melanomas tend to show low internal reflectivity as well as an intrinsic acoustic quiet zone on ultrasound. Most are dome shaped, but a collar stud or ‘mushroom’ configuration is highly suggestive of melanoma.[7] The shape occurs following a break in Bruch’s membrane, a structure of the retina. The larger the apical and basal dimensions, the greater the likelihood that the lesion is neoplastic. Some reports suggest a correlation between increased tumor thickness and risk of distant metastasis. Most experts agree that a lesion greater than 3 mm in apical height is likely a melanoma.

Rarely is a clinical biopsy necessary to confirm the diagnosis. The Collaborative Ocular Melanoma Study (COMS) had a greater than 99% diagnostic accuracy for eyes enucleated with typical features.[8] In some instances, a diagnostic biopsy may be indicated, particularly when the lesion is amelanotic or difficult to assess due to vitreous hemorrhage or debris. Fine needle aspiration can be performed but requires the assistance of a skilled cytologist familiar with ocular pathology.[9] Diagnostic biopsy must be distinguished from prognostic

biopsy (where the tumor is assessed for genetics and risk of future metastasis). The utility of a prognostic biopsy for risk stratification is described here, subsequently.

Primary treatment

Prior to ocular therapy, a systemic work up should be performed to demonstrate lack of distant metastasis (see section below on surveillance); once confirmed to be limited to the eye, local ophthalmic therapy can be focused on the primary neoplasm. Distant metastasis is rare at the time of initial ocular presentation, occurring less than 5% of the time. If distant disease is present, local therapy for the eye may be deferred in favor of systemic treatment, although this is dependent upon symptomatology of the patient with regards to the eye. It cannot be emphasized enough that the management of uveal melanoma is highly individualized; what follows are general guidelines and principles used by leading ocular oncologists in North America and Western Europe.

1. Close serial observation. In most instances, this approach is best considered in patients with ocular lesions with indeterminate findings not typical for melanoma. Often the ophthalmologist will monitor for definitive features such as rapid growth or development of subretinal fluid. In very rare instances observation may be the preferred approach when the patient is too frail for surgical intervention to either enucleate or place a radionuclide plaque.

2. Laser therapy. Diode laser therapy also referred to as transpupillary thermotherapy (TTT), is well-tolerated but of limited value due to local relapse rates as high as 20 %.[10] Rate of tumor control with laser therapy varies inversely with tumor size. Therefore, it is best considered for small tumors (< 3mm in thickness), arising at a distance from the macula and optic nerve. More commonly, this modality is used in an adjuvant setting following radiation (see below).

3. Radiation therapy. Focal radiation therapy is the most common globe salvaging approach used by ocular oncologists. The Collaborative Ocular Melanoma Study (COMS) medium size trial randomized patients with tumors 2.5 mm – 10.0 mm in apical height between primary brachytherapy (with Iodine-125 plaques) and enucleation. It found no statistically significant difference in melanoma-related mortality between the two cohorts.[11] Since then, ocular brachytherapy has emerged as the most common globe-sparing modality for tumors within these parameters. Melanomas with apical height greater than 10.0 mm can be also be treated with this approach but are more likely to succumb to severe radiation retinopathy and visual loss. In the U.S., Iodine-125 is the most commonly used isotope. Other radioisotopes are also used, with Ruthenium-106, a preferred source in many European centers.[12] Where available, charged particle radiation, proton-beam, is an alternative to brachytherapy. Most clinicians agree both modalities have high rates of local tumor control reported as high as 98 % in some series.[13]

4. Surgery. Enucleation, removal of the globe, remains a reasonable option for very large tumors and in cases where radiotherapy is likely to be complicated by

severe ocular and visual complications. Placement of an orbital implant at the time of surgery generally results in excellent cosmesis. Uvectomy, selective excision of the tumor with retention of the globe, is best limited to small anterior tumors of the eye such as iris melanomas. Patients who undergo selective choroidal resection of their melanomas may benefit from adjuvant plaque radiotherapy to reduce the risk of ocular recurrence.[14] Surgery affords the most detailed histopathologic assessment and can confirm microscopic extraocular extension. Epithelioid cell type and presence of microvascular loops are associated with a worse prognosis.[15] Exenteration, surgical removal of the globe and adjacent orbital contents, is rarely indicated. It is limited to extreme cases of massive orbital involvement and palliative care.

Survival and risk of distant relapse in patients with uveal melanoma are thought to be independent of the method selected for management of the primary tumor. Some authorities have suggested micrometastatic disease precedes local therapy. However since metastatic risk correlates with the size of the primary some ocular oncologists now take a more aggressive local approach to the management of smaller primary and indeterminate tumors.

Genetic prognostic testing

The clinical behavior of uveal melanomas can be segregated into two main groups: a) those that are diagnosed and confined locally to the eye, and b) those that metastasize and are ultimately fatal from distant disease. Uveal melanomas with chromosome 3 loss confer the worst prognosis, while those with 6p gain have the best outcomes.[16–19] Karyotyping via fluorescence in situ hybridization (FISH) is tissue-and labor-intensive and has a technical failure rate as high as 50% with fine needle aspiration sampling.[20] By contrast, gene expression profiling using an RNA-based assay demonstrates clustering into Class 1 tumors, those with low metastatic potential, and Class 2 tumors, those with high metastatic potential.[21, 22] This test, marketed in the United States as DecisionDx-UM® (Castle Biosciences, Friendswood, TX) has a technical failure rate of only 3% and requires much less tissue than FISH. Another uveal melanoma prognostic test from Impact Genetics (Ontario, Canada) assays copy numbers of chromosomes 1p, 3, 6, and 8, along with microsatellite analysis of chromosome 3 and confirmation of *GNAQ* or *GNA11* gene mutation status. This DNA-based test also has a low technical failure rate, but comes with at least a 10% inconclusive rate meaning the report cannot confirm that tumor rather than non-tumor stroma was analyzed if the molecular analysis is negative for *GNAQ* and *GNA11.* There are insufficient data regarding the optimal assay for tumors that recur locally following radiotherapy. Outside the United States, multiplex ligand-dependent probe amplification which detects 31 loci across chromosomes 1p, 3, 6, and 8 is a commonly used stand-alone test that predicts high-risk and low-risk tumors and is most efficiently tested on fresh or snap-frozen tissue.[23] Regardless of the technique used, the modern era of prognostic genetic testing is superior to histopathologic criteria such as tumor size, cell type, and tumor location and provides uveal melanoma patients with more powerful information moving forward.

Surveillance

The initial work up of a patient with uveal melanoma involves imaging of the abdomen given the propensity of this tumor to spread to the liver, although initial presentation with metastatic disease is rare. Since melanoma is ^{18}FDG-avid, staging with fused PET/CT imaging is common, although very small lesions in the liver may be missed due to both the size-dependent FDG-aviditiy and the background hepatic avidity due to normal metabolism. [24] Recent studies have raised the potential risks of radiation exposure associated with frequent PET/CT pointing to abdominal MR imaging as a radiation-free alternative with increased detection of smaller lesions.[25]

Triple-phase CT is also highly effective in distinguishing solid hepatic lesions from cystic and vascular structures such as hemangiomas. European centers have historically used abdominal ultrasonography and liver function tests, but the latter is not sensitive for small or few lesions and is rarely used by most North American practitioners.

The benefits, type and frequency of followup surveillance tests are highly debated amongst ocular and medical oncologists. No study has documented improved survival with early detection of metastatic disease. However, in some tertiary centers, the opportunity for enrollment in clinical trials lends itself toward identifying patients with early metastasis and minimal tumor burden who generally have a good performance status and preserved organ function. In select cases patients, with a single isolated hepatic or pulmonary metastatic nodule may be amenable to focal surgical resection.[26]

Most clinicians agree that if frequent screening is recommended, it is most appropriate for patients at high risk of relapse. Those whose primary tumors have a Class 2 gene expression profile, monosomy 3 or were greater than 8 mm in apical dimension are in the highest risk group. These patients may benefit from a surveillance regimen that includes hepatic imaging (CT/MRI) and liver function tests obtained in a three- to six-month interval for the first five years followed by six- to twelve-month intervals thereafter. Although surveillance regimens vary, some studies suggest LDH and GGT are the most sensitive liver function tests for uveal melanoma and are most often elevated with advanced hepatic involvement.[27–29]

Local and distant metastasis has been reported decades after primary therapy, but in view of the lack of evidence for the benefit of any specific surveillance strategy, particularly for late relapse, recommendations to these patients and their providers remain uncertain.

Adjuvant Treatment

A few adjuvant studies have been conducted in uveal melanoma in an attempt to prevent metastatic disease. However, none of these studies demonstrated meaningful metastasis free survival benefit or overall survival (OS) benefit, including a small Phase III using methanol-extracted residue of Bacille Calmette-Guerin (BCG)[30] and 2 single-arm studies of interferon-α using matched historical controls.

Adjuvant intra-arterial hepatic infusion of the alkylating agent, fotemustine, was studied in an effort to reduce the occurrence of liver metastasis, since the liver is the most common site

of and cause of death from uveal melanoma.[31] In this study, 22 uveal melanoma patients with choroidal involvement, largest basal diameter >20mm, extrascleral extension or tumor height >15mm were treated with fotemustine for 6 months. In this small study, adjuvant intra-arterial hepatic fotemustine was not shown to improve survival compared to matched historical controls.

There are several ongoing clinical trials of adjuvant therapy – none of which are randomized - such as ipilimumab, sunitinib, valproic acid and crizotinib for high risk patients in the U.S. These agents or classes of cagents have been chosen for study based on molecular characteristics of uveal melanoma cells (crizotinib, a met inhibitor, valproic acid or other histone deacetylase inhibitors) or expected immunomodulatory or microenvironment effects (sunitinib, ipilimumab[32]) (Table 1).

Treatment of Metastatic Disease

Liver-directed therapy

Since the liver is the first and only site of metastasis in most patients with uveal melanoma, and the prognosis of patients with metastatic uveal melanoma is highly dependent on the presence of liver metastasis and progression of disease in liver,[33–35] liver-directed local treatments such as surgical resection, hepatic artery embolization, hepatic arterial infusion of chemotherapy and radiofrequency ablation have been utilized in patients with metastatic uveal melanoma.

Surgical resection of liver metastasis has demonstrated survival benefit compared with non-surgical control groups in multiple retrospective studies, but this benefit is limited to those with minimal tumor volume that is limited ot the liver who are also fit enough for surgery (in a population whose average age at diagnosis is 70), and by these criteria, less than 10% of patients with metastatic uveal mleanoma are candidates for liver resection.[36–38] The median OS of patients undergoing hepatic metastatectomy with curative intent is greater than 12 months, but local relapse is common, and surgery has not been shown in randomized trials to enhance survival over best available systemic therapy.

Direct targeting of the hepatic arterial circulation is an enticing anatomical option for patients with liver-predominant disease, as normal liver will receive blood supply from the portal system, while metastatic tumor is generally supplied predominantly by the hepatic artery.[39] Hepatic arterial infusion of fotemustine has been studied in patients with uveal melanoma metastatic to the liver in a randomized phase III study that assigned 171 patients to receive fotemustine either intravenously (IV) or via hepatic arterial infusion.[40] While hepatic arterial infusion of fotemustine significantly improved progression free survival (PFS) compared to IV administration, (median PFS 4.5 months vs 3.5; hazard ratio [HR] 0.62; 95% confidence interval [CI] 0.45–0.84, P=0.002), there was no improvement in OS (median OS: 14.6 months vs 13.8, P=0.59).

Isolated hepatic perfusion (IHP) is another option but, in contrast to hepatic arterial infusion, IHP is a closed circuit perfusion that delivers high doses of chemotherapy to the liver with minimized systemic drug exposure. IHP is an invasive and precise operative procedure

requiring great skill and a period of extracorporeal circulation and is therefore limited to centers of excellence. A simple derivative percutaneous procedure known as percutaneous hepatic perfusion (PHP) has been developed. In a phase III trial, 93 patients were randomized to either PHP with melphalan or best supportive care, and crossover to PHP was allowed for those in the best supportive care arm following hepatic progression.[41] There was significant improvement of median hepatic PFS (245 days vs 49, P<0.001) and overall response rate (34.1% vs 2% P<0.001) compared with best supportive care. However, no survival benefit was observed in the study, in which 28 patients randomized to initial best supportive care crossed over to PHP.

Chemoembolization which combines hepatic artery embolization with infusion of concentrated doses of chemotherapeutic agents including cisplatin and 1,3-bis(2-cholorethyl)-1-nitrosourea (BCNU), is another commonly used liver-directed therapy for metastatic uveal melanoma. Gelatin sponge and non-spherical polyvinyl alcohol particles have been widely used as embolic agents for chemoembolization. Since these embolic agents have an unpredictable level of arterial occlusion due to their irregular shape and heterogeneous calibration, spherical embolic agents and drug-eluting microspheres have been developed and increasingly used.[42] In a retrospective study of 201 patients with uveal melanoma involving the liver, systemic chemotherapy, intra-arterial hepatic chemotherapy and chemoembolization were compared.[35] While the objective response rate of systemic treatment was less than 1%, chemoembolization induced 36% objective response with median duration of response 6 months. However, no meaningful survival benefit was observed, and one-third of the chemoembolization group received dacarbazine or vinblastine intravenously in addition to chemoembolization with cisplatin and polyvinyl alcohol. Patients with low tumor burden (<20% liver involvement) benefited the most from chemoembolization with significantly improved OS whereas patients with >75% liver involvement had poor clinical responses with a high incidence of major complications.[43, 44]

Immunoembolization with GM-CSF is hypothesized to increase local recruitment and maturation of dendritic cells to the tumor bed after ischemic necrosis of tumor by embolization. Among 31 evaluable patients treated with immunoembolization in a Phase I trial, a 33% response rate was reported.[45] However, a subsequent randomized phase II study of embolization with GM-CSF failed to show longer survival with the immunomodulator than with embolization using normal saline and gelatin sponge.[46] In addition, median PFS in liver metastasis embolized with GM-CSF was significantly shorter than control (3.7 months vs 7.2, P=0.01).

Radioembolization using yttrium-90 (^{90}Y) radiospheres is another liver-directed approach. ^{90}Y is small enough to pass deep into tumor vessels (2–4mm tissue penetration of radiation) but not through the capillary, thus sparing normal liver surrounding the tumor. Two retrospective studies of ^{90}Y showed high response rate of up to 62% (8/13) with median OS of 7–10 months.[47, 48] Currently, a prospective phase II study of ^{90}Y is ongoing to evaluate the clinical activity in well-characterized patients with uveal melanoma metastatic to the liver (Table 2).

Systemic therapy

Chemotherapy—Uveal melanoma is highly resistant to systemic cytotoxic chemotherapy. Several clinical trials of single agent or combination chemotherapy have shown disappointing results, with objective response rates of less than 1%.[49–55] Based on promising activity in advanced cutaneous melanoma, biochemotherapy with either bleomycin, vincristine, lomustine, dacarbazine, and interferon-α or fotemustine, interferon-α and interleukin-2 has been studied in 4 phase II trials for patients with metastatic uveal melanoma.[56–59] Objective response rates were less than 20%, and median OS was only 12 months with significant pulmonary toxicities, neurotoxicities and myelosuppression. To date, there is no clear role for chemotherapy or biochemotherapy in metastatic uveal melanoma.

Immunotherapy—In March of 2011, ipilimumab, a human antibody blocking the immune checkpoint interaction between CTLA4 and B7.1 on antigen-presenting cells and/or target tumor cells, was approved for the treatment of advanced melanoma based on improved OS in a large randomized phase III study.[60] While ipilimumab has been extensively studied in cutaneous melanoma, only limited data for ipilimumab are available in uveal melanoma. In a retrospective review of 39 patients with metastatic uveal melanoma who received ipilimumab at either 3mg/kg (N=34) or 10mg/kg (N=5),.[61] the objective response and "disease control rate" (adding patients with stable disease at 12 weeks to objective responders) was 2.6% and 46% at week 12, and 2.6% and 28.2% at week 23, respectively. The median OS was only 9.6 months. The efficacy of ipilimumab in uveal melanoma was also investigated in 3 expanded access programs (EAP).[62–64] The range of reported responses was 0–5%. Median PFS and OS were up to 3.6 months and 10.3 months, respectively. In another EAP, 13 patients with metastatic uveal melanoma received 10mg/kg of ipilimumab and no objective responses were observed with median OS of 36 weeks.[65] A recent phase II study of ipilimumab (3mg/kg) in 45 European patients with metastatic uveal melanoma has failed to demonstrate any objective clinical response. In the study, median OS and median PFS were only 6.8 months and 2.8 months, respectively with grade 3/4 adverse events of 36% (19 patients).[66] A similar phase II study in the U.S. using ipilimumab for metastatic uveal melanoma has not yet been published (NCT01585194).

The programmed death 1 protein (PD-1) is another important immune checkpoint receptor expressed on the surface of T cells. PD-1 has two known ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC). The ligation of PD-1 and PD-L1 inhibits T cell proliferation and activation and induces apoptosis of antigen specific T cells to suppress anti-tumor immunity. Recently, pembrolizumab (humanized) and nivolumab (human) IgG4 anti-PD1 monoclonal antibodies, were approved by the U.S. FDA for the treatment of metastatic melanoma following ipilimumab (and BRAF inhibitor therapy, for patients with BRAF v600-mutant melanoma). The efficacy of PD-1 blockade treatment has not yet been reported in metastatic uveal melanoma. In a single center EAP, 7 patients with metastatic uveal melanoma received 2mg/kg of pembrolizumab every 3 weeks.[67] Two patients had objective responses (1 complete response and 1 partial response), and median PFS was 12.2 weeks in the study.

Currently, several clinical trials of immunotherapy in metastatic uveal melanoma including adoptive cell therapy and combination of ipilimumab and nivolumab are under way to find effective immunotherapeutic approaches in metastatic uveal melanoma (Table 2). Since there are many differences in the tumor-immune microenvironment (nearly always the liver) as well as tumor biology (far fewer mutations and different mutational spectrum) of uveal melanoma compared with cutaneous (and other, such as mucosal) sites of primary melanoma, it is likely that outcomes reported for metastatic cutaneous melanoma will not be replicated in uveal melanoma, and that other trial designs will need to be considered.

Targeted therapy—Uveal melanomas are not known to harbor *BRAF* or *NRAS* mutations. Instead, 80% of uveal melanomas have oncogenic mutations in *GNAQ* or *GNA11*, which are potential drivers of MAPK activation similar to oncogenic *BRAF* mutations in cutaneous melanoma.[68] Therefore, inhibition of MAPK pathway has been studied in metastatic uveal melanoma. A recent randomized phase II trial of selumetinib, a selective MEK inhibitor, has shown promising clinical outcomes for uveal melanoma.[69] In the study, 101 patients with metastatic uveal melanoma were randomized to receive either selumetinib or temozolomide (or dacarbazine). The median PFS in the selumetinib group was 15.9 weeks with median OS of 11.8 months, whereas the chemotherapy group had a median PFS and OS of 7 weeks and 9.1 months, respectively (P=0.09 for OS). It was the first randomized study to demonstrate improved PFS in metastatic uveal melanoma, although OS benefit was not observed. Currently, several MEK inhibitor-based clinical trials are underway or completed, including a randomized double blind phase III study called SUMIT comparing selumetinib plus dacarbazine to placebo plus dacarbazine (completed, results pending) and a randomized phase II study of trametinib (a selective MEK inhibitor) with or without an AKT inhibitor (Table 2). These studies will provide insight on the role of MEK inhibitors, their molecular targets and other interacting pathways in the treatment of metastatic uveal melanoma.

There have been several small phase I and II trials targeting pathways other than MAPK,such as gefitinib (an epidermal growth factor inhibitor)[70], thalidomide[71], lenalidomide[72] (immunomodulators), bevacizumab (a vascular endothelial growth factor (VEGF-blocking antibody)plus interferon-α[73], bevacizumab plus temozolomide[74], aflibercept (a “decoy” receptor binding circulating VEGF)[75], carboplatin/paclitaxel/ sorafenib (a multikinase inhibitor)[54], imatinib (a KIT inhibitor)[76, 77], and sunitinib (a multiple receptor tyrosine kinase inhibitor)[78]. Unfortunately, none of these agents or combinations provided meaningful responses in metastatic uveal melanoma. Nevertheless, there are several ongoing clinical trials of other targeted therapies in metastatic uveal melanoma, including vorinostat and everoliumus (an mTOR inhibitor) plus pasireotide (a somatostatin analog) (Table 2).

Cytogenetics of uveal melanoma: Cytogenetic changes in uveal melanoma are nonrandom and are characterized by monosomy 3, trisomy 8, deletions in chromosome 1 and structural or numerical abnormalities of chromosome 6. Changes in chromosome 9p are less frequently observed.

Chromosomal aberrations: Cytogenetic investigation of uveal melanoma has revealed that monosomy 3 is the most frequent karyotypic abnormality, present in approximately 50–60% of cases. The pattern of loss of heterozygosity in these tumors indicates the presence of deletions around 3p25–26 and on 3q, and a region at 3p11–14 is preferentially deleted.[79–81] Loss of the long arm and gain of the short arm of chromosome 6 are frequently observed chromosomal aberrations in uveal melanoma. Loss in chromosome 6 may span the region ranging from 6q16.1 to 6q22 while a region of gain from 6pter to 6p21.2 was also demonstrated.[82] Gain of chromosome arms 18q or 21q was reported in a small number of uveal melanomas but the significance of this is not clear.[83] The loss of the entire short arm of chromosome 1 was only observed in tumors with monosomy 3 and 1p31 was proposed to be involved in progression of monosomy 3 uveal melanoma.[84] Singh et. al., studied the chromosome 3 and 8 aberrations in metastatic liver lesions from ten patients with uveal melanoma who underwent needle core biopsy and confirmed the presence of these in the metastatic tumors.[85]

Prognostic value: Monosomy of chromosome 3 and additional copies of 8q correlated with reduced survival.[79, 80] Also deletions in chromosome 1 concurrent with monosomy 3 were shown to be independent predictor of disease free survival.[86] The combination of monosomy 3 with cell type analysis or tumor diameter has been shown to have a greater prognostic impact than monosomy 3 alone.[87] In a very small number of cases, there may be heterogeneity in the chromosome 3 status in a single primary uveal melanoma, an observation that should be validated with larger numbers in order to understand how this information should be used. [88] Moreover the frequencies of such non-uniform chromosome 3 alterations, as reported in the published literature, vary from 0 to 48%. Abdel-Rahman et.al., in their study of 47 uveal melanomas and median follow-up of 36 months, showed that partial chromosome 3 alteration is not associated with the highly aggressive uveal melanoma that metastasizes within the first 3 years post treatment.[89] Contrary to loss of chromosome 3, a gain of chromosome 6p is usually associated with non-metastatic uveal melanoma.[90]

Detection/Testing: Accurate detection of the chromosome aberrations used to predict the risk of metastasis and death from uveal melanoma is important for patient management and may also impact follow-up recommendations. Historically, karyotyping and FISH on fresh tumor biopsies were used to identify chromosomal changes. Many alternative methods including microsatellite analysis, multiple ligation-dependent probe amplification, and, most recently, genome-wide single-nucleotide polymorphism array analysis are being tested for detecting chromosomal abnormalities in uveal melanoma.[91] Microarray analysis can provide whole genome data, detecting partial chromosome loss, LOH, or abnormalities not detectable by FISH probes. Frozen tissue is conventionally used for microarray analysis. Minca et. al. assessed the feasibility of DNA microarray analysis for high resolution interrogation of uveal melanoma using formalin-fixed paraffin-embedded tissue as an alternative to frozen tissue.[92] They conclude that in cases of chromosomal abnormalities larger than 1 Mb, formalin fixed samples performed very well, and showed high concordance with the matched frozen tissue material. Thus formalin fixed paraffin embedded archival tissues could be a feasible source of single nucleotide polymorphism analysis and correlates with clinical data.

Genetic mutations in uveal melanoma: Oncogene and tumor suppressor mutations that are common in other cancers are mostly absent in uveal melanoma, a disease characterized by low mutation burden. It also differs in genetic mutation profile from conventional cutaneous melanoma where *BRAF* and *NRAS* mutations dominate. These "driver" mutations that control the biology of up to 70% of cutaneous melanomas are absent/rare in uveal melanoma. New genomic sequencing technologies have rapidly advanced our understanding of the molecular landscape of uveal melanoma. Dono et al. analyzed 50 cases of primary uveal melanoma obtained from enucleation for mutations in the genes *GNAQ, GNA11, BAP1, SF3B1, EIFAX1* and *TERT*. They analyzed gene expression levels using microarrays and gene copy numbers by SNP arrays. They found that 42.2% of uveal melanomas harbored mutated *GNAQ*, 32.6% *GNA11*, 31.5% *BAP1,* 9.7% *SF3B1*, 18.9% *EIF1AX* and 1% *TERT*.[93] Of these, *GNAQ* and *GNA11* are usually mutually exclusive but both can co-exist with *BAP1* or *SF3B1* mutations.[94, 95] Likewise, *BAP1* and *SF3B1* are mutually exclusive as are *EIF1AX* and *SF3B1* mutations, *TERT* mutations appear to co-exist specifically with *GNA11* or *EIF1AX* mutations.[93, 96–99]

GNAQ/GNA11: The majority of uveal melanomas have one of two mutually exclusive activating mutations in the very homologous genes encoding Gα subunits, *GNAQ* (Gαq) and *GNA11* (Gα11) (19–21). Interestingly, the *GNAQ* mutation is more frequently found in benign blue nevi, while the *GNA11* mutation is frequent in malignant uveal melanoma.[68, 100] G protein coupled receptors are signal transducers that transmit signals from extracellular environment to intracellular. As a result, a G protein mutation can affect many physiological processes in a cell and thus play a significant role in oncogenic behavior of a cell. Recently Yu et al. and Feng et al. showed that the GNAQ/11 mutations activate YAP, a major effector of the Hippo tumor suppressor pathway, and YAP mediates the oncogenic properties of GNAQ/GNA11 mutations[101, 102].

BAP1: Harbour et al. first described inactivating somatic mutations in *BAP1* gene (BRCA1-associated protein 1), on chromosome 3p21.1 in 26 of 31 (84%) metastasizing tumors. This included 15 mutations causing premature protein termination and 5 affecting its ubiquitin carboxyl-terminal hydrolase domain. One tumor had a germ line frame-shift mutation representing a susceptibility allele. The connection of *BAP1* loss to uveal melanoma metastasis has been reinforced by multiple independent studies.[103, 104] This also raised the possibility of targeting deubiquitinating enzymes in uveal melanoma.[103] Subsequently, more germline mutations of *BAP1* have been described in uveal melanoma patients suggesting that *BAP1* screening can identify people with predisposition to uveal melanoma.[105, 106] These reports of mutation screens in patients with uveal melanoma suggest younger patients may harbor a germline *BAP1* mutation. For now, there is no consensus amongst genetic counseling groups regarding who should be screened and surveillance strategies for a patient with germline *BAP1* aberrancy. A role for BAP1 protein in regulating cell cycle progression has been suggested but the underlying mechanism is not clear. Pan et al. have indicated that BAP1 may interact with promoters regulated by *E2F1* and affect the cell cycle progression genes controlled by E2F.[104]

SF3B1: *SF3B1* gene encodes the splicing factor 3B subunit 1. Uveal melanoma is among a small group of cancers associated with *SF3B1* mutations. These mutations define a genetic subset of uveal melanoma that have been reported by Harbour et al. to be associated with favorable prognostic features and to be nearly always mutually exclusive of *BAP1* mutations.[94] *SF3B1* mutations are observed in codon 65 and mostly in tumors without loss of all or part of chromosome 3. Furney et al. have reported an association of these mutations with alternative splicing of transcripts.[96] SF3B1 is observed in about 15% of primary uveal melanomas and has been reported in the hepatic metastasis of uveal melanoma as well.[98]

EIF1AX: Using exome sequencing, Martin et al. identified recurrent somatic mutations in *EIF1AX* along with the *SF3B1*, specifically occurring in uveal melanomas with disomy 3, which rarely metastasize. *EIF1AX* mutations are infrequent in monosomy 3 uveal melanomas.[93, 97]

Advances in uveal melanoma research: Half of the patients with uveal melanoma develop metastatic disease and eventually die of melanoma. Research in the uveal melanoma field is therefore focused on prognostic factors, detection, and therapeutic approaches for metastatic disease.

Prognostic and predictive factors: Classically, the diagnosis of uveal melanoma and prognostic prediction was based on the clinical presentation and histopathological evaluation. Molecular prognostic testing for genetic mutations, chromosomal abnormalities, and gene expression profiling, as discussed above, are becoming more common in uveal melanoma and have led to the identification and enrollment of high risk patients in adjuvant therapy trials. Microarray approaches, detailed above have been shown to perform better in predicting outcome compared to standard clinical or histopathological parameters.[82]

Translational approaches: Mutation profiling has given us an opportunity for optimal attempts at targeted therapy for uveal melanoma patients. *GNAQ* and *GNA11* mutations activate pathways that may provide a rationale for the use of a MEK or Akt inhibitor, while HDAC inhibitors may be the choice for treating *BAP1*-mutated uveal melanoma.[95] The identification of downstream effectors of *GNAQ/11* mutations, like the components of the Hippo pathway, gives us an alternative to targeting the MAPK pathway, which, to date, has been disappointing.[107] The lack of a suitable animal model has slowed down translational research in uveal melanoma considerably. However, patient-derived xenograft (PDX)-based mouse studies with uveal melanoma tumors by Nemati et al. have brought alternative approaches of developing targeted therapy in focus.[108] They used well-characterized PDX from primary uveal melanoma in mice to study the effect of small molecule inhibitors of Bcl-2/Bcl-XL on uveal melanoma tumor growth. Primary uveal melanoma has been reported to have high expression of the anti-apoptotic protein, Bcl-2.[109] Recently, Schiffner et al. attempted to develop a transgenic mouse model for uveal melanoma, since spontaneous models are not available. They evaluated the Tg(Grm1) that expresses a metabotropic glutamate receptor under the transcriptional control of a melanoma-specific dopachrome tautomerase, in studying spontaneous development of uveal melanoma. [110] Several attempts at building functional animal models to test experimental therapies include a recent zebrafish

xenograft embryo model.[111] The major aim was to screen large libraries of compounds for drug discovery and all uveal melanoma cell lines tested in this model showed proliferation and migration, failing to be inhibited by the drugs tested. Surriga et al. tested the efficacy of crizotinib, a MET inhibitor, in a mouse model where retroorbital injection of uveal melanoma cells resulted in development of melanoma in the eye as well as metastasis in the liver and lung.[112] Mice treated with crizotinib showed a significant reduction in the development of metastasis as compared to untreated control mice. Thus, inhibition of MET may prevent uveal melanoma metastasis and crizotinib could represent a potential adjuvant therapy strategy for patients with primary uveal melanoma at risk for distant disease.

Improved prognostic and detection techniques in the recent years has not translated into improved outcomes for uveal melanoma. The search for effective targeted therapy approaches as well as effective immunotherapy for metastatic disease continues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology. 2011; 118:1881–1885. [PubMed: 21704381]
2. Hammer H, Olah J, Toth-Molnar E. Dysplastic nevi are a risk factor for uveal melanoma. Eur J Ophthalmol. 1996; 6:472–474. [PubMed: 8997595]
3. Carbone M, Ferris LK, Baumann F, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs. J Transl Med. 2012; 10:179. [PubMed: 22935333]
4. Eskelin S, Kivela T. Mode of presentation and time to treatment of uveal melanoma in Finland. Br J Ophthalmol. 2002; 86:333–338. [PubMed: 11864894]
5. Eagle RC Jr, Grossniklaus HE, Syed N, Hogan RN, Lloyd WC 3rd, Folberg R. Inadvertent evisceration of eyes containing uveal melanoma. Arch Ophthalmol. 2009; 127:141–145. [PubMed: 19204229]
6. The Collaborative Ocular Melanoma Study Group. Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No. 5. Arch Ophthalmol. 1997; 115:1537–1544. [PubMed: 9400787]
7. Bedi DG, Gombos DS, Ng CS, Singh S. Sonography of the eye. AJR Am J Roentgenol. 2006; 187:1061–1072. [PubMed: 16985158]
8. Accuracy of diagnosis of choroidal melanomas in the Collaborative Ocular Melanoma Study. COMS report no. 1. Arch Ophthalmol. 1990; 108:1268–1273. [PubMed: 2205183]
9. Char DH, Miller T. Accuracy of presumed uveal melanoma diagnosis before alternative therapy. Br J Ophthalmol. 1995; 79:692–696. [PubMed: 7662638]
10. Shields CL, Shields JA, Perez N, Singh AD, Cater J. Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations. Ophthalmology. 2002; 109:225–234. [PubMed: 11825800]

11. Diener-West M, Earle JD, Fine SL, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS Report No. 18. Arch Ophthalmol. 2001; 119:969–982. [PubMed: 11448319]
12. Takiar V, Gombos DS, Mourtada F, et al. Disease control and toxicity outcomes using ruthenium eye plaque brachytherapy in the treatment of uveal melanoma. Pract Radiat Oncol. 2014; 4:e189–194. [PubMed: 25012839]
13. Egger E, Zografos L, Schalenbourg A, et al. Eye retention after proton beam radiotherapy for uveal melanoma. Int J Radiat Oncol Biol Phys. 2003; 55:867–880. [PubMed: 12605964]
14. Damato, BEFW. Retina. 4. CV Mosby; St Louis: 2005. Surgical Resection of Choroidal Melanoma (Chapter 40); p. 1
15. Folberg R, Rummelt V, Parys-Van Ginderdeuren R, et al. The prognostic value of tumor blood vessel morphology in primary uveal melanoma. Ophthalmology. 1993; 100:1389–1398. [PubMed: 8371929]
16. Prescher G, Bornfeld N, Hirche H, Horsthemke B, Jockel KH, Becher R. Prognostic implications of monosomy 3 in uveal melanoma. Lancet. 1996; 347:1222–1225. [PubMed: 8622452]
17. White VA, Chambers JD, Courtright PD, Chang WY, Horsman DE. Correlation of cytogenetic abnormalities with the outcome of patients with uveal melanoma. Cancer. 1998; 83:354–359. [PubMed: 9669819]
18. Shields CL, Ganguly A, Bianciotto CG, Turaka K, Tavallali A, Shields JA. Prognosis of uveal melanoma in 500 cases using genetic testing of fine-needle aspiration biopsy specimens. Ophthalmology. 2011; 118:396–401. [PubMed: 20869116]
19. Kilic E, van Gils W, Lodder E, et al. Clinical and cytogenetic analyses in uveal melanoma. Invest Ophthalmol Vis Sci. 2006; 47:3703–3707. [PubMed: 16936076]
20. Young TA, Rao NP, Glasgow BJ, Moral JN, Straatsma BR. Fluorescent in situ hybridization for monosomy 3 via 30-gauge fine-needle aspiration biopsy of choroidal melanoma in vivo. Ophthalmology. 2007; 114:142–146. [PubMed: 17097737]
21. Onken MD, Worley LA, Tuscan MD, Harbour JW. An accurate, clinically feasible multi-gene expression assay for predicting metastasis in uveal melanoma. J Mol Diagn. 2010; 12:461–468. [PubMed: 20413675]
22. Onken MD, Worley LA, Char DH, et al. Collaborative Ocular Oncology Group Report Number 1: Prospective Validation of a Multi-Gene Prognostic Assay in Uveal Melanoma. Ophthalmology. 2012; 119:1596–1603. [PubMed: 22521086]
23. Lake SL, Kalirai H, Dopierala J, Damato BE, Coupland SE. Comparison of formalin-fixed and snap-frozen samples analyzed by multiplex ligation-dependent probe amplification for prognostic testing in uveal melanoma. Invest Ophthalmol Vis Sci. 2012; 53:2647–2652. [PubMed: 22427594]
24. Finger PT, Kurli M, Reddy S, Tena LB, Pavlick AC. Whole body PET/CT for initial staging of choroidal melanoma. Br J Ophthalmol. 2005; 89:1270–1274. [PubMed: 16170114]
25. Wen JC, Sai V, Straatsma BR, McCannel TA. Radiation-related cancer risk associated with surveillance imaging for metastasis from choroidal melanoma. JAMA Ophthalmol. 2013; 131:56–61. [PubMed: 23307209]
26. Aoyama T, Mastrangelo MJ, Berd D, et al. Protracted survival after resection of metastatic uveal melanoma. Cancer. 2000; 89:1561–1568. [PubMed: 11013372]
27. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Screening for metastasis from choroidal melanoma: the Collaborative Ocular Melanoma Study Group Report 23. J Clin Oncol. 2004; 22:2438–2444. [PubMed: 15197206]
28. Hendler K, Pe'er J, Kaiserman I, et al. Trends in liver function tests: a comparison with serum tumor markers in metastatic uveal melanoma (part 2). Anticancer Res. 2011; 31:351–357. [PubMed: 21273623]
29. Felberg NT, Shields JA, Maguire J, Piperata S, Amsel J. Gamma-glutamyl transpeptidase in the prognosis of patients with uveal malignant melanoma. Am J Ophthalmol. 1983; 95:467–473. [PubMed: 6132555]
30. McLean IW, Berd D, Mastrangelo MJ, et al. A randomized study of methanol-extraction residue of bacille Calmette-Guerin as postsurgical adjuvant therapy of uveal melanoma. Am J Ophthalmol. 1990; 110:522–526. [PubMed: 2240139]

31. Voelter V, Schalenbourg A, Pampallona S, et al. Adjuvant intra-arterial hepatic fotemustine for high-risk uveal melanoma patients. Melanoma Res. 2008; 18:220–224. [PubMed: 18477897]
32. Landreville S, Agapova OA, Matatall KA, et al. Histone deacetylase inhibitors induce growth arrest and differentiation in uveal melanoma. Clin Cancer Res. 2012; 18:408–416. [PubMed: 22038994]
33. Gragoudas ES, Egan KM, Seddon JM, et al. Survival of patients with metastases from uveal melanoma. Ophthalmology. 1991; 98:383–389. discussion 390. [PubMed: 2023760]
34. Bedikian AY, Kantarjian H, Young SE, Bodey GP. Prognosis in metastatic choroidal melanoma. South Med J. 1981; 74:574–577. [PubMed: 7244714]
35. Bedikian AY, Legha SS, Mavligit G, et al. Treatment of uveal melanoma metastatic to the liver: a review of the M. D. Anderson Cancer Center experience and prognostic factors. Cancer. 1995; 76:1665–1670. [PubMed: 8635073]
36. Mariani P, Piperno-Neumann S, Servois V, et al. Surgical management of liver metastases from uveal melanoma: 16 years' experience at the Institut Curie. Eur J Surg Oncol. 2009; 35:1192–1197. [PubMed: 19329272]
37. Frenkel S, Nir I, Hendler K, et al. Long-term survival of uveal melanoma patients after surgery for liver metastases. Br J Ophthalmol. 2009; 93:1042–1046. [PubMed: 19429579]
38. Rivoire M, Kodjikian L, Baldo S, Kaemmerlen P, Negrier S, Grange JD. Treatment of liver metastases from uveal melanoma. Ann Surg Oncol. 2005; 12:422–428. [PubMed: 15886904]
39. Ackerman NB, Lien WM, Silverman NA. The blood supply of experimental liver metastases. 3. The effects of acute ligation of the hepatic artery or portal vein. Surgery. 1972; 71:636–641. [PubMed: 5021077]
40. Leyvraz S, Piperno-Neumann S, Suciu S, et al. Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial. Ann Oncol. 2014; 25:742–746. [PubMed: 24510314]
41. Pingpank, JF., Hughes, MS., Faries, MB., et al. A phase III random assignment trial comparing percutaneous hepatic perfusion with melphalan (PHP-mel) to standard of care for patients with hepatic metastases from metastatic ocular or cutaneous melanoma. 2010 ASCO Annual Meeting; Chicago. 2010;
42. Osuga K, Maeda N, Higashihara H, et al. Current status of embolic agents for liver tumor embolization. Int J Clin Oncol. 2012; 17:306–315. [PubMed: 22806426]
43. Patel K, Sullivan K, Berd D, et al. Chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma: results of a phase II study. Melanoma Res. 2005; 15:297–304. [PubMed: 16034309]
44. Gupta S, Bedikian AY, Ahrar J, et al. Hepatic artery chemoembolization in patients with ocular melanoma metastatic to the liver: response, survival, and prognostic factors. Am J Clin Oncol. 2010; 33:474–480. [PubMed: 19935383]
45. Sato T, Eschelman DJ, Gonsalves CF, et al. Immunoembolization of malignant liver tumors, including uveal melanoma, using granulocyte-macrophage colony-stimulating factor. J Clin Oncol. 2008; 26:5436–5442. [PubMed: 18838710]
46. Eschelman, DJ., Gonsalves, CF., Terai, M., et al. The results of a randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor (GM-CSF) in uveal melanoma patients with hepatic metastasis. 2011 ASCO Annual Meeting; Chicago. 2011;
47. Gonsalves CF, Eschelman DJ, Sullivan KL, Anne PR, Doyle L, Sato T. Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience. AJR Am J Roentgenol. 2011; 196:468–473. [PubMed: 21257902]
48. Klingenstein A, Haug AR, Zech CJ, Schaller UC. Radioembolization as locoregional therapy of hepatic metastases in uveal melanoma patients. Cardiovasc Intervent Radiol. 2013; 36:158–165. [PubMed: 22526099]
49. Bedikian AY, Papadopoulos N, Plager C, Eton O, Ring S. Phase II evaluation of temozolomide in metastatic choroidal melanoma. Melanoma Res. 2003; 13:303–306. [PubMed: 12777987]
50. Schmidt-Hieber M, Schmittel A, Thiel E, Keilholz U. A phase II study of bendamustine chemotherapy as second-line treatment in metastatic uveal melanoma. Melanoma Res. 2004; 14:439–442. [PubMed: 15577312]

51. Schmittel A, Schmidt-Hieber M, Martus P, et al. A randomized phase II trial of gemcitabine plus treosulfan versus treosulfan alone in patients with metastatic uveal melanoma. Ann Oncol. 2006; 17:1826–1829. [PubMed: 16971664]
52. Atzpodien J, Terfloth K, Fluck M, Reitz M. Cisplatin, gemcitabine and treosulfan is effective in chemotherapy-pretreated relapsed stage IV uveal melanoma patients. Cancer Chemother Pharmacol. 2008; 62:685–688. [PubMed: 18084763]
53. O'Neill PA, Butt M, Eswar CV, Gillis P, Marshall E. A prospective single arm phase II study of dacarbazine and treosulfan as first-line therapy in metastatic uveal melanoma. Melanoma Res. 2006; 16:245–248. [PubMed: 16718271]
54. Bhatia S, Moon J, Margolin KA, et al. Phase II trial of sorafenib in combination with carboplatin and paclitaxel in patients with metastatic uveal melanoma: SWOG S0512. PLoS One. 2012; 7:e48787. [PubMed: 23226204]
55. Buder K, Gesierich A, Gelbrich G, Goebeler M. Systemic treatment of metastatic uveal melanoma: review of literature and future perspectives. Cancer Med. 2013; 2:674–686. [PubMed: 24403233]
56. Becker JC, Terheyden P, Kampgen E, et al. Treatment of disseminated ocular melanoma with sequential fotemustine, interferon alpha, and interleukin 2. Br J Cancer. 2002; 87:840–845. [PubMed: 12373596]
57. Kivela T, Suciu S, Hansson J, et al. Bleomycin, vincristine, lomustine and dacarbazine (BOLD) in combination with recombinant interferon alpha-2b for metastatic uveal melanoma. Eur J Cancer. 2003; 39:1115–1120. [PubMed: 12736111]
58. Nathan FE, Berd D, Sato T, et al. BOLD+interferon in the treatment of metastatic uveal melanoma: first report of active systemic therapy. J Exp Clin Cancer Res. 1997; 16:201–208. [PubMed: 9261748]
59. Pyrhonen S, Hahka-Kemppinen M, Muhonen T, et al. Chemoimmunotherapy with bleomycin, vincristine, lomustine, dacarbazine (BOLD), and human leukocyte interferon for metastatic uveal melanoma. Cancer. 2002; 95:2366–2372. [PubMed: 12436444]
60. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363:711–723. [PubMed: 20525992]
61. Luke JJ, Callahan MK, Postow MA, et al. Clinical activity of ipilimumab for metastatic uveal melanoma: a retrospective review of the Dana-Farber Cancer Institute, Massachusetts General Hospital, Memorial Sloan-Kettering Cancer Center, and University Hospital of Lausanne experience. Cancer. 2013; 119:3687–3695. [PubMed: 23913718]
62. Khattak MA, Fisher R, Hughes P, Gore M, Larkin J. Ipilimumab activity in advanced uveal melanoma. Melanoma Res. 2013; 23:79–81. [PubMed: 23211837]
63. Kelderman S, van der Kooij MK, van den Eertwegh AJ, et al. Ipilimumab in pretreated metastastic uveal melanoma patients. Results of the Dutch Working group on Immunotherapy of Oncology (WIN-O). Acta Oncol. 2013; 52:1786–1788. [PubMed: 23607756]
64. Maio M, Danielli R, Chiarion-Sileni V, et al. Efficacy and safety of ipilimumab in patients with pre-treated, uveal melanoma. Ann Oncol. 2013; 24:2911–2915. [PubMed: 24067719]
65. Danielli R, Ridolfi R, Chiarion-Sileni V, et al. Ipilimumab in pretreated patients with metastatic uveal melanoma: safety and clinical efficacy. Cancer Immunol Immunother. 2012; 61:41–48. [PubMed: 21833591]
66. Zimmer L, Vaubel J, Mohr P, et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naive patients with metastatic uveal melanoma. PLoS One. 2015; 10:e0118564. [PubMed: 25761109]
67. Kottschade, L., McWilliams, R., Markovic, S., et al. The use of pembrolizumab for the treatment of metastatic uveal melanoma. 2015 ASCO Annual Meeting; Chicago. 2015;
68. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA11 in uveal melanoma. N Engl J Med. 2010; 363:2191–2199. [PubMed: 21083380]
69. Carvajal RD, Sosman JA, Quevedo JF, et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. JAMA. 2014; 311:2397–2405. [PubMed: 24938562]
70. Patel SP, Kim KB, Papadopoulos NE, et al. A phase II study of gefitinib in patients with metastatic melanoma. Melanoma Res. 2011; 21:357–363. [PubMed: 21738104]

71. Reiriz AB, Richter MF, Fernandes S, et al. Phase II study of thalidomide in patients with metastatic malignant melanoma. Melanoma Res. 2004; 14:527–531. [PubMed: 15577325]
72. zeldis, JB., Heller, C., Seidel, G., et al. A randomized phase II trial comparing two doses of lenalidomide for the treatment of stage IV ocular melanoma. 2009 ASCO Annual Meeting; Chicago. 2009;
73. Guenterberg KD, Grignol VP, Relekar KV, et al. A pilot study of bevacizumab and interferon-alpha2b in ocular melanoma. Am J Clin Oncol. 2011; 34:87–91. [PubMed: 20458209]
74. Piperno-Neumann, S., Servois, V., Bidard, FC., et al. BEVATEM: Phase II study of bevacizumab (B) in combination with temozolomide (T) in patients (pts) with first-line metastatic uveal melanoma (MUM): Final results; 2013 ASCO Annual Meeting; Chicago. 2013;
75. Tarhini AA, Frankel P, Margolin KA, et al. Aflibercept (VEGF Trap) in inoperable stage III or stage iv melanoma of cutaneous or uveal origin. Clin Cancer Res. 2011; 17:6574–6581. [PubMed: 21880788]
76. Hofmann UB, Kauczok-Vetter CS, Houben R, Becker JC. Overexpression of the KIT/SCF in uveal melanoma does not translate into clinical efficacy of imatinib mesylate. Clin Cancer Res. 2009; 15:324–329. [PubMed: 19118061]
77. Penel N, Delcambre C, Durando X, et al. O-Mel-Inib: a Cancero-pole Nord-Ouest multicenter phase II trial of high-dose imatinib mesylate in metastatic uveal melanoma. Invest New Drugs. 2008; 26:561–565. [PubMed: 18551246]
78. Mahipal A, Tijani L, Chan K, Laudadio M, Mastrangelo MJ, Sato T. A pilot study of sunitinib malate in patients with metastatic uveal melanoma. Melanoma Res. 2012; 22:440–446. [PubMed: 23114504]
79. Sisley K, Rennie IG, Parsons MA, et al. Abnormalities of chromosomes 3 and 8 in posterior uveal melanoma correlate with prognosis. Genes Chromosomes Cancer. 1997; 19:22–28. [PubMed: 9135991]
80. White JS, Becker RL, McLean IW, Director-Myska AE, Nath J. Molecular cytogenetic evaluation of 10 uveal melanoma cell lines. Cancer Genet Cytogenet. 2006; 168:11–21. [PubMed: 16772116]
81. Cross NA, Ganesh A, Parpia M, Murray AK, Rennie IG, Sisley K. Multiple locations on chromosome 3 are the targets of specific deletions in uveal melanoma. Eye (Lond). 2006; 20:476–481. [PubMed: 15920570]
82. van Gils W, Lodder EM, Mensink HW, et al. Gene expression profiling in uveal melanoma: two regions on 3p related to prognosis. Invest Ophthalmol Vis Sci. 2008; 49:4254–4262. [PubMed: 18552379]
83. Mensink HW, Kilic E, Vaarwater J, Douben H, Paridaens D, de Klein A. Molecular cytogenetic analysis of archival uveal melanoma with known clinical outcome. Cancer Genet Cytogenet. 2008; 181:108–111. [PubMed: 18295662]
84. Hausler T, Stang A, Anastassiou G, et al. Loss of heterozygosity of 1p in uveal melanomas with monosomy 3. Int J Cancer. 2005; 116:909–913. [PubMed: 15849744]
85. Singh AD, Tubbs R, Biscotti C, Schoenfield L, Trizzoi P. Chromosomal 3 and 8 status within hepatic metastasis of uveal melanoma. Arch Pathol Lab Med. 2009; 133:1223–1227. [PubMed: 19653714]
86. Kilic E, Naus NC, van Gils W, et al. Concurrent loss of chromosome arm 1p and chromosome 3 predicts a decreased disease-free survival in uveal melanoma patients. Invest Ophthalmol Vis Sci. 2005; 46:2253–2257. [PubMed: 15980208]
87. Damato B, Duke C, Coupland SE, et al. Cytogenetics of uveal melanoma: a 7-year clinical experience. Ophthalmology. 2007; 114:1925–1931. [PubMed: 17719643]
88. Mensink HW, Vaarwater J, Kilic E, et al. Chromosome 3 intratumor heterogeneity in uveal melanoma. Invest Ophthalmol Vis Sci. 2009; 50:500–504. [PubMed: 18824727]
89. Abdel-Rahman MH, Christopher BN, Faramawi MF, et al. Frequency, molecular pathology and potential clinical significance of partial chromosome 3 aberrations in uveal melanoma. Mod Pathol. 2011; 24:954–962. [PubMed: 21499235]
90. Landreville S, Agapova OA, Harbour JW. Emerging insights into the molecular pathogenesis of uveal melanoma. Future Oncol. 2008; 4:629–636. [PubMed: 18922120]

91. Singh AD, Aronow ME, Sun Y, et al. Chromosome 3 status in uveal melanoma: a comparison of fluorescence in situ hybridization and single-nucleotide polymorphism array. Invest Ophthalmol Vis Sci. 2012; 53:3331–3339. [PubMed: 22511634]
92. Minca EC, Tubbs RR, Portier BP, et al. Genomic microarray analysis on formalin-fixed paraffin-embedded material for uveal melanoma prognostication. Cancer Genet. 2014; 207:306–315. [PubMed: 25442074]
93. Dono M, Angelini G, Cecconi M, et al. Mutation frequencies of GNAQ, GNA11, BAP1, SF3B1, EIF1AX and TERT in uveal melanoma: detection of an activating mutation in the TERT gene promoter in a single case of uveal melanoma. Br J Cancer. 2014; 110:1058–1065. [PubMed: 24423917]
94. Harbour JW, Roberson ED, Anbunathan H, Onken MD, Worley LA, Bowcock AM. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. Nat Genet. 2013; 45:133–135. [PubMed: 23313955]
95. Field MG, Harbour JW. Recent developments in prognostic and predictive testing in uveal melanoma. Curr Opin Ophthalmol. 2014; 25:234–239. [PubMed: 24713608]
96. Furney SJ, Pedersen M, Gentien D, et al. SF3B1 mutations are associated with alternative splicing in uveal melanoma. Cancer Discov. 2013; 3:1122–1129. [PubMed: 23861464]
97. Martin M, Masshofer L, Temming P, et al. Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. Nat Genet. 2013; 45:933–936. [PubMed: 23793026]
98. Luscan A, Just PA, Briand A, et al. Uveal melanoma hepatic metastases mutation spectrum analysis using targeted next-generation sequencing of 400 cancer genes. Br J Ophthalmol. 2015; 99:437–439. [PubMed: 25361747]
99. Rodrigues MJ, Stern MH. Genetic landscape of uveal melanoma. J Fr Ophtalmol. 2015; 38:522–525. [PubMed: 25976133]
100. Van Raamsdonk CD, Bezrookove V, Green G, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature. 2009; 457:599–602. [PubMed: 19078957]
101. Yu FX, Luo J, Mo JS, et al. Mutant Gq/11 promote uveal melanoma tumorigenesis by activating YAP. Cancer Cell. 2014; 25:822–830. [PubMed: 24882516]
102. Feng X, Degese MS, Iglesias-Bartolome R, et al. Hippo-independent activation of YAP by the GNAQ uveal melanoma oncogene through a trio-regulated rho GTPase signaling circuitry. Cancer Cell. 2014; 25:831–845. [PubMed: 24882515]
103. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. Science. 2010; 330:1410–1413. [PubMed: 21051595]
104. Pan H, Jia R, Zhang L, et al. BAP1 regulates cell cycle progression through E2F1 target genes and mediates transcriptional silencing via H2A monoubiquitination in uveal melanoma cells. Int J Biochem Cell Biol. 2015; 60:176–184. [PubMed: 25582751]
105. Aoude LG, Vajdic CM, Kricker A, Armstrong B, Hayward NK. Prevalence of germline BAP1 mutation in a population-based sample of uveal melanoma cases. Pigment Cell Melanoma Res. 2013; 26:278–279. [PubMed: 23171164]
106. Cebulla CM, Binkley EM, Pilarski R, et al. Analysis of BAP1 Germline Gene Mutation in Young Uveal Melanoma Patients. Ophthalmic Genet. 2015:1–6. [PubMed: 23834555]
107. Yu FX, Zhang K, Guan KL. YAP as oncotarget in uveal melanoma. Oncoscience. 2014; 1:480–481. [PubMed: 25594048]
108. Nemati F, de Montrion C, Lang G, et al. Targeting Bcl-2/Bcl-XL induces antitumor activity in uveal melanoma patient-derived xenografts. PLoS One. 2014; 9:e80836. [PubMed: 24454684]
109. Sulkowska M, Famulski W, Bakunowicz-Lazarczyk A, Chyczewski L, Sulkowski S. Bcl-2 expression in primary uveal melanoma. Tumori. 2001; 87:54–57. [PubMed: 11669559]
110. Schiffner S, Braunger BM, de Jel MM, Coupland SE, Tamm ER, Bosserhoff AK. Tg(Grm1) transgenic mice: a murine model that mimics spontaneous uveal melanoma in humans? Exp Eye Res. 2014; 127:59–68. [PubMed: 25051141]
111. van der Ent W, Burrello C, Teunisse AF, et al. Modeling of human uveal melanoma in zebrafish xenograft embryos. Invest Ophthalmol Vis Sci. 2014; 55:6612–6622. [PubMed: 25249605]

112. Surriga O, Rajasekhar VK, Ambrosini G, Dogan Y, Huang R, Schwartz GK. Crizotinib, a c-Met inhibitor, prevents metastasis in a metastatic uveal melanoma model. Mol Cancer Ther. 2013; 12:2817–2826. [PubMed: 24140933]

Table 1

Adjuvant trials for uveal melanoma in the U.S.

Clinical trials No.	Treatment	Phase	N	Eligibility	Status	Primary end point
NCT00489944	Suntinib + tamoxifen + cisplatin	II	50	Basal diameter≥16mm, apical diameter≥10mm, extrascleral extension, ciliary body involvement or epithelioid cell type	Recruiting	Disease-free survival, overall survival and toxicity
NCT01100528	DTIC + interferon α	II	36	Monosomy 3	Closed	Disease-free survival
NCT01585194	Ipilimumab	I/II	12	Class 2 tumor, monosomy 3, or apical thickness ≥8mm	Closed	Distant metastasis-free survival
NCT02068586	Sunitinib or valproic acid	II	90	Monosomy 3 and 8q amplification or Class 2 tumor	Recruiting	Overall survival
NCT02223819	Crizotinib	II	30	Class 2 tumor	Recruiting	Relapse-free survival
NCT02336763	External Beam Radiation Therapy to the Liver	II	50	Monosomy 3 or Class 2 tumor	Recruiting	Progression-free survival

Table 2

Ongoing studies for metastatic uveal melanoma in the U.S.

Clinical trials No.	Treatment	Phase	N	Status	Primary end point
NCT01473004	Cabozantinib (MET inhibitor) vs Temozolomide	II	69	Recruiting	Progression-free survival at 4 months
NCT01585194	Ipilimumab + nivolumab (combination checkpoint blockade)	II	52	Recruiting	Objective response rate
NCT01814046	Adoptive T cell therapy + high dose IL-2 vs adoptive T cell therapy (T cell therapy)	II	57	Recruiting	Objective response rate
NCT01252251	Everolimus (mTOR inhibitor) + pasireotide (somatostatin analog)	II	25	Recruiting	Clinical benefit rate
NCT01587352	Vorinostat (histone deacetylase inhibitor)	II	40	Recruiting	Objective response rate
NCT01979523	Trametinib (MEK inhibitor) vs Trametinib + GSK2141795 (AKT inhibitor)	II	80	Recruiting	Progression-free survival
NCT02359851	Pembrolizumab (anti-PD1 antibody)	II	29	Recruiting	Objective response rate
NCT02273219	AEB071 (protein kinase C inhibitor) + BYL719 (PI3Kα inhibitor)	I	50	Recruiting	Maximum tolerated dose
NCT02363282	Glembatumumab vedotin (antibody-drug conjugate)	II	34	Not yet open	Objective response rate
NCT01730157	Radioembolization (Y90) with Ipilimumab (anti-CTLA4 antibody)	0	12	Active, not recruiting	Toxicity, hepatic response rate