# Management of metastatic uveal melanoma

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**INTRODUCTION** — Uveal melanoma is a rare malignancy that arises from melanocytes within the uveal tract of the eye, which includes the iris, ciliary body, and choroid. Uveal melanoma comprises approximately 95 percent of melanomas arising from the eye, with the remainder arising from the conjunctiva.

The molecular pathogenesis, clinical presentation, and management of metastatic uveal melanoma are discussed here. The initial management of uveal and conjunctival melanomas is discussed separately. (See "Initial management of uveal and conjunctival melanomas".)

**MOLECULAR PATHOGENESIS** — The molecular pathogenesis of uveal melanoma is incompletely understood but is distinct from that of cutaneous melanoma and other melanoma subtypes, including conjunctival melanoma. Unlike cutaneous melanoma, uveal melanoma is genetically characterized by a small number of alterations. Advances in understanding the molecular pathogenesis may eventually provide important opportunities for targeted therapy in patients with metastatic disease. (See "The molecular biology of melanoma", section on 'MAPK pathway'.)

Uveal melanoma is characterized by a low mutational burden, with approximately 2000 predicted somatic single-nucleotide variants per tumor and low levels of aneuploidy [1]. Furthermore, uveal melanoma does not harbor recurrent mutations in *BRAF* or *NRAS* as are present in cutaneous disease. Rather, recurrent alterations in *GNAQ*, *GNA11*, *BAP1*, *PLCB4*, *CYSLTR2*, *SF3B1*, and *EIF1AX* are observed.

- *GNAQ* and *GNA11* are genes encoding for G protein alpha subunits and are mutated in over 90 percent of uveal melanomas [2]. These mutations lead to activation of downstream signaling pathways, including the MAPK pathway, in an analogous fashion to *BRAF* mutations in cutaneous melanoma, as well as the PI3K/AKT pathway and Yap/Hippo pathway [3-7].

- Additional mutations in *PLCB4* have been found in cases without *GNAQ* or *GNA11* mutations. *PLCB4* is a downstream effector of *GNAQ*/*GNA11* that was found to be mutated in 3 out of 28 uveal melanoma samples without *GNAQ*/*GNA11* mutations [8].

- Recurrent activating mutations in the G protein coupled receptor *CYSLTR2* have been found in uveal melanoma without *GNAQ*/*GNA11* or *PCLB4* mutations [9].

- The *BAP1* gene is a nuclear deubiquitinase located on chromosome 3p21.1 that functions as a tumor suppressor and has an important role in transcription and the DNA damage response. Inactivating mutations in *BAP1* are present in approximately 47 percent of primary uveal melanomas and 84 percent of metastatic uveal melanomas, implicating loss of *BAP1* in the progression of uveal melanoma [10]. Germline mutations

have been identified in *BAP1* in approximately 5 percent of patients with uveal melanomas, and these have been associated with larger tumors and involvement of the ciliary body [11].

- *SF3B1* encodes for splicing factor 3B subunit 1, which is involved in pre-messenger-RNA splicing. Recurring mutations occurring exclusively at codon 625 of *SF3B1* were identified in 18.6 percent of primary uveal melanomas and were associated with a relatively good prognosis [12]. *SF3B1* mutations, however, appear to be associated with the development of delayed metastasis within a median of 8.2 years [13].

- *EIF1AX* encodes for eukaryotic translation initiation factor 1A, X-linked, which stimulates transfer of methionine transfer RNA to the small ribosomal subunit. Recurrent somatic mutations in *EIF1AX* have been identified in 48 percent of primary uveal melanomas, and they were mutually exclusive of *BAP1* and *SF3B1* mutations and were associated with a good prognosis. All *EIF1AX* mutations caused in-frame changes affecting the N terminus of the protein [14].

**CLINICAL PRESENTATION AND PROGNOSIS** — Despite aggressive therapy of the primary lesion, distant recurrence is common and occurs in approximately 50 percent of all cases [15]. The most common initial sites of metastasis include the liver (60.5 percent), lung (24.4 percent), skin/soft tissue (10.9 percent), and bone (8.4 percent) [16].

Approximately 20 to 30 percent of patients diagnosed with a primary uveal melanoma die of systemic metastases within five years of diagnosis, with 45 percent dead within 15 years [15,17]. Of those who develop metastases and die of uveal melanoma, 62 and 90 percent do so within 5 and 15 years of the original diagnosis, respectively. The extent of metastatic disease is incorporated into the tumor, node, metastasis (TNM) staging system (table 1 and table 2), and its impact on overall survival is illustrated in the figure (figure 1).

The rarity of uveal melanoma has made it challenging to delineate the natural course and prognosis of patients with metastatic disease. A meta-analysis of individual patient-level data from phase Ib/II trials was conducted under the auspices of the International Rare Cancers Initiative (IRCI) Rare Melanoma Subgroup [18]. Data were available from 968 patients treated in 29 studies conducted between 2000 and 2015:

- Response data (best response achieved on trial) were available for 796 patients; 5 (0.6 percent) and 77 (9.7 percent) achieved a complete response and a partial response, respectively. Stable disease was achieved in 368 patients (46 percent). Thus, clinical benefit (complete response, partial response, and stable disease) was seen in 450 patients (57 percent).

- Median progression-free survival (PFS) was 3.3 months (95% CI 2.9-3.6), with a PFS rate at six months of 27 percent (95% CI 24-30). Factors significantly associated with shorter PFS on multivariate analysis included male sex, elevated lactate dehydrogenase (LDH), elevated alkaline phosphatase (ALP), and increased diameter of the largest liver metastasis (≥44.5 versus <44.5 mm).

- Median overall survival was 10.2 months (95% CI 9.6-11.0), with a one-year overall survival rate of 43 percent (95% CI 40-47). Significant prognostic factors for shorter overall survival by multivariable analysis were Eastern Cooperative Oncology Group (ECOG) performance status (≥1 versus 0), male sex, elevated LDH, elevated ALP, and larger diameter of the largest liver metastasis.

- There were numerically superior median PFS and overall survival for patients treated with liver-directed modalities; however, after adjusting for prognostic factors, only the PFS benefit of liver-directed therapies over other systemic regimens remained.

**OVERVIEW OF MANAGEMENT** — Advances in treatment of metastatic melanoma using targeted therapy and immunotherapy have led to prolongation of overall survival for patients with metastatic cutaneous melanoma.

These approaches are being explored for patients with metastatic uveal melanoma, but they do not have an established role in uveal melanoma. (See 'Systemic therapy' below.)

Currently, there are no US Food and Drug Administration (FDA)-approved systemic therapies for uveal melanoma in the adjuvant or metastatic settings, and no therapy has been shown to improve overall survival. As a result, there is no standard-of-care therapy, and participation in a clinical trial should be prioritized for patients with metastatic disease.

Although surgery or ablative procedures such as radiofrequency ablation, cryotherapy, or stereotactic radiation therapy can be performed with curative intent in cases of oligometastatic disease recurrence [19], such cases are rare. There are no randomized trials that have compared metastasectomy or ablation with systemic therapy or best supportive care. A comprehensive review of the role of surgery in this setting suggested that patients who were able to have their liver metastases completely resected did better than patients for whom a complete resection was not feasible [20]. However, only an estimated 2 to 7 percent of patients are candidates for resection of hepatic metastases, and the apparent improvement in survival may simply be a reflection of patient selection. (See "Surgical management of metastatic melanoma".)

A broad range of other treatment modalities have been evaluated to date, including systemic chemotherapy, immunotherapy, and molecularly targeted agents for the MAPK pathway and others. In many patients with metastatic uveal melanoma, the predominant site of metastatic disease is the liver, and this has led to extensive evaluation of treatments targeting hepatic disease, such as bland embolization, chemoembolization, radioembolization, immunoembolization, and hepatic arterial infusion of chemotherapy. (See 'Liver-directed therapeutic strategies' below.)

**LIVER-DIRECTED THERAPEUTIC STRATEGIES** — Among patients with hepatic metastases, therapy directed specifically toward the liver metastases has been associated with responses that may have clinical utility. Some liver-directed therapies take advantage of the dual blood supply of the liver in order to deliver treatments more directly to the metastases through the hepatic artery. Recruited hepatic artery branches vascularize the melanoma, whereas portal circulation provides the majority of the blood to the normal liver tissue. Intrahepatic therapeutic approaches include bland embolization, intraarterial administration of chemotherapy, isolated hepatic perfusion, intraarterial hepatic chemoembolization, and immunoembolization [21,22].

Both fotemustine and melphalan given by intrahepatic artery infusion have been compared with systemic chemotherapy in phase III trials. In both trials, no significant improvement in overall survival was observed despite differences in progression-free survival (PFS) or response rate [23-25].

- Fotemustine – In one trial, 171 patients with uveal melanoma and metastases limited to the liver were randomly assigned to fotemustine given either intraarterially or intravenously [24]. At a median follow-up of 1.6 years, 155 patients (91 percent) had died. Although there was a statistically significant improvement in PFS (median 4.5 versus 3.5 months), there was no improvement in overall survival with the intraarterial approach (median 14.6 versus 13.8 months, hazard ratio 1.09, 95% CI 0.79-1.50).

- Melphalan – In another trial, percutaneous hepatic perfusion of melphalan was compared with best alternative care in 93 patients with melanoma liver metastases. Approximately 89 percent of patients treated in this study had uveal melanoma. Hepatic PFS was significantly prolonged with the melphalan infusion (median 7.0 versus 1.6 months). However, there was no difference in overall survival (median 10.6 versus 10.0 months) [25].

**SYSTEMIC THERAPY** — No therapy has been shown to improve overall survival for patients with uveal melanoma, and thus, there is no standard of care. Enrollment in formal clinical trials is recommended whenever possible.

The majority of prospective trials conducted in uveal melanoma have been single-arm phase II studies, which have generally demonstrated response rates under 10 percent, progression-free survival (PFS) less than five months, and overall survival less than one year. Only seven randomized clinical trials have been conducted and presented or published for patients with advanced uveal melanoma [24,26-30].

**Chemotherapy** — No chemotherapeutic agent, alone or in combination, has been found to extend overall survival in patients with metastatic disease, with response rates generally under 10 percent. Agents studied have included dacarbazine, temozolomide, cisplatin, bendamustine, treosulfan, fotemustine-based regimens, and others.

In an analysis of 64 patients treated for metastatic uveal melanoma with a variety of regimens that included cisplatin and dacarbazine, only one complete response and five partial responses were observed (9 percent) [31]. Only two responses were seen in the 56 patients with hepatic metastases. Other studies have not resulted in consistently higher response rates [32,33]. (See "Cytotoxic chemotherapy for metastatic melanoma".)

**Immunotherapy** — Despite the dramatic efficacy of checkpoint inhibitors targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death receptor 1 (PD-1) in cutaneous melanoma, only limited activity has been observed in uveal melanoma.

**Ipilimumab** — In the phase III trial that established the survival benefit of ipilimumab for metastatic cutaneous melanoma, patients with uveal melanoma were excluded [34]. However, more recent data suggest that CTLA-4 inhibition with ipilimumab or tremelimumab has limited activity in uveal melanoma [35-38]. (See "Immunotherapy of advanced melanoma with immune checkpoint inhibition".)

- The Spanish Melanoma Group evaluated the efficacy of 10 mg/kg ipilimumab in 32 patients with treatment-naïve metastatic uveal melanoma [37]. With a median follow-up of 5.5 months, 13 patients were evaluable for response. Of these, one achieved a partial response (7.7 percent), and six achieved stable disease (46.2 percent). Median overall survival was 9.8 months.

- A phase II study of ipilimumab (3 mg/kg) in 45 pretreated and 8 treatment-naïve patients with metastatic uveal melanoma was performed by the Dermatologic Cooperative Oncology Group [38]. Sixteen patients had stable disease (47 percent), and none experienced a partial or complete response. One- and two-year overall survival rates were 22 and 7 percent, respectively. Median overall survival was 6.8 months (95% CI 3.7–8.1), and median PFS was 2.8 months (95% CI 2.5–2.9).

- Tremelimumab, another anti-CTLA-4 antibody, failed to demonstrate activity in 11 patients in a prospective phase II study of advanced uveal melanoma in patients who had not received prior immunotherapy; the study was terminated for lack of efficacy [39].

**Anti-PD-1 or PD-L1 antibodies** — Although at least one small series has observed activity with the anti-PD-1 antibody pembrolizumab [40], more extensive experience suggests that responses and clinical benefit are much more limited than with advanced cutaneous melanoma.

The most extensive results come from a multicenter retrospective series of 56 patients with metastatic uveal melanoma [41]. Treatment utilized pembrolizumab, nivolumab, and atezolizumab in 38, 16, and 2 cases, respectively; 36 (62 percent) had received prior ipilimumab. There were two partial responses (3.6 percent), and stable disease for ≥6 months was observed in five cases (8.9 percent). Median PFS and overall survival were 2.8 and 7.6 months, respectively.

**Other immunotherapy approaches** — Preliminary evidence from a phase 2 study indicated that autologous tumor-infiltrating lymphocytes (TILs) could mediate regression of metastatic uveal melanoma [42]. Additional clinical study will be required to further assess this approach.

Clinical activity has also been reported in patients with uveal melanoma treated with IMCgp100, a bispecific molecule comprised of a targeting end that constitutes a soluble T cell receptor targeting glycoprotein 100, a uveal melanoma antigen, and an effector end targeting CD3. In the first in-human study of IMCgp100, of 15 evaluable uveal melanoma patients, three patients (20 percent) achieved a partial response and seven patients (47 percent) had stable disease at eight weeks. The disease control rate was 53 percent at 16 weeks and 40 percent at 24 weeks [43].

In a subsequent phase I trial of this agent using an intrapatient dose escalation strategy, of the 19 evaluable patients treated on the dose escalation portion of the study, with a median follow-up of 24.3 weeks, there were two objective responses (11 percent), with 12 additional patients with stable disease (63 percent). The disease control rate at 16 weeks was 53 percent, with a median PFS of 24.3 weeks. The estimated 52-week overall survival was 79.5 percent [44].

Additional clinical study will be required to further assess these novel approaches.

**Molecularly targeted agents** — Uveal melanoma has a different molecular pathogenesis than cutaneous melanoma. *BRAF* mutations are typically not seen, and thus, BRAF inhibitors are not indicated [45]. (See "The molecular biology of melanoma", section on 'MAPK pathway' and "Molecularly targeted therapy for metastatic melanoma", section on 'Approach to treatment'.)

The near universal presence of either *GNAQ* and *GNA11* mutations or other mutations in genes such as *PLCB4* or *CYSLTR2* affirms the importance of G protein alpha subunit signaling in this disease, with downstream activation of pathways such as the MAPK, PI3K/AKT, and YAP pathways. Molecularly targeted therapies for the MAPK and/or the PI3K/AKT pathways have been conducted in metastatic uveal melanoma.

A randomized phase II study of the MEK inhibitor selumetinib versus chemotherapy in advanced uveal melanoma demonstrated a modest improvement in PFS with selumetinib treatment, but no overall survival benefit [26]. A subsequent phase III study of selumetinib and dacarbazine versus dacarbazine alone showed no improvement in either PFS or overall survival [46].

**Epigenetic therapies** — Given that uveal melanoma is a genetically simple disease characterized by few somatic variants compared with cutaneous melanoma, other factors, such as epigenetic alterations, may be important in the pathogenesis of uveal melanoma.

Preclinical data in uveal melanoma cell lines support the role of histone deacetylase (HDAC) inhibitors in reversing the phenotypic and biochemical cell changes associated with *BAP1* loss and metastatic potential in uveal melanoma cells, with induction of G1 cell-cycle arrest, melanocytic differentiation, and gene-expression changes consistent with reversion to a class I phenotype [47,48].

Preclinical data suggest that epigenetic therapies targeting the bromodomain and extra-terminal domain (BET) family of proteins may be a promising new strategy in uveal melanoma. JQ1, a first-generation BET inhibitor that competitively displaces BRD4 from acetylated histones, demonstrated potent cytotoxic activity in *GNAQ* and *GNA11* mutant cell lines but not wild-type cells [49]. Microarray analysis of cell lines treated with JQ1 revealed changes in expression in genes involved in cell-cycle regulation, apoptosis, and the DNA damage response. Interestingly, concomitant silencing of Bcl-xL and Rad51, regulators of apoptosis and the DNA damage response, respectively, was sufficient to induce apoptosis independent of Myc expression.

Studies of HDAC inhibitors and BET protein inhibitors are currently in clinical development for uveal melanoma.

## SUMMARY AND RECOMMENDATIONS

- For patients who present with metastatic disease or who develop metastatic disease after treatment of their primary tumor, the prognosis is poor. (See 'Clinical presentation and prognosis' above.)
- Limited data exists regarding the optimal selection of patients best suited for localized, regional, or systemic therapy, but they may be performed based upon clinical factors such as the number and location of metastatic lesions, the disease-free interval, and the availability of clinical trials.
- Resection or ablation of oligometastatic disease can lead to long-term clinical benefit in appropriately selected patients. (See 'Overview of management' above.)
- Regional liver-directed therapy may achieve disease control that is more durable than that achieved with the available systemic therapeutic options; however, there does not appear to be an overall survival advantage when adjusting for prognostic factors. (See 'Liver-directed therapeutic strategies' above.)
- There appears to be limited clinical efficacy achieved with currently available immunological checkpoint inhibitors targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death ligand 1 (PD-L1). (See 'Immunotherapy' above.)
- Therapy for these patients remains generally palliative, and clinical trial participation remains the standard of care.



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## GRAPHICS

### Choroidal and ciliary body melanoma TNM staging AJCC UICC 2017

**Primary tumor (T)**

| T category | T criteria |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor size category 1 |
| T1a | Tumor size category 1 without ciliary body involvement and extraocular extension |
| T1b | Tumor size category 1 with ciliary body involvement |
| T1c | Tumor size category 1 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter |
| T1d | Tumor size category 1 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter |
| T2 | Tumor size category 2 |
| T2a | Tumor size category 2 without ciliary body involvement and extraocular extension |
| T2b | Tumor size category 2 with ciliary body involvement |
| T2c | Tumor size category 2 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter |
| T2d | Tumor size category 2 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter |
| T3 | Tumor size category 3 |
| T3a | Tumor size category 3 without ciliary body involvement and extraocular extension |
| T3b | Tumor size category 3 with ciliary body involvement |
| T3c | Tumor size category 3 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter |
| T3d | Tumor size category 3 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter |
| T4 | Tumor size category 4 |
| T4a | Tumor size category 4 without ciliary body involvement and extraocular extension |
| T4b | Tumor size category 4 with ciliary body involvement |
| T4c | Tumor size category 4 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter |
| T4d | Tumor size category 4 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter |
| T4e | Any tumor size category with extraocular extension >5 mm in largest diameter |

*NOTES:*

1. Primary ciliary body and choroidal melanomas are classified according to the four tumor size categories defined in figure entitled "Classification for ciliary body and choroid uveal melanoma based on thickness and diameter."
2. In clinical practice, the largest tumor basal diameter may be estimated in optic disc diameters (DD; average: 1 DD = 1.5 mm), and tumor thickness may be estimated in diopters (average: 2.5 diopters = 1 mm). Ultrasonography and fundus photography are used to provide more accurate measurements.
3. When histopathologic measurements are recorded after fixation, tumor diameter and thickness may be underestimated because of tissue shrinkage.

**Classification for ciliary body and choroid uveal melanoma based on thickness and diameter**

| | Largest basal diameter (mm) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Thickness (mm)** | **≤3.0** | **3.1 to 6.0** | **6.1 to 9.0** | **9.1 to 12.0** | **12.1 to 15.0** | **15.1 to 18.0** | **>18.0** |
| **>15.0** | | | | | 4 | 4 | 4 |
| **12.1 to 15.0** | | | | 3 | 3 | 4 | 4 |
| **9.1 to 12.0** | | 3 | 3 | 3 | 3 | 3 | 4 |
| **6.1 to 9.0** | 2 | 2 | 2 | 2 | 3 | 3 | 4 |
| **3.1 to 6.0** | 1 | 1 | 1 | 2 | 2 | 3 | 4 |
| **≤3.0** | 1 | 1 | 1 | 1 | 2 | 2 | 4 |

**Regional lymph nodes (N)**

| N category | N criteria |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node involvement |
| N1 | Regional lymph node metastases or discrete tumor deposits in the orbit |
| N1a | Metastasis in one or more regional lymph node(s) |
| N1b | No regional lymph nodes are positive, but there are discrete tumor deposits in the orbit that are not contiguous to the eye (choroidal and ciliary body) |

**Distant metastasis (M)**

| M category | M criteria |
|---|---|
| M0 | No distant metastasis by clinical classification |
| M1 | Distant metastasis |
| M1a | Largest diameter of the largest metastasis ≤3.0 cm |
| M1b | Largest diameter of the largest metastasis 3.1-8.0 cm |
| M1c | Largest diameter of the largest metastasis ≥8.1 cm |

**Prognostic stage groups**

| When T is... | And N is... | And M is... | Then the stage group is... |
|---|---|---|---|
| T1a | N0 | M0 | I |
| T1b-d | N0 | M0 | IIA |
| T2a | N0 | M0 | IIA |
| T2b | N0 | M0 | IIB |
| T3a | N0 | M0 | IIB |
| T2c-d | N0 | M0 | IIIA |
| T3b-c | N0 | M0 | IIIA |
| T4a | N0 | M0 | IIIA |
| T3d | N0 | M0 | IIIB |
| T4b-c | N0 | M0 | IIIB |
| T4d-e | N0 | M0 | IIIC |
| Any T | N1 | M0 | IV |
| Any T | Any N | M1a-c | IV |

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 110766 Version 3.0

## Iris melanoma TNM staging AJCC UICC 2017

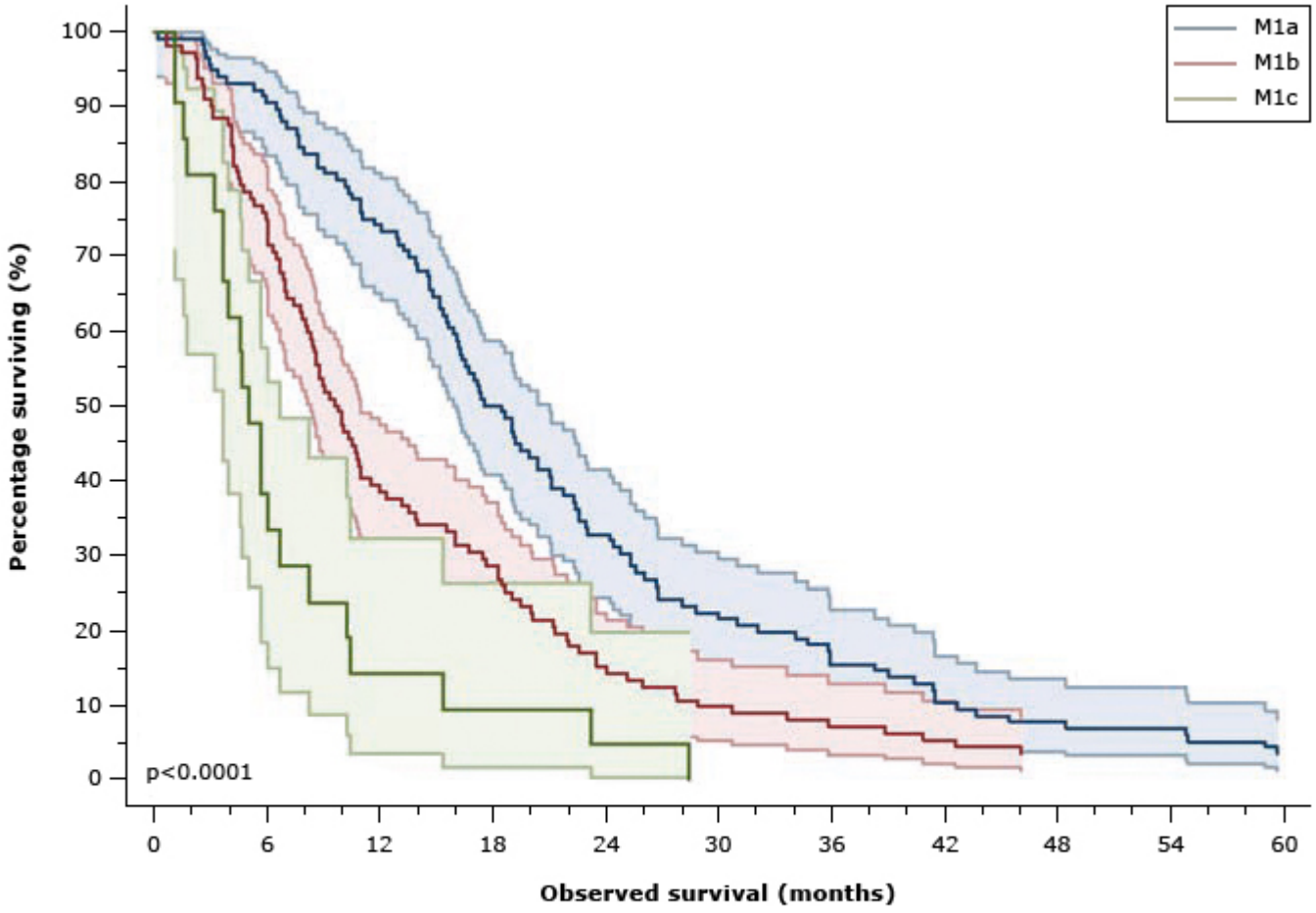
| Primary tumor (T) | |
|---|---|
| **T category** | **T criteria** |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor limited to the iris |
| T1a | Tumor limited to the iris, not more than 3 clock hours in size |
| T1b | Tumor limited to the iris, more than 3 clock hours in size |
| T1c | Tumor limited to the iris with secondary glaucoma |
| T2 | Tumor confluent with or extending into the ciliary body, choroid, or both |
| T2a | Tumor confluent with or extending into the ciliary body, without secondary glaucoma |
| T2b | Tumor confluent with or extending into the ciliary body and choroid, without secondary glaucoma |
| T2c | Tumor confluent with or extending into the ciliary body, choroid, or both, with secondary glaucoma |
| T3 | Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension |
| T4 | Tumor with extrascleral extension |
| T4a | Tumor with extrascleral extension ≤5 mm in largest diameter |
| T4b | Tumor with extrascleral extension >5 mm in largest diameter |
| *NOTE:* Iris melanomas originate from, and are predominately located in, this region of the uvea. If less than half the tumor volume is located within the iris, the tumor may have originated in the ciliary body, and consideration should be given to classifying it accordingly. | |
| **Regional lymph nodes (N)** | |
| **N category** | **N criteria** |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node involvement |
| N1 | Regional lymph node metastases or discrete tumor deposits in the orbit |
| N1a | Metastasis in one or more regional lymph node(s) |
| N1b | No regional lymph nodes are positive, but there are discrete tumor deposits in the orbit that are not contiguous to the eye (choroidal and ciliary body) |
| **Distant metastasis (M)** | |
| **M category** | **M criteria** |
| M0 | No distant metastasis by clinical classification |
| M1 | Distant metastasis |
| M1a | Largest diameter of the largest metastasis ≤3.0 cm |
| M1b | Largest diameter of the largest metastasis 3.1-8.0 cm |
| M1c | Largest diameter of the largest metastasis ≥8.1 cm |

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.



Graphic 110765 Version 2.0

## Observed melanoma-related overall Kaplan-Meier survival rates metastatic primary choroidal and ciliary body melanomas




**Number at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M1a | 116 | 105 | 86 | 58 | 38 | 26 | 18 | 12 | 9 | 8 | 4 |
| M1b | 112 | 84 | 43 | 32 | 17 | 11 | 8 | 6 | 4 | 4 | 4 |
| M1c | 21 | 8 | 3 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

Observed melanoma-related overall Kaplan-Meier survival rates for metastatic primary choroidal and ciliary body melanomas.



Graphic 112190 Version 2.0

## Contributor Disclosures

**Richard D Carvajal, MD** Consultant/Advisory Boards: Castle Biosciences [Melanoma (DecisionDX)]; Iconic Therapeutics [Melanoma (ICON1)]; BMS [Melanoma (Ipilimumab, nivolumab)]; Novartis [Melanoma (Imatinib, nilotinib)]; AstraZeneca [Melanoma (Selumetinib)]; Immunocore [Melanoma (IMCgp100)]; Merck [Melanoma (Pembrolizumab)]; Aura Biosciences [Melanoma (AU-011)]. **Michael B Atkins, MD** Grant/Research/Clinical Trial Support: BMS [Melanoma and RCC (Nivolumab and ipilimumab)]; Roche [Melanoma (Vemurafenib and cobimetinib); RCC (Atezolizumab and bevacizumab)]; Novartis [Melanoma (Dabrafenib and trametinib); RCC (Pazopanib and everolimus)]. Consultant/Advisory Boards: BMS; Merck; Novartis; Pfizer; Roche; Exelixis; Eisai [Melanoma; RCC; immunotherapy (Everoliumus, pazopanib; dabrafenib/trametinib; axitinib, sunitinib, avelumab; vemurafenib/cobimetinib, atezolizumab; ipilimumab/nivolumab; pembrolizumab, interferon; cabozantinib; lenvatinib)]. **Jonathan Trobe, MD** Nothing to disclose **Russell S Berman, MD** Nothing to disclose **Michael E Ross, MD** Nothing to disclose

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