

COMBINATION THERAPY FOR METASTATIC UVEAL MELANOMA



A look at the response of large choroidal metastatic melanoma to treatment with darovasertib and crizotinib.

BY LAUREN B. YEAGER, MD, AND BRIAN P. MARR, MD

Uveal melanoma (UM) is the most common intraocular tumor in adults. Plaque brachytherapy has been the mainstay of treatment for UM tumors since the pivotal COMS trial, which proved the noninferiority of brachytherapy compared with enucleation for the treatment of medium-sized tumors. While brachytherapy offers a globe-salvaging treatment with more than 95% effectiveness, significant visual impairments occur in more than half of patients, mainly due to radiation-related complications.^{1,2} Current research focuses on enhancing brachytherapy by reducing complications, improving visual outcomes, and expanding indications for use. Enucleation remains necessary for large tumors that exceed 11 mm in thickness and/or those that cannot be adequately covered by the plaque.

Metastatic UM (MUM) develops in up to 50% of patients diagnosed with UM.³ The prognosis is historically poor in cases of MUM, and treatment options remain limited, although clinical trials on targeted therapies are making slow and steady progress. Nearly 90% of UM cases are associated with *GNAQ/GNA11* mutations, which lead to consistent activation of the protein kinase C (PKC) and the mitogen-activated protein kinase pathway, driving tumor progression.⁴ Studies have shown that PKC inhibition slows the growth of *GNAQ/GNA11*-mutated melanomas⁵; however, the results of PKC inhibitors when used alone are suboptimal.⁶ This may be due, in part, to hepatocyte growth factors (HGF) binding to *c-Met*, a receptor tyrosine kinase, leading to cell proliferation,⁷ and evidence suggests *c-Met* inhibition combined with PKC inhibition may have a synergistic effect.⁸ This has led to ongoing clinical trials evaluating darovasertib, a small-molecule PKC inhibitor for *GNAQ*-mutated cancers, as a monotherapy or in combination with

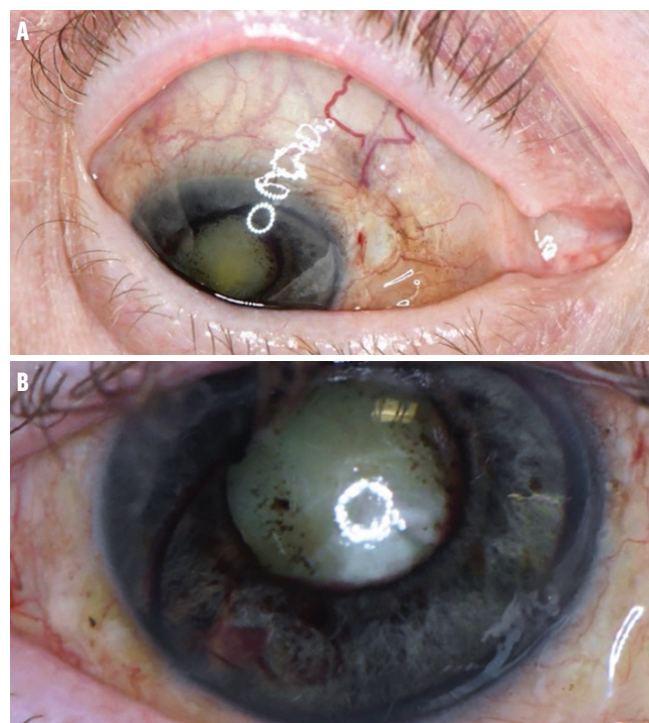


Figure 1. External photographs at presentation showed diffuse subconjunctival pigmentation (A). Note the scattered pigment in the anterior chamber and on the anterior lens capsule (B). Layered hemorrhage was visualized inferiorly, and a dense white cataract obstructed the posterior view.

a *c-Met* inhibitor, such as crizotinib or binimetinib.

Herein, we report a case of MUM that spread to the liver and was successfully treated with darovasertib and crizotinib, highlighting the dramatic response of the primary tumor and the potential role of this combination therapy for ocular treatment, particularly in the neoadjuvant setting.



Figure 2. MRI of the orbits showed an enhancing intraocular mass occupying most of the globe in the T-1 post-contrast image.

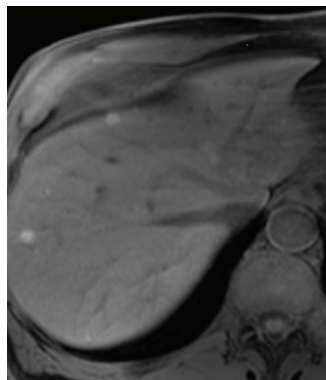


Figure 3. A pre-contrast axial T-1 image of the abdomen performed at the time of diagnosis demonstrated multiple intrinsically enhancing lesions consistent with MUM.

CASE REPORT

A 73-year-old man presented to our service for a tertiary opinion. Four months prior, he was diagnosed at an outside hospital with a retinal detachment and presumed subretinal and choroidal hemorrhage, for which he underwent pars plana vitrectomy. His postoperative course was complicated by multiple redetachments requiring two repeat surgeries; in the most recent surgery, the surgeon noted intraocular brown pigment.

The patient's past medical, family, and social history were noncontributory. At presentation, VA was light perception OD and 20/25 OS, and IOP was normal. On anterior examination, there was fine, diffusely scattered subconjunctival pigment; diffuse pigment on the corneal endothelium; iris neovascularization; and a dense cataract

(Figure 1). Vitreous hemorrhage obscured the posterior view. He was taking oral acetazolamide (Diamox, Teva Pharmaceuticals), as well as topical prednisolone acetate and 2%/0.5% dorzolamide HCl timolol maleate ophthalmic solution (Cosopt PF, Théa) in the right eye.

Ultrasonography of the right eye was limited due to the presence of silicone oil but suspicious for a large intraocular mass. Globe transillumination showed diffuse darkening without discrete borders. UM was suspected, and an MRI of the orbits was performed that revealed a 2.0 cm x 1.3 cm intraocular mass with intrinsic T-1 hyperintensity and relative diffuse restriction, consistent with a melanocytic tumor and UM (Figure 2). There was no gross orbital extension on MRI; however, the subconjunctival pigment was consistent with extraocular spread. Systemic workup with CT of the chest and MRI of the abdomen showed multiple small, T-1-enhancing liver lesions (Figure 3). CT-guided liver biopsy confirmed MUM with GNAQ mutation.

Treatment options were reviewed with the patient, including enucleation. Given the need for systemic management and that the patient was pain-free, surgery was deferred. Systemic treatment options included immune checkpoint blockade, liver-directed therapy, and clinical trials. The patient was HLA-A*02:01 negative and, thus, not a candidate for tebentafusp (Kimmtrak, Immunocore). He was enrolled in a clinical trial and started on treatment with oral darovasertib and crizotinib. He experienced moderate but tolerable side effects, including nausea, vomiting, edema, and facial rash; each was controlled medically.

At 2 months post-treatment, liver disease was reduced by 28%. At 3 months post-treatment, orbital MRI showed a greater-than 50% reduction of the ocular tumor (Figure 4). Six months post-diagnosis, the patient has decreased disease burden (Figure 5).

EMERGING NEOADJUVANT THERAPIES

Therapeutic options for MUM remain limited. Checkpoint inhibitors, which revolutionized the treatment of metastatic cutaneous melanoma, show disappointing results in UM.⁹ Recent advances include the FDA approval of tebentafusp, a bispecific gp100-CD3 T-cell engager for HLA-A*02:01-positive patients that improves median overall survival to 21.6 months compared with 16 months in the control group. The overall survival benefit does not correlate with response rates, which are limited to 9% versus 5% in control populations.¹⁰ While tebentafusp is currently first-line therapy for HLA-A*02:01-positive patients, eligibility for the drug is limited. HLA-A*02:01 seropositivity occurs in about 50% of the White population.¹¹

There remains an urgent need for treatments that will target broader populations. Early trial data showed that darovasertib/crizotinib therapy for the treatment of MUM may have a 90% disease control rate and median



Figure 4. MRI of the orbits 3 months post-treatment initiation showed that the mass had decreased by more than half.

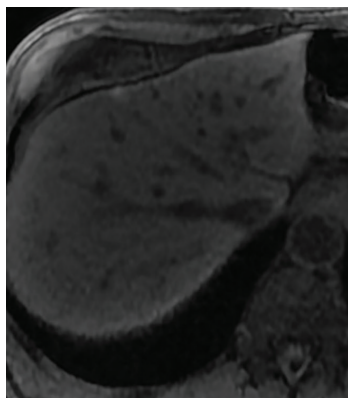


Figure 5. A pre-contrast, axial T-1 image of the abdomen performed 6 months post-treatment showed that the lesions had significantly reduced in size and number.

progression-free survival of 7 months, offering a potential first-line treatment for HLA-A*02:01-negative patients.¹²

Research focuses on the potential of neoadjuvant treatments for primary UM. Neoadjuvant treatment is used to shrink the ocular tumor prior to definitive therapy. Current treatment with tebentafusp and immune checkpoint inhibitors offers poor response rates of 0% to 9%, making them unsuitable for neoadjuvant use.^{10,13,14} Our patient experienced 50% shrinkage of his ocular tumor with darovasertib/crizotinib therapy; this marked response is supported by clinical data. Darovasertib/crizotinib combination has an overall response rate of 45% and decreased tumor size in 100% of patients with UM to date.¹² Hoing et al recently published the first prospective case of successful neoadjuvant

treatment using combined darovasertib/crizotinib in a patient with a large UM in his only seeing eye. At 4 months, there was an 80% reduction in tumor size, sparing the patient enucleation and allowing for plaque brachytherapy.¹⁵ These data have prompted a phase 2 clinical trial evaluating darovasertib as a neoadjuvant therapy in ocular melanoma.

POTENTIAL TO SPARE ENUCLEATION

Decreasing tumor size prior to definitive therapy has the potential to allow for malignancies to be treated with globe-salvaging approaches and improved visual outcomes post-brachytherapy through lowering radiation dosage, a known risk factor for visual impairment.¹⁶ ■

Acknowledgement: The authors would like to thank Volkan Beylergil, MD, radiologist at Memorial Sloan Kettering Cancer Center, New York City, for his contributions to the article.

1. Melia BM, Abramson DH, Albert DM, et al; Collaborative Ocular Melanoma Study Group. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16. *Ophthalmology*. 2001;108(2):348-366.
2. Shields CL, Shields JA, Cater J, et al. Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1106 consecutive patients. *Archives of Ophthalmology*. 2000;118(9):1219-1228.
3. Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci*. 2003;44(11):4651-4659.
4. Van Raamsdonk CD, Bezrookove V, Green G, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature*. 2009;457(7229):599-602.
5. Wu X, Li J, Zhu M, Fletcher JA, Hodi FS. Protein kinase C inhibitor AEB071 targets ocular melanoma harboring GNAQ mutations via effects on the PKC/Erk1/2 and PKC/NF-kappaB pathways. *Mol Cancer Ther*. 2012;11(9):1905-1914.
6. Chen X, Wu Q, Tan L, et al. Combined PKC and MEK inhibition in uveal melanoma with GNAQ and GNA11 mutations. *Oncogene*. 2014;33(39):4724-4734.
7. Cheng H, Terai M, Kageyama K, et al. Paracrine effect of NRG1 and HGF drives resistance to MEK inhibitors in metastatic uveal melanoma. *Cancer Res*. 2015;75(13):2737-2748.
8. Cao L, Chen S, Sun R, et al. Darovasertib, a novel treatment for metastatic uveal melanoma [published online ahead of print July 28, 2023]. *Front Pharmacol*.
9. Yang J, Manson DK, Marr BP, Carvajal RD. Treatment of uveal melanoma: where are we now? [published online ahead of print February 12, 2018]. *Ther Adv Med Oncol*.
10. Nathan P, Hassel JC, Rutkowski P, et al. Overall survival benefit with tebentafusp in metastatic uveal melanoma. *N Engl J Med*. 2021;385(13):1196-1206.
11. Ellis JM, Henson V, Slack R, Ng J, Hartzman RJ, Hurley CK. Frequencies of HLA-A2 alleles in five US population groups: predominance of A*02011 and identification of FHLA-A*0231. *Hum Immunology*. 2000; 61(3):334-340.
12. IDEAYA announces positive interim phase 2 data for darovasertib and crizotinib combination and successful FDA type C meeting on registrational trial design for accelerated approval in first-line metastatic uveal melanoma. IDEAYA Biosciences. April 23, 2023. tinyurl.com/yvkv3xzh
13. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381(16):1535-1546.
14. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol*. 2015;33(17):1974-1982.
15. Hiong A, O'Day R, Fog LS, et al. Globe salvage and vision preservation by neoadjuvant darovasertib and crizotinib in uveal melanoma. *Ophthalmol Retina*. 2024;8(4):325-330.
16. Shields CL, Dalvin LA, Chang M, et al. Visual outcome at 4 years following plaque radiotherapy and prophylactic intravitreal bevacizumab (every 4 months for 2 years) for uveal melanoma: comparison with nonrandomized historical control individuals. *JAMA Ophthalmol*. 2020;138(2):136-146.

BRIAN P. MARR, MD

- Ophthalmologist, Edward S. Harkness Eye Institute, Columbia University Irving Medical Center, New York, New York
- Financial disclosure: None

LAUREN B. YEAGER, MD

- Ophthalmologist, Edward S. Harkness Eye Institute, Columbia University Irving Medical Center, New York, New York
- ly2292@cumc.columbia.edu
- Financial disclosure: None