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What does the future hold for uveal melanoma, a historically untreatable disease?

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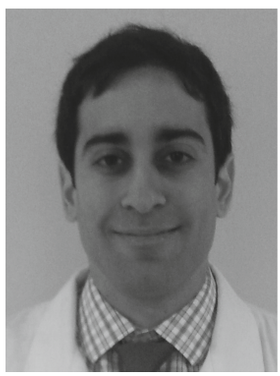

"...with a better understanding of the genetic and epigenetic changes that underlie distinct classes of tumor behavior, future interventions may be identified..."

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Uveal melanoma (UM), which encompasses pigmented tumors arising from the iris, ciliary body and choroid, is the most common primary intraocular malignancy in adults, with an incidence of approximately five cases per million [1]. A total of 98% of patients with UM are Caucasian and incidence increases with age. Approximately half of all patients develop metastatic disease within 15–20 years of initial diagnosis, with up to 90% of patients developing hepatic metastases [1]. Metastatic UM has historically portended a dismal prognosis, with an overall survival of less than 1 year from diagnosis. Outcome can be predicted using either cytogenetic or gene expression analysis of the primary tumor. Starting in the late 1980s, cytogenetic analysis of metastatic UMs led to the finding that monosomy 3 (and specifically 3p loss) and 8q24 duplication portended a worse prognosis than disomy 3 and 6p gain [2]. More recently, gene expression profiling demonstrated that UMs fall into two distinct classes with diverging 5-year risk of metastasis – Class I, with as low as 2% risk, and Class II, with approximately 72% risk [3].

Once metastases occur, therapeutic options are limited. Over the past decade, multiple Phase II trials have been conducted with traditional cytotoxic chemotherapeutic agents such as temozolomide, immunologic agents such as interferon, and targeted agents such as imatinib, among others. The overall objective response rates on these trials are universally low, with observed progression-free survivals typically less than 3 months. Hepatic-directed therapy has demonstrated reasonable objective response rates, but the impact of these therapies on overall survival is not clear [4].

Multiple agents have recently been approved by the US FDA for treatment of advanced melanoma, including the BRAF inhibitors vemurafenib [5] and dabrafenib [6]; the MEK inhibitor trametinib and the CTLA-4 inhibitor ipilimumab [7]. Although vemurafenib and dabrafenib have been demonstrated to improve survival in patients with cutaneous melanoma harboring *BRAF* mutations, they are not a viable therapeutic option for patients with UM, a disease that only rarely harbors such mutations [8]. Immune checkpoint inhibitors such as ipilimumab, which also improves survival in patients with advanced cutaneous melanoma [7], represent another potential treatment approach for those with advanced UM. A retrospective review of clinical outcomes of metastatic UM patients receiving ipilimumab identified an immune-related response rate of 5% and the disease-control rate was 28% at 24 weeks, results that appear similar to that seen in cutaneous melanoma [9]. A smaller series reported an identical disease control rate at 23 weeks [10].

Recent advances in our understanding of the biology of UM have provided potential therapeutic strategies. A critical insight into the mechanism of UM tumor

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growth came in 2009–2010, when van Raamsdonk and colleagues reported two mutually exclusive activating mutations in G-α subunits (*GNAQ* and *GNA11*) of UM cells that resulted in constitutive signaling downstream of G-protein coupled receptors [11,12]. As a result, several downstream growth signaling pathways are upregulated, including MAPK, PKC and PI3K/mTOR/Akt [13]. This discovery has led to the development of a new generation of clinical trials based upon preclinical work by our group and others demonstrating the mutation-dependent antitumor effects of MEK and PKC pathway inhibition [14,15].

We led a randomized Phase II trial of the MEK inhibitor selumetinib versus chemotherapy with either temozolomide or dacarbazine (investigator's choice) that was the first study to ever demonstrate clinical efficacy of any agent in a randomized fashion in metastatic UM. Progression-free survivals increased from 7 weeks with chemotherapy to 16 weeks with selumetinib [16]. Sustained MAPK pathway inhibition was documented on tumor samples after 14 days of selumetinib treatment. Specifically, phosphorylated ERK (pERK) and cyclinD1, downstream effectors of MEK, were decreased by a median of 48 and 76%, respectively. Radiologic response to selumetinib was significantly correlated with pERK inhibition, and there was a trend towards correlation between pERK inhibition and clinical benefit.

The success of MEK inhibition supports the hypothesis that inhibition of growth pathways constitutively activated by the *GNAQ* and *GNA11* mutations can lead to clinical benefit. The efficacy of selumetinib in this disease supports the evaluation of other MEK inhibitors with more potent MEK inhibitory activity in this disease. Although only limited data are available regarding the efficacy of trametinib, another inhibitor of MEK in UM, some antitumor effects have been observed. Of 16 heavily pretreated patients with advanced UM treated on the Phase I study of trametinib, two achieved a 24% tumor reduction and 50% achieved stable disease. Four patients received treatment for 16 weeks or longer, and two received treatment for at least 40 weeks [17].

Future studies are focusing on combination regimens that aim to inhibit multiple pathways in an effort to increase the clinical benefit achieved with single-agent therapy. The majority of these trials will be utilizing MEK inhibition as the backbone. A randomized Phase II trial is being developed by AstraZeneca (Macclesfield, UK) comparing selumetinib alone with selumetinib plus dacarbazine. This study will test the hypothesis that modulation of key apoptotic proteins by MEK inhibition can enhance the cytotoxic effects of chemotherapy. A second randomized trial of trametinib with or without the AKT inhibitor GSK2141795, sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute (MD, USA), will test the hypothesis that dual pathway inhibition will result in greater antitumor effects than MEK inhibition alone.

Another approach to targeting the downstream effects of *GNAQ* and *GNA11* mutations is the inhibition of PKC, which lies downstream of *GNAQ* and *GNA11* [13]. A multicenter Phase I trial of the *PKC* inhibitor sotrastaurin (AEB071) is currently recruiting patients [101]. A study combining MEK and PKC inhibition with MEK162 and sotrastaurin is also open for accrual [102]. Finally, a Phase Ib/II trial combining sotrastaurin with the PI3K-α specific inhibitor BYL719 is currently being planned.

Other recent advances in our understanding of the biology of UM will likely be critical in the successful development of effective therapies of this disease. In 2010, Harbour's group identified a novel tumor suppressor gene, *BAP1*, on chromosome 3p that is associated with UM progression [18]. BAP1 was initially described as a deubiquitinating enzyme thought to mediate tumor suppression through *BRCA1*, but further studies have demonstrated that BAP1 affects a myriad of cellular pathways independent of *BRCA1*. BAP1 targets include multiple genes implicated in development that may underlie the dedifferentiated phenotype in *BAP1*-mutant UM cells [19]. Further elucidation of these pathways may identify other treatment targets. Recently, for example, an *in silico* screen and confirmatory *in vitro* analyses identified HDAC inhibitors as agents that may reverse the dedifferentiation and growth induced by BAP1 loss [19]. This has led to the development of an ongoing Phase II study of the HDAC inhibitor vorinostat in metastatic UM [103].

Earlier this year, Harbour's group reported that 20% of UMs had mutations in codon 625 of *SF3B1*, a gene encoding a splice factor known to process pre-mRNAs [20]. Various *SF3B1* mutations were originally described in hematologic malignancies, with varying impact on prognosis depending on the tumor type. In UM, *SF3B1* mutations were largely found in good prognosis, Class I, tumors. Interestingly, only one of the 17 *SF3B1*-mutant tumors was *BAP1* mutant, suggesting that these changes are largely mutually exclusive and may represent alternate pathways for tumor progression [20]. It is currently unclear how *SF3B1* mutations influence UM cellular behavior. Despite its role as a splice factor, *SF3B1* mutant UM cells were not associated with global changes in splice donor and acceptor sites [20]. Thus, further study is needed to determine how *SF3B1* mutations contribute to UM tumor progression and whether there are any potential therapeutic implications.

Overall, over the past decade, there has been a great deal of progress in understanding the molecular basis

of UM. With the discovery of distinct mutations that activate intracellular growth pathways, it is now clearly recognized as a disease entity distinct from cutaneous melanoma. Ongoing and future studies are focusing on targeting these molecular pathways and harnessing the immune system to improve outcomes. In the years ahead, it is likely that this work will lead to new effective treatment options for patients with metastatic disease. It is already possible to predict the development of metastatic disease and, with a better understanding of the genetic and epigenetic changes that underlie distinct classes of tumor behavior, future interventions may be identified to prevent distant spread and achieve cure in a greater number of patients.

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