The purpose of this study, then, is to evaluate a series of metastatic uveal melanoma patients profiled at our facility. There is a great need for improved therapy as the prognosis is poor for advanced-stage disease. Our study undertakes to investigate the presence of novel therapeutic targets.

Methods: We analyzed 49 uveal melanoma patients with immunohistochemistry for 23 markers including AR, AR27, BCRP, 6D171, c-kit, 8F11, cMET, 88.2%, KIT (44.8%), ERCC1 (41.4%), GART (41.4%), SPARC (41.4%), PGP (C494), PR (1E2), PTEN (6H2.1), RRM1 (polyclonal), SPARCm (1222511), SPARCp (polyclonal), TLE3 (polyclonal), TOP101 (1D6), TOP2A (polyclonal), TLE3 (polyclonal), (shown below) are graphical illustrations showing the top overexpressors, ranked by percentage.

Conclusions: Our data on BRAF suggests that it is a promising target in uveal melanoma. Low expression of BRAF is in about 95% of our patients may indicate the likelihood of favorable response to select agents like dacarbazine or temozolomide. These are currently several clinical trials investigating various BRAF inhibitors, as well as imatinib in advanced uveal melanoma patients. Our findings highlight the importance of molecular profiling uveal melanoma patients.

Background: Uveal melanoma, which arises from neuroectodermal cells, is the most common intraocular malignancy of the adult eye and differs considerably from cutaneous melanoma in its etiology, histology, and genetic features. This disease arises from either the choroid, ciliary body, or iris. In the United States, malignancy of the adult eye and differs considerably from cutaneous melanoma in its etiology, histology, and genetic features. The disease arises from either the choroid, ciliary body, or iris. Approximately 50% of patients will develop metastases when available, involve small cohorts.

Results: Overexpression of KIT at the protein and RNA level was 74% (24 of 33) and 34.5% (6 of 17), respectively. Expression of KIT did not correlate with gain of KIT mutations in any of the 34 samples tested. In our study, MET was overexpressed. In total, 15 out of 17 cases at the RNA level and MET was high in each of our patients indicating poor prognosis. No mutations in the MET pathway were observed in the majority of uveal melanoma patients. MET was split into 10 patients. Similarly, no BRAF or MEK mutations were detected. Protein and RNA expression of PTEN was low in our patients. IHC testing was used of 14 of 43 patients, indicating the PI3K pathway is not activated in the majority of uveal melanoma patients. MET was split into 10 patients. These results were evaluated by board-certified pathologists and categorized into above threshold, below threshold, or negative based on defined, evidence-based cut-offs.

Malignancy, DNA damage, immunohistochemistry, protein expression, and its correlation with clinicopathological features was analyzed. Fluorescent in-situ hybridization (FISH) and DNA direct sequencing were also performed, sometimes based on physician request.

IHC results from 49 patients profiled at our facility are shown in Table 1 below. Several results are associated with benefit to fluorouracil (TYMS) and temozolomide/chemotherapy (Table 4). Results achieved in our laboratory are consistent with what has been reported in the medical literature. For instance, c-kit IHC overexpression (74% protein overexpression in this group) with no amplification. Note how EGFR by FISH results indicate a lack of clinical benefit to anti-EGFR-targeted therapy, in keeping with previous reports. Sequencing was also utilized to interrogate biomarkers. In our cohort, the biomarkers, BCRP, BRAF, and RUNX1, showed no mutations or rearrangements.

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Conclusions

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• Many of the results obtained herein reinforce what has been shown about the biology of uveal melanoma. As the disease has spread, control with chemotherapy becomes difficult. However, biomarkers utilized at our facility could provide valuable targets to the decision-making whether to utilize a certain agent, especially when organ-sparing metastatic ressection has occurred outside the brain, to give the best chance at survival.

• Future studies could correlate accepted clinical practice to these biomarkers. For instance, MET scores can be correlated to response to MET inhibitors (pending approval AMG)- turnaround.

• Prognostic markers could be composed of histopathological and/or functional features that predict the future course of disease.

• Metformin (MET, IRS-1, IRS-2), a non-competitive dual inhibitor of PKA and PKC, is being investigated as potential targets in uveal melanoma and is currently performed in our laboratory.

References


