



[A Cure In Sight at AACR - April 2025:](#)

[SUMMARY of Uveal Melanoma Abstracts and Posters](#)

Kevin (our ACIS Research Coordinator) attended the AACR meeting in Chicago. This scientific meeting is mostly focused on laboratory and translational research, which leads to the identification of new targets within cancers, and advances in therapies and treatment strategies that are then tested in patients in clinical trials.

CLINICAL Abstracts:

Abstract # 1014 (Poster) Detection of reportable germline BAP1 mutations in patients with uveal melanoma. Amy C. Schefler, Retina Consultants of Texas, Houston, TX

ACIS Take-away: This study of uveal melanoma patients collected blood and cheek swab samples to determine if high-risk “BAP-1 loss” genomic change can be detected in these samples separately from the tumor sample, and if the BAP-1 loss might be associated with “germline” (hereditary, family) gene mutations. The investigators found 24% of the 45 patients studied had germline mutations. They suggest that UM patients who have the Castle 15-gene GEP genomic test and find BAP-1 loss (Class 2) as a result, may want to also have simple blood/cheek swab sampling to determine the possible risk of risk of BAP-1 cancers (BAP-1 Tumor Predisposition Syndrome) in other family members (kidney cancer, mesothelioma, skin cancers, meningioma). This would be entirely up to the patient and family to decide.

Purpose: The reported rate of pathogenic germline mutations in the *BAP1* gene range from 2% in unselected population to up to 50% in patients with familial uveal melanoma (UM) and are associated with an increased risk of developing *BAP1*-Tumor Predisposition Syndrome (TPDS)-related cancers. The primary objective of this study was to determine more accurately the rate of germline *BAP1* mutations in a clinically representative sample population of UM patients with a known somatic mutation in *BAP1*, using clinically available 7-gene UM next-generation sequencing (NGS) panel DecisionDx-UMSeq.

Conclusions: Among 45 patients with a diagnosis of uveal melanoma, the DecisionDx-UMSeq panel accurately identified reportable germline *BAP1* mutations in both buccal swab and blood samples from patients with previously reported somatic *BAP1* mutations. A quarter of patients in this cohort had a reportable germline mutation, including patients without a family history suggestive of typical *BAP1*-TPDS cancers, thus indicating that the rate of *BAP1* germline mutations may be higher in this cohort than reported elsewhere. This study supports the routine implementation of the DecisionDx-UMSeq panel for *BAP1* germline testing in all patients with a somatic *BAP1* mutation, enabling improved critical clinical decision-making and genetic counseling for patients and family members at risk of *BAP1*-related TPDS.

Abstract # 2055 (Poster) - Molecular profiling of the PI3K δ inhibitor roginolisib in metastatic uveal melanoma and its correlation with clinical outcomes Alessio Bevilacqua, iOnctura

ACIS Take-away: This abstract provides additional laboratory findings from the recent roginolisib Phase I study. A major finding was treatment with “rogi” (including metastatic uveal melanoma patients) increased CD39CD8 T-cells, which in other cancer studies has been associated with response to immune checkpoint inhibitors. Also, pre-treatment baseline expression of 325 genes, including “GPCR”, which was then down-regulation with rogi treatment. These findings with rogi were noted in UM patients who had then experienced Stable Disease, forming a group that contributed to the overall survival findings emerging from this Phase I study. Among patients who did not respond to rogi (progressive disease) there was increased signaling of PI3K, which is the target for rogi inhibition in cancer cells. These laboratory results will help further identify markers in the new roginolisib Phase II study* to evaluate patients who achieve clinical response and stable disease, and those who progress.

Introduction: Uveal melanoma (UM) is a rare orphan disease with significant unmet clinical need. Unlike cutaneous melanoma, UM has a low tumor mutational burden and a highly immunosuppressive microenvironment, rendering it largely unresponsive to checkpoint inhibitor therapies. PI3K δ is involved in the pathophysiology of the disease, by enhancing regulatory T cell activity and supporting tumor cell survival. Roginolisib, a PI3K δ inhibitor, was evaluated in 23 UM patients at an 80 mg biological effective dose (BED). Here, we report data from a comprehensive translational analyses of genomic, transcriptomic, proteomic and cellular data from UM patients, supporting PI3K δ as a suitable therapeutic target for UM patients.

Results: The roginolisib Phase I study (IOA-244-101, NCT04328844) was conducted in patients with advanced cancer, which included metastatic uveal melanoma patients. Roginolisib treatment induced progressive decrease of circulating regulatory T cells and increased CD39+CD8T cells, accompanied by reduction of soluble PD1, CCL22 and increase of IL15 and IFNGR2. We identified a subpopulation of mUM patients that particularly benefited from roginolisib treatment. Patients with RECIST 1.1-defined stable disease (SD) at 16 weeks experienced significantly longer median overall survival (28.5 months) compared to those with progressive disease (PD) (10.9 months). SD patients had enhanced CD8⁺ T cell/Treg ratios and downregulation of PI3K/mTOR-associated proteins in plasma. Conversely, PD patients showed upregulation of these proteins after 8 weeks of treatment, suggesting a potential resistance mechanism. Transcriptomic analysis of tumor biopsies revealed that SD patients had higher baseline expression of 325 genes, including 61 GPCR (G-protein coupled receptors), which were downregulated post-treatment. Longitudinal ctDNA profiling further demonstrated dynamic tumor evolution, with specific variants emerging or disappearing over time.

Conclusion: These findings highlight the importance of immune modulation, PI3K/mTOR signaling, and GPCR gene expression in potentially driving treatment outcomes, and encourage further evaluation of Roginolisib in a Phase 2 randomized study (*Open for enrollment in US and EU: NCT06717126).

Session LBPO.CL02 - Late-Breaking Research: Clinical Research 2 / Endocrinology

LB262 / 11 Section 51 - Development of a clinically feasible aqueous proteomic signature to assess the malignant potential of small uveal melanocytic tumors Olga Zolochovska, Castle

ACIS Take-away: Some patients with uveal melanocytic tumors receive a pathologic diagnosis of “indeterminate malignant potential.” Investigators at Castle Bioscience and several US ocular oncology centers of excellence examined the use of clinic-based samples from the aqueous humor of the affected eye, to follow and identify patients who may be of high risk of transformation of their tumor to cancer. This may result in development of a future in-office diagnostic and prognostic procedure.

Purpose: With a prevalence of approximately 5% in the U.S., uveal melanocytic tumors of indeterminate malignant potential (UMTIP) are primarily managed by observation for growth prior to treatment. While the malignant potential of these lesions can be assessed by intraocular tumor biopsy and genetic testing, serial tumor biopsy in the operating room is not feasible for routine management of UMTIPs. On the other hand, the aqueous humor (AH) from the anterior chamber of the eye can be easily and safely obtained by an office-based procedure that can be repeated periodically. Proteomic signatures in aqueous fluid could potentially allow early detection of UMTIPs at high risk of having undergone malignant transformation, thus identifying patients who would benefit from a definitive tumor biopsy and earlier treatment as indicated.

Results: The sample distribution was representative of a typical UM cohort: mean age 64.8 ± 14.5 years, mean tumor diameter 11.02 ± 3.40 mm, mean tumor thickness 4.61 ± 3.14 mm.

DecisionDx-UM identified 57/79 (72%) of tumors as Class 1 and 22/79 (28%) of tumors as Class 2. Approximately 1400 out of 3072 proteins were detected in AH samples. Proteins with statistically significant differences between Class 1 and 2 ($N=386$, $p < 0.0001$) were included in further analyses. The best fitting models were k-nearest neighbor, random forest, and neural networks with accuracies of 76%, 83%, and 83%, and kappa 0.25, 0.40, and 0.36, respectively. Within the Explorer3072 panel, proteins grouped into the Immune Response and Oncology subpanels achieved an average accuracy of 81-85% and 77-89%, respectively.

Conclusions: Several promising risk prediction models were identified by proteomic profiling of AH from UM patients. The proteins from the highest-performing models will be utilized in the development and validation of a testing platform that is feasible for office-based clinical testing to identify high-risk UMTIPs that would benefit from definitive risk assessment using tumor biopsy-based testing.

NON-CLINICAL (Laboratory) Abstracts

Abstract # 1271 (Poster) Generation and optimization of humanized mice models in metastatic uveal melanoma. Sota Deguchi, Jefferson University

ACIS Take-away: Investigators in the Sato Lab at Jefferson have developed another “humanized” mouse model, and these mice with metastatic uveal melanoma cells can now be studied with immunotherapies which closely model the human immune response to cancer.

Background: Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, with poor prognosis in cases of liver metastasis. Tebentafusp, a bispecific T cell engager, has shown survival benefits in patients with metastatic uveal melanoma (MUM); however, the response rate is low (<10%), and there is an unmet need to improve the outcome of immunotherapy against MUM. A major challenge of translational research in MUM immunotherapy is the lack of suitable preclinical models. To address this, we developed a humanized mouse model using human bone marrow (BM)-derived CD34⁺ hematopoietic stem cells (HSCs).

Result: Three weeks post-injection, human CD45⁺ cells were confirmed in the blood, indicating the differentiation of injected human CD34⁺ HSCs. Flow cytometry detected human CD3⁺, CD19⁺, CD14⁺, CD11c⁺, and CD56⁺ cells in hematological organs. Monocytes and B cells predominated in the spleen at 9 weeks, while T cells were more abundant in the peripheral blood at 20 weeks. Human TNF- α production with LPS was detected from human CD45⁺ cells obtained from the mouse BM. IFN- γ production with phytohemagglutinin (PHA) was also confirmed in 21.1% of human CD3⁺ T cells obtained from the mouse BM. In the spleen, B cells and T cells were confirmed, but those cells were rarely seen in other organs. Interestingly, human CD45⁺ cells infiltrated the MUM tumors in the liver of humanized mice (on poster: mainly CD68⁺ macrophages and CD11c dendritic cells).

Conclusion: NSG-hFLT3 mice successfully adopted human CD34⁺ HSCs and developed the chimerism with functional human immune cells. This indicates that this mouse model can be utilized to study the interaction between MUM tumors and human immune cells and serve as a platform for investigating the efficacy and resistance mechanisms of cancer immunotherapies. This approach may also be used for an autologous humanized mouse model using CD34⁺ cells and patient-derived xenograft (PDX) from the same patients.

Abstract # 2578 (Poster) CAFs and Beyond: A Central Role for the Tumor Microenvironment in Cancer - GDF15 reprograms the microenvironment to drive the development of uveal melanoma liver metastases. Sathya N. Sriramareddy, Moffitt Cancer Center

ACIS Take-away: Investigators in the Smalley Lab at Moffitt have identified a new target “GDF15” in uveal melanoma cells which metastasize to the liver (hepatic stellate cells).

Little is known about how interactions between the uveal melanoma (UM) and host cells in the tumor microenvironment (TME) drive the progression of liver metastases. Single cell RNA-seq analysis of UM samples identified marked differences in cell-cell communication between primary and metastatic UM characterized by increased signaling strength and numbers of interactions emanating from the hepatic stellate cells (HSCs) and endothelial cells in the metastatic samples. In co-culture, HSCs modulated the transcriptional heterogeneity of the UM cells, enriching for cell states that expressed genes implicated in cell survival, metabolic reprogramming and the angiogenic response. Co-culture of HSCs and UM cells also led to increased expression of growth factors and receptors implicated in angiogenesis including IL-8, VCAM1, VEGF and ICAM1. One candidate driver of HSC reprogramming was the TGF-beta family member GDF15. Increased expression of GDF15 was associated with a Class 2 metastatic UM phenotype in clinical UM samples and UM cell lines, with silencing of BAP1 in UM cells increasing both GDF15 expression and H3K27ac marks at the GDF15 promoter. Treatment of HSCs with GDF15 led to increased expression of multiple ECM proteins, inflammatory cytokines and angiogenic factors, including IL-8. Both exogenous GDF15, IL-8 and conditioned media from UM-HSC co-cultures increased endothelial cell network formation in vitro, an effect that could be blocked by anti-GDF15 antibodies. In an eye->liver metastasis model of UM, silencing of GDF15 did not prevent the seeding of UM cells to the liver, but did inhibit the outgrowth of metastatic lesions. Although the GDF15-silenced UM cells were proliferative they did not recruit endothelial cells, leading to a significant reduction in metastatic burden. In sum, we provide the first evidence that UM liver metastasis development is dependent upon GDF15-mediated remodeling of the liver microenvironment leading to an angiogenic response that supports tumor growth.

Abstract # 2723 (Poster) - Unveiling epigenetic mechanisms driving RasGRP3 upregulation via oncogenic Gαq signaling in uveal melanoma. Zaizhou Liu

ACIS Take-away: Researchers at the Bastian Melanoma Lab at UCSF have further investigated the very common GNAQ gene mutation (found in >80% of uveal melanoma mutations). They identified a unique protein in the GNAQ-related RAS oncogene pathway “RasGRP3” which appears to have enhanced cancer activity in uveal melanoma cell proliferation (multiplication of cells). They suggest further study may look at using existing class of drugs (histone modifiers) as a targeted approach to stopping this cancer-driver pathway in UM cells.

Uveal melanoma (UM) is a rare but aggressive cancer originating from melanocytes within the eye. It is distinct from cutaneous melanoma (CM) and genetically defined by somatic mutations activating the Gαq signaling pathway, most commonly affecting the Gαq subunits GNAQ or GNA11. UM remains a highly lethal melanoma subtype that cannot be effectively treated by current treatment regimens, including immune checkpoint blockade and targeted therapies. RasGRP3 (RAS Guanyl Releasing Protein 3), a guanine nucleotide exchange factor (GEF) for Ras,

is markedly (>100-fold mRNA levels compared to CM) and selectively upregulated in UM and serves as a critical signaling hub connecting Gαq signaling to the MAPK pathway. Elucidating the mechanisms underlying the RasGRP3 upregulation unique for UM promises to unveil alternative therapeutic targets. We compared the epigenetic landscape of the RasGRP3 locus in UM and CM cells using ChIP-seq for H3K27ac (marking active enhancer/promoters), H3K4me1 (active enhancers), and H3K4me3 (active promoter). In UM but not CM cells, the RasGRP3 locus was highly enriched for H3K27ac and H3K4me1 modifications, and two of its three transcription start sites were marked with elevated H3K4me3 levels, indicating the expression of two major isoforms in UM. Treatment of UM cells with the Gαq inhibitor YM-254890 (YM) or the PKC inhibitor LXS-196 (LXS) for 24 hours significantly reduced all three histone modifications (H3K4me3, H3K27ac, H3K4me1) at the RasGRP3 locus. No changes were observed in CM cells. Our findings indicate an active super-enhancer that regulates RasGRP3 expression in UM, which is under control of the Gαq pathway through epigenetic modifications at its promoter and enhancer regions. These findings explain the selective upregulation RasGRP3 characteristics of UM. Ongoing investigations aim to delineate the precise mechanisms by which Gαq signaling drives these epigenetic changes. Our results highlight the potential of targeting specific histone modifiers as a novel therapeutic strategy for UM treatment.

Abstract # 4906 (Poster) - A prospective analysis identified mismatch repair genes as predisposing for uveal melanoma. Marc-Henri Stern, Institut Curie- Paris

ACIS Take-away: This evaluation of 381 UM patients at Institut Curie examined the patients' germline DNA for gene mutations which may place patients at further high-risk for metastasis. The investigators found 29 genes that may warrant further monitoring, including genes termed "mis-match repair" may also be associate with Lynch Syndrome (familial gene mutations which may cause a variety of cancers).

Background and Aim: Uveal melanoma (UM) is the most common intraocular malignancy in adults. Thus far, germline mutations of two genes have been identified to be predisposing to UM with a high penetrance: *BAP1*, responsible for the *BAP1* tumor predisposition syndrome (*BAP1*-TPDS), and *MBD4*, which germline alterations are associated with tumor predisposition, specific tumor mutational signature and response to immunotherapy. However, only a fraction of familial and bilateral/multifocal forms of UM can be explained by these germline alterations, suggesting the existence of other predisposing factors.

Methods: We analyzed a panel of 122 candidate cancer predisposing genes by target sequencing on germline DNA from a prospective unbiased cohort of 381 patients diagnosed with UM at Institut Curie between July 2021 and February 2023.

Results: We identified 29 pathogenic variants (PVs) in genes that are relevant for patient monitoring and genetic counselling (6 in *MBD4*, 3 in *BAP1*, 3 in *BRCA2*, 1 in *ATM*, 3 in *FAN1*, 2 in *FANCL*, 3 in *FANCM*, 1 in *MLH1*, 1 in *MSH2*, 2 in *MSH6* and 4 in *PMS2*). Two patients had PVs in *MSH6*, 4 in *PMS2*, 1 in *MLH1* and 1 in *MSH2*. The frequencies of the 3 MisMatch Repair (MMR)

genes *MLH1*, *MSH2* and *MSH6* were significantly higher than in the gnomAD (v2.1.1) non-Finnish European database as a matched control sub-cohort ($p=0.00073$, OR: 10.4 [2.8-27.5]). *PMS2* was excluded from this statistical analysis because its pseudogene prevents the interpretation of public data. One UM tumor sample was further characterized from the patient carrying the germline *MLH1* PV. This UM displayed biallelic inactivation of *MLH1*, loss of *MLH1* and *PMS2* expression by immuno-histochemistry, a prominent Substitution Mutational Signature 6 (SBS6) associated with MMR deficiency from whole Genome Sequencing (WGS) and an MSI-H phenotype.

Conclusions: This study confirms MMR genes as predisposing factors in UM, as suggested by two previous case reports identifying *MLH1* germline PVs and biallelic inactivation in UM cases (Lobo et al. *Virchows Arch* 2017;470:347; Abdel-Rahman et al. *Ophthalmology* 2020;127:668). Further analyses will be needed to define the risk of developing UM for patients with a Lynch syndrome.

Abstract # 6817 (Poster) - Targeting XPO1 eliminates cancer stem-like cells and abrogate hepatic metastasis in uveal melanoma. Bei Jin, Guang Zhou, China

ACIS Take-away: Investigators in Chona identified yet another cancer driver protein in the nucleus of uveal melanoma cells “XPO1.” Blocking this protein with several different molecules caused cell death, and in one model reduced the overall size of metastatic UM liver metastases in mice.

Uveal melanoma originating from the uveal tract are a rare form of the malignancy with a biology and clinical feature distinct from its more common cutaneous counterparts. Yet, UM is the most common primary intraocular tumor in adults. Despite effective treatment in primary UM with eye-sparing radiation-based techniques or enucleation, ~50% of UM patients ultimately develop distant metastasis, most commonly in the liver. XPO1 (also referred as CRM1), a key member of the importin β superfamily of nuclear transport receptors, mediates nuclear export of tumor suppressors and growth factors. We found that XPO1 was highly overexpressed in UM cells and positively correlated with poor prognosis of UM. Depletion of XPO1 by shRNA or its small molecular inhibitor KPT-330 significantly inhibited growth of UM cells *in vitro* and *in vivo*. Treatment with KPT-330 markedly induced apoptosis in UM cells via reducing the protein level of Survivin. Meanwhile, silencing of XPO1 by lentiviral shRNA or incubated with KPT-330 significantly decreased the percentage of ALDH⁺ cells and dampened self-renewal capacity in UM cells. Targeting XPO1 by KPT-330 profoundly alleviated liver metastasis burden in liver metastasis mouse model. These results suggest XPO1 may be a potential therapeutic target for patients with metastatic UM.

7217 / 23 Section 35- Synergistic anti-cancer effects of dual IGF-1R and EGFR targeting in uveal melanoma Pei-Chi Tsai, Johns Hopkins Univ.

ACIS Take-away: These investigators tested an inhibitor of a known cancer driver in uveal melanoma cells (which did not work in clinical trials), now in combination with another drug which appears to provide an additive effect on inhibiting cell growth and cell colony formation in UM cell cultures (not in animals or humans). They suggest the possibility of combining these two drugs in a clinical trial in UM patients (perhaps after more proof in animal UM models).

Uveal melanoma arises from melanocytes in the eye, with approximately 7,000 patients reported worldwide every year. IGF-1R plays an important role in uveal melanoma metastatic progression, and promotes tumor cell proliferation and survival. However, in previously reported clinical trials, targeting IGF-1R did not significantly inhibit uveal melanoma metastatic spread or patient survival. This could be due to compensatory activation of other receptor signaling pathways. Therefore, the aim of this study is to find other activated receptors in uveal melanoma cells following IGF-1R inhibition which could be co-targeted in a novel combination treatment for metastatic uveal melanoma. Using several uveal melanoma cell lines (Mel202, Omm2.3, Omm2.5, Omm1, 92.1, MP38 and MM28), we found that treatment with linsitinib, an IGF-1R inhibitor, increased EGFR protein expression and activity. Targeting IGF-1R alone with linsitinib, or EGFR alone with gefitinib, did not significantly inhibit growth of uveal melanoma cells. However, combination treatment with linsitinib (10 μ M) and gefitinib (5 μ M) significantly inhibited both cell growth and anchorage-dependent/independent colony formation abilities in uveal melanoma cultures. Moreover, Linsitinib and gefitinib co-treatment dramatically increased cleaved PARP protein, an apoptotic maker. Our research suggests that dual targeting of IGF-1R and EGFR could be a novel treatment strategy to inhibit uveal melanoma metastatic dissemination and growth.

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