Immune Profiling of Metastatic Uveal Melanoma and Response to Immune Checkpoint Inhibitors

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Background

The immune profile of primary uveal melanoma (UM) differs significantly from cutaneous melanoma (CM)[1,2]. However, limited data exists about the immune profile of metastatic uveal melanoma (mUM) and its correlation with prognosis. Furthermore, the response to immune checkpoint inhibitors (ICI) in mUM is low as compared to CM[3,4]. We aimed to understand the immune profile of mUM in correlation with survival and identify markers predictive of improved survival in patients treated with ICI.

Methods

Tumor samples of UM patients were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes assay or whole exome sequencing) and RNA (whole transcriptome sequencing). Somatic mutations were totaled to calculate tumor mutational burden (TMB) and cutoff for high vs low was 10 mt/MB. PDL1 was tested with immunohistochemistry for tumor staining and cutoff for PDL1 was ≥2+, 5% for high vs low. HLA genes were tested using WTS. *NCOA2* gene amplification was considered a surrogate for gain of chromosome 8q (cutoff ≥6). Median RNA expression level for LAG3 was calculated for each cohort and used as cutoff for high vs low. All ICI treated patients were considered to have metastatic disease. Real-world overall survival (rwOS) was obtained from insurance claims data and calculated from tissue collection to last contact. Time on treatment (TOT) was calculated from start to finish of ICI treatment and was considered as surrogate for progression-free survival (PFS). Comparison of survival was performed by Kaplan-Meier analysis.

Results

Table 1: Testing Characteristics

Population	N
Total UM	450
Primary	47
Metastatic	338
Immune Checkpoint Inhibitor Treated	108
Testing Method	
Whole Exome/ Next Generation Sequencing	334
Whole Transcriptome Sequencing	116

Table 2: Immune Characteristics of Tumor Samples

Tumor Marker	Total UM % (N)	Metastatic UM % (N)	ICI Treated % (N)
PDL1 High	14 (39/279)	14 (35/249)	38 (34/89)
TMB High	2.3 (6/263)	NA	NA
HLA class I High	47 (37/78)	52 (32/66)	50 (7/14)
HLA Class II High	52 (33/63)	54 (31/57)	45 (5/11)

Immune Profiling and Correlation with Survival

Figure 1: Real World Overall Survival of all uveal melanoma by tumor mutational burden

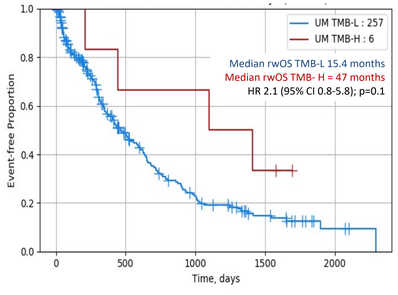


Figure 2: Real World Survival of all metastatic uveal melanoma by PDL1 Status

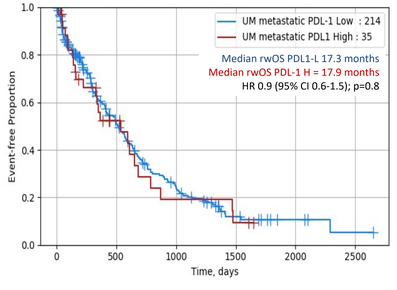


Figure 3: Real World Overall Survival of metastatic uveal melanoma by HLA Class I Status

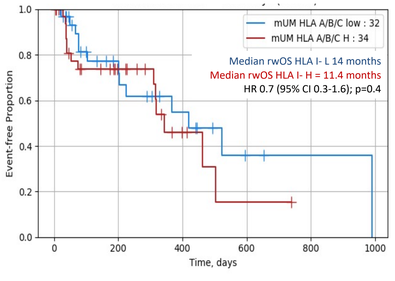
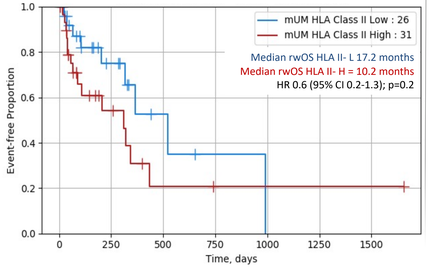


Figure 4: Real World Survival of all metastatic uveal melanoma by HLA Class II Status



Immune Profiling and Response to Checkpoint Inhibitors

Figure 5: Time on Treatment with Immune Checkpoint Inhibitors by PDL1 Status

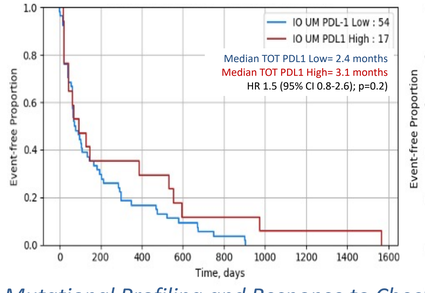
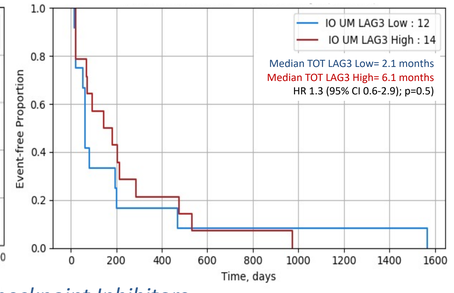


Figure 6: Time on Treatment with Immune Checkpoint Inhibitors by LAG3 Status



Mutational Profiling and Response to Checkpoint Inhibitors

Figure 7: Real World Survival with Immune Checkpoint Inhibitors by NF1 Mutation Status

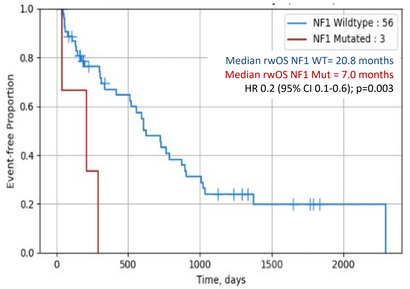
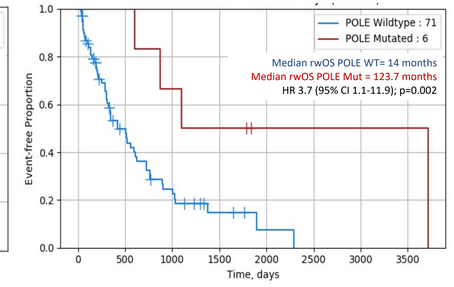


Figure 8: Real World Survival with Immune Checkpoint Inhibitors by POLE Mutation Status



Conclusions

- UM lacks traditional markers of response to ICI with only 14% high for PDL1 and 2.3% high for TMB[1]
- TMB did not serve as a prognostic marker for UM in our study.
- PDL1, HLA Class I and HLA Class II were not prognostic for mUM. This is in contrast to primary UM where high expression of HLA Class I and II is associated with worse survival. However, RNA expression of HLA was evaluated in our study which may not correlate with protein expression and survival[5]
- PDL1 status and LAG3 expression did not serve as a predictive markers of response to ICI in our study. An IHC based assay for evaluation of LAG3 expression may be more appropriate in this context.[6]
- *NF1* mutation was correlated with poor survival with ICI. NF1 is an upstream regulator of RAS/MAPK pathway[7]. Implications of *NF1* mutation in UM warrant further investigation
- *POLE* mutation was associated with improved survival with ICI. POLE is critical in DNA repair. Faulty DNA repair and accumulation of neoantigens may allow for increased cancer clearance in the presence of ICI[8].

References

1. Thorsson V, Gibbs DL, Brown SD, et al. The Immune Landscape of Cancer. Immunity. 2018 Apr 17;48(4):812-830.e14
2. Hoefsmit EP, Rozeman EA, Van TM, et al. Comprehensive analysis of cutaneous and uveal melanoma liver metastases. J Immunother Cancer. 2020 Dec;8(2)
3. Piulats JM, Espinosa E, de la Cruz Merino L, et al. Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). J Clin Oncol. 2021 Feb 20;39(6):586-598
4. Pelster MS, Gruschkus SK, Bassett R, Gombos DS, et al. Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study. J Clin Oncol. 2021 Feb 20;39(6):599-607
5. Ericsson C, Seregard S, Bartolazzi A, et al. Invest Ophthalmol Vis Sci. 2001 Sep;42(10):2153-6.
6. Tawbi HA, Schadendorf D, Lipson EJ, et al. RELATIVITY-047 Investigators. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med. 2022 Jan 6;386(1):24-34
7. Kiuru M, Busam KJ. The NF1 gene in tumor syndromes and melanoma. Lab Invest. 2017 Feb;97(2):146-157
8. Wang F, Zhao Q, Wang YN, Jin Y, He MM, Liu ZX, Xu RH. Evaluation of POLE and POLD1 Mutations as Biomarkers for Immunotherapy Outcomes Across Multiple Cancer Types. JAMA Oncol. 2019 Oct 1;5(10):1504-1506