180 EVALUATION OF ASSOCIATION OF MUTATION IN ARID FAMILY OF GENES WITH OUTCOMES IN CUTANEOUS MELANOMA

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Background ARID genes encode subunits of SWI/SNF chromatin remodeling complexes and are frequently mutated in human cancers. We investigated the correlation between ARID mutations, molecular features, and clinical outcomes in melanoma patients.

Methods Cutaneous melanoma samples (n=4094) were analyzed by next-generation sequencing. Samples were stratified by pathogenic/likely pathogenic mutation in ARID genes (ARID1A/2/1B/5B). PD-L1 expression was assessed using IHC (SP142; positive (+): $\geq$ 1%). Tumor mutation burden (TMB)-high was defined as $\geq$ 10 mutations/Mb. Transcriptomic signatures predictive of response to immune checkpoint inhibitors – interferon gamma (IFN-g; Ayers, 2017) and T-cell inflamed score (T-cell; Bao et al., 2020) were calculated. Real-world overall survival (OS) information was obtained from insurance claims data, with Kaplan-Meier estimates calculated from time of tissue collection until last date of contact. Mann-Whitney U, Chi-square, and Fisher exact tests were applied where appropriate, with p-values adjusted for multiple comparisons.

Results ARID2 mutations were more prevalent in cutaneous melanoma compared to ARID1A (11.0%: n = 451 vs 2.8%: n = 113), with concurrent ARID1A/ARID2 mutation in 1.1% (n = 46) of samples. ARID mutations were associated with a high prevalence of RAS pathway mutations – NF1 (ARID1A, 52.6%; ARID2, 48.5%; ARID1A/2, 63.6%; and ARID-WT, 13.3%; p<0.0001) and KRAS (ARID1A, 3.5%; ARID2, 3.1%; ARID1A/2, 6.5%; and ARID-WT, 1.0%; p=0.018)), although BRAF mutations were less common in ARID-mutated cohorts (ARID1A, 31.9%; ARID2, 35.6%; ARID1A/2, 26.1%; and ARID-WT, 50.4%; p<0.0001). TMB-H was more common in ARID-mutated samples (ARID1A, 80.9%; ARID2, 89.9%; ARID1A/2, 100%; and ARID-WT, 49.4%; p<0.0001), while PD-L1 positivity was similar across subgroups (ARID1A, 43.8%; ARID2, 51.1%; ARID1A/2, 52.5%; and ARID-WT, 44.9%; p=0.109). Patients with ARID1A mutations had a higher prevalence of dMMR/MSI-H compared to those with ARID-WT (2.7% vs 0.2%, p = 0.030). Median IFN-g and T-cell signatures were higher in ARID2-mutated samples compared to ARID-WT (IFN-g: -0.15 vs -0.21, p =0.0066; T-cell: 23.5 vs -18.5, p =0.041). ARID mutations collectively were not associated with differences in OS (HR = 1.13 [95% CI: 0.9 – 1.3], p = 0.099). However, ARID2-mutated patients had improved survival compared to ARID-WT; (HR: 1.22 [95% CI: 1.0 – 1.5], p = 0.022). No additional OS benefit was observed with anti-PD-1 therapy for ARID2 mutation.

Conclusions Melanoma patients with ARID mutations exhibited higher prevalence of markers associated with ICI response, including TMB-H, PD-L1 and immune-related signatures. Our data also suggests improved survival outcome in patients with ARID2 mutations, although no additional OS benefit was observed with anti-PD-L1 therapy.

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