137 MAJORITY OF MUTATIONS IN CUTANEOUS SQUAMOUS CELL CARCINOMA ARE UNIQUE TO INDIVIDUAL TUMORS

[1,2]Elizabeth S Borden*, [2,3]Anngela C Adams, [1,2]Anne M Macy, [1]Tiffany Y Juan, [4]Denise J Roe, [5]Kenneth H Buetow, [5]Melissa A Wilson, [1,2]Karen Taraszka Hastings. *[1]University of Arizona College of Medicine – Phoenix, Phoenix, AZ, USA; [2]Phoenix Veterans Affairs Health Care System, Phoenix, AZ, USA; [3]University of Arizona, Phoenix, AZ, USA; [4]University of Arizona, Tucson, AZ, USA; [5]Arizona State University, Tempe, AZ, USA*

Background Determining the shared and unique neoantigen profiles in cutaneous squamous cell carcinoma (cSCC) is critical to selecting immunotherapeutic approaches for improved prevention and treatment of cSCC. Nonmelanoma skin cancer, including cSCC, is the most common cancer in the United States. Immune checkpoint inhibitors have been approved for treatment of cSCC, but are only effective in 32–46% of patients. Determining the extent to which neoantigens are shared between tumors will guide future development and selection of immunotherapeutic approaches for cSCC.

Methods We characterized the mutational profiles of human cSCC and a physiologically-relevant murine model to determine the likelihood of shared neoantigens in cSCC. Variant calls from 88 publicly available human cSCC tumors[1] and three solar-simulated UV light-induced murine cSCC cell lines generated in our laboratory[2] were analyzed for shared mutations. The murine cSCC cell lines were characterized to determine if their mutational profile and driver mutations recapitulated that of human cSCC. Finally, two clonal murine cSCC cell lines were analyzed for cross-protection with a prophylactic irradiated tumor cell vaccine.

Results Across the 88 human cSCC tumors, the majority of mutations are unique to individual tumors with only 27 (0.075%) shared in three or four tumors and no mutations recurring in greater than four tumors. The combination of the 27 shared mutations covers 53.4% of the tumors. The murine cSCC cell lines have a mutational signature that recapitulates that of human disease with an equivalent proportion of C>T and G>A mutations. Each murine cell line contains putative driver mutations in TP53 that overlap with human cSCC tumors. The shared driver mutations and mutational signature support the physiological relevance of the mouse model. Despite the shared genetic background and UV exposure of the murine cell lines, there were no missense mutations shared across all three cell lines and only 17 missense mutations shared across any two cell lines. Prophylactic vaccination with the same cell line provides complete protection from tumor challenge, but vaccination with an independent cell line, sharing three mutations and the highest number of shared predicted binding neoantigens, does not constrain tumor growth.

Conclusions This work demonstrates a low number of shared neoantigens in human cSCC as well as in a physiologically-relevant mouse model. The lack of shared mutations and ineffective cross-protection suggests that immunotherapeutic approaches for cSCC need to be agnostic to the neoantigen or personalized.

Acknowledgements This work was supported by the Training Oncology Physician Scientists Award from the University of Arizona Cancer Center (E.S.B), NIH (F30CA281056, E.S.B; T32CA009213, A.C.A: F30CA257622, A.C.A; P30CA023074, D.J.R; P01CA229112, K.T.H), and American Skin Association (A.C.A).

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Ethics Approval This study was approved by the University of Arizona's Institutional Animal Care and Use Committee (Protocol #13–469).

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0137