70 NOVEL IMMUNOTHERAPEUTIC TARGETS IN CANCER OF UNKNOWN PRIMARY (CUP)

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Background Cancer of unknown primary (CUP) is a rare tumor type accounting for 2% of solid cancers. In the subset of CUP cases where tumor of origin is posited and treated as such, no clear clinical benefit has been demonstrated. Furthermore, CUP patients treated by empiric platinum-based regimens have low response and survival rates of approximately 20%.[1 2] Support of tissue-agnostic marker-directed immunotherapy is growing because it targets the immune system rather than the tumor, with some efficacy evidence emerging for CUP.[3] Identifying new targets for immunotherapeutic opportunities in this heterogeneous and difficult to treat patient group is a critical unmet need.

Methods Comprehensive genomic and immune marker profiling by NGS[4] was performed on FFPE tissue for CUP tumors (n=298) as indicated by physicians' test orders from >100 clinical practice sites. Histology was verified by a molecular pathologist as part of pre-analytic test quality control, with cases representing tumors with adenocarcinoma (58%), carcinoma (26%), squamous (10%), and neuroendocrine (6%) histologic features. RNA-expression levels of immune genes that are current targets in non-CUP immunotherapy clinical trials (n=36) were ranked against a reference population (≥75th percentile=high), and described by histologic type, along with PD-L1 IHC (22C3) expression, tumor mutational burden (TMB) and genomic variants.

Results 90% of all CUP tumors had at least 1 highly expressed immune gene target in active immunotherapy trials, with the most frequent being TGFB1 (47%) and CCL2 (39%). 55% of CUP tumors were PD-L1 IHC 22C3 positive (>=1% TPS), and 21% had high TMB (>=10 mut/Mb) in CUP tumors with neuroendocrine (32%), carcinoma (30%), squamous cell (21%), and adenocarcinoma (17%) histologic features. Overall, 26% of CUP patient tumors, mostly adenocarcinomas (28%) and carcinomas (27%), harbored genomic variants (n=77) with FDA approved targeted therapies in other tumor types. The most frequently immunogenic CUP tumors were carcinomas, showing high RNA-seq expression of 26/36 genes in at least 20% of patients, most represented by CD20, CD27, TLR8, and PD-L1. High expression of CD40, CSF1R, TIM3, and VISTA was most common in adenocarcinomas. Squamous cell carcinomas were relatively immunogenic, with frequent high expression of 17/36 immune genes, uniquely including MAGEA4. Neuroendocrine tumors were the least immunogenic, with frequent high expression in only 4/36 genes, including ADORA2A (42%) and MAGEA1 (37%).

Conclusions CUP tumors diversely express both standard marker and novel immunotherapeutic targets based on histology and may benefit from selective access to clinical trials for these therapies.

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Occult Primary (Cancer of Unknown Primary [CUP]), Version 2.2021. Fort Washington, Pennsylvania: National Comprehensive Cancer Network; 2021. https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf.
2. Laprovitera N, Riefolo M, Ambrosini E, Klec C, Pichler M, Ferracin M. Cancer of unknown primary: Challenges and progress in clinical management. *Cancers (Basel)* 2021;**13**(3):1–30. doi:10.3390/cancers130304513.
3. Naing A, Meric-Bernstam F, Stephen B, et al. Phase 2 study of pembrolizumab in patients with advanced rare cancers. *J Immunother Cancer* 2020;**8**(1):e000347. doi:10.1136/jitc-2019-0003474.
4. Conroy JM, Pabla S, Glenn ST, et al. Analytical validation of a next-generation sequencing assay to monitor immune responses in solid tumors. *J Mol Diagnostics* 2018;**20**(1):95–109. doi:10.1016/j.jmoldx.2017.10.001

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