Novel Immunotherapeutic Targets in Cancer of Unknown Primary (CUP)

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Introduction

Cancer of unknown primary (CUP) is a rare metastatic 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 specimens from CUP tumors (n=298) as indicated by physicians' test orders from >100 clinical practice sites (Figure 1). CUP 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 (0-100) 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 The Dako PD-L1 IHC 22C3 assay was used to measure PD-L1 protein expression and scored as the percentage of viable tumor cells showing % membrane staining as a tumor proportion score (%TPS). PD-L1 IHC TPS score was interpreted as <1% (negative), 1-49% (low), and >=50% (high).

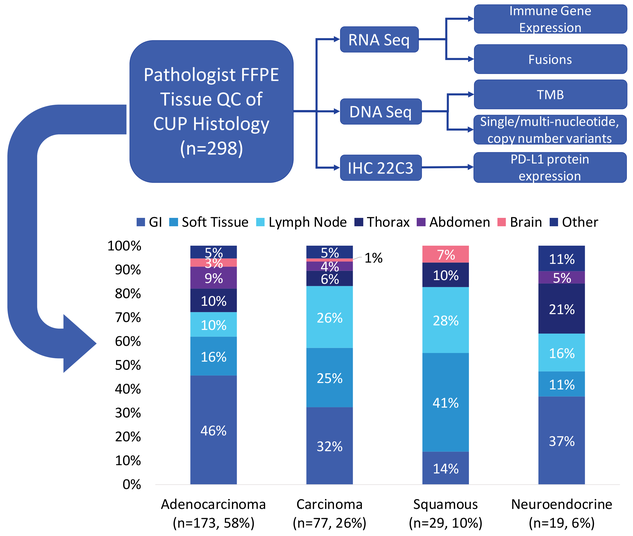

Figure 1. Comprehensive genomic and immune profiling. Tested CUP specimens with adenocarcinoma features were mostly represented by GI (liver) specimens (46%), while tumors with squamous features were mostly soft tissue (41%) and lymph node specimens (28%). CUP tumors with neuroendocrine features had the highest number of specimens from thorax sites (21%). Overall, brain tissue was the least common site tested (3%)

Results

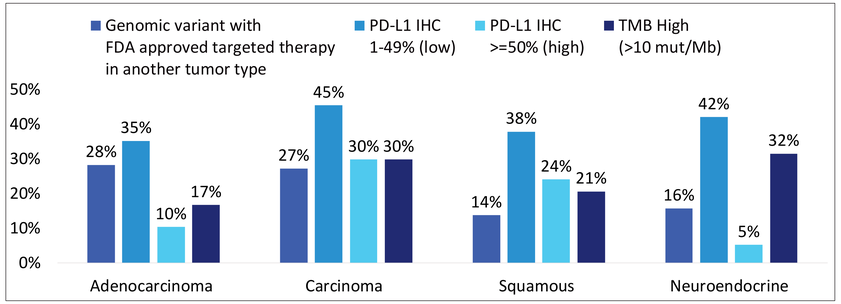

Figure 2. CUP tumor marker status for FDA approved therapies in other tumor types or all solid tumor types. Overall, 26% of CUP tumors, mostly adenocarcinomas (28%) and carcinomas (27%), harbored genomic variants with FDA-approved targeted therapies in other tumor types, including *ALK, BRAF, BRCA1/2, EGFR, ERBB2, FGFR3, KRAS, MET,* and PD-L1 High by IHC (30%), while neuroendocrine tumors were most frequently TMB High (32%).

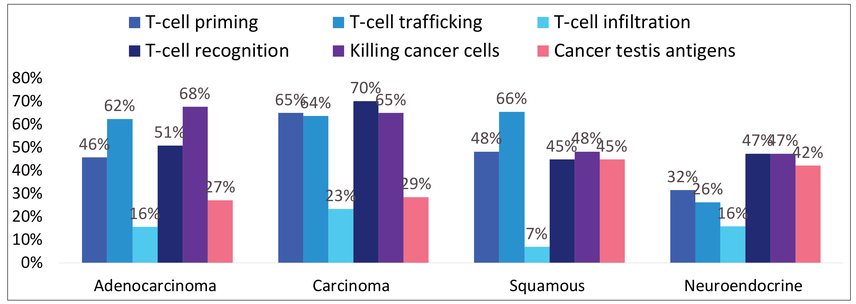

Figure 3. Highly expressed immunotherapy targets in clinical trials by immune cycle role. 90% of all CUP tumors had at least highly expressed immune gene target in active immunotherapeutic trials. While all histologies included cases with highly expressed T-cell infiltration genes, including CD8, the range was generally low (from 7% in squamous to 23% in carcinomas), indicating alternative immunotherapy treatment modalities are warranted in CUP.

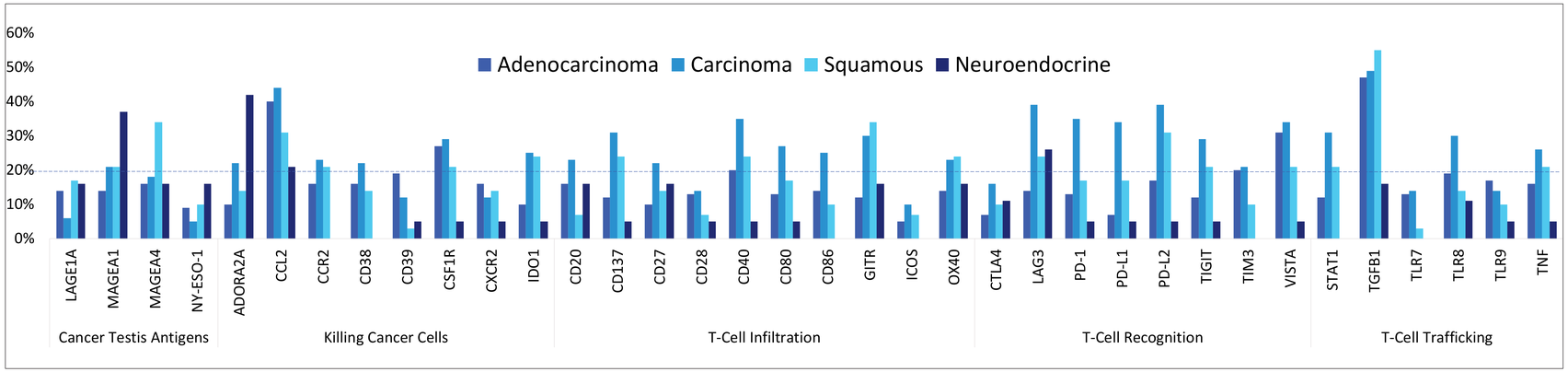

Figure 4. Highly expressed immunotherapy targets in CUP tumors. Across all CUP tumors, the most frequent highly expressed genes were TGFB1 (47%) and CCL2 (39%). The most immunogenic CUP tumors were those with carcinoma features, with high expression of 26/36 genes in at least 20% of patients, most frequently PD-L2 (39%), LAG3 (39%) and CD40 (35%), and uniquely PD-L1 (34%), TLR8 (30%), CD20 (23%) and CD27 (22%), High expression of VISTA (31%), CSF1R (27%), CD40 (20%), and TIM3 (20%) was most common in adenocarcinomas. Squamous cell carcinomas were relatively immunogenic, with frequent high expression of 17/36 immune genes, uniquely including MAGEA4 (34%). Neuroendocrine tumors were the least immunogenic, with frequent high expression in only 4/36 genes, including ADORA2A (42%) and MAGEA1 (37%).

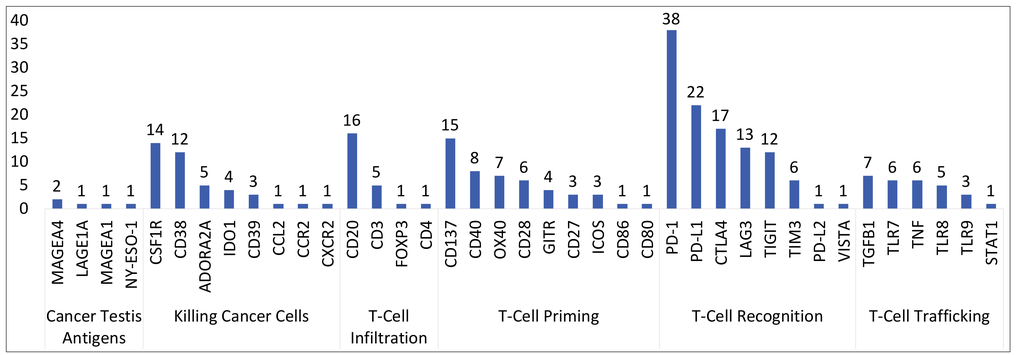

Figure 5. Number of immunotherapies in clinical development by target and immune cycle role. Based on open clinical trials in the United States [5].

Conclusion

CUP tumors diversely express both standard predictive markers associated with FDA approved therapies and novel immunotherapeutic targets in clinical trials based on histologic features. CUP patients 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/cancers13030451
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-2019-000347
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.
5. www.clinicaltrials.gov [Accessed August 1, 2021].

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