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Uncovering genomic differences between small and large cell extra-pulmonary neuroendocrine carcinomas

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BACKGROUND

Extra-pulmonary neuroendocrine carcinomas (EP-NECs) are rare and aggressive cancers that include two morphological subtypes: large cell NEC (LC-NEC) and small cell NEC (SC-NEC). Although they are treated with similar chemotherapy regimens, they are distinct diseases, and their genomic profiles have not been compared. We investigated the genomic profile of the extrapulmonary LC-NEC and SC-NEC to identify mutations that could enable more personalized therapy.

METHODS

Patients diagnosed with poorly differentiated extra-pulmonary NECs (LC-NEC and SC-NEC subtypes) were selected from the de-identified Tempus real-world multimodal database. Patient demographic/clinical characteristics and genomic/transcriptomic data were described as N (%) or median (IQR), min, and max and compared between subgroups by Chi-squared/Fisher's Exact tests or Wilcoxon rank-sum tests, as applicable. The prevalence of somatic mutations (SNVs, CNVs, and Fusions) was described and compared similarly, with a false-discovery rate correction for multiple comparisons. Analyses were two-sided, with statistical significance evaluated at the 0.05 alpha level.

RESULTS

307 patient samples (121 LC-NECs and 186 SC-NECs) were identified. There was no difference in race and ethnicity between LC and SC NECs. There were no significant differences in median TMB between LC and SC-NECs (3.1 vs 3.4 mut/Mb, p=0.2, respectively); the majority had low TMB (<10 mut/Mb). LC-NECs had higher frequency of deletions vs SC-NECs in *CDKN2A* (12% vs 1.6%, q=0.002), *CDKN2B* (12% vs 1.6%, q=0.002), and *MTAP* (9.9% vs 1.1%, q=0.002). SC-NECs had more frequent *RB1* loss compared to LC-NECs, although not significant after correction for multiple testing (16% vs 7.4%, q=0.2). LC-NECs have more common *CCND1, FGF3, FGF4, KDM5A, NOTCH1,* and *MYC* amplifications, but less common *SDHC, SLAMF1, FCGR2A, FCGR3A,* and *NIT1* amplifications compared to SC-NECs. SNVs in *APC, KRAS, BRAF, DAXX, NOTCH1,* and *SMARCA4* mutations were more common in LC-NECs, while *RB1, TERT, and FOXA1* mutations were more common in SC-NECs.

CONCLUSIONS

Our results demonstrated that EP-NECs display a broad pattern of genomic alterations according to their histological subtypes. These distinct molecular signatures could impact the development of future precision therapeutics for SC-NECs and LC-NECs.

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