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Prevalence of TP-53/Rb-1 Co-Mutation in Large Cell Neuroendocrine Carcinoma

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BACKGROUND: High grade poorly differentiated neuroendocrine carcinoma (HG-NEC) is a rare and highly aggressive neoplasm, which can arise from anywhere in the body. In 2016, Rekhtman et. al. differentiated genomic profiles of large cell NEC into: small cell lung cancer (SCLC)-like, characterized by TP53 + RB1 co-mutation/loss, and non-small cell lung cancer (NSCLC)-like, characterized by the lack of co-altered TP53 + RB1. TP53 and RB1 co-mutation was only found in 40% of their cohort. The objective of this study was to prospectively evaluate prevalence of TP53 + RB1 co-mutation in HG-NEC.

METHODS: HG-NEC patients were prospectively enrolled after IRB approval for tissues based somatic tumor mutation testing with help of Human Longevity Initiative's next generation sequencing platform.

RESULTS: 32 patients were consented. Only 15 patients had research quality tissue available for final analysis. Average age of cohort was 62 years with 46% females. Primary sites included Lung 4, Colo-Rectal 2, Pancreas 1, Esophagus 1, Parotid 1, Cervix 1, Ovary 1, Skin 1, Bladder 1, Trachea 1, Unknown Primary 1. 40% (6/15) patients were positive for TP 53 mutation and loss of Rb-1. As expected, the only two small cell lung cancer patients were positive for TP-53/Rb-1 co-mutation which is a universal biomarker of SCLC. However this was not found to be consistent for extrathoracic small cell as well as large cell neuroendocrine carcinoma. Median tumor mutation burden of cohort was 3.9. Parotid small cell carcinoma had highest TMB of 46.7 in our cohort.

CONCLUSION: Extra-thoracic high grade NEC are potentially molecularly distinct entities as compared to SCLC. Extrapolation of therapeutic strategies from SCLC to extra-thoracic HG-NEC might not be optimal. Large prospective studies are needed to refine our understanding of molecular differences between small cell

vs large cell NEC and thoracic vs extra-thoracic HG-NEC.

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