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Correlation of MEN1 and DAXX Mutational Status with Response to Capecitabine and Temozolomide (CAPTEM) in Pancreatic Neuroendocrine Tumors

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BACKGROUND

Capecitabine and temozolomide (CAPTEM) is a common regimen for the treatment of metastatic, well-differentiated pancreatic neuroendocrine tumors (PNETs). However, it is unknown whether certain genomic profiles predict response to CAPTEM. PNETs often contain mutations in *MEN1, ATRX, DAXX,* and the PI3K/AKT/mTOR pathway. We sought to determine whether the mutational status of these genes may correlate with progression-free survival (PFS) on CAPTEM.

METHODS

A retrospective cohort of PNET cases seen at Cedars-Sinai Medical Center or from Perthera's Real-World Evidence (RWE) Database (N=95) included 25 patients who were treated with first- or second-line CAPTEM and had tumor next-generation sequencing (NGS) performed. Relationships between commonly altered PNET genes and PFS on CAPTEM were analyzed using Perthera's RWE analytics tools. Differences in PFS outcomes by *MEN1*^{mut}/*DAXX*^{wt} status and potential confounders (e.g., line of therapy) were analyzed using univariate and multivariate Cox regression.

RESULTS

We analyzed 25 PNET patients, 4 (16%) of whom had documented functional tumors. We identified *MEN1* mutations as positively associated with CAPTEM response, but this effect was less pronounced for the subset with co-occurring *DAXX* mutations, which are commonly found alongside *MEN1* alterations. With and without accounting for line of therapy, we found that PFS on CAPTEM was significantly longer in *MEN1*-mutated, *DAXX*-wildtype tumors compared to other mutation profiles ($P < 0.01$, see **Table 1**). *ATRX* and *PTEN* alterations were also enriched in the *MEN1*-mutated/*DAXX*-wildtype subset; however, other PI3K/AKT/mTOR alterations were common across all *MEN1*-mutated cases.

PFS Strata (N=25)	Univariate Cox Significance (p)	Hazard Ratio (HR) [95% Conf. Interval]	Multivariate Cox Significance (p)	Hazard Ratio (HR) [95% Conf. Interval]
MEN1^{mut}/DAXX^{wt} vs Other NGS Profiles	p=0.0094	HR=0.16 [0.04-0.64]	p=0.0097	HR=0.16 [0.04-0.64]
1st Line CAPTEM vs 2nd Line CAPTEM	p=0.68	HR=0.8 [0.27-2.34]	p=0.86	HR=0.91 [0.32-2.58]

CONCLUSIONS

We describe a novel, exploratory genomic signature (*MEN1*-mut/*DAXX*-wt) that correlates with relative PNET response to CAPTEM. Prospective validation of these associations is warranted while taking into account other therapies, histopathologic factors, and other genomic correlates.

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