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PPM1D as a Potential Driver of Myeloid Malignancy Transformation in Neuroendocrine Tumor (NET) Pts: An Underrecognized Malignant CHIPerpetrator?

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BACKGROUND

Building on our prior work showing high baseline CHIP prevalence and cytopenias in NET pts receiving PRRT, we used NANETS support to analyze a new cohort with matched pre- (pre-tx) and post-treatment (post-tx) peripheral blood (PB) samples (pre-post chemotherapy/ctx, PRRT, or both). This expanded dataset enabled a deeper investigation of CHIP-associated hematologic toxicity, mutation dynamics, and high-risk mutation acquisition to validate earlier results, identify putative targets and inform predictive models of tx-related toxicity.

METHODS

Following IRB approval at CCF and Roswell, PB from NET pts was analyzed for CHIP using a 63-gene myeloid NGS panel (≥2% VAF cutoff). Sequencing was performed via anchored multiplex PCR and Illumina technology (>500× coverage). Clinical associations were assessed using chi-square and Mann-Whitney U tests, with significance set at $p < 0.05$.

RESULTS

At baseline/pre-tx, 8 of 41 pts (19.5%) were CHIP+ and had significantly older age (72.8 vs. 58.7 yrs, $p = 0.002$), lower ALC (1.1 vs. 1.5, $p=0.044$) and lower Hb (12.4 vs. 13.7 g/dL, $p = 0.063$, trend), suggesting reduced immune and marrow reserves. No associations were seen with sex, race, ECOG, WBC, ANC, platelets, or prior radiation/ctx. Majority of CHIP+ pts (5/8; 62.5%) at baseline had no prior RT/ctx exposure. Post-tx (post ctx, PRRT), pts who were CHIP+ at baseline demonstrated significantly higher mutation burden on follow up sequencing (2.0 ± 1.3 vs. 0.6 ± 1.1, $p = 0.005$), and greater clonal progression (88.9% vs. 10.0%, $p < 0.001$), compared to those who were CHIP-negative at baseline. Stable mutation profiles or clonal stability post-tx were more common in CHIP-neg pts (90.0% vs. 5.6%). Recurrent post-tx mutations included PPM1D, DNMT3A, TET2, and ASXL1, with PPM1D emerging in 31.7% (13 of 41) despite being present in only one patient at baseline. PPM1D mutations (PPM1Dm) were characterized by multiple clinically significant truncating variants that that were strongly selected for following tx. CHIP+ status was associated with greater clonal expansion post-tx and worse survival. Detailed mutation dynamics post-specific treatments will be presented.

CONCLUSIONS

Contrary to prior assumptions, PPM1Dm emerged post-tx in 31% of patients regardless of baseline CHIP status highlighting its role in therapy-related CHIP independent of initial mutation status. These

findings underscore the need for serial sequencing and long-term follow-up to detect clonal evolution early and enable timely intervention. Given PPM1D's link to impaired DNA repair and poor outcomes in overt myeloid malignancy (Fandrei et al., Clin Cancer Res. 2025), we plan a larger longitudinal study to validate these findings in the precursor CHIP state, map co-mutations, and identify progression drivers to inform prevention strategies.

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