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Tumor Biology

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Liquid Biopsies - Detecting and Tracking Circulating Cell Free Tumor Derived DNA in Patients with Neuroendocrine Neoplasms

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Introduction: There is a clinical need to develop novel and better biomarkers to monitor patients with neuroendocrine neoplasms (NENs). Circulating cell free tumor derived DNA (ctDNA), a form of liquid biopsy, is finding clinical utility in an ever increasing number of malignancies however has not been widely tested in patients with NENs. **Aims:** Our aim was to identify and track plasma ctDNA in a cohort of patients with NENs using a personalized, patient specific approach. **Materials and methods:** A total of 35 serial plasma samples were collected from 9 patients with metastatic, well differentiated NENs (6 small intestinal and 1 lung, 1 ovarian and 1 pelvic; range 2-5 plasma samples per patient) over the space of 2-25 months. For each patient, NEN specific somatic mutations (single nucleotide variants and insertions/deletions) were identified through whole exome sequencing of paired tumor-leucocyte DNA and were used to design a bespoke multi-variant Ampliseq™ HD ctDNA panel (5-20 variants per patient) for targeted next generation sequencing. Imaging and treatment were provided as per usual clinical care. **Results:** ctDNA was detectable in 6/9 patients and in 19/35 plasma samples. A rise in the number of ctDNA target variants and/or variant allele frequency was seen in 4/6 patients who experienced disease progression. Two of these

patients received peptide receptor radionuclide therapy after which ctDNA disappeared in one patient and substantially reduced in the other, which correlated with treatment response. The 3 patients who did not have detectable ctDNA at any time point all had grade 1 small intestinal NENs with stable disease during the observation period. **Discussion:** Our data provide exciting evidence for the feasibility of using ctDNA as a biomarker in NENs. By targeting multiple individualized variants using next generation sequencing, we have demonstrated that ctDNA can track changes in disease burden and can monitor response to treatment in patients. Of equal importance, ctDNA was not detectable in patients with quiescent disease. This could help identify patients who do not need intensive monitoring. Targeting bespoke, multiple variants per patient is a novel and powerful approach for NENs, especially given their heterogenous genetic landscape. This study provides important early evidence that ctDNA may be a clinically useful biomarker for detection and surveillance of NENs.

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