pre-treatment and on-treatment biopsies demonstrated intratumoral suppression of KYN production with EPA 600 mg BID.

**Conclusions** Using suppression of plasma KYN as a pharmacodynamic marker of EPA activity, we demonstrated that maximal blockade of IDO1 activity in the context of anti-PD-1 treatment requires doses of EPA substantially higher than those tested in prior clinical studies. These findings are now informing additional proof of concept clinical studies.

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**Ethics Approval**

 trial registration ECHO-202 [NCT02179722]; ECHO-204 [NCT02327078]; ECHO-210 [NCT01685255]; ECHO-301 [NCT02752074]; POD1UM-102 [NCT03589651]

**Ethics Approval** These studies were each approved by the institutional review board or independent ethics committee of participating institutions.

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**PROFILING TUMOR CIRCULATING CELL-FREE DNA WITH AN ENHANCED WHOLE-EXOME TO ENABLE SENSITIVE ASSESSMENT OF SOMATIC MUTATIONS**

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**Background** An increasing number of studies have demonstrated the potential use of circulating cell-free DNA (cfDNA) for diagnosis, prognosis, disease progression, and treatment monitoring. However, many of these studies use assays covering a limited set of genes and therefore miss biologically and clinically relevant genetic alterations involving immuno-modulatory pathways which confer treatment resistance, and leading to changes in neoantigen status. To address this, we developed a whole-exome scale cfDNA platform, NeXT Liquid Biopsy™, that enables sensitive detection and tracking of mutations in approximately 20000 genes.

**Methods** To enable sensitive detection across the exome, our enhanced exome assay and chemistry augments hard-to-sequence genomic regions, such as regions of high GC content, to enable more uniform coverage across the exome. We achieved a high mean sequencing depth of approximately 2000X exome-wide, with additionally boosted depth for 248 clinically relevant oncogenic and tumor suppressor genes to further enhance sensitivity. We developed a computational pipeline for our NeXT Liquid Biopsy assay optimized to lower the noise floor for variant detection, providing sensitive monitoring and de novo detection of variants over multiple time points.

**Results** We evaluated the sensitivity of our NeXT Liquid Biopsy platform in three ways. First, we evaluated the sensitivity within the coverage boosted regions using the SeraCare reference materials at multiple allele frequency (AF) dilutions. Our platform identified all 8 and 25 Horizon and SeraCare SNV events at 1% AF and above, respectively, and detected 24 out of 25 events at 0.5% for the SeraCare samples. Additionally, to enable sensitivity analysis at the whole-exome scale, we then developed a cell culture media system that models the shedding of tumor DNA fragments seen in human plasma samples and created tumor/normal dilution series in vitro. We achieved >95% sensitivity for variants with AF≥29%, and between 85% to 92% for mutations with AF of 1%-2%. Second, we evaluated false-positive rates on 12 cancer patients using digital droplet PCR. Third, we demonstrated our ability to longitudinally monitor treatment response using a clinical cancer cohort on checkpoint therapy, profiling putative tumor evolution while on therapy.

**Conclusions** In conclusion, we have developed a whole-exome scale liquid biopsy platform, NeXT Liquid Biopsy, that enables sensitive monitoring and detection of somatic SNVs from cfDNA across ~20000 genes. The platform enables broader monitoring of changes in response to cancer therapy, acquired mechanisms of resistance, and intra- and inter-tumor heterogeneity.

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**NLR (NEUTROPHIL LYMPHOCYTE RATIO) AND PLR (PLATELET LYMPHOCYTE RATIO) CHANGES AS A PREDICTOR OF EVENTUAL TREATMENT FAILURE AND DEATH ON NIVOLUMAB THERAPY IN RENAL CELL CARCINOMA**

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**Background** Elevated baseline neutrophil lymphocyte ratios (NLR) are now well established as a poor predictor of survival in renal cell carcinoma (RCC) and other cancers. Platelet Lymphocyte Ratios (PLR) have also recently shown similar effects. Despite these findings, the practical use of these ratios is still somewhat limited. We have previously shown that higher NLRs may be associated with increased concentrations of myeloid derived suppressor cells (MDSC). We hypothesized that increases in NLR or PLR (NLR/PLR failure) at 2 months while on immunotherapy could be a predictor of eventual treatment failure and overall survival.

**Methods** We analyzed patients who received nivolumab therapy for RCC at our institution from 3/2016 to 6/2019. Patients with complete data on NLR and PLR at time = 0 and +2 months and those who had accurate response and overall survival information available were selected (n = 37).

**Results** NLR failure was associated with a statistically significant increase in the risk of progression and death with NLR/PLR failure at 2 months (±2 weeks). Kaplan Meier graphs were constructed to trace survival functions for PFS and OS by NLR.

**Conclusions** NLR failure was associated with a statistically significant increase in the risk of progression on nivolumab therapy (HR 4.26, 95% CI [1.47–12.3], p = 0.007), in an adjusted cox regression model that included baseline NLR. In this adjusted model, the value of baseline NLR to predict