Comprehensive ctDNA monitoring provides early signal of clinical benefit with a novel personalized neoantigen directed immunotherapy for late-stage cancer patients


Abstract: Neoantigen directed immunotherapy holds promise for patients with solid tumors devoid of immune infiltration to benefit from immune checkpoint immunotherapy (CPI). A heterologous prime-boost vaccine approach consisting of a Chimpanzee Adenovirus (ChAd) prime and multiple self-amplifying mRNA (samRNA) boosts, delivering 20 neoantigens, has been evaluated in a Phase 1/2 clinical trial in late-stage solid tumor patients in combination with nivolumab and ipilimumab (NCT03639714). Neoantigen dynamics, tumor burden and genomic correlates of response were studied over time in 25 patients (12 GEA, 2 small cell lung cancer patients in combination with nivolumab and ipilimumab).

**Methods:** Exome sequences from archival (sample used for neoantigen selection), baseline (start of immunization) and on-treatment ctDNA samples were collected monthly from baseline. A heterologous prime-boost treatment (mean 7; range: 1-18) was administered. ctDNA was amplified from ctDNA using lipid nanoparticles encoding same mRNA or exome sequences from archival (sample used for neoantigen selection) and baseline (BL) when available.

**Conclusion:**
- Majority of neoantigens are retained in tumor while vaccine is being manufactured.
- Comprehensive ctDNA longitudinal monitoring enables real-time assessment of response/resistance and potentially provides more useful predictive information than traditional RECIST radiologic assessment in the context of this novel immunotherapy.
- Neoantigen-directed immunotherapy appears to drive clinical benefit in patients with advanced MSS-CRC, with molecular response elicited in 4/9 treated subjects and correlated with prolonged progression-free survival and overall survival.

**Figure: ctDNA molecular response is associated with OS in patients with advanced stage MSS-CRC**

1. ctDNA assessment based on GRANITE-developed, tumor-informed assay in 24 patients from the 3 most recently treated patients.
2. ctDNA assessment not available for the 3 most recently treated patients.
3. Patients G14 and G16 with PD at week 16 and G9, respectively set off control on subsequent scans through week 24.

**Conclusion:** Acquired resistance in antigen presentation pathway at 12 months of therapy suggesting vaccine induced immune pressure on tumor

**Figure: Differential Gene Expression Analysis**

**Conclusion:**

Differential gene expression analysis from panel 6 and post-vaccine biopsy (G10 and G11 MSS-CRC - G90 with molecular response) (M12) demonstrated significant upregulation in genes associated with immune infiltrated tumor microenvironment which includes pro-inflammatory immune responses and immune checkpoint genes. This data suggests a mechanism for neoantigen-directed immunotherapy.