Exploratory analysis of T cell repertoire dynamics upon systemic treatment with the oncolytic virus pelareorep in combination with pembrolizumab and chemotherapy in patients with advanced pancreatic adenocarcinoma (Abstract #2272)

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Abstract
Background: Pelareorep is an immunoo-oncolytic virus that induces an inflamed tumor phenotype in metastatic adenocarcinoma of the pancreas (MAP). Systemically delivered pelareorep in combination with chemotherapy achieves a 1 & 2 year-survival rates of 46% & 24% in MAP patients (pts), respectively. Analysis of tumor tissue from pts treated with pelareorep, chemotherapy and anti-PD-L1 have shown reverse RNA and protein replication, T cell infiltration, and upregulation of PD-L1, highlighting that effective T cell recognition of tumor antigens may be critical to success for this combination therapy. Thus, we hypothesized that pelareorep in combination with chemotherapy and pembrolizumab in pts with MAP would alter the peripheral T cell repertoire, creating new T cell clones via the release of novel neoantigens in addition to expanding existing T cell clones.

Methods: A phase I study enrolled 11 MAP pts who progressed after first-line treatment. Pts received pelareorep (4x106 IU, D1, D2, D7, D14, plus pembrolizumab (2 mg/kg, IV, D8) plus either 5-FU (400mg/m2, IV, D1, or 3 intravenous bolus, 5-FU 1250mg/m2, IV, D1) or 3 intravenous bolus, 5-FU 200mg/m2, IV, D1) at cycle 1 (C1) & C2 (approx. 3 weeks later) was analyzed using the ImmunoSEQ® Assay (Adaptive Biotechnologies, Seattle) sequenced the T cell receptor beta chain to interrogate changes in the T cell repertoire.

Results: The median Morisita index between C1 and D1 was 0.83 with three samples below 0.6, indicating of significant peripheral repertoire turnover. The median number of expanded clones equates to 4.43 x 10^5 cumulative total clones; normal variation over 4 weeks is ~ 5-10 expanded clones. Strikingly, most (median: 86%) peripheral clonal expansion occurred in clones below the limit of detection at cycle 1 (C1) (HR = 0.251, p = 0.019) and C2 (HR = 0.378, p = 0.013). Conclusions: High levels of peripheral T cell repertoire turnover occur between C1 and C2. Repertoire turnover is accompanied by significant clonal expansion, mostly by expansion of new clones (i.e. undetected in C1). Higher peripheral clonality is associated with better prognosis at C1, and overall survival at C1 and C2. This research highlights the potential utility of T cell clonality as a predictive and prognostic biomarker to pelareorep therapy and warrants further clinical investigation.

Background
Study Design and Schedule

Primary endpoint: Dose-limiting toxicities
Secondary Endpoints: ORR, PFS, OS, biomarkers

Efficacy Findings

Results
Low Morisita Indices Between C1 and D1 Suggests High Repertoire Turnover

- Morisita Index takes into account both repertoire overlap and clonal frequencies between the two samples. A perfectly ideal repertoire is 1, and two completely disparate samples would be 0.
- Normal variation over a month is ~0.9–0.95.
- The median Morisita between C1 and D1 is 0.83 with 3 samples below 0.6. This suggests significant peripheral repertoire turnover.

Significant Peripheral Clonal Expansion Over Treatment

- Peripheral expanded clones were detected between C1 and C2.
- Normal variation over 4 weeks is ~ 5-10 expanded clones
- Median values are greater than 40 in both cases. Only 1 sample had less than 18 expanded clones

Most Peripherally Expanded Clones Are Newly Identified at C2D1

- Newly expanded clones can be either expansion of existing clones or newly identified clones (i.e. undetected in the first time point).
- Most peripheral clonal expansion is observed from new clones (Median: 86%).

Results cont.
Peripheral Clonality and Diversity at C1D1 Correlate with Progression Free Survival

- Variables were treated as continuous variables for cox regression.
- Clonality was scaled to a unit of 0.1
- Clonality was scaled to a unit of 100
- Clonality and diversity are correlated with progression free survival and show a significant association with C1D1. Higher peripheral clonality and lower diversity are associated with longer progression free survival.

Peripheral Clonality and Diversity at C1D1 and C2D1 Correlate with Survival Time

- Variables were treated as continuous variables for cox regression.
- Clonality was scaled to a unit of 0.1
- Clonality was scaled to a unit of 100
- Clonality and diversity are correlated with overall survival and show a significant p-value at C2D1. Higher peripheral clonality and lower diversity are associated with better outcome.

Long Term Survivors Have Greater Peripheral Clonality at C2D1

- Responders and long term survivors have greater peripheral clonality at C2D1.
- Long term survivors (LTS): > 6 months.
- Short term survivors (STS): < 6 months.

Early Expanded Clones Most Strongly Correlate With Survival Time

- Both numbers of early and durable clones are associated with longer overall survival times.
- The strongest correlation is seen with the number of early expanded clones.
- Early vs. late clonal expansion may be influenced by the type of response pelareorep is eliciting.

Conclusion

- Higher peripheral clonality and lower diversity are associated with better overall survival.
- High levels of peripheral repertoire turnover occur between C1D1 and C2D1.
- Repertoire turnover is accompanied by significant clonal expansion, mostly by increases in "new" clones (clones that were undetected in C1D1).
- The number of early expanded clones (prior to pembrolizumab) is associated with longer overall survival. There is no correlation with either durable or late expanded clones and clinical outcome.

A study by Hopkins et al. has also shown that peripheral T cell repertoire analysis with survival in MAP pts treated with nivolumab and a pancreatic cancer vaccine.

References