Abstracts

show that non-GCB subjects had a higher proportion of clinical response (4/8, 50%), compared to 3/10 (30%) in GCB subjects. DPX-Survivac-induced T cell responses were observed in 8/19 subjects (42.1%) including 6 subjects with clinical response (PR, CR), one SD and one PD. Multiplex-IHC analyses demonstrated baseline tumor PD-L1 expression in 6/7 subjects with a clinical response (85.7%, p<0.05). Similarly, subjects with higher baseline CD4+ and CD8+ T cell infiltration demonstrated a trend towards clinical response (table 1).

Conclusions DPX-Survivac, intermittent low-dose CPA and pembrolizumab is generally well tolerated and can induce clinical responses in subjects with t/r DLBCL (7/11, 63.6% of evaluable subjects), including subjects with both non-GCB and GCB subtypes. Pre-treatment biopsies of clinical responders were characterized by higher baseline tumor PD-L1 expression and CD4 and CD8 infiltration. Extending this exploratory data in a larger cohort may define a t/r DLBCL patient population with a higher likelihood to respond to this novel combination immunotherapy.

Trial Registration NCT03349450

Ethics Approval This study was approved by the Ontario Cancer Research Ethics Board, approval number 0981.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0356

TAK-573, AN ANTI-CD38–ATTENUATED INTERFERON ALPHA (IFNα) FUSION PROTEIN (ATTENUKINE™), HAS DEMONSTRATED IFNα RECEPTOR (IFNAR) PATHWAY MODULATION IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA


Background TAK-573, a humanized, anti-CD38, IgG4, monoclonal antibody genetically fused to two attenuated IFNαb2 molecules, was designed for targeted delivery of attenuated IFNαb2 to CD38 expressing (CD38+) cells, utilizing a unique epitope of CD38 that does not compete with current anti-CD38 therapies. Preclinical evaluation of TAK-573 confirmed activation of type I IFN signaling in CD38+ cells inducing direct anti-proliferative effects on multiple myeloma (MM) cells and direct and indirect immune cell activation. Here we provide the preliminary analyses of the pharmacodynamic data currently available from the ongoing Ph I/II TAK-573-1501 clinical study in patients with relapsed/refractory MM (NCT03215030).

Methods Peripheral blood (PB) and bone marrow (BM) aspirates were collected from patients at pre- and post-dose time points for exploratory biomarker analyses. CD38 receptor occupancy (RO) and receptor density (RD) were determined using a 9-color flow cytometry assay. Whole transcriptome sequencing of bulk RNA was performed and analyzed to assess the type I IFN gene signature. Serum samples were analyzed using Olink’s Proximity Extension Assay Immuno-Oncology panel to measure changes in cytokine levels. Mass cytometry-based immunophenotyping was utilized to characterize changes in immune cell prevalence and activation status of cryopreserved cells.

Results Administration of TAK-573 resulted in a dose dependent increase in CD38 RO of PB-derived immune cells with saturation detected 4 hours after the end of infusion (EOI) at doses ≥ 0.2 mg/kg. The duration of saturation was dose dependent with doses ≥ 0.75 mg/kg saturating CD38 RO through 24 hours. All dose levels tested resulted in increases in the type I IFN gene signature at 24 hours. Consistent with CD38 being an IFN stimulated gene, TAK-573 treatment resulted in CD38 RD increases most notably on NK cells, but also on other CD38+ cells including MM cells. Circulating levels of IFN-α associated cytokines were also elevated, with maximal induction 4 hours after the EOI. CD8+ T-cells in BM showed increased CD69 expression in 7 of 9 patients analyzed, 3 of whom also showed increases in both IFNα and granzyyme B positivity suggesting TAK-573 treatment results in increased BM cytolytic CD8+ T-cells, in a subset of patients.

Conclusions These preliminary biomarker data indicate that TAK-573 is a pharmacologically active molecule that mediates its effect through IFNAR pathway modulation. Additional data are being collected to further refine the mechanism of action (Image 1), which will inform the recommended phase 2 dose and optimal schedule of administration for the development of TAK-573.

Trial Registration ClinicalTrials.gov: NCT03215030

Ethics Approval The TAK-573-1501 study is approved by WIRB-Copernicus Group, University of Nebraska Medical Center, Dana Farber Cancer Institute and Advarra IRBs.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0357

TRIAL IN PROGRESS: A PILOT STUDY OF COMBINED IMMUNE CHECKPOINT INHIBITION IN COMBINATION WITH ABLATIVE THERAPIES IN SUBJECTS WITH HEPATOCELLULAR CARCINOMA (HCC)

1Hailey Carroll*, 2Umar Aleem, 3Pooya Varghese, 4Marie Galligan, 5Michèle Bourke, 6Katherine Hoey, 7Ronan Ryan, 8Peter Donan, 9Stephen Stewart, 10Cliona O’Farrell, 11Tim Greten, 12Briandoulouliaurhan, 13Raymond McDermott, 14Austin Duffy, 15Mater Hospital, Dublin, Ireland; 16St. Vincent’s University Hospital, Dublin, Ireland; 17University College Dublin, Dublin, Ireland; 18Trinity College, Dublin, Ireland; 19NIH, Bethesda, MD, USA

Background Locoregional therapies for hepatocellular carcinoma, such as transcatether arterial chemoembolization (TACE) or ablation, can induce a peripheral anti-tumor immune response. This may be amplified by immune checkpoint inhibitors (ICI). Early and higher anti-CTLA4 dosing could potentially lead to better priming and a stronger immune response. Recent data has suggested that early (Day 1 only), increased doses of anti-CTLA4 therapy, was associated with encouraging clinical activity and a tolerable safety profile. This study will evaluate dual immune checkpoint, CTLA4 (tremelimumab, day 1 only) and PD-L1 (durvalumab) blockade in combination with TACE in patients with advanced

Abstract 357 Figure 1 Proposed Mechanism of Action of TAK-573