Background NKTR-255, an investigational IL-15Rα-dependent polymer-conjugated recombinant human IL-15 (rhIL-15) agonist, maintains the full spectrum of IL-15 biology and provides sustained pharmacodynamic (PD) responses without the need for daily dosing. NKTR-255 engages IL-15Rα and IL-2/IL-15Rβγ leading to natural killer(NK) and CD8+ T-cell expansion, proliferation and activation. In preclinical studies, NKTR-255 enhanced antibody-dependent cellular cytotoxicity(ADCC) of each of daratumumab, rituximab, trastuzumab and cetuximab, resulting in synergistic antitumor activity. This ongoing phase 1 trial (NCT04136756) evaluates NKTR-255 in patients with hematologic malignancies.

Methods Heavily pretreated patients with relapsed/refractory multiple myeloma(MM) or non-Hodgkin lymphoma(NHL) received escalating doses of NKTR-255 intravenously q3w. Patients were observed for 3 weeks following the first NKTR-255 dose for dose-limiting toxicity(DLT). Preliminary safety, PK and PD were evaluated in all patients and bone marrow biopsy was evaluated in one patient. NKTR-255-mediated activation of the immune system was assessed by flow cytometry and plasma cytokine analysis.

Results As of June 25, 2020, 4 patients were dosed(1.5µg/kg:3 patients; 3µg/kg:1 patient). NKTR-255 was well tolerated. Most common treatment-related adverse events(AEs): flu-like symptoms, muscle stiffness, and myalgia. One Grade 3 event(pyrexia) was reported, resolving <24 hours with over-the-counter medications. No NKTR-255-related DLTs or serious AEs occurred. Clinical activity was observed in 2/4 patients(NHL and MM). The NHL patient achieved reduced metabolic activity in all prespecified target lesions after 5 cycles. The MM patient achieved stable disease after 3 cycles on NKTR-255 monotherapy. This 63 y/o male had high-risk recurrent stage III MM with complex cytogenetics (relapsing after VRd, DRd, and carfilzomib plus dexamethasone). Preliminary PK analyses(1.5µg/kg) showed mean half-life of >24 hours with no accumulation following repeat dosing. NKTR-255 at 1.5µg/kg expanded NK and CD8+ T-cells in peripheral blood, with peak fold-changes in cell numbers of approx 5-fold and approx 3-fold respectively, maintained during the cycle. Bone marrow biopsy data indicate 7-fold(cycle 5) to 13-fold (cycle 9) increase from baseline in the CD56+ population in the MM patient. Proliferative capacity for NK and CD8+ T-cells was maintained across multiple treatment cycles. NKTR-255-dependent changes in inflammatory cytokines, including MCP-1 and IL-6, peaked by 6 hours and resolved to baseline levels by 24 hours, further supporting the safety of NKTR-255.

Conclusions In heavily pretreated patients with hematologic malignancies, NKTR-255 is biologically active and demonstrated sustained increases in NK and CD8+ T-cells. NKTR-255 was well tolerated, with minimal treatment-related toxicities. Our preclinical and preliminary clinical data provide evidence of synergistic effects enhancing ADCC and support continued dose escalation of NKTR-255.

Trial Registration NCT04136756

Ethics Approval The study was approved by the institutional review board of each participating site.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0355
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 r/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 r/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

Abstract 357 Figure 1 Proposed Mechanism of Action of TAK-573
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 RΔ increases most notably on NK cells, but also on other CD38+ cells including MM cells. Circulating levels of IFN-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 granzyne 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

Abstract 358 TRIAL IN PROGRESS: A PILOT STUDY OF COMBINED IMMUNE CHECKPOINT INHIBITION IN COMBINATION WITH ABLATIVE THERAPIES IN SUBJECTS WITH HEPATOCELLULAR CARCINOMA (HCC)

Background Locoregional therapies for hepatocellular carcinoma, such as transcatheter 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 (pembrolizumab, day 1 only dosing) and PD-L1 (durvalumab) blockade in combination with TACE in patients with advanced