PHASE 1/2 STUDY OF THOR-707 (SAR444245), A PEGYLATED RECOMBINANT NON-ALPHA IL-2, AS MONOTHERAPY AND IN COMBINATION WITH PEMBROLIZUMAB OR CETUXIMAB IN PATIENTS (PTS) WITH ADVANCED SOLID TUMORS

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Background THOR-707 (SAR444245) is a recombinant human IL-2 molecule irreversibly bound to a PEG chain to block alpha-binding while retaining near-native affinity for beta/gamma IL-2 receptor subunits. We report updated results from the ongoing HAMMER phase 1/2 trial.

Methods SAR444245 was given via IV infusion as monotherapy Q2W [A] or Q3W [B], with pembrolizumab 200mg IV Q3W [C], or Q3W with cetuximab 400mg/m² IV on D1 then 250mg/m² IV QW [D] after pre-medication and peri-infusion hydration. A 3+3 design was used to identify the MTD/RP2D in pts with advanced solid tumors. Key objectives included assessments of safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD).

Results 68 pts, median age 61.5 (37–78) yrs with median 3 (1–10) prior therapies enrolled. Most common tumors: melanoma (n=10), colorectal (n=11). Doses tested by cohort: [A]: 8–16 µg/kg (n=9); [B]: 8–40 µg/kg (n=29); [C]: 8–32 µg/kg (n=20); [D]: 16–24 µg/kg (n=10). The most common (>30%) AEs included pyrexia (52.5%), nausea (50.0%), flu-like symptoms (44.1%), vomiting (36.8%), chills (32.4%), fatigue (32.4%), AST elevation (30.9%). AEs generally resolved promptly with supportive care. Grade(G) 3/4 (>5%) related AEs included ALT/AST elevation (5.9%), and decreased lymphocyte count (26.5% within first 24 hrs, recovering by 48–72 hrs, this lymphocyte migration is mechanistically consistent with immune cell margination). G3/4 CRS was observed in 2 pts. Two DLTs occurred: G3 infusion reaction (32 µg/kg [B]) and G3 AST/ALT/G2 bilirubin elevation with G2 CRS (24 µg/kg [C]). No vascular leak syndrome, QTc prolongation, cardiac, or end organ toxicity was observed. Half-life was ~10 h. Sustained increases in CD8 T and NK cells were observed (fold relative to baseline): monotherapy (1–9.4x and 2–43.3x); with pembrolizumab (0.5–5.78x and 1.5–26.9x); with cetuximab (1.3–7.57x and 3.6–45.4x). Max CD4 and eosinophils increased to 136 cell/µL and 1078 cell/µL. No IL-5 elevation or ADAs were observed. Transient IL-6 increases in 4 pts (500, 627, 1000, 1100 pg/mL) were not associated with AEs. Four pts had confirmed PRs (1 PD1-treated SCC, unknown primary [B]; 2 PD1-naïve BCC and 1 PD1-treated HNSCC [C]); 3 pts had minor responses – prostate (-24%) and PD1-treated melanoma (-17%) [B]; PD1-treated NSCLC (-29%) [C] – after ≥2 scans. 23 pts completed ≥5 cycles.

Conclusions SAR444245 was well tolerated and demonstrated antitumor activity in heavily pretreated patients, including prior checkpoint inhibitor therapy. Clinical safety, efficacy and PD suggest a wide therapeutic window. Combination with

pembrolizumab and cetuximab leveraged SAR444245's effects on CD8 T and NK cells.

Trial Registration NCT04009681

Ethics Approval The clinical trial was approved by each institutions ethics' and review board prior to beginning study enrollment.

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