PHASE 1/2A CLINICAL TRIAL OF BI-1808, A MONOCLONAL ANTIBODY TO TUMOR NECROSIS FACTOR RECEPTOR 2 (TNFR2) AS SINGLE AGENT AND IN COMBINATION WITH PEMBROLIZUMAB

Background BI-1808 is a human IgG1 monoclonal antibody targeting TNFR2 by blocking the interaction of TNFR2 with its ligand TNF-α, conferring FcγR-dependent depletion of intratumoral Tregs and mediating expansion of intratumoral CD8+ T cells. Upon co-administration of BI-1808 and anti-PD-1 surrogate antibodies to immunocompetent tumor-bearing mice, with partial sensitivity to checkpoint blockade, complete cures were observed in all treated mice, indicating a potentially synergistic activity.

Methods Safety and tolerability of BI-1808 as a single agent and in combination with pembrolizumab is currently investigated in the Phase 1/2a trial 19-BI-1808–01 in patients with advanced malignancies or cutaneous T-cell lymphoma (CTCL). The trial consists of Phase 1 Parts A and B (dose escalation with single agent and combination with pembrolizumab, respectively), and Phase 2a Parts A and B (dose expansion with single agent and combination therapy, respectively). Dose escalation uses a modified toxicity probability interval-2 protocol (mTPI-2), investigating ascending dose levels of 25–1000 mg every three weeks (Q3W). Dose escalation aims to select both single agent RP2D and combination RP2D of BI-1808 for Phase 2a.

Patients are sampled for pharmacokinetics (PK) of BI-1808, antidrug-antibodies and pharmacodynamics including lymphocyte subsets, regulatory T cells, memory T cells, soluble TNFR2 serum concentration (sTNFR2) and BI-1808 receptor occupancy (RO).

Results As of June 19th, 2023, 24 subjects with various advanced solid malignancies received doses of up to 1000 mg BI-1808 as single-agent treatment, and 7 subject received 225 mg doses of BI-1808 with pembrolizumab.

Across the completed monotherapy arm, no Grade 3/4 AEs, AE related to BI-1808 and no DLTs were observed. No MTD was defined. The number of potentially related AEs of Gr 1/2 are evenly distributed across the dose range, with no target system organ class of special notice identified. Best clinical response recorded are stable disease (SD) in 7/19 evaluable patients in the monotherapy arm. The first dose cohort for BI-1808 at 225 mg in combination with pembrolizumab is currently ongoing.

BI-1808 exhibits a non-linear PK. At doses > 675 mg Q3W, t½ was approximately 1 week resulting in accumulation of drug, with complete RO throughout the dosing interval.

Conclusions Preliminary data from the BI-1808 monotherapy arm from the clinical trial 19-BI-1808–01 is promising. BI-1808 has a favorable safety profile, with no DLTs observed. SD was observed in 7/19 evaluable patients. Doses of 675 mg and higher are expected to provide complete RO throughout the dose interval, and will be further explored in Ph2a.

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