Background SAR445710 is a targeted cytokine comprised of a fusion antibody combining a fully human, high affinity anti-human Programmed Death Ligand 1 (PD-L1) IgG1 antibody with the human IL-15 receptor alpha (IL-15Ra) sushi domain and human IL-15. SAR445710 and its mouse cross-reactive surrogate molecule have been extensively characterized by in vitro and in vivo studies and demonstrated robust efficacy and therapeutic benefits compared to IL-15 alone. Specifically, SAR445710, potentially leverages PD-L1 targeting to deliver IL-15 to the tumor microenvironment.

Methods This was a phase 1, open-label, multiple ascending dose, multi-center study in patients with metastatic or locally advanced solid tumors (NCT04242147). Dose escalation followed a ‘3+3’ design with the occurrence of dose limiting toxicity (DLT) evaluated over the first 28 days. Bi-weekly (Q2W) and weekly (QW) dosing schedules were evaluated at doses ranging from 3–400 mg/kg (Q2W) and 50–300 mg/kg (QW). The primary objective was to assess the safety and tolerability of SAR445710 monotherapy.

Results As of July 31, 2023, 39 patients (median age, 61.5 years, and 46.15% females) were treated in dose escalation with 27 patients on Q2W schedule and 12 on QW schedule. There were three DLTs in the Q2W dose escalation, two Grade 3 cytokine release syndrome at 400 mg/kg and one Grade 3 pneumonitis at 200 mg/kg. No DLTs were observed in the QW schedule. The maximum tolerated dose (MTD) in the Q2W schedule was 200 mg/kg. Pyrexia (57.1%) and chills (42.9%) were the most common treatment-related adverse events. These were mostly Grade 1–2 that resolved with supportive management. Best overall response achieved among the Q2W and QW schedules was stable disease. On-target and expected pharmacodynamics for IL-15 agonisms were observed. SAR445710 had a potent effect on peripheral NK and CD8 T cell expansion. Ki67 expression in NK and T cells peaked on day 2 to day 3 post-treatment. There was no clear sign that T cells developed an exhaustion phenotype after repeated SAR445710 dosing. SAR445710 showed a non-linear pharmacokinetic profile from 3–400 μg/kg (Q2W), as expected for targeted antibodies. Enrolment continues in the QW schedule.

Conclusions SAR445710 demonstrated a manageable toxicity profile with on-mechanism pharmacodynamics consistent with IL-15 agonism.

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Trial Registration NCT04242147

Ethics Approval This study obtained ethics approval from WIRB.

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