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Blood 142 (2023) 3396–3397

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

A Phase 1, First-in-Human, Dose Escalation and Dose-Expansion Study of a BCMAxCD38xCD3 Targeting Trispecific Antibody ISB 2001 in Subjects with Relapsed/Refractory Multiple Myeloma

Hanlon Sia[1], *Vinu Menon*[2], *Andrew Garton, PhD*[3], *Eileen Wolff*[3], *Tejas Shah*[3], *Colleen Charpentier*[4], *Dominique Duchesne*[3], *Maria Pihlgren*[5], *Jeppe Koch-Olsen*[4], *Adam Drake*[6], *Mario Perro, PhD*[6], *Eugene Zhukovsky*[7], *Lida Pacaud, MD*[2], *Cyril Konto, MD*[2]

[1] Pindara Private Hospital, Benowa, AUS
[2] Ichnos Sciences, New York, NY
[3] Ichnos Sciences Inc., New York
[4] Ichnos Sciences, New York
[5] Ichnos Sciences SA, Epalinges, Switzerland
[6] Ichnos Sciences Biotherapeutics SA, Epalinges, Switzerland
[7] Ichnos Sciences Biotherapeutics SA, Lausanne, Switzerland

Background

Despite advances, multiple myeloma (MM) remains an incurable disease and resistance mechanisms are emerging. ISB 2001 has been designed to overcome those resistance mechanisms inherent to current MM therapies such as monoclonal antibodies (e.g. daratumumab), BCMA-targeted therapies, proteasome inhibitors(PIs), or immunomodulatory drugs(IMiDs). ISB 2001 is a first in class Trispecific T cell engager (TCE) that redirects cytotoxic T cells to BCMA and/or CD38 expressing myeloma cells. Simultaneous targeting of the two tumor associated antigens (TAA) may increase binding to tumor cells through avidity even with heterogeneous or low expression of the targeted TAA (BCMA or CD38). Therefore, it may overcome tumor escape mechanisms associated with low tumor antigenic expression inherent to current MM targeted therapies. Preclinically, ISB 2001 has demonstrated improved activity when compared to other BCMA or CD38 targeted molecules either alone or in combination across different MM models (M. Pihlgren et al., Blood. 140, 858-859 (2022), M. Pihlgren et al., Cancer Res. 83, 2970-2970 (2023)).

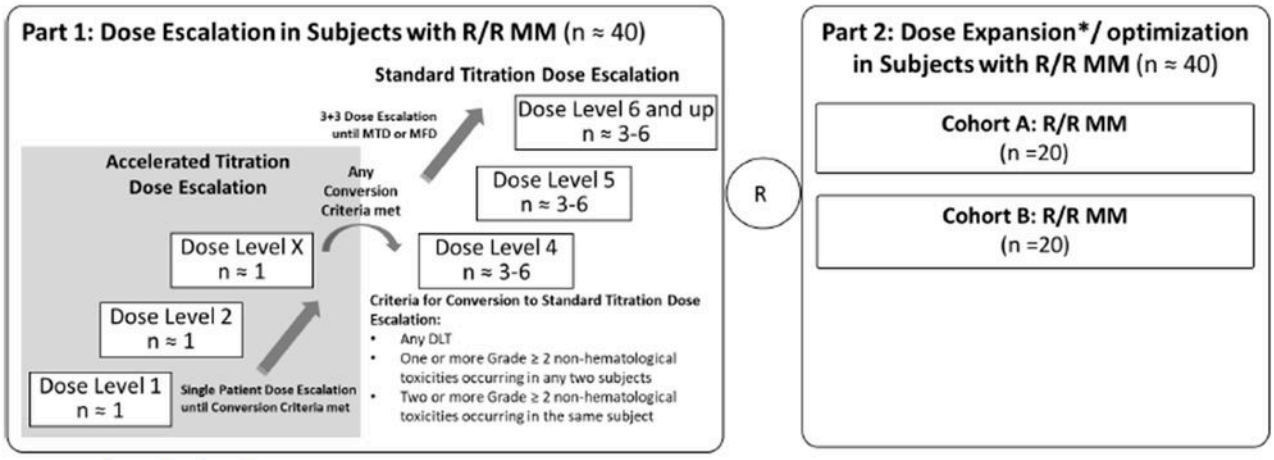
Study design and methods

This first-in-human, multicenter, open label Phase 1 study is assessing the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of ISB 2001 in relapsed/refractory multiple myeloma (RRMM) patients. This study will enroll subjects treated with prior IMiDs, PIs, and anti-CD38 therapies, or intolerant of, established therapies known to provide benefit (prior BCMA therapies, or prior transplantation and cellular therapies allowed).be conducted in two parts (Part 1: Dose escalation and Part 2: Dose expansion) (Figure 1). Criteria for enrollment in this study include patients with RRMM with measurable disease who have been treated with an anti-CD38 antibody, IMiDs, PIs either in combination or as a single agent, and /or intolerant of established therapies known to provide clinical benefit. ISB 2001 is being administered weekly by subcutaneous (SC) injection in 28-day cycles, with two step-up doses on cycle 1 day 1 (C1D1) and C1D4 before administering the full dose on C1D8. The first-in-human dose was derived by integrating both in vitro and in vivo preclinical data benchmarked to teclistamab utilizing a quantitative systems pharmacology (QSP) model guided approach. The fractionated step-up dosing before administering the full dose on C1D8 was included in every cohort preemptively to minimize the potential cytokine release syndrome (CRS) risk. The study will follow a rapid titration single patient dose escalation design until the completion of cohort 3 or until one of the safety conversion criteria are met, whichever comes first, after which the design will be converted to a conventional 3+3 dose escalation. The primary outcome measure is the number of DLTs during the first 28 days after the first study treatment (ie, Cycle 1) in each cohort. Once a potential safe and efficacious dose range is identified, the Part 2 expansion will start enrollment in two arms at two putative recommended Part 2 doses with 1:1 randomization with at least 20 patients per arm (FDA Project Optimus). The primary objective of Part 2 is to confirm safety and to select the recommended Phase 2 dose (RP2D). Secondary endpoints include PK parameters, immunogenicity incidence, ORR, CRR and DOR based on IMWG criteria. Exploratory endpoints include levels of cytokines, chemokines, sCD38, sBCMA, APRIL and BAFF in peripheral blood, immunophenotyping in peripheral blood and bone marrow, and MRD negative rate. Approximately 40 patients will

be enrolled in Part 1 at sites in Australia, France and the United States. A total of approximately 40 evaluable patients will be enrolled in Part 2. The study is currently open for enrollment (Clinicaltrials.gov identifier: NCT05862012).

Disclosures Menon: *Ichnos Sciences:* Current Employment. **Garton:** *Ichnos Sciences:* Current Employment. **Wolff:** *Ichnos Sciences Inc.:* Current Employment. **Shah:** *Ichnos Sciences:* Current Employment. **Duchesne:** *Ichnos Sciences:* Current Employment. **Pihlgren:** *Ichnos Sciences Biotherapeutics SA:* Current Employment; *AC Immune SA:* Current equity holder in publicly-traded company. **Koch-Olsen:** *Ichnos Sciences Inc.:* Current Employment. **Drake:** *Ichnos Sciences Biotherapeutics SA:* Current Employment. **Perro:** *Ichnos Sciences Biotherapeutics SA:* Current Employment. **Zhukovsky:** *Ichnos Sciences Inc.:* Current Employment. **Pacaud:** *Ichnos Sciences Inc.:* Current Employment, Current holder of *stock options* in a privately-held company. **Konto:** *Ichnos Sciences:* Current Employment.

Figure 1: Trial design of ISB 2001



n = number of subjects.
R = randomization.
X = The dose level in the accelerated titration design at which the conversion criteria is met.
DLT = dose-limiting toxicity; MFD = maximum feasible dose; MM = multiple myeloma; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose; R/R = relapsed/refractory.
* Dose levels to be determined.

Figure 1

https://doi.org/10.1182/blood-2023-187106