P871 ISB 1442, A FIRST-IN-CLASS CD38 AND CD47 BISPECIFIC ANTIBODY INNATE CELL MODULATOR FOR THE TREATMENT OF CD38 POSITIVE HEMATOLOGICAL MALIGNANCIES

**Topic:** 13. Myeloma and other monoclonal gammopathies - Biology & Translational Research

Camille Grandclement1, Carole Estoppey1, Elie Dheilly1, Maria Panagopoulou1, Evangelia Martini1, Valentina Labanca1, Stefania De Angelis1, Julia Frei1, Adam Drake1, Alain Rubod1, Girish Gudi2, Venkatesha Udupa3, Jeppe Koch Olsen4, Roberto Giovannini4, Marie Agnes Doucey1, Eric Feldman2, Cyril Konto2, Ankita Srivastava1, Mario Perro3, Stefano Sammicheli1

1 Ichnos Sciences, Epalinges, Switzerland; 2 Ichnos Sciences, New York, United States; 3 Glenmark Pharmaceuticals Limited, Mahape, India; 4 Ichnos Sciences, La Chaux-de-Fonds, Switzerland

**Background:**

ISB 1442 is a first in class 2+1 biparatopic bispecific antibody targeting CD38 x CD47 using the BEAT® 2.0 (Bispecific Engagement by Antibodies based on the TCR) platform. The CD38 binding arm consists of bi-paratopic Fabs that strongly bind to CD38 in two different epitopes on tumor cells and do not functionally compete with daratumumab. The anti-CD47 arm comprises a single Fab arm designed to block the interaction between CD47 and the signal-regulatory protein alpha (SIRPα) receptor present on phagocytes (including macrophages, monocytes and dendritic cells). With this design, the high affinity anti-CD38 Fab arms preferentially drive binding to tumor cells and enables blocking of proximal CD47 receptors on the same cell via avidity-induced binding. The Fc portion of ISB 1442 is engineered to enhance antibody dependent cell phagocytosis (ADCP), antibody dependent cell cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).

**Aims:**

ISB 1442 was developed for the treatment of hematologic malignancies that express CD38, including multiple myeloma (MM), acute myeloid leukemia (AML), and T-acute lymphoblastic leukemia (T-ALL), with the intention of overcoming mechanisms of resistance to CD38-targeted therapies such as daratumumab and isatuximab, and minimizing hemagglutination/hemolysis on red blood cell (RBC) observed with anti-CD47 monoclonal antibodies (mAb) such as magrolimab.

**Methods:**

ISB 1442 was tested for its capacity in vitro to induce ADCP, ADCC and CDC relative to daratumumab and magrolimab across a broad range of MM, AML and T-ALL cell lines expressing different levels of CD38 and CD47. To assess the complex mechanisms of action of ISB 1442 in a single system, a multiple mode of action of killing (MMoAK) assay was established to allow for simultaneous killing by natural killer cells (ADCC), autologous macrophages (ADCP), and complement from human serum (CDC). In vivo, ISB 1442 was assessed in a therapeutic model of subcutaneously established Raji tumor xenograft in CB17/SCID mice compared to daratumumab and magrolimab. On-target specificity was evaluated in vitro in human and monkey whole blood assays.

**Results:**

In vitro, ISB 1442 exhibited higher killing potency compared to daratumumab across a range of CD38-expressing MM, AML and T-ALL tumor cells. Additionally, ISB 1442 showed in vitro tumor killing potency through phagocytosis comparable to magrolimab, acting mostly through ADCP. In the CDC, ADCC and MMoAK assays, ISB 1442 exhibited tumor cell killing that was twice as high as daratumumab in MM cell lines.

In vivo, ISB 1442 induced higher tumor growth inhibition than daratumumab and comparable tumor regression to...
magrolimab.

ISB 1442 did not cause any detectable hemolysis, RBC depletion or platelet aggregation and showed markedly lower hemagglutination relative to magrolimab, suggesting a more favorable on-target specificity profile in humans. In monkeys, ISB 1442 showed more pronounced binding on RBC than magrolimab due to higher expression of CD38, suggesting that monkey is a more sensitive species than human for toxicological evaluation of CD38-targeted therapies.

Summary/Conclusion:

In summary, we report a novel approach for the treatment for CD38 positive hematologic malignancies by co-targeting CD38 and CD47 using a first in class multispecific antibody. Based on its unique design and multiple mechanisms of action, ISB 1442 is anticipated to enhance antitumor activity in patients relative to anti-CD38 mAbs by overcoming primary and acquired tumor escape mechanisms of resistance.