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A Phase 1a/1b, first-in-human, dose-escalation study to evaluate the safety, tolerability, and efficacy of IOS-1002, a LILRB1, LILRB2, and KIR3DL1 targeting HLA-based fusion protein administered alone and in combination with Pembrolizumab in patients with advanced solid tumors.

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Background

IOS-1002 is a recombinant homodimer of the human leukocyte antigen B57 free heavy chain linked to a human IgG4 Fc backbone associated with human β2 macroglobulin (Fig. 1). The binding of IOS-1002 to LILRB1, LILRB2, and KIR3DL1 receptors blocks the interaction of endogenous ligands such as HLA-G. Through this mechanism, IOS-1002 enhances the immune response of diverse sets of both innate and adaptive immune cells and leads to tumor cell killing (Fig. 2). The anti-tumor effect is enhanced by combining IOS-1002 with a PD1 checkpoint inhibitor in pre-clinical models. The current first-in-human study (FIH) will evaluate the safety and efficacy of IOS-1002 as monotherapy and in combination with Pembrolizumab.

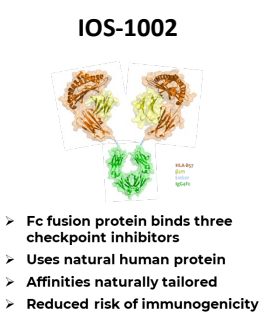


Fig. 1: IOS-1002 Compound

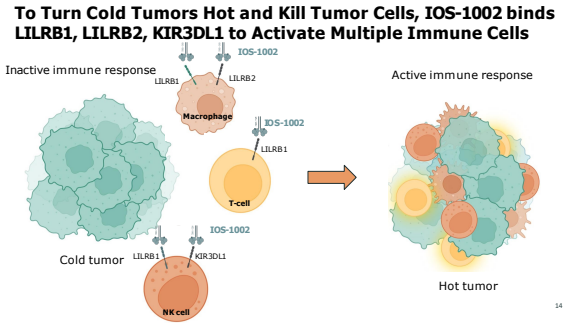
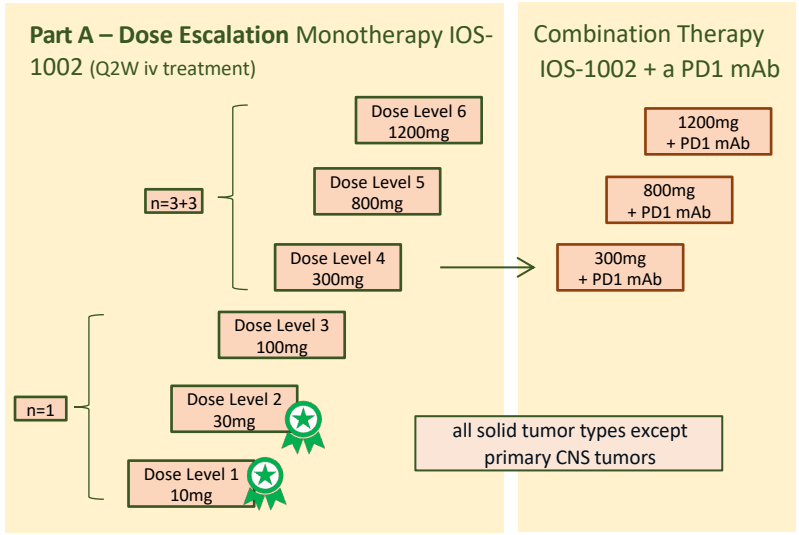


Fig. 2: IOS-1002 Mode of Action targeting LILRB1/2 and KIR3DL1 receptors on macrophages, NK- and T-cells leading to immune activation.

Study Design

Guided by the dose-limiting toxicities (DLTs) observed, an accelerated dose titration design is used for the first 3 dose levels followed by a 3+3 dose escalation. The DLT period is defined as 4 weeks following cycle 1 day 1 infusion.



Following the toxicity and activity profile observed in part A, a tumor-specific cohort expansion study in up to 6 potential disease entities with 20 patients per cohort will be initiated (Part B and Part C) at MTD / MAD or alternate doses. Dose level 1 and 2 have been successfully completed ( ).

Part B – Dose Expansion

Monotherapy IOS-1002 (Q2W iv treatment)

- **Cohort 1 (n=20)** Metastatic / recurrent NSCLC 2L
- **Cohort 2 (n=20)** Metastatic / recurrent colon / pancreatic / gastric cancer
- **Cohort 3 (n=20)** Metastatic / recurrent gynaecologic / breast cancer

Part C – Dose Expansion

Combination Therapy IOS-1002 + Pembrolizumab

- **Cohort 4 (n=20)** Metastatic / recurrent NSCLC
- **Cohort 5 (n=20)** Metastatic / recurrent ovarian cancer
- **Cohort 6 (n=20)** Metastatic / recurrent H&N or GU or GI cancer

Depending on the disease entity and line of treatment, the combination cohort will include PD-1/PD-L1 treatment naïve, pre-exposed and refractory patients, respectively.

Key Message

- The study is actively enrolling patients with advanced solid organ tumors
- Dose escalation for monotherapy started at 10 mg flat dose
- The combination therapy cohorts with standard dose Pembrolizumab will open once the dose level of 300 mg IOS-1002 has been cleared

Objectives

Primary

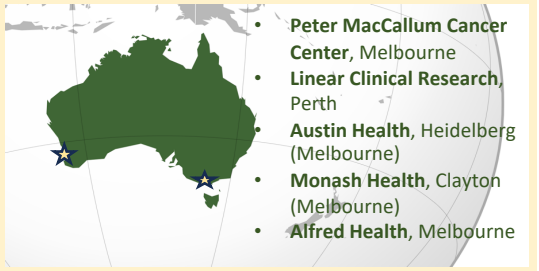
- Safety
- Tolerability
- DLT / MAD / RP2D

Secondary

- Preliminary antitumor activity of IOS-1002 and in combination with the Pembrolizumab
- PK of IOS-1002 alone and in combination with Pembrolizumab.
- Immunogenicity of IOS-1002 alone and in combination with Pembrolizumab.

Study Sites

Part A is conducted in Australia only. For parts B and C, additional sites in South Korea are planned.



The corresponding author has no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript. CB, CR, MG and AR are employees of the company and hold shares. We certify that the submission is original work and is not under review at any other publication.

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