A First-In-Human Phase 1 Trial of IO-108, An Antagonist Antibody Targeting LILRB2 (ILT4), as Monotherapy and in Combination with Pembrolizumab in Adult Patients with Advanced Relapsed or Refractory Solid Tumors

AACR Poster # CT209

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1 Background and Rationale

Cancer immunotherapy has entered the mainstream with approval of T-cell checkpoint inhibitors. However, most patients with advanced solid tumors do not derive benefit, or relapse after T-cell checkpoint blockade. Myeloid checkpoint inhibition is a new approach to cancer immunotherapy.

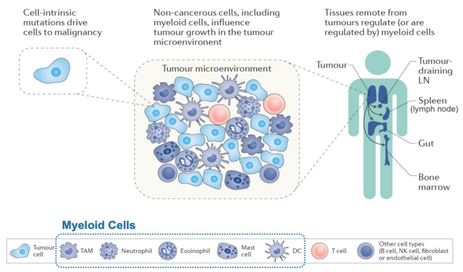
LILRB2 is primarily expressed by myeloid cells and its expression in tumors is associated with high macrophage infiltration. Several LILRB2 ligands (HLA-G, ANGPTL2, and SEMA4A) are known to contribute to the immune suppressive microenvironment of solid tumors. Blockade of the LILRB2 pathway has the potential to reactivate or enhance anti-tumor T-cell immune responses.

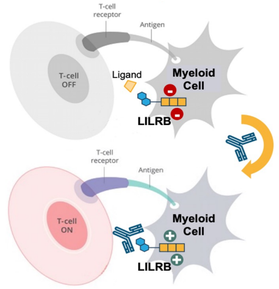
IO-108 is a IgG4 monoclonal antibody that specifically binds LILRB2 to block ligand interaction and activation of LILRB2. In vitro, IO-108 treatment of primary immune cells results in increased pro inflammatory responses and enhanced antigen presenting cell phenotypes. A Good Laboratory Practice repeat-dose, 15-day toxicology study in cynomolgus monkeys at 0 (control), 1, 10, or 100 mg/kg/dose administered intravenously once weekly for a total of 3 doses showed that IO-108 was well tolerated at all dose levels, with only non-statistically significant reduction of thyroid gland weight. No-observed-adverse-effect-level (NOAEL) of 100 mg/kg provided a sufficient safety margin for the IO-108 starting dose of 60 mg, which was derived using a MABEL (minimum anticipated biological effect level) approach.

2 Myeloid Checkpoint Inhibition Through LILRB2

Targeting Myeloid Cells to Overcome Limitations of Current Treatment Options

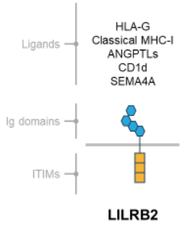
Myeloid cells modulate key cancer-associated activities, including **immune evasion**, and affect virtually all types of cancer therapy [1]





Blocking myeloid checkpoints will:
- Increase antigen presentation
- Reprogram myeloid phenotypes
- Release proinflammatory cytokines
- Attract and activate effector cells (T, NK, etc.)

LILRB2 Activation in Myeloid Cells Promotes Immune Inhibitory Signals [2,3,4,5,6,7]

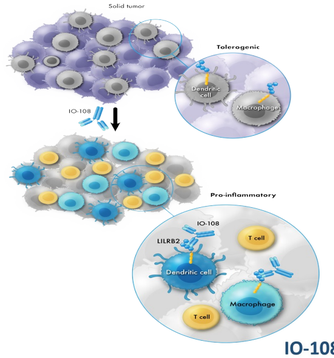


- **Mostly expressed on myeloid cells** (monocyte, DC, macrophage, neutrophil)
- Receptor with **dual immune inhibitory activity**
  1. Inhibits Ca++ signaling through SHP-1 recruitment
  2. Competes with CD8 for MHC class I binding
- **Promotes tumor immune evasion** via interaction of LILRB2 with HLA-G and other ligands
- **LILRB2 expression is a contributing factor to anti-PD1 resistance,** as demonstrated by LILRB2 blockade in clinic

ITIM = immunoreceptor tyrosine-based inhibition motif

3 IO-108 Mechanism of Action

IO-108 (Anti-LILRB2): **Re-Programs Myeloid Cells** to Activate T Cells



Therapeutic Mechanism of Action

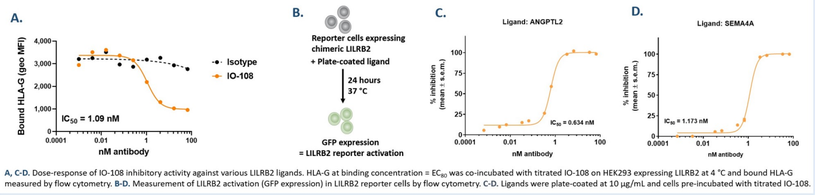
LILRB2 blockade causes **re-programming** of immune suppressive myeloid cells to pro-inflammatory cells in the tumor microenvironment leading to activation of T cells

LILRB2 (ILT4) Antagonist Antibody

Specific, high affinity binding to LILRB2 and blocks binding of LILRB2 to multiple cancer-relevant ligands (HLA-G, ANGPTL2, SEMA4A, CD1d)

IO-108 is a potent antagonist of LILRB2

Competitive binding with HLA-G | **Inhibition of LILRB2 reporter cell activation**



A, C-D. Dose-response of IO-108 inhibitory activity against various LILRB2 ligands. HLA-G at binding concentration = EC_{80}, was co-incubated with titrated IO-108 on HEK293 expressing LILRB2 at 4 °C and bound HLA-G measured by flow cytometry. B-D. Measurement of LILRB2 activation (GFP expression) in LILRB2 reporter cells by flow cytometry. C-D. Ligands were plate-coated at 10 µg/mL and cells pre-incubated with titrated IO-108.

4 Phase 1 Clinical Study Objectives

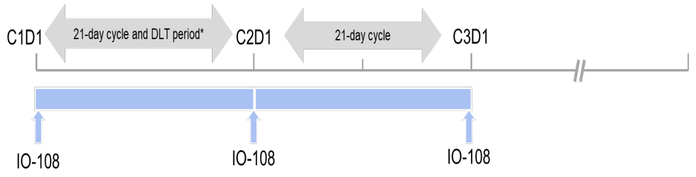
Primary
- To assess safety and tolerability at increasing dose levels of IO-108 in successive cohorts of participants with advanced relapsed or refractory solid tumors in order to estimate the maximum tolerated dose (MTD) or maximum administered dose (MAD) as monotherapy and in combination with pembrolizumab, and select the recommended Phase 2 dose (RP2D)

Secondary
- To characterize the PK of IO-108
- To evaluate the immunogenicity of IO-108 and its impact on other endpoints
- To evaluate preliminary anti-tumor activity of IO-108

Exploratory
- To characterize potential PD effects of IO-108 in the periphery and tumor microenvironment

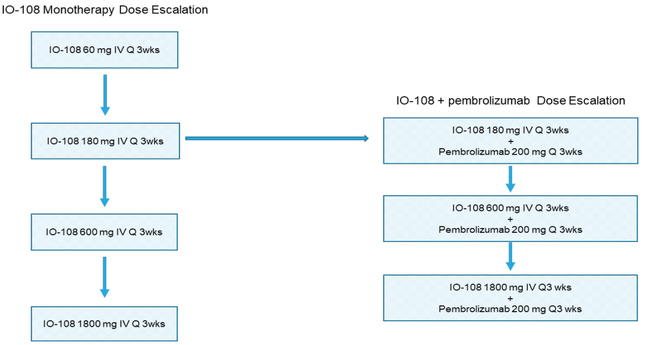
5 Phase 1 Study Design

This clinical trial is a first-in-human, Phase 1, multicenter, open-label, dose-escalation, safety, pharmacokinetic (PK), and pharmacodynamic evaluation of intravenously administered IO-108, both as monotherapy and in combination with pembrolizumab, in adult patients with solid tumors that have failed standard of care therapies. It is estimated that up to 36 patients will be enrolled in the dose escalation portion of the study. IO-108 will be administered every 21 days, with a dose-limiting toxicity (DLT) evaluation period of 21 days. Patients will be enrolled into sequential cohorts and treated with increasing doses of IO-108 using mTPI (modified Toxicity Probability Interval) method. Safety, PK, and clinical activity will be evaluated on an ongoing basis.



Combination therapy initiated after the first two dose levels in monotherapy are cleared

6 IO-108 Phase 1 Dose Escalation



7 Key Eligibility

- **Patients must be ≥18.**
- **Has any histologically- or cytologically confirmed advanced/metastatic solid tumor by pathology report and has received, has been intolerant to, or has been ineligible for standard systemic therapy known to confer clinical benefit. Solid tumors of any type are eligible for enrollment. Patients with asymptomatic central nervous system (CNS) disease may be enrolled.**
- **Patient has measurable disease by Response Evaluation in Solid Tumors version 1.1 (RECIST 1.1) as assessed by local site.**

8 Biomarker Plan

- **IO-108 target engagement by determining LILRB2 receptor occupancy in peripheral blood myeloid cells**
- **Potential PD effects of IO-108 monotherapy and IO-108 + pembrolizumab in the TME and periphery:**
  - **Myeloid cell phenotyping**
  - **T cell profiling**
  - **Gene expression profiles of tumor tissues**
- **Correlations between baseline LILRB2 expression and tumor gene expression profile with safety, clinical activity, PK and PD of IO-108 monotherapy and IO-108 + pembrolizumab**

9 Summary

- **Myeloid checkpoint inhibition through blockade of the LILRB2 pathway has the potential to reactivate or enhance anti-tumor T cell immune responses.**
- **IO-108 is a fully human IgG4 anti-LILRB2 antibody displaying high affinity, specificity and potent antagonistic activity that promotes pro-inflammatory phenotype and differentiation of myeloid cells, enhances immune cell activation and alleviates myeloid cell suppressive activity**
- **This is a first-in-human study of IO-108 in solid tumor patients as monotherapy or in combination with pembrolizumab to evaluate safety/tolerability and determine the MTD/RP2D**
- **Key eligibility include patients ≥18 years with confirmed advanced/metastatic solid tumors of any type who have received or are ineligible for standard of care therapies**
- **The trial is continuing as planned. As of March 2022, DLT has not been reached.**

References:
1. **Adapted from Nat Rev Cancer. 16:447-62 (2016)**
2. **Siu et al., Clin. Cancer Res., 2021**
3. **Colonna et al., Journal Immunol., 1998**
4. **Fanger et al., Eur. J. Immunol., 1998**
5. **Chang et al., Nat Immunol., 2002**
6. **Shiroishi et al., PNAS, 2003**
7. **Chen et al., JCI, 2018**