BioInvent

Trial-in-Progress 1073

A phase 1/2a first in-human phase 1 study of BI-1910, a monoclonal antibody agonistic to TNFR2, as a ainge agent and in combination with pembrolizumab in subjects with advanced solid tumors

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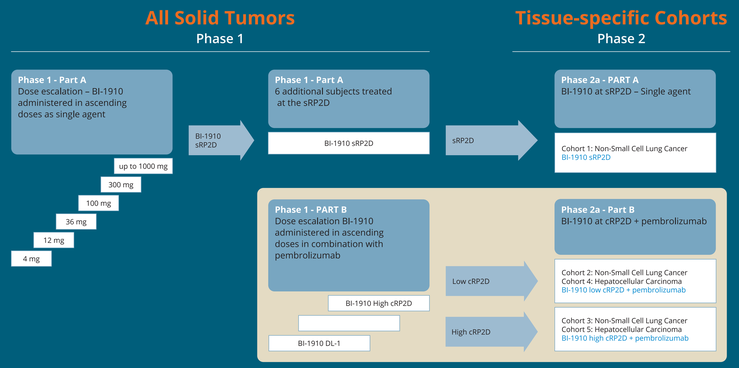
Study 22-BI-1910-01 explores the safety and preliminary antitumor activity of a novel agonist to TNFR2

BI-1910 has demonstrated robust T-cell mediated antitumor activity in the preclinical setting, with additive effects after combination with anti-PD-1 therapy. Monotherapy dose escalation started in December 2023, and enrollment into first cohort with pembrolizumab co-treatment is expected to start in Q4 2024.

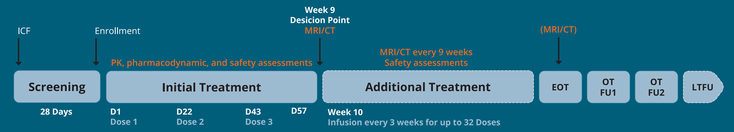


Study Treatment Design

BI-1910 will be administered as IV infusion once every 3 weeks (Q3W).

Pembrolizumab (Keytruda®) will be administered as 400 mg IV infusion once every 6 weeks (Q6W).

A response assessment will be made at every 9 weeks, and patients with stable disease or an objective response may continue treatment for up until 2 years.



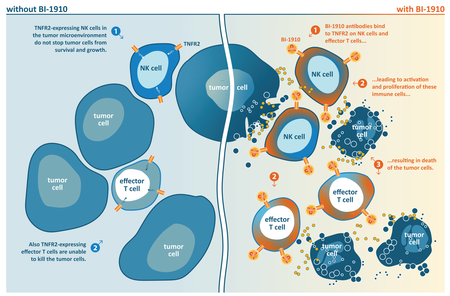
CT = Computed Tomography / EOT = End of Treatment / ICF = Informed Consent Form / MRI = Magnetic Resonance Imaging
OTFU = Off Treatment Follow Up / LTFU = Long-term Follow-up / PK=Pharmacokinetics

Rationale for Developing BI-1910

TNFR2 is a novel promising target for cancer immune therapy, and TNFR2 has been proposed as a costimulatory receptor for T cell activation. Early clinical development of ligand-blocking mAbs targeting TNFR2, such as BI-1808, indicate that modulating the pathway may lead to clinical responses with favourable tolerability.

We have developed BI-1910, a TNFR2 targeting agonist. BI-1910 does not block the interaction between TNFR2 and its ligand TNF-α. Non-clinical in vivo data demonstrate enhancement of functional activity of TNFR2-expressing lymphocytes, including CD8+ and CD4+ T-cells, as well as NK cells, resulting in tumor regression and ultimately immune rejection.

Furthermore, BI-1910 show additive effects with anti–PD-1 therapy in several murine tumor models.



Background

Tumor necrosis factor (TNF) is a potent pro-inflammatory cytokine known to induce an inflammatory response and cell death, and anti-TNF drugs are used to treat autoimmune diseases. TNF has two receptors: TNFR1, which is broadly expressed on many different cell types, and TNFR2, with expression largely restricted to immune cells. TNFR2 is a type I transmembrane protein with typically high expression in myeloid cells and specific T cell subsets. Macrophages and T regs constitutively express TNFR2. In effector T cells TNFR2 expression is upregulated after T cell receptor stimulation. The role of TNFR2 in inflammation is unclear, with both proinflammatory and immunoregulatory roles postulated.

TNFR2 is important for T reg survival, while simultaneously acting as a potent costimulatory molecule on CD8+ T cells thereby promoting inflammatory activity. Given the costimulatory functions of TNFR2 in different immune cells, TNFR2 has in recent years been suggested as a promising novel target for anticancer treatment. We are developing BI-1910, an agonistic human IgG2 mAb targeting TNFR2. BI-1910 agonizes T cells and mediates CD4+ and CD8+ T cell activation. It binds human TNFR2 selectively but does not block the interaction between the receptor and its ligand, TNF-α. BI-1910 combined with anti-PD-1 showed additive anti-tumor effect in several murine tumor models including B16 melanoma cancer, MC38 colon cancer, and CT26 colon cancer, providing rationale to clinically evaluate this antibody in combination with pembrolizumab.

Trial Design

This is a Phase 1/2a dose escalation clinical trial of BI-1910, as single agent and in combination with pembrolizumab, in subjects with advanced/metastatic solid tumors who progressed after standard therapy. It aims to establish safety/tolerability profile, pharmacokinetics, pharmacodynamics and preliminary efficacy of BI-1910 as monotherapy and in combination. Phase 1 dose escalation is guided by a BLRM design, with flexibility in cohort size based on emerging data. The Phase 1/2a study is expected to enroll a total of approximately 180 patients.

Phase 2a will be performed in advanced/metastatic NSCLC and HCC patients in parallel cohorts. Safety and efficacy of BI-1910 when combined with pembrolizumab will be evaluated at two well separated dose levels for dose optimization.

Study Objectives

The primary objectives of Study 22-BI-1910-01 is to assess the safety and tolerability profile of BI-1910 as a single agent and in combination with pembrolizumab in subjects with advanced solid tumors. In addition the trial intend to asess any preliminary efficacy, and to define dose level(s) to explore for future studies.

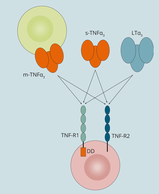
In addition to safety, tolerability and tumor response information, the study will generate data on pharmacokinetics, receptor occupancy, cytokine and immune cell response. Selection of dose levels will be made based on an integrated pharmacometric evaluation of all data available, to maximize the benefit-risk of treatment with BI-1910 as single agent or in combination with pembrolizumab.

Forward Looking Plans

Single agent dose escalation has reached its fifth planned cohort, and is expected to complete by year-end 2024, leading to opening Phase 2a with BI-1910 monotherapy in NSCLC in first half of 2025. Phase 1 Part B dose escalation of BI-1910 in combination with pembrolizumab is expected to commence Q4 2024.

About TNFR2

- **High expression on T regs, activated/memory CD8+ T cells, NK cells, also DC's and several myeloid cells, e.g. monocytes**
  - Shares ligands with TNFR1
  - Membrane bound TNF-α binds and signals through TNFR2
  - Soluble TNF-α and LT-α primarily signals through TNFR1
- **TNFR2 bind soluble TNF-α and LT-α but the signaling efficacy of this bindings is not clear**
- **TNFR2 has been shown to be critical for T reg proliferation and survival**
- **Proposed as a co-stimulatory factor for T cells proliferation and activation (similar to e.g. OX40 or 41BB)**



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ClinicalTrials.gov ID: NCT06205706

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA