TIG-007: Study Of EOS884448/GSK4428859A Alone, and in Combination with Iberdomide with or without Dexamethasone, in Participants With Relapsed or Refractory Multiple Myeloma.

Abstract #152395

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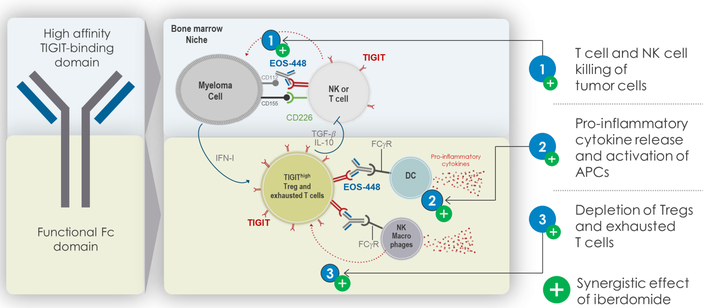
Background and Rationale

- Multiple Myeloma (MM) is the third most common blood cancer and remains largely incurable despite significant progress in therapeutic approaches.
- The tumor microenvironment (TME), including immunosuppressive T-regulatory (Treg) cells, plays an important role in sustaining the progression and immune evasion of MM cells.
- T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is an inhibitory immune checkpoint receptor expressed on subsets of T cells and NK cells.
- In multiple myeloma, TIGIT expression increases as the disease progresses and correlates with defective T cell effector functions[1] in parallel to an imbalance with immunosuppressive T-regulatory (Treg) cells [2,3].
- Higher TIGIT expression was observed in MM bone marrow CD8+ T cells in mice and patients compared to other immune checkpoint inhibitors, including PD-1, TIM-3, LAG-3, or CTLA-4 [1,4,5]
- EOS884448/GSK4428859A (EOS-448) is a potent and highly selective fully human antagonist IgG1 antibody targeting TIGIT. Preclinically, in murine MM models, an anti-TIGIT Ab elicits superior anti-tumor immune responses compared to anti-PD1 mAbs [1].
- In MM models, an Fc-enabled a-TIGIT Ab elicits effective control of MM disease progression, while an Fc-disabled version is inactive. In addition, an Fc-enabled a-TIGIT mAb provides significant synergistic activity when combined with an Immunomodulatory imide drug (IMiD) **(Minnie, SA. et al, Abstract 154087).**
- Iberdomide (also known as CC-220) is a novel potent cereblon (CRBN) E3 ligase modulating compound (CELMoD coumpond), the primary cellular target of imid agent that regulates degradation of multiple transcription factors within immune cells. In parallel with the direct MM cells cytotoxicity, cereblon modulation also leads to activation of T-cells and NK-Cells, stimulates antigen presenting cells (APCs) and increases antibody mediated cytotoxicity and immune response[6].
- Iberdomide in combination with dexamethasone or other antimyeloma agents has shown notable clinical activity and acceptable tolerability in heavily pre-treated patients with relapsed or refractory multiple myeloma (RRMM), including those refractory to prior imid agents[7].
- Given the dominant role of TIGIT and Tregs in the immune suppression associated with MM, we hypothesize that TIGIT is an ideal checkpoint to target in MM with an Fc-enabled monoclonal antibody, either alone or in combination with a CELMoD agent to further disrupt the TME and generate a long-lasting antimyeloma immune response.

Proposed Mechanism of Action of EOS-448 ± iberdomide in MM

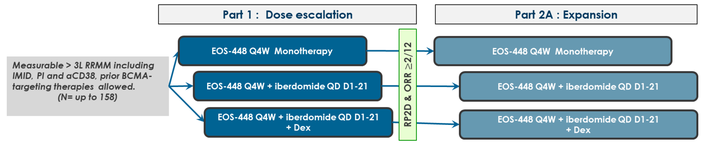


Study

Design

- This is a phase I/II, open-label, multicenter, dose-escalation and expansion study to assess the safety, tolerability and preliminary activity of EOS-448 as monotherapy and in combination with iberdomide with or without dexamethasone in adults with RRMM, who have progressed after prior treatment with IMiD, PI and anti-CD38.
- In Part 1, the safety and tolerability of escalating doses of EOS-448 as monotherapy and in combination with iberdomide with or without dexamethasone will be assessed in cohorts of up to 12 participants to identify the recommended phase II dose (RP2D) in each of the 3 treatment arms.
- In Part 2, the safety, tolerability and activity at the RP2D will be assessed in each of the treatment arms which demonstrate response in at least 2 out of 12 participants in Part 1.

Study Schematic



Objectives And Endpoints

Primary

- Safety and tolerability
  - AEs
  - Laboratory abnormalities
- Recommended Phase 2 dose
  - Dose-limiting toxicities
  - Dose-level safety PK/PD and activity
- Antitumor Efficacy (Expansion)
  - Overall response rate assessed according to the International Myeloma Working Group (IMWG) Uniform Response Criteria

Secondary

- Safety and Tolerability at RP2D (Expansion)
- Antitumor activity (All Parts)
  - Overall response rate assessed according to the International Myeloma Working Group (IMWG) Uniform Response Criteria, Progression-free survival, duration of response and time to response
- PK and Immunogenicity

Eligibility Criteria

Key Inclusion Criteria

- Age ≥ 18 yr
- Patients with measurable MM (IMWG)
- R/R > 3L including IMiDs, Proteasome inhibitors or Anti-CD38, prior BCMA-targeting therapies allowed
- Adequate organ and hematopoietic function
- ECOG 0-2
- Written ICF

Key Exclusion Criteria

- Prior chemotherapy, targeted small-molecule therapy, immunotherapy, treatment with biologic agents, or use of other investigational anticancer therapy within 28 days before the first dose of study treatment
- Prior discontinuation of immunotherapy for life-threatening toxicity.
- Active graft versus host disease after allogeneic stem cell transplantation
- Clinical evidence of central nervous system (CNS) or pulmonary leukostasis, or disseminated intravascular coagulation
- Uncontrolled active infection requiring systemic antibiotics, antivirals, or antifungals within 14 days prior to first dose
- Active, unstable cardiovascular dysfunction

Assessments

- Safety assessments will include the incidence of adverse events, clinical laboratory tests, vital signs, physical examinations, ECGs and cardiac function tests.
- Blood samples for EOS-448 and iberdomide pharmacokinetic analysis will be collected from participants
- Systemic and tumor-based pharmacodynamic effects of EOS-448 with or without iberdomide ± dexamethasone will be evaluated.
- Efficacy assessment will include measurement of myeloma protein in serum and urine, serum-calcium corrected for albumin, bone marrow examination, skeletal survey and documentation of extramedullary plasmacytoma.

Conclusion

- This study is aiming to assess if EOS-448 alone or in combination with iberdomide with or without dexamethasone may provide a therapeutic opportunity to amplify myeloma-specific T-cell anti-tumor responses in difficult to treat RRMM patients previously exposed to IMiDs, proteasome inhibitors (PIs) and anti-CD38.
- The study plan is to enroll participants in North America and Europe.

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Disclosures
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