This is the first study evaluating the mechanism of action of the clinical-stage B-cell Maturation Antigen (BCMA) is a cell surface receptor highly expressed in plasma cell malignancies. In line with engagement of the host immune system, combinations with anti-BCMA monoclonal antibody (aka., belantamab or GSK2857914) conjugates to monomethyl auristatin E (MMAE)-containing ADCs can kill tumor cells, either by apoptosis after cytotoxic drug is released inside the cells or by antibody-dependent cellular cytotoxicity (ADCC).  

**Background**

● Multiple myeloma (MM) is the second most common hematological malignancy and remains an incurable disease. Novel targeted therapies are urgently needed.

● B-Cell Maturation Antigen (BCMA) is a cell surface receptor highly expressed in multiple myeloma and other B cell malignancies with a key role in plasma cell survival.

● Belantamab mafodotin or GSK2857916 is a humanized, afucosylated, IgG1 anti-BCMA monoclonal antibody (aka, belantamab or GSK2857914) conjugated to monomethyl auristatin E (MMAE)-containing ADCs can kill tumor cells, either by apoptosis after cytotoxic drug is released inside the cells or by antibody-dependent cellular cytotoxicity (ADCC).

**Aims**

● MM&F is a member of the deubiquitinating family of microtubule inhibitors, potent anti-tumor agents that can lead to immunogenic cell death (ICD), a type of cell death that stimulates host immune response. We evaluated and characterized ICD as a mechanism of action for belantamab mafodotin.

● We leveraged ICD and explored GSK2857916 immune-modulatory activities as single agent and in combination with immune-modulators, in particular OX40, in an immune-competent mouse model.

**Results**

Figure 1. GSK2857916 Induces Hallmarks of Immunogenic Cell Death in EL4-BCMA Cells

Treatment of EL4-BCMA cells with GSK2857916 leads to ICD as measured by cell surface expression of calreticulin and HSP90 (A) and increased secretion of calreticulin (B) HSP90 (C), and HSPB (D) Mice or no effects were observed using IgG1 MAF or un conjugated antibody (1541) controls.

Figure 2. Syngeneic EL4-hBCMA T cell Lymphoma Model Development & Characterization

PD changes following treatment with GSK2857916 in the EL4-hBCMA model. Mice were treated with 2 doses of GSK2857916 (15 mg/kg) and tumors were harvested 24 hours after the 2nd dose. Immunophenotyping revealed significant increases in tumor infiltration of CD8 T cells and dendritic cells (A), activation markers CD86 (A), CD40, CD80 and ICOS (B), the co-stimulatory molecule CD40 (C), and cytotoxic Granzyme B (C) GSK2857916 also induced a modest but reproducible increase in membrane expression of major histocompatibility complex (MHC) class I and II molecules (A) and the type I interferon signature (B), both ICD markers. Immunohistochemistry for CD8 reactive cells (B).  

Figure 3. GSK2857916 Induces Immunogenic Cell Death in EL4-BCMA Cells

EL4-BCMA tumors were established (as in Figure 4) and animals were treated on days 1, 3, 6, 9, 13, and 16 with GSK2857916 or IgG1 MAF (ADC, red line). T cell depletion doses of anti-CD8 (100 µg/mouse) were administered on days 1, 3, 9, and 16 (Depot, blue line). Depletion of CD8+ T cells abrogated the anti-tumor activity of GSK2857916 (C & D). Depletion of CD+ T cells was verified on day 15 by flow cytometry (not shown). The numbers in the bottom right corner indicate the number of tumor free mice.

Figure 4. Anti-tumor Activity of GSK2857916 is Mediated by the Host Adaptive Immune Response and Permits Tumor Antigen Spreading

Therapeutic efficacy (left) and survival (right) in EL4-BCMA tumor-bearing mice dosed with 10 mg/kg of GSK2857916 (10 mg/kg) and tumors were harvested 48 hours after the 2nd dose. (A) GSK2857916 administered at 10 mg/kg achieved a 60% overall response rate, with a median duration of response of 14.3 months.

Figure 5. Anti-tumor Activity of GSK2857916 is MAF-dependent

Therapeutic efficacy (left) and survival (right) in EL4-BCMA tumor-bearing mice dosed with 10 mg/kg of GSK2857916 (10 mg/kg) and tumors were harvested 48 hours after the 2nd dose. (B) GSK2857916 administered at 10 mg/kg achieved a 60% overall response rate, with a median duration of response of 14.3 months.

**Conclusions**

● This is the first study evaluating the mechanism of action of the clinical-stage anti-BCMA antibody GSK2857916 in a newly-developed immune-competent EL4-BCMA mouse model.

● GSK2857916 potently delays tumor growth and promotes durable complete responses of EL4-hBCMA tumor xenografts.

● GSK2857916 anti-tumor activity is associated with increased tumor T lymphocyte and DC infiltration and activation, and is abrogated upon depletion of CD8+ T cells.

● Induction of ICD and engagement of the host immune system potentiates the anti-tumor activity of GSK2857916 in an immune-competent setting and constitutes key mechanisms of GSK2857916 activity.

● In line with an engagement of the host immune system, combinations with immune-modulatory agents such as anti-OX40 synergize with GSK2857916.

● Results from this preclinical work provide rationale to support clinical evaluation of belantamab mafodotin in combination with an anti-OX40 agonist in a planned trial (DREAMM-5).

**References**


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