The anti-BCMA Antibody-Drug Conjugate Belantamab Mafodotin (GSK2857916) Drives Immune-Mediated Anti-Tumor Responses, and in Combination with an OX40 Agonist Potentiates in vivo Activity

Abstract: GSK2857916 does not cross-react with murine BCMA. The EL4 T cell lymphoma line was engineered to express human BCMA (EL4-hBCMA). (A) Expression of BCMA on the cell surface was evaluated by flow cytometry in KCl-H929 (C), EL4 parental (G), and EL4-hBCMA (E) cells with an anti-BCMA antibody or isotype (E, EL4-hBCMA). (B) Expression of hBCMA in the EL4 cell line (red) increases 4x to GSK2857916 but not to the unmodified EL4-H929 controls, as determined by 3 day cell viability assay.

Figure 1. GSK2857916 Induces Hallmarks of Immune Cell Death and Dendritic Cell Activation in NCI-H929 Cells

Results

Treatment of NCI-H929 H929 cells with GSK2857916 (100 g/mL) induces endoplasmic reticulum (ER) stress (A) and JNK (B-D). (A) Induction of phosphorylation of the ER stress kinase PERK (pPERK). (B) Increased surface expression of calreticulin by flow cytometry and (C) secretion of HMGB1 by ELISA. Minimal or no effects were observed using control ADC (IgG-MMAF) or unmodified antibody GSK2857914 (914). Silfotrostatin (MTX) as an ER stress controller.

Figure 2. Synergic EL4-hBCMA T cell Lymphoma Model Development and Characterization

Figure 3. GSK2857916 Induces Immune Cell Death in EL4-hBCMA Cells

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

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

Figure 6. Depletion of CD8+ T Cells Abrogates GSK2857916 Anti-Tumor Activity

Figure 7. GSK2857916 Promotes Tumor Lymphocyte Infiltration and Activation

Conclusions

- This is the first study evaluating the mechanism of action of the clinical-stage BCMA-targeting ADC, GSK2857916, in a newly-developed immune-competent EL4-hBCMA mouse model.
- GSK2857916 potently delays tumor growth and promotes durable complete responses.
- 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 IC3 and engagement of the host immune system potentiates the anti-tumor activity of GSK2857916 in an immune-competent setting and constitutive key mechanisms of GSK2857916 activity.
- In line with an engagement of the host immune system, combinations with immune-modulatory agonists 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 OX40 agonist in a planned trial (DREAMM-5).

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References


Pharmacological characterization of the novel antibody-drug conjugate Belantamab mafodotin (GSK2857916) demonstrated its potent activity in vitro and in vivo, with significant antitumor effects. The antibody-drug conjugate elicits immune-mediated anti-tumor activity, which is further poteniated by combination with an OX40 agonist. These findings lay the groundwork for further clinical development of this promising immunotherapeutic agent.