Multiple myeloma (MM) is a hematological malignancy that affects plasma cells and leads to devastating clinical features. Typically, front line and relapsed/refractory MM (RRMM) treatments comprised standard care (SOC) combinations that include proteasome inhibitors (e.g., bortezomib [Bor]), immunomodulatory drugs (e.g., lenalidomide [Len] or pomalidomide [Pom]) and/or a steroid (e.g., dexamethasone [Dex]). While these therapies have significantly improved patient outcomes, the disease remains incurable and novel targeted therapies are urgently needed.1

Belantamab mafodotin (belamab, GSK2857916) is a promising candidate for the treatment of MM. In the primary analysis of the pivotal Phase 1 study GSK469325-M2 (NCT03252578), single-agent belantamab demonstrated an acceptable safety profile and rapid, deep and durable clinical responses (at a follow-up of 13 months, overall survival was 14.9 and 14.0 months and duration of response was 11 and 12.3 months in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively) in patients with heavily pretreated RRMM in the DREAMM-6 trial.2

Belantamab mafodotin targets the B-cell maturation antigen (BCMA) protein, highly expressed in MM and other B-cell malignancies. Belantamab mafodotin is an immunotoxin that consists of a humanized afucosylated anti-BCMA monoclonal antibody (GSK2857914) conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF) that enables anti-tumor activity by: 1) direct cell kill (ADC), 2) antibody-dependent cellular cytotoxicity or cellular phagocytosis (ADCC/ADCP), and 3) immunogenic cell death (ICD). Figure 1.1

To determine potential combinatorial activity, we conducted in vitro and in vivo studies of belantamab mafodotin in double and/or triple combinations with MM SOC agents (Bor, Dex, Len, or Pom) in two MM models: MOLP-8 and OPM-2.

Methods

We evaluated direct cell kill activity of GSK2857916, GSK2857914 (naked antibody without MMAF linker) and SOC agents (Len, Pom, Bor, Dex) in two human MM cell lines.

Additionally, we evaluated tumor growth inhibition and effects on survival of GSK2857916 or IgG-MMAF in combination with other combination in murine subcutaneous xenograft models using the same two MM cell lines.

Results

GSK2857916 has direct cell kill activity in OPM-2 and MOLP-8 MM cell lines compared with the naked antibody GSK2857914. The half-maximal inhibitory concentration (IC50) values were 0.5 and 1.77 µg/mL, respectively, for each cell line after a 72 h exposure to GSK2857916. Captopril was used as a positive control.

In vitro, belantamab mafodotin was found to synergize in vitro and potentiate in vivo anti-tumor activity in multiple myeloma models.

Conclusions

Belantamab mafodotin combinations with immuno-modulatory drugs (IMiDs) (e.g., Len or Pom) or Bor provided additional benefit compared with each single agent by significantly increasing tumor growth inhibition and survival in the OPM-2 model. Similar results were obtained with the MOLP-8 model, but to a lesser extent. Combining belantamab mafodotin with Dex in double or triple combinations did not provide significant added benefit compared to single agents or double combinations, respectively.

References

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