Combinations of belantamab mafodotin with lenalidomide, pomalidomide, bortezomib and/or dexamethasone synergize *in vitro* and potentiate *in vivo* anti-tumor activity in multiple myeloma

Poster No. 6711

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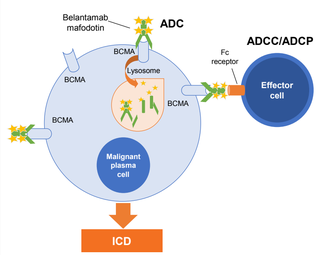
Background

- 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 comprise standard of care (SOC) combinations that include proteasome inhibitors (e.g., bortezomib [Bor]), immunostimulatory 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 (belamaf; GSK2857916) is a promising candidate for the treatment of MM. In the primary analysis of the pivotal, Phase II study DREAMM-2 (NCT03525678), single-agent belamaf 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 6.2 months in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively) in patients with heavily pretreated MM.[2,3]
- Belantamab mafodotin targets the B-cell maturation antigen (BCMA) protein, highly expressed in MM and other B cell malignancies. Belantamab mafodotin is an immunoconjugate 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**).[4]

Figure 1. Mechanisms of action of belantamab mafodotin



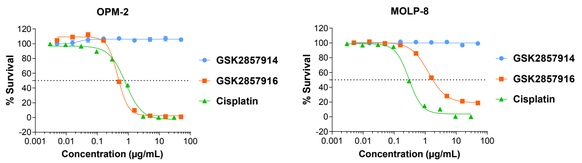
- To determine potential combinatorial activity, we conducted *in vitro* and *in vivo* studies of belantamab mafodotin in double and/or triple combinations with MM SOC agents (Bor, Dex, Len, or Pom) in two MM models: OPM-2 and MOLP-8.

Methods

- We evaluated direct cell kill activity of GSK2857916, GSK2857914 (naked antibody without MMAF toxin) 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 and SOC as single agents and/or in combination in murine subcutaneous xenograft models using the same two MM cell lines.

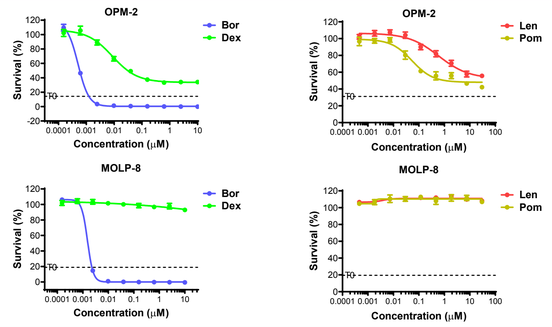
Results

Figure 2. Single-agent activity of belantamab mafodotin (GSK2857916) versus unconjugated antibody (GSK2857914) in two MM cell lines



- 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 (IC_{50}) values were 0.5 and 1.77 µg/mL, respectively, for each cell line after a 72 h exposure to GSK2857916. Cisplatin was used as a positive control.

Figure 3. Single-agent activity of bortezomib, lenalidomide, pomalidomide, and dexamethasone in two MM cell lines



- Treatment of OPM-2 cells with Bor, Dex, Len, or Pom led to direct cell kill.
- Direct cell kill of MOLP-8 cells was only observed with Bor treatment.
- IC_{50} (µM) and maximum growth inhibition (%) values are shown in **Table 1**.

Table 1. IC_{50} and maximum growth inhibition

Compound	MOLP-8		OPM-2	
	IC_{50} (µM)	Max inh.(%)	IC_{50} (µM)	Max inh.(%)
GSK2857916	1.77	81.3%	0.5	99.1%
GSK2857914	NA	0.7	NA	NA
Bor	0.002	100.6%	0.001	100.1%
Dex	NA	7.1%	0.031	65.9%
Len	NA	-8.1%	NA	44.4%
Pom	NA	-6.9%	1.110	57.8%

Figure 4. Activity of belantamab mafodotin in combination with bortezomib, lenalidomide, pomalidomide, and dexamethasone in two MM cell lines

Concentrations tested	GSK2857916 (µg/mL)	Bor (µM)	Dex (µM)	Len (µM)	Pom (µM)
MOLP-8	50, 12.5, 3.125, 0.7813, 0.1953, 0.0488, 0.0122	0.01, 0.0033, 0.0011, 0.00037, 0.00012	10, 3.333, 1.111, 0.3704, 0.1235	30, 10, 3.333, 1.111, 0.3704	30, 10, 3.333, 1.111, 0.3704
OPM-2	50, 12.5, 3.125, 0.7813, 0.1953, 0.0488, 0.0122	0.01, 0.0033, 0.0011, 0.00037, 0.00012	0.3, 0.1, 0.033, 0.011, 0.0037	10, 2, 0.4, 0.08, 0.016	10, 2, 0.4, 0.08, 0.016

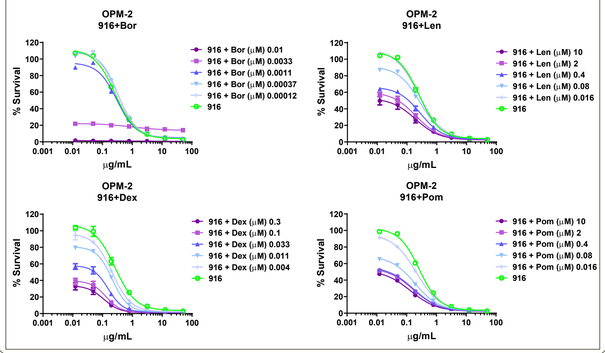
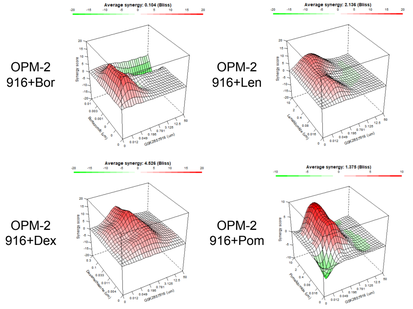


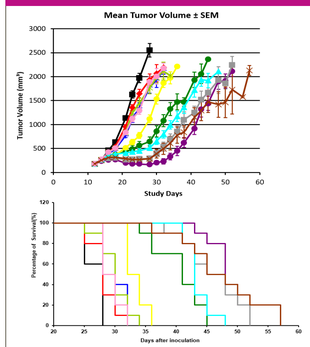
Figure 5. Activity of belantamab mafodotin in combination with bortezomib, lenalidomide, pomalidomide and dexamethasone in two MM cell lines (cont.)



- Dose response curves and Bliss 3D response surface plots show synergy between belantamab mafodotin and SOC agents in OPM-2 cells.
- Similar *in vitro* combinatorial activity was obtained in the MOLP-8 cells (not shown), but to a lesser extent.

Synergy score (Bliss) 3D response surface plots.

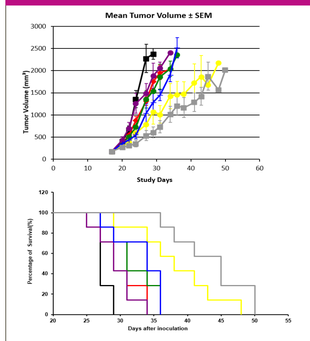
Figure 6. *In vivo* combination of belantamab mafodotin with lenalidomide, bortezomib and/or dexamethasone in the OPM-2 xenograft model



Dosing started at Day 12 after cell inoculation. 916 or IgG-MMAF (isotype control) were dosed BIW x 2 wk at 2 mg/kg. Len was dosed QDx4 x 2 wk at 10 mg/kg. Bor was dosed BIW x 2 wk at 1 mg/kg. Dex was dosed QD x 2 wk at 3 mg/kg.

BIW, twice per week; QD, once per day; IgG, immunoglobulin G.

Figure 7. *In vivo* combination of belatamab mafodotin with pomalidomide and/or dexamethasone in the OPM-2 xenograft model



Dosing started at Day 17 after cell inoculation. 916 or IgG-MMAF (isotype control) were dosed BIW x 2 wk at 2 mg/kg. Pom was dosed QD x 2 wk at 2.5 mg/kg. Dex was dosed QD x 2 wk at 3 mg/kg.

- *In vitro* combination synergy was analyzed based on the Bliss independence principle, which is appropriate when two drugs are mutually nonexclusive and/or have different mechanisms of action.[5]
- The Bliss model showed potential synergy in both cell lines with all agents to varying degrees, particularly when the combinations employed lower doses of each drug than those used when delivered as single agents.
- Belantamab mafodotin had significant tumor growth inhibition efficacy and provided a survival advantage when administered as monotherapy in the OPM-2 and MOLP-8 (not shown) MM xenograft models.
- Belantamab mafodotin combinations with immunomodulatory 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.

Conclusions

- *In vitro*, belantamab mafodotin as a single agent demonstrated direct cell kill activity in OPM-2 and MOLP-8 cells after 72 hours of exposure. Treatment of OPM-2 cells with Bor, Dex, Len or Pom also led to direct cell kill. However, direct cell kill of MOLP-8 cells was only observed with Bor treatment. Combining belantamab mafodotin with each SOC agent led to synergistic activity in both cell lines.
- *In vivo,* belantamab mafodotin induced tumor growth inhibition and provided survival advantage when administered as monotherapy to immune-compromised mice bearing OPM-2 and MOLP-8 xenografts. Combinations with Len, Pom, or Bor enhanced this anti-tumor activity and provided additional survival benefit compared to each single agent.
- The observed synergy in *in vitro* cell cultures and *in vivo* xenograft models provided preclinical evidence for combining belantamab mafodotin with IMiDs or Bor in MM. Selected combinations are currently under clinical evaluation in RRMM in the DREAMM-6 trial.

References

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