Synergistic Activity of Belantamab Mafodotin (anti-BCMA immuno-conjugate) with Nirogacestat (PF-03084014, gamma-secretase inhibitor) in BCMA-Expressing Cancer Cell Lines

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Abstract

Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation of plasma cells within the bone marrow. B-cell maturation antigen (BCMA) is a cell-surface receptor required for the survival of plasma cells and is also ubiquitously expressed on MM cells. Belantamab mafodotin (GSK2857916) is a humanized monoclonal anti-BCMA antibody, which is afucosylated and conjugated to the microtubule-disrupting agent monomethyl auristatin-F (MMAF). Upon binding to BCMA on the cell surface, belantamab mafodotin is rapidly internalized and the cytotoxic moiety (cys-mcMMAF) is released, leading to direct cell death.

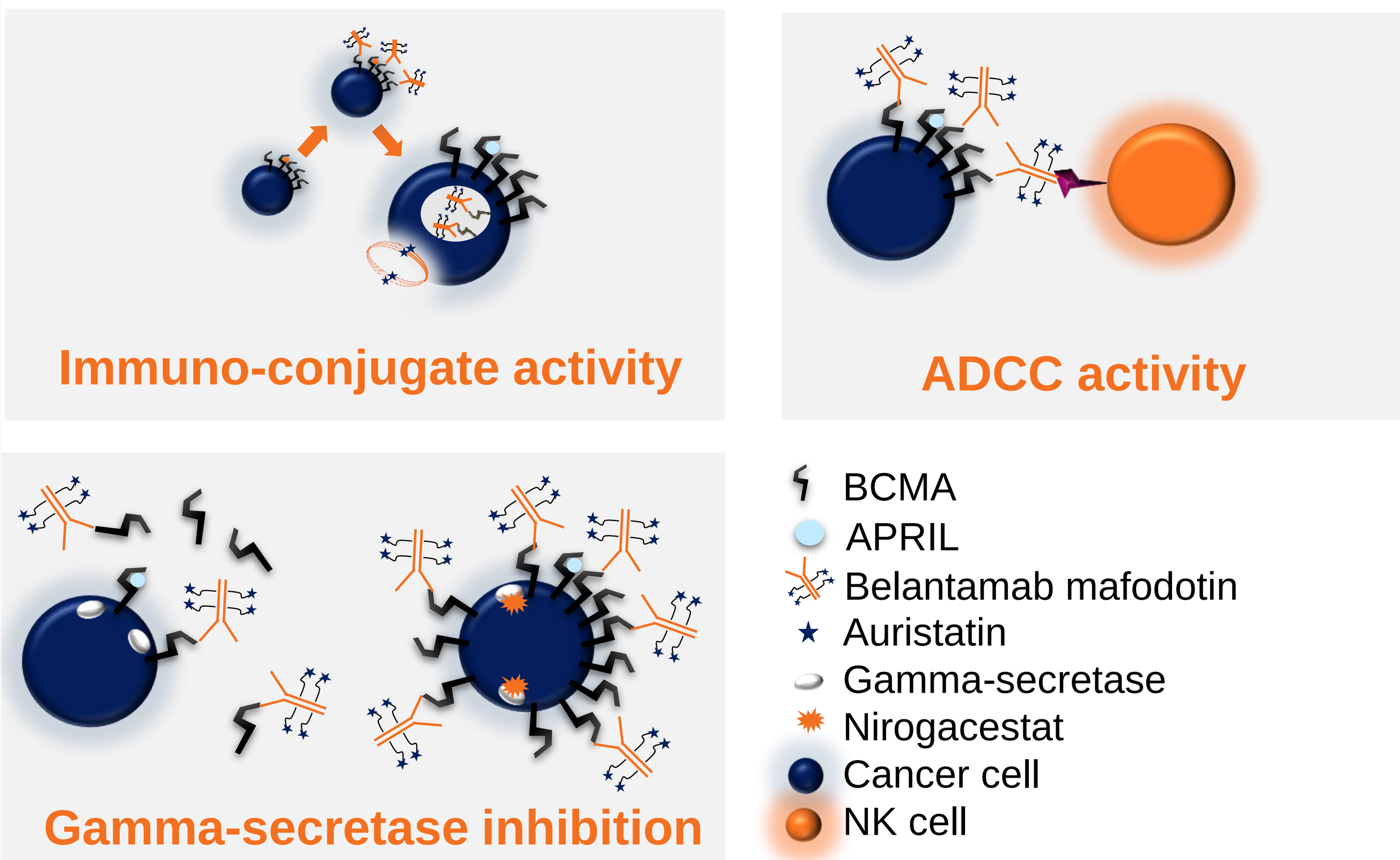
BCMA is directly shed from the plasma membrane by gamma-secretase, a type-I sheddase. In order to further enhance belantamab mafodotin activity, we sought to increase cell surface levels of BCMA by blocking shedding of BCMA with a gamma-secretase inhibitor (GSI). We then determined the effect on the activity of belantamab mafodotin by combining Belantamab mafodotin with nirogacestat (PF-03084014), a highly-selective GSI. In order to understand combination effects against immuno-conjugate activity, a 3-day proliferation assay on a panel of multiple myeloma and lymphoma cell lines with varying levels of BCMA expression was conducted. The assay showed a 50 to 3,000-fold EC50 shift in cell lines sensitive to belantamab mafodotin across multiple lymphoma cell types.

Antibody-dependent cellular cytotoxicity (ADCC) activity of Belantamab mafodotin in combination with nirogacestat was also examined. In a 24-hour ADCC Jurkat reporter assay, an EC50 shift across multiple BCMA-expressing cell lines was observed. Even cell lines with very low BCMA expression, such as Raji, showed a synergistic increase in ADCC activity in combination with nirogacestat. Cell lines that were non-responsive in the cell proliferation assay, showed activity in the ADCC assay, indicating low-expressing BCMA cell lines remain sensitive to belantamab mafodotin, alone and in combination with nirogacestat.

Synergistic effect from this preclinical work provided rationale to support clinical evaluation of belantamab mafodotin in combination with Nirogacestat in a planned clinical trial (DREAMM-5).

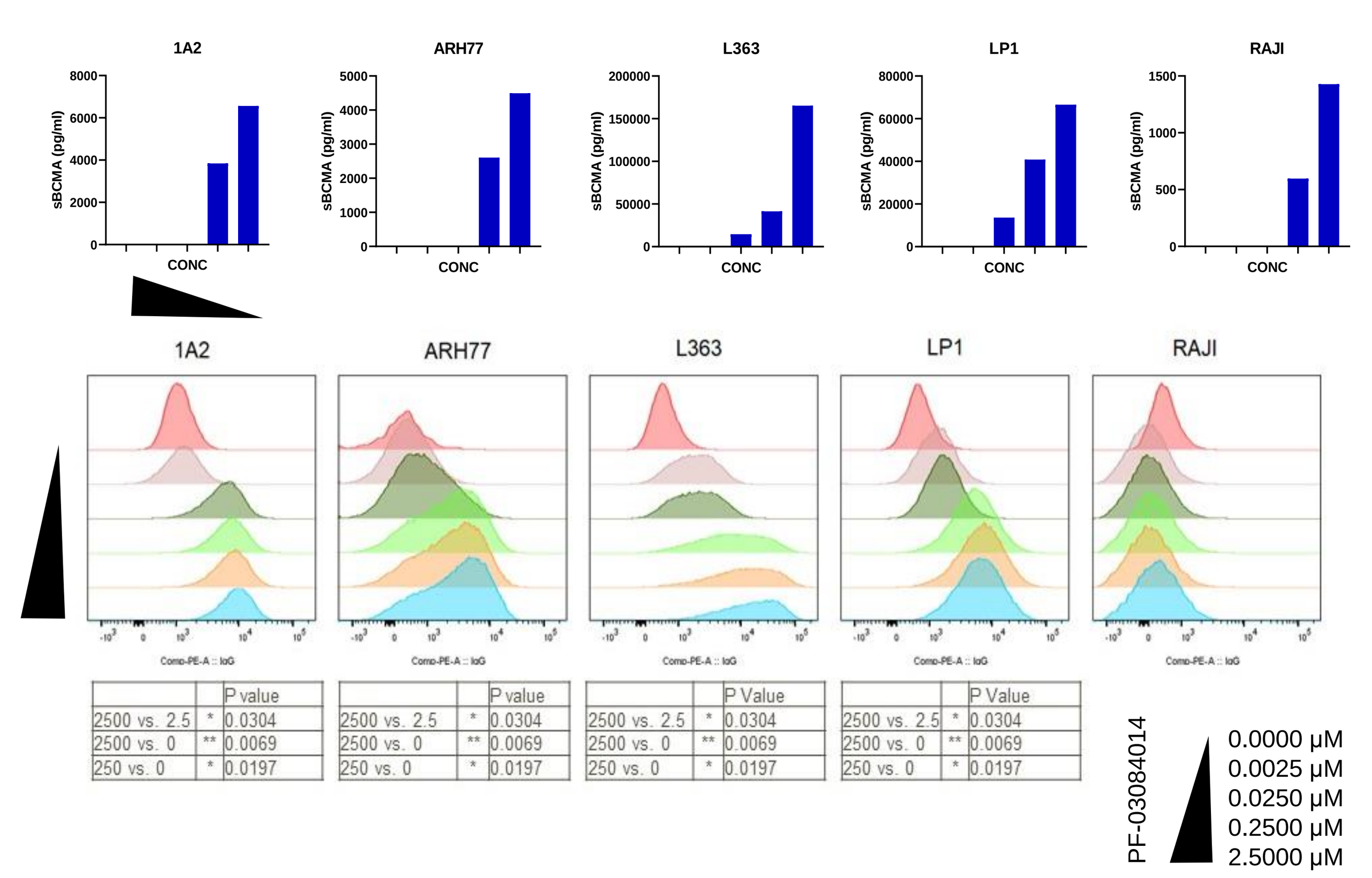
Results

Belantamab mafodotin



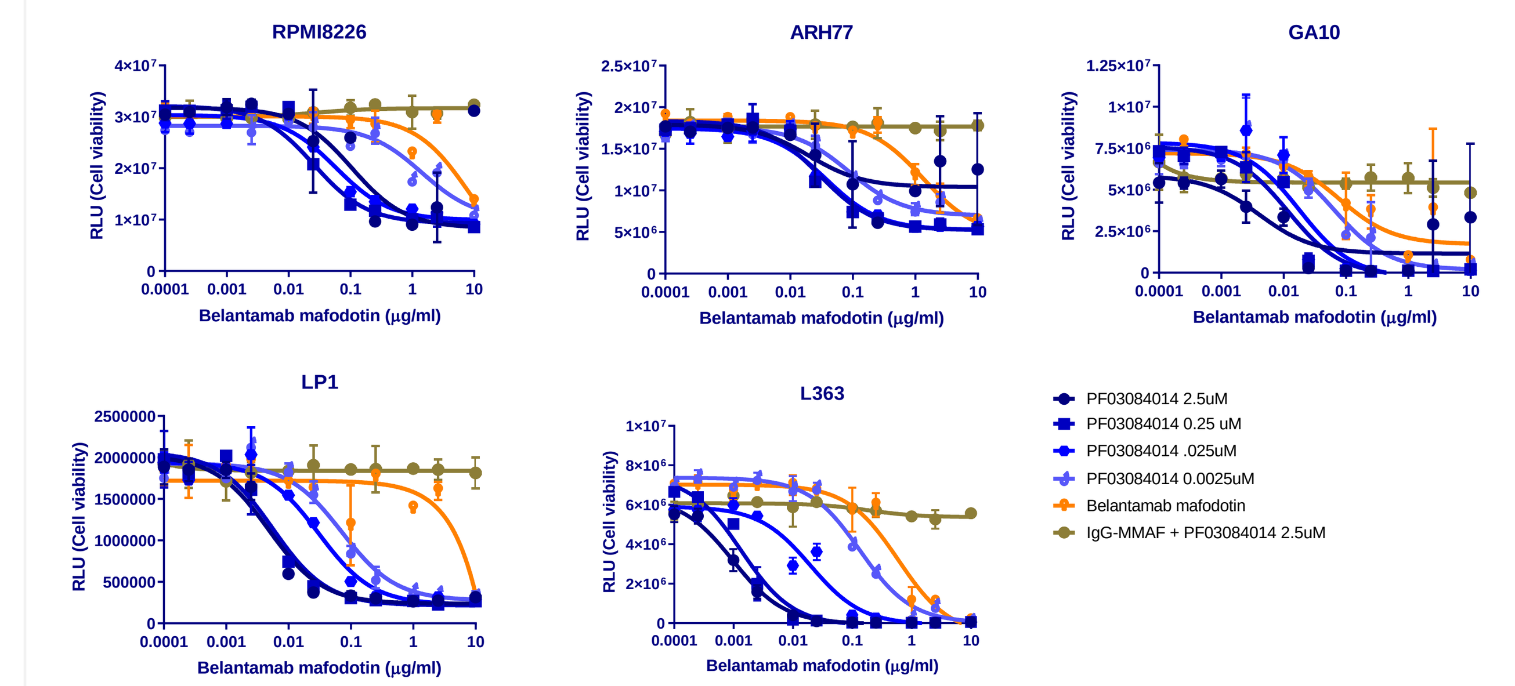
Belantamab mafodotin uses both immuno-conjugate activity and ADCC activity against BCMA-expressing cancer cells. The use of the gamma-secretase inhibitor, nirogacestat, increases cell surface levels of BCMA and increases BCMA-targeted engagement of belantamab mafodotin.

Effects of gamma-secretase inhibitor Nirogacestat on BCMA



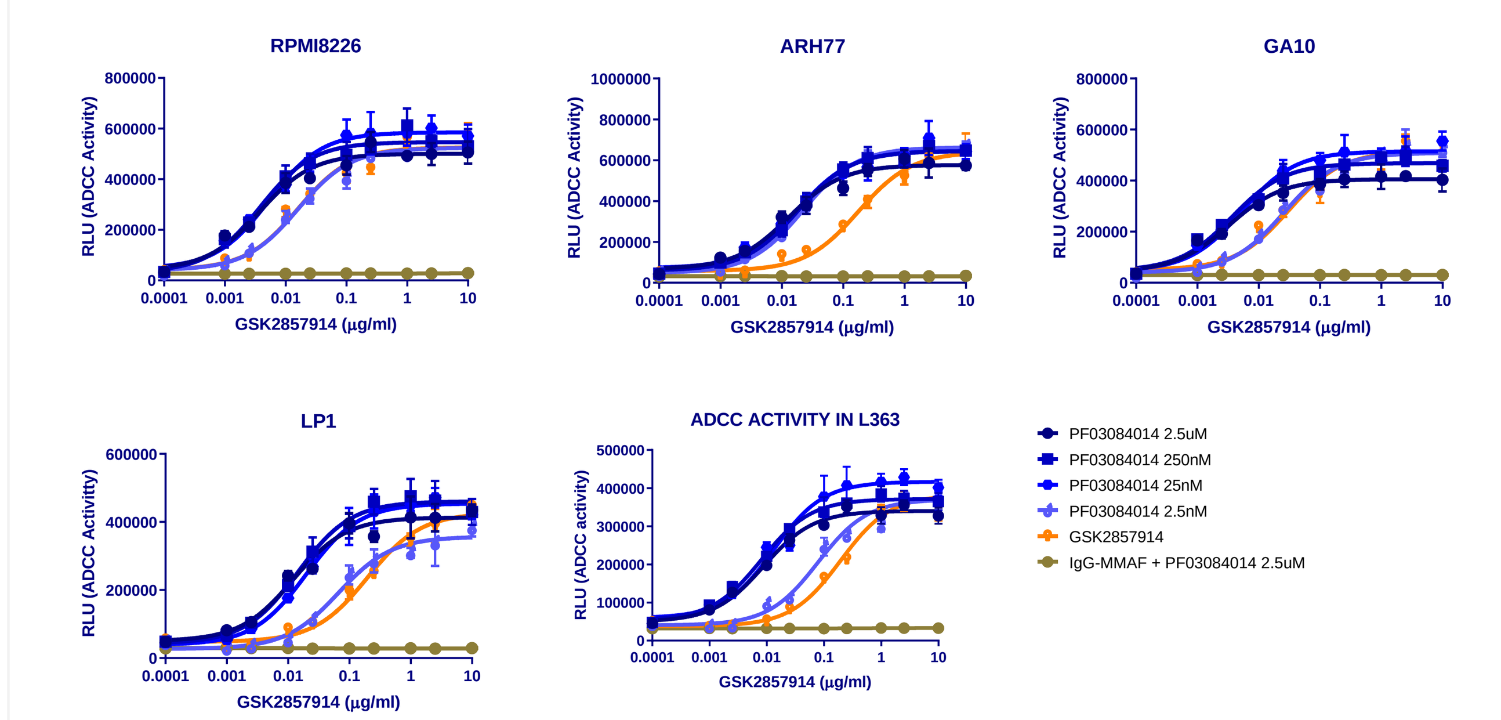
sBCMA is diminished following treatment with nirogacestat, even in low-expressing BCMA cell lines such as Raji. Cell surface BCMA levels are increased in a dose-dependent manner following 3-day treatment with nirogacestat.

Immuno-conjugate activity



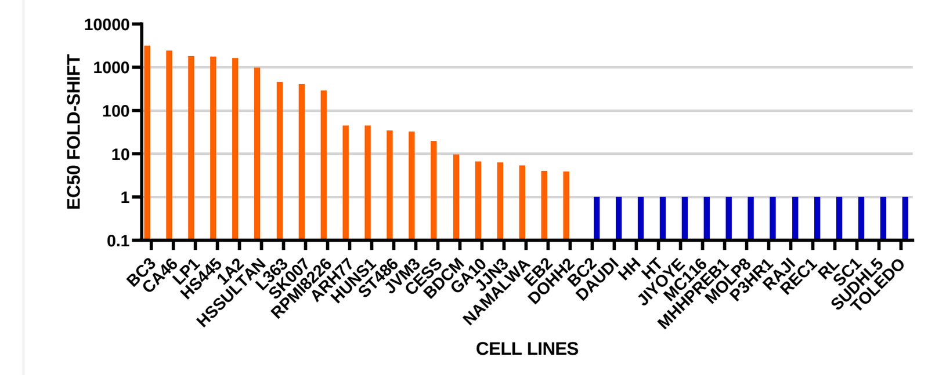
A three-day proliferation assay (Cell-Titre Glo) was conducted using fixed doses of nirogacestat with serial dilutions of belantamab mafodotin. Our combination results show a dose-dependent increase in EC50 in clinically relevant doses.

ADCC activity.



ADCC activity was measured using Promega's Jurkat ADCC assay. The 24-hour assay was conducted using fixed doses of nirogacestat with serial dilutions of belantamab mafodotin. Combination results show a dose-dependent increase in ADCC activity.

Figure 3.



	GSK2857916	GSK2857916 PF-03084014			
		2.5 uM	.25uM	0.025uM	0.0025uM
1A2	10.000	0.0955	0.0062	0.0056	0.0587
SK007	0.124	0.0008	0.0003	0.0003	0.0014
JJN3	0.002	0.0002	0.0003	0.0009	0.0015
L363	0.602	0.0010	0.0013	0.0198	0.1340
BC3	10.000	0.0015	0.0032	0.0155	0.0762
CA46	10.000	0.0219	0.0041	0.0094	0.0898
BDCM	0.040	0.0553	0.0042	0.0232	0.0163
LP1	10.000	0.0048	0.0056	0.0305	0.0713
HS445	10.000	0.0005	0.0057	0.0287	0.1619
HSSULTAN	10.000	0.0135	0.0101	0.0166	0.0330
GA10	0.078	0.0041	0.0117	0.0180	0.0644
EB2	0.051	0.0066	0.0130	0.0099	0.0061
JVM3	0.562	0.0124	0.0170	0.0150	0.3011
NAMALWA	0.100	0.2660	0.0189	0.0070	0.0425
CESS	0.376	0.0455	0.0191	0.0213	0.0293
HUNS1	1.234	0.0336	0.0277	0.0750	0.9804
ST486	0.981	0.0371	0.0287	0.0326	0.0535
ARH77	1.336	0.0200	0.0299	0.0372	0.0866
DOHH2	0.123	0.0148	0.0317	0.0128	0.1606
RPMI8226	10.000	0.0390	0.0351	0.0578	1.4170
EB3	0.280	0.0552	1.5320	0.1342	0.0437

Immuno-conjugate activity across a panel of BCMA-expressing cell lines shows increased activity upon combination treatment with nirogacestat. Low BCMA-expressing cell lines are insensitive to combination treatment.

Conclusions

- Treatment of BCMA-expressing cancer cell lines with Nirogacestat shows increased levels of BCMA cell surface expression and corresponding decreased levels of soluble BCMA
- Combination therapy of belantamab mafodotin with nirogacestat results in synergistic immuno-conjugate activity. We have identified up to 3,000-fold increase in sensitivity to Belantamab mafodotin.
- In a 24-hour assay assay to measure ADCC activity, we showed increased sensitivity to belantamab mafodotin when in combination with nirogacestat.
- Cell lines sensitive to belantamab mafodotin as a single agent showed increased immuno-conjugate and ADCC activity, regardless of lymphoma type.
- A clinical trial evaluating belantamab mafodotin with nirogacestat will be examined in DREAMM-5 platform trial (Study 208887; NCT04126200).

An audio recording accompanies this poster – this is available via the QR code

References

1. Laurent SA, et al. *Nat. Comm.* 2015;Volume:6–7333.

Disclosures

- Drug linker technology licensed from Seattle Genetics; monoclonal antibody produced using POTELLIGENT Technology licensed from BioWa.
- SE, CS, IG, JK, CB, PB, JS, and AH are employees of GSK and share/stockholders in GSK

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