HMPL-A067 (HMA800067), a novel CD38-targeting antibody-drug conjugate (ADC), demonstrated superior anti-tumor activity to daratumumab in preclinical B-cell malignancies models

Abstract #1890

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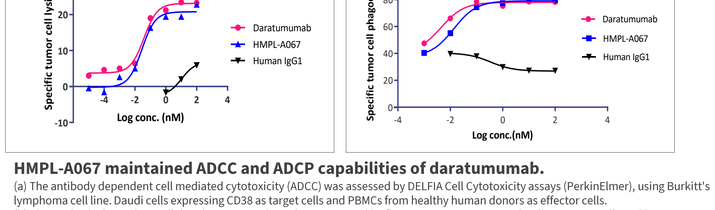
BACKGROUND

- Daratumumab, an anti-CD38 monoclonal antibody, has been widely used in the treatment of multiple myeloma (MM). However, some of MM patients exhibit primary or acquired resistance to daratumumab therapy [1].
- HMPL-A067, a novel CD38 targeting antibody-drug conjugate (ADC), is developed by conjugating daratumumab with cytotoxic payload Monomethyl auristatin E (MMAE) via a novel linker, aiming for superior anti-tumor efficacy to daratumumab, including in subjects with resistance to daratumumab treatment.
- Herein we report superior anti-tumor effect of HMPL-A067 to daratumumab in varied preclinical B-cell malignancies models.

RESULTS

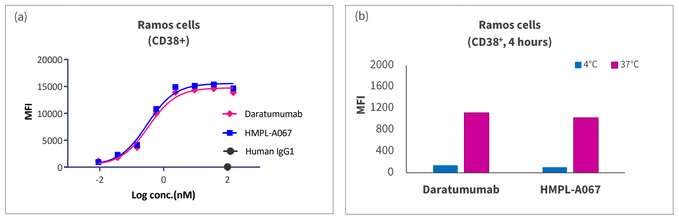
A. Binding affinity of HMPL-A067 to CD38 protein from multiple species



HMPL-A067 and daratumumab showed high and comparable binding affinity to human CD38 protein, without any binding to cynomolgus, mouse or rat CD38 protein.

Binding to purified human (a), cynomolgus monkey (b), mouse (c) and rat CD38 (d) was determined using ELISA.

B. Binding and internalization of HMPL-A067 to CD38⁺ human lymphoma Ramos cells



HMPL-A067 displayed high binding affinity and efficient internalization to CD38⁺ Ramos cells, compared to daratumumab.

(a) The binding of HMPL-A067 to cellular CD38 was determined by FACS in CD38⁺ human lymphoma Ramos cells.
(b) Levels of surface-localized PE anti-human IgG Fc binding to daratumumab or HMPL-A067 in the control (4°C) and the internalization (37°C, 4 h) samples determined by an acid dissociation [2], which can remove non-internalized daratumumab or HMPL-A067 on cell surface, without affecting levels of daratumumab or HMPL-A067 internalized into cytoplasm.

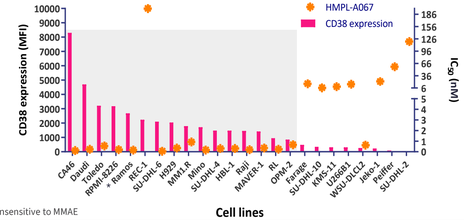
C. ADCC and ADCP activity of HMPL-A067

HMPL-A067 maintained ADCC and ADCP capabilities of daratumumab.

(a) The antibody dependent cell mediated cytotoxicity (ADCC) was assessed by DELFIA Cell Cytotoxicity assays (PerkinElmer), using Burkitt's lymphoma cell line. Daudi cells expressing CD38 as target cells and PBMCs from healthy human donors as effector cells.
(b) The antibody dependent cellular phagocytosis (ADCP) was assessed by flow cytometry, using Daudi cells as target cells and human M0 macrophages as effector cells.

RESULTS

D. Cytotoxicity of HMPL-A067 on hematologic malignant tumor cell growth

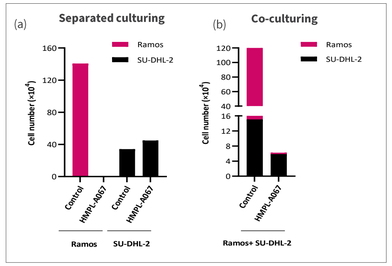


*: REC-1 cell insensitive to MMAE

HMPL-A067 exhibited a CD38-dependent cytotoxic activity against a panel of 24 tumor cell lines.

In vitro cytotoxicity was evaluated with CellTiter-Glo® 2.0 assay. CD38 expression was determined by flow cytometry with daratumumab as primary antibody. Fifteen in 16 cell lines with CD38 MFI >800 showed IC_{50}s value < 1.0 nM (median 0.24nM).

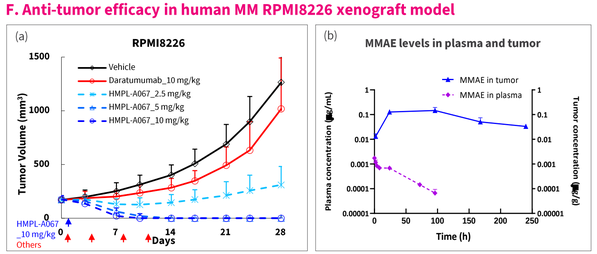
E. Bystander killing effect of HMPL-A067 on CD38-negative hematologic cells



HMPL-A067 killed CD38 negative tumor cells effectively through bystander effect.

(a) In separated cell culture, HMPL-A067 at 0.5 nM killed all the CD38 positive Ramos cells, while no inhibition on CD38 negative SU-DHL-2 cells.
(b) In co-culture of Ramos and SU-DHL-2 cells, HMPL-A067 effectively killed not only CD38 positive Ramos cells, but also CD38 negative SU-DHL-2 cells, suggesting the bystander killing effect of HMPL-A067.

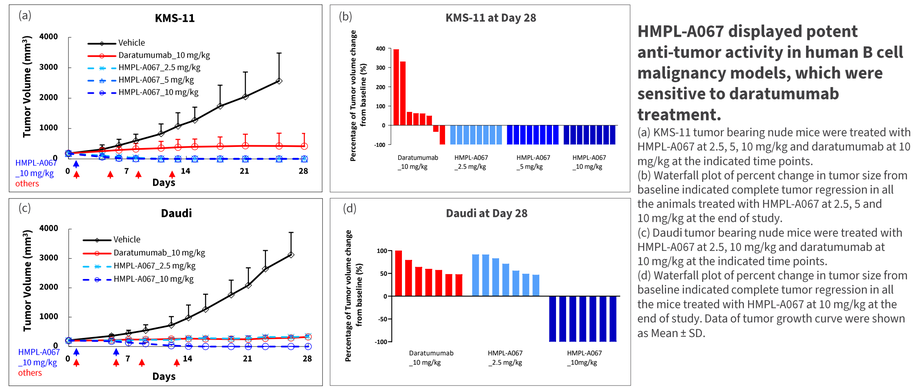
F. Anti-tumor efficacy in human MM RPMI8226 xenograft model



HMPL-A067 demonstrated potent anti-tumor efficacy in daratumumab insensitive RPMI-8226 xenograft model in a dose-dependent manner, with the sustainable high exposure of MMAE in the tumor and low release of free MMAE in plasma.

(a) RPMI-8226 tumor bearing nude mice were treated with HMPL-A067 at 2.5, 5, 10 mg/kg and daratumumab at 10 mg/kg at the indicated time points. HMPL-A067 showed potent anti-tumor activity, with complete tumor regression in all the animals treated with HMPL-A067 at 5 mg/kg and 10 mg/kg, superior to daratumumab at the dose of 10 mg/kg. HMPL-A067 treatment was well tolerated.
(b) MMAE levels were determined in plasma and tumor post HMPL-A067 single dose at 10 mg/kg in RPMI-8226 tumor bearing mice. Data were shown as Mean ± SD.

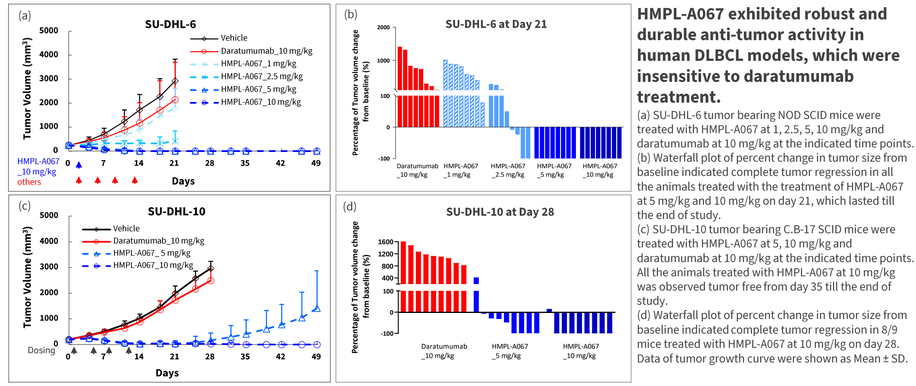
G. Potent anti-tumor activity of HMPL-A067 in human B-cell malignancy xenograft models



HMPL-A067 displayed potent anti-tumor activity in human B cell malignancy models, which were sensitive to daratumumab treatment.

(a) KMS-11 tumor bearing nude mice were treated with HMPL-A067 at 2.5, 5, 10 mg/kg and daratumumab at 10 mg/kg at the indicated time points.
(b) Waterfall plot of percent change in tumor size from baseline indicated complete tumor regression in all the animals treated with HMPL-A067 at 2.5, 5 and 10 mg/kg at the end of study.
(c) Daudi tumor bearing nude mice were treated with HMPL-A067 at 2.5, 10 mg/kg and daratumumab at 10 mg/kg at the indicated time points.
(d) Waterfall plot of percent change in tumor size from baseline indicated complete tumor regression in all the mice treated with HMPL-A067 at 10 mg/kg at the end of study. Data of tumor growth curve were shown as Mean ± SD.

H. Durable anti-tumor activity of HMPL-A067 in human DLBCL xenograft models



HMPL-A067 exhibited robust and durable anti-tumor activity in human DLBCL models, which were insensitive to daratumumab treatment.

(a) SU-DHL-6 tumor bearing NOD SCID mice were treated with HMPL-A067 at 1, 2.5, 5, 10 mg/kg and daratumumab at 10 mg/kg at the indicated time points.
(b) Waterfall plot of percent change in tumor size from baseline indicated complete tumor regression in all the animals treated with the treatment of HMPL-A067 at 5 mg/kg and 10 mg/kg on day 21, which lasted till the end of study.
(c) SU-DHL-10 tumor bearing C.B-17 SCID mice were treated with HMPL-A067 at 5, 10 mg/kg and daratumumab at 10 mg/kg at the indicated time points. All the animals treated with HMPL-A067 at 10 mg/kg was observed tumor free from day 35 till the end of study.
(d) Waterfall plot of percent change in tumor size from baseline indicated complete tumor regression in 8/9 mice treated with HMPL-A067 at 10 mg/kg on day 28. Data of tumor growth curve were shown as Mean ± SD.

CONCLUSION

- **HMPL-A067, as a novel CD38 targeting ADC, demonstrated potent anti-tumor activities in multiple B-cell malignant tumor models *in vitro* and *in vivo* with favorable PK profile.**
- **HMPL-A067 exhibited superior anti-tumor activity in either daratumumab sensitive or insensitive B cell malignancy models, with durable tumor-free status.**
- **Our results supported further development of HMPL-A067, as a superior therapeutic option for treatment of patients with CD38⁺ B cell malignancies.**

References:
[1] . Eur J Haematol. 2018 May;100(5):494-501.
[2]Pharm Res. 2015 Jan;32(1):286-99.

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