Introduction

Despite the introduction of immunomodulators and proteasome inhibitors (PI), outcomes remain poor for patients with relapsed/refractory multiple myeloma (RRMM).

The tumour necrosis superfamily cell-surface receptor, B-cell maturation antigen (BCMA), is an ideal target for targeted therapies with reduced toxicity. BCMA is a potential therapeutic target in MM.

Belantamab mafodotin (GSK2857916) is a novel anti-BCMA monoclonal antibody (mAb) conjugated to the microtubule-disrupting agent monomethyl auristatin F via a pseudo-resistant maleimido-cys linker (mMMAF), after uptake of the antibody-drug conjugate (ADC) the active form Cys-mcMMAF is released.1

Interim analysis of the first-in-human study of belantamab mafodotin in patients with RRMM (BMA117155; DREAMM1, NCT02054387) reported an overall response rate (ORR) of 60% (95% confidence interval [CI] 42.7–76.1) at the recommended Phase 2 dose, and progression-free survival (PFS) of 7.9 months (95% CI: 3.1–not estimable).

Aims

Here we present the final analysis, a further 14 months after interim analysis of the efficacy, safety, pharmacokinetic (PK) and biomarker findings from DREAMM1.

Methods

Study design and patient population

This open-label, 2-part Phase 1 study (BMA117155; NCT02054387) was conducted in 9 centres in the USA. Canaletto in adults with MM and progressive disease after stem cell transplantation (or considered for transplantation) with high levels of baseline circulating free soluble BCMA (sBCMA), as biomarkers for response to belantamab mafodotin.


Assessments

Primary endpoints were safety, maximum tolerated dose and recommended Phase 2 dose.

Secondary endpoints included clinical activity (percentage of patients achieving at least a partial response [response rate, [RR]], safety and tolerability as adverse event [AE] reporting and PK parameters).

PK parameters were collected during the first cycle in Part 1. PK parameters for the ADC, total mAb and Cys-mcMMAF were determined by noncompartmental analysis.

MM biomarkers were used, including BCMA expression in bone marrow mononuclear cells and plasma cells by immunohistochemistry, and circulating free soluble BCMA (sBCMA) levels by immunoassay in serum.

Results

Patient population

In Part 1, 28 patients were enrolled and analysed, with a mean (range) age of 59 (39–79) years. Thirty-four patients were enrolled in Part 2 with a mean (range) age of 61 (46–75) years; patients completed a median (range) of 12.5 (7–23) months of follow-up.

Safety and efficacy

Sixty-three patients achieved at least a partial response [overall response rate], safety and tolerability as adverse event (AE) reporting and PK parameters.

PK parameters were summarised in Table 1.

Table 1. Summary of PK parameters

<table>
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<th>Dose (mg/kg)</th>
<th>C0h (µg/mL)</th>
<th>AUC (0-24 h) (µg h/mL)</th>
<th>t1/2 (h)</th>
<th>Vss (L)</th>
<th>tmax (h)</th>
<th>t1/2 (h)</th>
<th>Vss (L)</th>
<th>tmax (h)</th>
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</table>

Figures 2–5 show data for the recommended Phase 2 dose (3.4 mg/kg) and at the 4.6 mg/kg dose.

Safety

The ORR was 60% (95% CI: 42.1–76.1). Median PFS was 12.0 months (95% CI: 3.1–not estimable).

Pharmacokinetic

The Q3W dosing regimen was selected based on preclinical data and on the projected half-life (~18 months of follow-up [cut-off: 31 August 2018]).

PK

Combining all dose levels in Part 1, geometric mean clearance of belantamab mafodotin was 18 mL/h, steady-state volume of distribution was 4.1 L, and half-life was 4.7 days (n=18) and the median time to maximum concentration (tmax) was 2.0 h (n=29). Similar PK parameter values were observed for total mAb (mAb with/without MMAF). The median tmax, t1/2, and high levels of baseline sBCMA, ranging from <10 ng/mL up to 262 ng/mL (n=38). Patients without prior IMiD and PI, 15/21 (71.4%; 95% CI: 47.8–88.7) patients without prior PI with prior daratumumab treatment.

Figures 2–5 show data for the recommended Phase 2 dose (3.4 mg/kg) and at the 4.6 mg/kg dose.

Toxicities were manageable and the most common adverse events were infusion-related reactions (2/35; 6.0%) and lymphopenia (2/35; 6.0%).

Belantamab mafodotin binds sBCMA in the circulation and is reduced by free sBCMA at day 28 post-infusion. Greater than 50% reductions in free sBCMA were observed at 4.6 mg/kg with no relationship between response and free sBCMA reduction, indicating that sBCMA is saturated at higher doses of belantamab mafodotin (Figure 4). Free sBCMA concentrations increased over time after the initial decrease observed with belantamab mafodotin administration.

Median baseline sBCMA was 45 ng/mL (7.9–210.24 ng/mL). In responders (n=21), 80 ng/mL (13.3–100 ng/mL) in nonresponders (n=14). Response was achieved in patients with both low and high levels of baseline sBCMA, ranging from <10 ng/mL up to 262 ng/mL.

Conclusions

Belantamab mafodotin was well tolerated and demonstrated rapid deep and durable responses in heavily pre-treated patients with RRMM. With additional follow-up, more complete responses and considerably longer PFS was observed in the final analysis compared with interim analysis.

The PK profile was characterised by slow clearance, a small volume of distribution and half-life of 4.7 days.

No clear relationship between baseline sBCMA expression level and patient response was identified.

Circum and thrombocytopenia events were consistent with the known toxicities of other MMAF-linked antibody-drug conjugates.

Belantamab mafodotin engaged sBCMA in a dose-dependent manner. Clinical responses were observed in patients across a wide range of baseline sBCMA levels.

Further investigations are needed to understand the value of BCMA expression on MM cells and circulating free sBCMA levels as biomarkers for response to belantamab mafodotin.

References


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