DREAMM 4: A Phase I/II single-arm open-label study to explore safety and clinical activity of belantamab mafodotin (GSK2857916) administered in combination with pembrolizumab in patients with relapsed/refractory multiple myeloma (RRMM)

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Background

BCMA is a cell-surface receptor highly expressed in MM and other B-cell malignancies[1,2]

BCMA promotes the growth and survival of MM cells and is virtually absent on naïve and memory B cells,[1,3,4] making it an ideal therapeutic target in MM[5-9]

Belantamab mafodotin (GSK2857916) is a first-in-class, anti-BCMA immune-conjugate with an afucosylated, humanized anti-BCMA mAb conjugated by a protease-resistant cysteine linker to a microtubule disrupting agent, MMAF

Preclinical data indicate that belantamab mafodotin specifically binds to BCMA, eliminating myeloma cells by multimodal mechanisms, including delivery of MMAF to BCMA-expressing malignant plasma cells, enhancing antibody-dependent cellular cytotoxicity and leveraging immunogenic cell death[2,10]

A favourable safety profile and clinical activity of belantamab mafodotin as a monotherapy has been shown in heavily pre-treated participants with MM, with deep and durable responses reported (NCT02064387): ORR was 60% with a mPFS of 12 months (95% CI: 3.1–not estimable).[11] Of those participants without prior daratumumab treatment an ORR of 71.4% (95% CI: 47.8–88.7) was achieved; whereas in participants with prior daratumumab treatment and refractory to both immunomodulators and proteasome inhibitors an ORR of 38.5% (95% CI: 13.9–68.4) was achieved

PD-L1 overexpression may be a mechanism of immune evasion in MM[12]

Pembrolizumab, a selective, humanised IgG4 anti-PD-1 monoclonal antibody that blocks the interaction of PD-1 with PD-L1 and PD-L2, may synergise with immunomodulatory drugs to enhance tumour suppression

We hypothesised that T cell-dependent anti-tumour response induced by belantamab mafodotin may be augmented by combining with pembrolizumab

Trial objectives

To evaluate safety and determine the RP2D and preliminary clinical activity of belantamab mafodotin in combination with pembrolizumab in participants with RRMM previously treated with ≥3 prior lines

Trial design: DREAMM 4 (NCT03848845)

Phase I/II | 2-part | open-label | single-arm

Key inclusion criteria:

- ≥18 years of age
- ECOG PS 0–1
- 3 or more prior lines of anti-myeloma therapies including an IMiD, proteasome inhibitor, and anti-CD38 antibody
- Measurable disease

Prior anti-BCMA treatments, including belantamab mafodotin, are not excluded

Key exclusion criteria:

- Any prior anti-MM therapy or investigational drug within 14 days
- Prior treatment with a monoclonal antibody within 30 days
- Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE
- Corneal epithelial disease except mild punctate keratopathy
- Major surgery within the last 4 weeks
- Active renal condition, liver or biliary disease, or infection
- Active CNS metastases and/or carcinomatous meningitis
- Autoimmune disease that has required systemic treatment in the past 2 years
- Diagnosed immunodeficiency or any form of immunosuppressive therapy within 7 days
- Prior allogenic tissue/solid organ transplant

1 Part 1: Dose escalation N≤12

Belantamab mafodotin

1.92 | **2.5 (mg/kg)** | 3.4

(Belantamab mafodotin dose of 1.92 mg/kg may be tested if starting dose level of 2.5 mg/kg is not tolerated)

\+

Pembrolizumab 200 mg

Q21Days

OBJECTIVE
- Determine safety, tolerability, and establish the RP2D of the combination of belantamab mafodotin and pembrolizumab

1 PRIMARY ENDPOINT
- Percentage of participants with AE/DLT

2 SECONDARY ENDPOINTS
- ORR
- PK/ADA profiles

During the dose escalation, at least 3 evaluable participants will be tested per dose level. mTPI[13] design will guide dose escalation and RP2D of belantamab mafodotin

2 Part 2: Dose expansion N≤28

Belantamab mafodotin

RP2D optimal dose (mg/kg)

\+

Pembrolizumab 200 mg

Q21Days

OBJECTIVE
- Evaluate clinical activity, confirm safety and collect PK information for belantamab mafodotin, administered in combination with pembrolizumab dosing schedules identified in Part 1

1 PRIMARY ENDPOINT
- ORR

2 SECONDARY ENDPOINTS
- Ocular findings on ophthalmic exam
- Percentage of participants with AE
- Clinical benefit rate
- Duration of response
- Progression-free survival
- Time to disease progression
- OS
- PK/ADA profile

EXPLORATORY ENDPOINTS
- MRD in participants who achieve ≥VGPR
- BCMA expression and clinical response
- Genetic variations and clinical response
- Treatment and disease-related PROs
- Health-related quality of life

Safety data will be examined on an ongoing basis to support dose-escalation decisions

Participants will be treated until disease progression, intolerable toxicity, informed consent withdrawal, or for a maximum of 35 cycles (approximately 2 years)

Disease progression is assessed according to IMWG 2016 response criteria[14]

Safety monitoring

An independent safety review committee will review safety data

An additional stopping rule for Part 2 may stop enrolment early if (starting from 5 participants dosed) the observed rate of treatment-related ≥Grade 4 AEs equal or exceeds the specified rate (12%) at one-sided alpha level of 0.025 based on the 11% Grade 4 or higher AEs observed in the monotherapy study (NCT02064387)

Participants will undergo a corneal examination prior to dosing, then every 3 weeks. If there are no corneal signs, after cycle 4 of belantamab mafodotin treatment, the examinations may be decreased to once every 12 weeks

- Corneal events will be managed through prophylaxis with steroid eyedrops. Prophylactic preservative-free artificial tears should be administered in each eye at least 4–8 times daily, beginning on Day 1 until the end of treatment

Current status

Enrolment for Part 1 began in **March 2019**

As of 16 Sep 2019

3 participants have been enroled into the 2.5 mg/kg treatment group

&

3 participants have been enroled into the 3.4 mg/kg treatment group

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Abbreviations

ADA, anti-drug antibodies; AE, adverse event; BCMA, B-cell maturation antigen; CD, cluster of differentiation; CI, confidence interval; CNS, central nervous system; CTLA, cytotoxic T-lymphocyte-associated protein; DLT, dose-limiting toxicities; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; IMiD, immunomodulatory imide drugs; IMWG, International Myeloma Working Group; irAE, immune-related adverse event; MM, multiple myeloma; MMAF, microtubule inhibitor monomethyl auristatin F; mPFS, median progression-free survival; MRD, minimal residual disease; mTPI: modified toxicity probability interval; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L, programmed cell death ligand; PK, pharmacokinetics; PR, partial response; PRO, patient-reported outcome; RP2D, recommended Phase II dose; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response

Disclosures

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