DREAMM-9: Phase III Study of Belantamab Mafodotin Plus VRd vs VRd Alone in Transplant-Ineligible Newly Diagnosed Multiple Myeloma (TI NDMM)

Poster No. 456

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Background

BCMA and belantamab mafodotin

BCMA is a cell-surface receptor, expressed on MM cells but absent on naïve and memory B cells, that promotes plasma cell survival.[1]

Belantamab mafodotin (**belamaf; GSK2857916**) is a first-in-class BCMA-binding, humanized, afucosylated, monoclonal antibody-drug conjugate with multimodal activity involving immune-independent ADC-mediated apoptosis as well as immune-dependent mechanisms such as ICD and ADCC/ADCP.[2]

In the pivotal Phase II DREAMM-2 study (NCT03525678), single-agent **belamaf** demonstrated deep and durable responses, was well tolerated, and had an acceptable safety profile in patients with heavily pretreated RRMM.[3]

In the 2.5-mg/kg (n=97) cohort:

ORR	Median PFS	Median DoR
31% (97.5% CI 21.7–43.6)	2.9 months (95% CI 1.6–3.6)	not reached

In the 3.4-mg/kg (n=99) cohort:

ORR	Median PFS	Median DoR
34% (97.5% CI 24.8–47.0)	4.9 months (95% CI 2.0–5.8)	not reached

This was sustained during 13 months' follow-up.[4]

VRd combination therapy

Bortezomib, lenalidomide, and dexamethasone (**VRd**) is standard of care as first-line treatment for transplant-eligible with TI NDMM. Clinical studies have demonstrated a manageable safety profile and PFS of 43 months with this regimen for patients with TI NDMM.[5] However, relapse is usually inevitable and outcomes diminish with each relapse,[6] highlighting the need for novel, effective therapies.

Combining **belamaf** with bortezomib or lenalidomide inhibits tumor growth and increases survival in preclinical models (data on file).

The promising clinical activity with single-agent **belamaf** in RRMM, along with the potential that lenalidomide and bortezomib could enhance **belamaf**-mediated ICD, suggest that this combination could improve outcomes in patients with TI NDDM. **Belamaf** demonstrated clinically meaningful activity with an acceptable safety profile as a single-agent and in combination with Vd.[7] Studies in combination with Rd are ongoing.

Study Objective

The DREAMM-9 study was designed to determine the efficacy and safety of combining single-agent **belamaf** with **VRd** versus **VRd** alone in patients with TI NDMM.

Methods

DREAMM-9 (NCT04091126) is a:

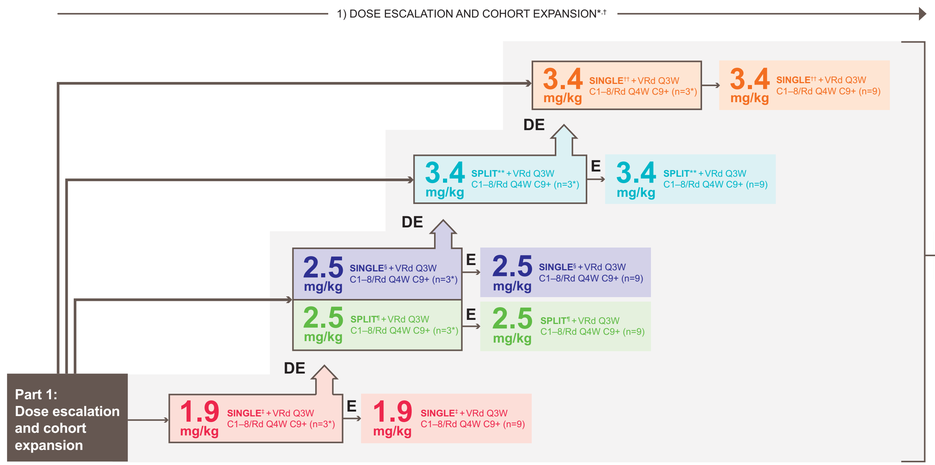
3 Phase III | Open-label | Randomized | Multicenter study

Part 1

Will evaluate the safety and tolerability of different doses and dosing regimens of **belamaf** in combination with **VRd** (≤12 patients per cohort, with an additional 6 patients in the cohort most likely to be selected as RP3D) with the objective of establishing the RP3D of **belamaf** plus **VRd**.

Part 2

Is the open-label, randomized, Phase III portion of the study to evaluate the efficacy and safety of the selected RP3D of the combination versus **VRd** alone (~750 patients will be randomized 1:1).



Patients in Part 1 are:

- not allowed to switch to Part 2
- not allowed to alter their allocated dose
- permitted dose reduction

Patients will receive study treatment until disease progression or unacceptable toxicity occurs.

Part 2: Randomized‡‡ Phase III

2) Dose selection

Induction Treatment	Maintenance Treatment
Belamaf selected dose + **VRd**	**Belamaf** selected dose + **Rd**
VRd Cycles 1–8	**Rd** Cycles 9+

VRd Q3W C1–8/Rd Q4W C9+ = VRd (bortezomib, lenalidomide, dexamethasone) Q3W to C8, Rd (lenalidomide, dexamethasone) Q4W for C9 onward.

*Dose escalation cohort may be expanded in accordance with the mTPI method; †an additional 6 participants may be added to cohort(s) considered most likely to be selected as the RP3D; ‡1.9 SINGLE = belamaf 1.9 mg/kg on Day 1 Q3W to C8 and Q4W for C9 onward; §2.5 SINGLE = belamaf 2.5 mg/kg on Day 1 Q3W to C8 and Q4W for C9 onward; ¶2.5 SPLIT = belamaf 1.25 mg/kg on Day 1 and 1.25 mg/kg on Day 8 Q3W to C8 and Q4W for C9 onward; **3.4 SPLIT = belamaf 1.7 mg/kg on Day 1 and 1.7 mg/kg on Day 8 Q3W to C8 and Q4W for C9 onward; ††3.4 SINGLE = belamaf 3.4 mg/kg on Day 1 Q3W to C8 and Q4W for C9 onward; ‡‡Two arms randomized 1:1.

Key assessments:

Primary dual endpoints, PFS and MRD negativity rate, will be assessed.

Safety: AEs and serious AEs will be recorded throughout the study.

Key inclusion criteria

- Age ≥18 years
- Confirmed diagnosis of MM (IMWG criteria)[8]
- Ineligible* for high-dose chemotherapy with ASCT
  *At the investigator's discretion.
- Measurable disease (according to serum and/or urine M protein and/or serum free light chain levels)
- ECOG PS 0–2
- Adequate organ function

Key exclusion criteria

- Smoldering MM
- Prior systemic antimyeloma therapy, or investigational drug <14 days or 5 half-lives prior to first dose of study treatment
- Peripheral neuropathy or neuropathic pain Grade 2 or higher, NCI-CTCAE v5.0
- Major surgery <4 weeks prior to first dose of study treatment
- Active renal condition, internal bleeding, liver or biliary disease
- Previous/concurrent malignancies other than MM, unless considered medically stable for ≥2 years
- Evidence of cardiovascular risk
- Active infection or HIV
- HBV surface antigen or core antibody present, or positive for HCV at screening or ≤3 months prior to first dose of study treatment
- Current corneal epithelial disease, except mild punctate keratopathy
- Light chain amyloidosis, active POEMS syndrome, or active plasma cell leukemia

Study Endpoints

Part 1: Dose Selection

Primary endpoints

- DLTs (NCI-CTCAE v5.0; GSK scale for corneal events)
- AEs (NCI-CTCAE v5.0)

Secondary endpoints

- Lenalidomide RDI and bortezomib RDI after 4 cycles of **belamaf** + **VRd**
- Cumulative administered dose of belamaf after 4 cycles of **belamaf** + **VRd**
- PK parameters
- ADA incidence

Exploratory endpoints

- Efficacy*:
  - ORR (≥PR)
  - CRR (CR or sCR)
  - ≥VGPR (VGPR, CR, or sCR)
- Belamaf exposure-response relationship
- Changes in BCMA expression, serum BCMA, and circulating free-DNA levels
- Host genetic variation

*Clinical responses will be investigator-assessed according to IMWG 2016 criteria.[9]

Part 2: Phase III

Primary endpoints

- MRD-negativity rate (10^{-5} sensitivity by NGS)
- PFS

Secondary endpoints

- Efficacy*:
  - ORR (≥PR)
  - CRR (CR or sCR)
  - ≥VGPR (VGPR, CR, or sCR)
  - DoR
  - TTP
  - OS
  - Sustained MRD negativity
- Safety:
  - AEs (NCI-CTCAE v5.0)
  - Ocular findings on ophthalmic exam
- Belamaf exposure
- ADA incidence
- HRQoL: EORTC-QLQ, PRO-CTCAE, and OSDI

Exploratory endpoints

- PET-CT imaging for MRD negativity
- PFS2
- TTBR
- Changes in safety assessments
- HRQoL: EQ-5D-3L, PGIS, PGIC, FACT GP5
- HCRU
- **Belamaf** PK parameters and exposure-response relationship
- Changes in BCMA expression, serum BCMA, and circulating free-DNA levels
- Host genetic variation

Summary

- **Belamaf represents a new treatment option for patients with RRMM.**
- **Screening for the DREAMM-9 study began in 2019, and the study is currently recruiting.**
- **Single-agent belamaf is being evaluated in other clinical trials in various combination strategies (oral presentation no. 8502 and poster no. 452), in addition to evaluation as monotherapy (poster nos. 436, 419 and 441) in various MM settings.**

Abbreviations

ADA, anti-drug antibody; ADC, antibody-drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; AE, adverse event; ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; belamaf, belantamab mafodotin; C, Cycle; CI, confidence interval; CR, complete response; CRR, complete response rate; CTCAE, Common Terminology Criteria for Adverse Events; DE, dose escalation; DLT dose-limiting toxicity; DoR, duration of response; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; E, expansion; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC-QLQ, European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimension 3 Level; FACT-GP5, Functional Assessment of Cancer Therapy General, Point 5; GSK, GlaxoSmithKline; HBV, hepatitis B virus; HCRU, healthcare resource utilization; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; ICD, immunogenic cell death; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; mTPI, modified toxicity probability interval; NCI, National Cancer Institute; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; NR, not reached; ORR, overall response rate; OS, overall survival; OSDI, Ocular Surface Disease Index; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PFS2, progression-free survival on subsequent line of therapy; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; POEMS, plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; PR, partial response; PRO, patient-reported outcome; Q3W, every 3 weeks; Q4W, every 4 weeks; Rd, lenalidomide and dexamethasone; RDI, relative dose intensity; RP3D, recommended Phase III dose; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; TI, transplant-ineligible; TTBR, time to best response; TTP, time to progression; VGPR, very good partial response; VRd, bortezomib, lenalidomide, and dexamethasone

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Ethics approval statement

This Master Protocol (IGNYTE-ESO) will be conducted under approval by the appropriate institutional review boards and independent ethics committees.

Disclosures

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