4567

MagnetisMM-4: An Open-Label, Phase 1b/2 Umbrella Study of Elranatamab in Combination With Other Anti-Cancer Treatments for Patients With Multiple Myeloma

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Objective

- The phase 1b/2 MagnetisMM-4 study will determine the recommended dose and clinical benefit of elranatamab in combination with other anti-cancer therapies in patients with RRMM who are refractory to at least 1 immunomodulatory drug, 1 proteasome inhibitor, and 1 anti-CD38 antibody

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Acknowledgments:
This study was sponsored by Pfizer. Medical writing support was provided by Steven Moore, PhD, of Engage Scientific Solutions and was funded by Pfizer.
Nirogacestat for this study was provided by SpringWorks Therapeutics, Inc. under a clinical trial collaboration agreement with Pfizer.
For more information about this clinical trial, please call 1-800-718-1021 or email clinicaltrials.gov_inquiries@pfizer.com
ClinicalTrials.gov ID: NCT05090566

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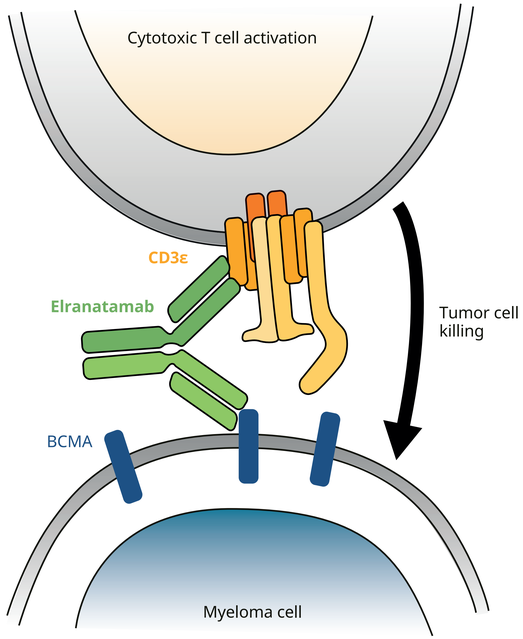
Presented at the 64th American Society of Hematology (ASH) Annual Meeting, December 10–13, 2022, New Orleans, LA, USA

Background

- Multiple myeloma (MM) is a B-cell malignancy that results in bone destruction and marrow failure[1]
- Despite recent advances, MM remains an incurable disease for most patients and initial remission will be followed by relapses that require therapy[2,3]
- B-cell maturation antigen (BCMA) is preferentially expressed by mature B lymphocytes and is overexpressed on MM cells[4]
- Elranatamab (PF-06863135) is a humanized bispecific antibody that targets BCMA on myeloma cells and CD3 on T cells to induce T-cell–mediated cytotoxicity (**Figure 1**)[4]

Figure 1: Elranatamab targets BCMA on myeloma cells and CD3 on T cells



BCMA=B-cell maturation antigen

- In MagnetisMM-1 (NCT03269136), an ongoing, phase 1 study in patients with relapsed or refractory MM (RRMM), subcutaneous (SC) elranatamab yielded an overall response rate (ORR) of 64% and had a manageable safety profile[5]
- In the phase 2 MagnetisMM-3 (NCT04649359) study in patients with heavily pretreated RRMM, SC elranatamab was well tolerated and yielded an ORR of 61% at the recommended phase 2 dose[6]

Methods

STUDY DESIGN

- MagnetisMM-4 (NCT05090566) is a phase 1b/2, open-label, non-randomized, multicenter, umbrella study of elranatamab in combination with other anti-cancer treatments for patients with MM
- The estimated enrollment is 105 patients
- Key patient inclusion and exclusion criteria are shown in **Table 1**

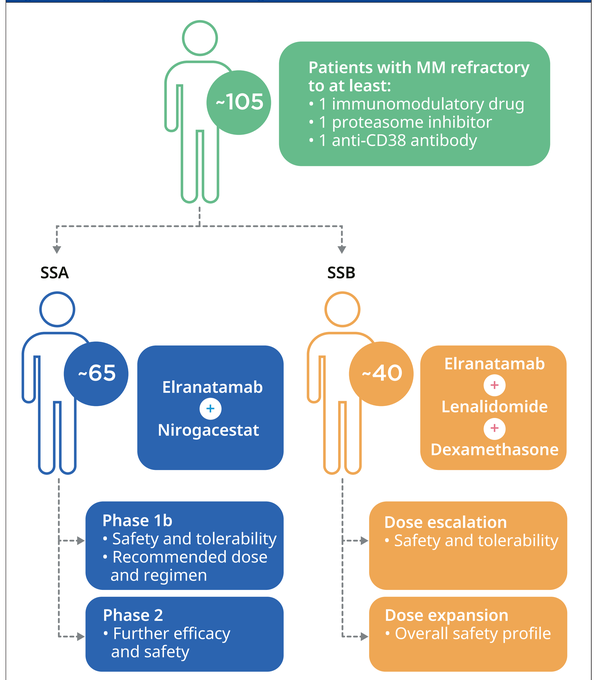
Table 1: Key eligibility criteria

Key inclusion criteria	Key exclusion criteria
Age ≥18 y	Active plasma cell leukemia
RRMM with ≥3 prior lines of therapy	Amyloidosis
Refractory to at least 1 immunomodulatory drug, 1 proteasome inhibitor, and 1 anti-CD38 antibody	Stem cell transplant within 12 wks prior to enrollment, or active GVHD
Measurable disease defined by at least 1 of the following: 1. Serum M-protein ≥0.5 g/dL 2. Urinary M-protein excretion ≥200 mg/24 h 3. Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa to lambda FLC ratio	POEMS syndrome
Eastern Cooperative Oncology Group performance status ≤1	Any active uncontrolled bacterial, fungal, or viral infection
	Impaired cardiovascular function or clinically significant cardiovascular diseases within 6 mo prior to enrollment
	Previous administration with an investigational drug within 30 d or 5 half-lives preceding the first dose of study treatment
	SSA only: Previous treatment with BCMA-bispecific antibody
	SSB only: Previous treatment with BCMA-directed therapy

BCMA=B-cell maturation antigen; FLC=free light chain; GVHD=graft-versus-host disease; POEMS=Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes; RRMM=relapsed or refractory multiple myeloma; SSA=substudy A; SSB=substudy B

- The study is split into 2 substudies (**Figure 2**)

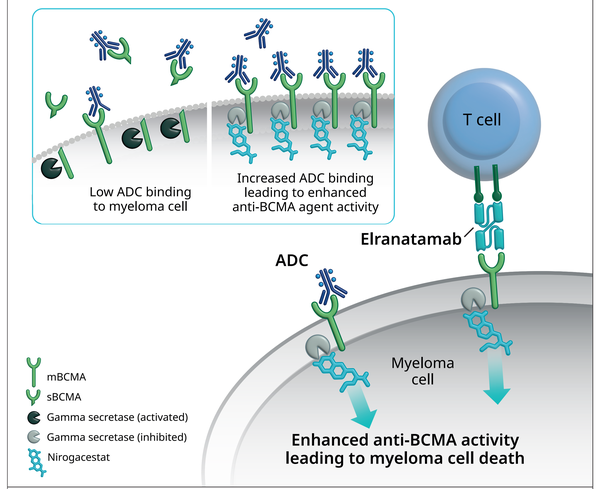
Figure 2: MagnetisMM-4 trial design



MM=multiple myeloma; SSA=substudy A; SSB=substudy B

- In substudy A (SSA), patients will receive SC elranatamab + the gamma secretase inhibitor (GSI) nirogacestat orally
  - Studies have shown that GSIs block BCMA cleavage and can potentially enhance BCMA-directed therapy (**Figure 3**)[7-9]

Figure 3: Nirogacestat may enhance BCMA-directed therapy



The gamma secretase inhibitor nirogacestat blocks the cleavage of mBCMA, potentially enhancing BCMA-directed therapies such as elranatamab
ADC=antibody–drug conjugate; BCMA=B-cell maturation antigen; mBCMA=membrane-bound BCMA; sBCMA=soluble BCMA

- Phase 1 of SSA will evaluate the safety, tolerability, and select a recommended dose and regimen for the combination of elranatamab and nirogacestat
- Phase 2 of SSA will further evaluate the efficacy and safety of the combination of elranatamab and nirogacestat
- In substudy B (SSB), patients will receive SC elranatamab + oral lenalidomide + oral dexamethasone
- The dose-escalation part of SSB will assess the safety and tolerability of elranatamab in combination with lenalidomide and dexamethasone
- The dose-expansion part of SSB will evaluate the overall safety profile of elranatamab in combination with lenalidomide and dexamethasone
- In each substudy, step-up priming doses of elranatamab will be employed to mitigate the risk of cytokine release syndrome
  - A Bayesian logistic regression model will be utilized for dose escalation
- The primary and secondary endpoints are shown in **Table 2**

Table 2: Study endpoints

	SSA	SSB
Primary endpoints	DLT up to 35 d (phase 1)	DLT up to 42 d (dose-escalation phase)
	ORR[a] (phase 2)	TEAEs[b] and lab abnormalities (dose-expansion phase)
Key secondary endpoints	TEAEs[b]	ORR[a]
Shared secondary endpoints	Time to response,[a] duration of response,[a] CR rate,[a] duration of CR,[a] progression-free survival,[a] overall survival, minimal residual disease negativity rate,[a] immunogenicity to elranatamab, and elranatamab pharmacokinetics	

[a] Per IMWG response criteria
[b] Per NCI CTCAE v5, cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome assessed per ASTCT criteria
ASTCT=American Society for Transplantation and Cellular Therapy; CR=complete response; DLT=dose-limiting toxicity; IMWG=International Myeloma Working Group; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=objective response rate; SSA=substudy A; SSB=substudy B; TEAE=treatment-emergent adverse event

STUDY STATUS

- The study is enrolling the phase 1 portions and is being opened at multiple sites in the United States and Canada