# PHASE 1, MULTICENTER, OPEN-LABEL STUDY OF SINGLE-AGENT BISPECIFIC ANTIBODY T CELL ENGAGER GBR 1342 IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

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## ABSTRACT

### Background

Available therapies have improved outcomes in multiple myeloma but patients eventually relapse, requiring treatment with agents that are active in refractory disease. CD38, a transmembrane glycoprotein, is upregulated on myeloma cells and is a validated disease target, evidenced by the anti-myeloma activity of daratumumab, an anti-CD38 human IgG1κ monoclonal antibody. GBR 1342 is a CD3xCD38 bispecific antibody engineered (using Glenmark's BEAT® platform) to direct T cells to CD38-expressing myeloma cells. In preclinical studies, GBR 1342 redirected the cytotoxic potential of T cells to human myeloma cell lines in vitro and in mouse xenograft models. This ongoing, 2-part, first-in-human study aims to: (1) evaluate the safety profile and maximum tolerable dose (MTD) of GBR 1342 monotherapy in subjects with relapsed/refractory multiple myeloma (>3 prior therapies); and (2) further elucidate the safety, tolerability, and preliminary clinical activity of GBR 1342 at the MTD. The study is also evaluating the mechanisms by which GBR 1342 redirects T cells to tumor and enhances cytolytic activity of cytotoxic T cells.

### Methods

In Part 1, intravenous GBR 1342 is administered on Day 1 and Day 15 in 28-day treatment cycles at escalating dose levels. The first 4 cohorts consist of a single subject. Subsequent cohorts will enroll using a 3+3 design. In Part 2, 65 evaluable subjects will be treated at the MTD identified in Part 1 until disease progression or unacceptable toxicity occurs. Primary endpoints include frequency and severity of AEs, number of dose-limiting toxicities during Cycle 1 (Part 1 only), and objective response to GBR 1342 (Part 2 only). Secondary endpoints include pharmacokinetics and anti-tumor activity of GBR 1342 (objective response, progression-free and overall survival).

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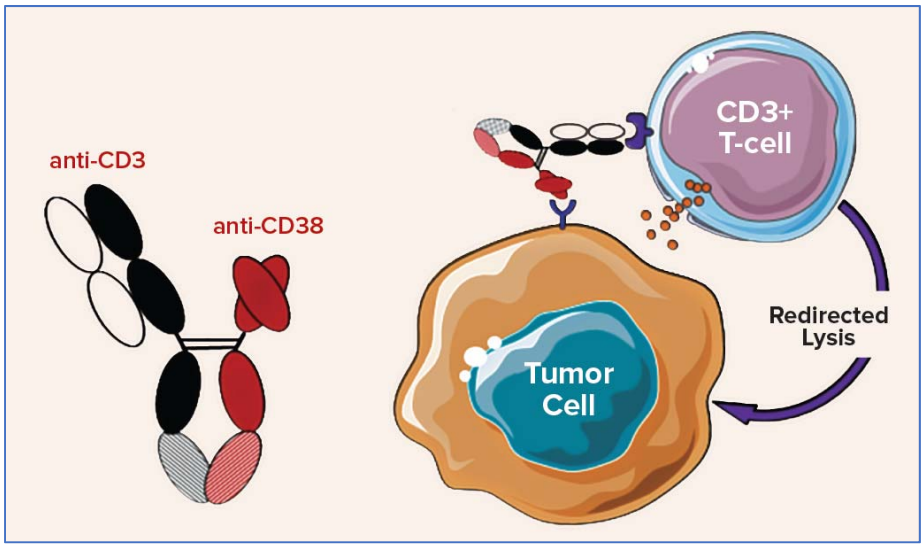
# KEY FINDINGS

## GBR 1342 OVERVIEW

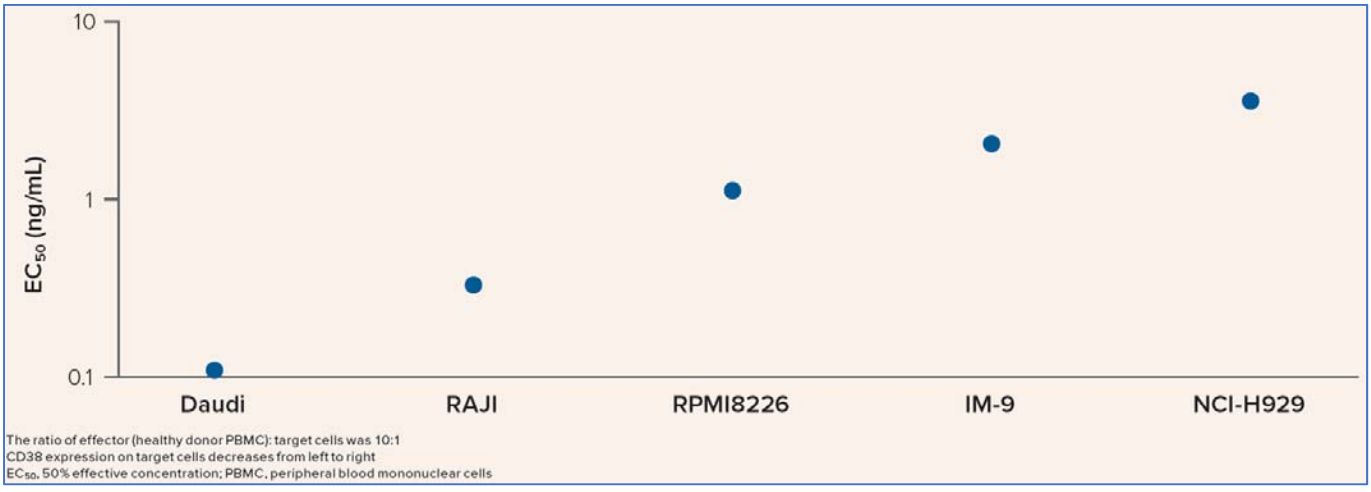
- GBR 1342 is a novel CD3xCD38 bispecific antibody engineered (using the Glenmark Bispecific Engagement by Antibodies based on the T cell receptor [BEAT®] platform) to direct T cells to CD38-expressing myeloma cells by engaging the CD3 molecule on T lymphocytes and the CD38 antigen on tumor cells, thereby killing the bound target cells through redirected lysis (**Figure 1**)
  - Includes a single chain, variable fragment arm with anti-CD38 specificity and a fragment antigen binding (Fab) arm with anti-CD3ε specificity
  - GBR 1342 has full antibody-like pharmacokinetics (PK) with a long elimination half-life of approximately 110 hours (in rats), which is similar to IgG and therefore permits intermittent dosing
  - GBR 1342 has low immunogenicity potential

**Figure 1. GBR 1342 Design**




- In preclinical studies, GBR 1342 demonstrated potent killing of CD38-overexpressing cancer cell lines, including multiple myeloma cell lines (**Figure 2**)
  - A direct correlation was observed between CD38 expression levels and efficacy of killing by GBR 1342, with greater antigen expression resulting in more potent killing

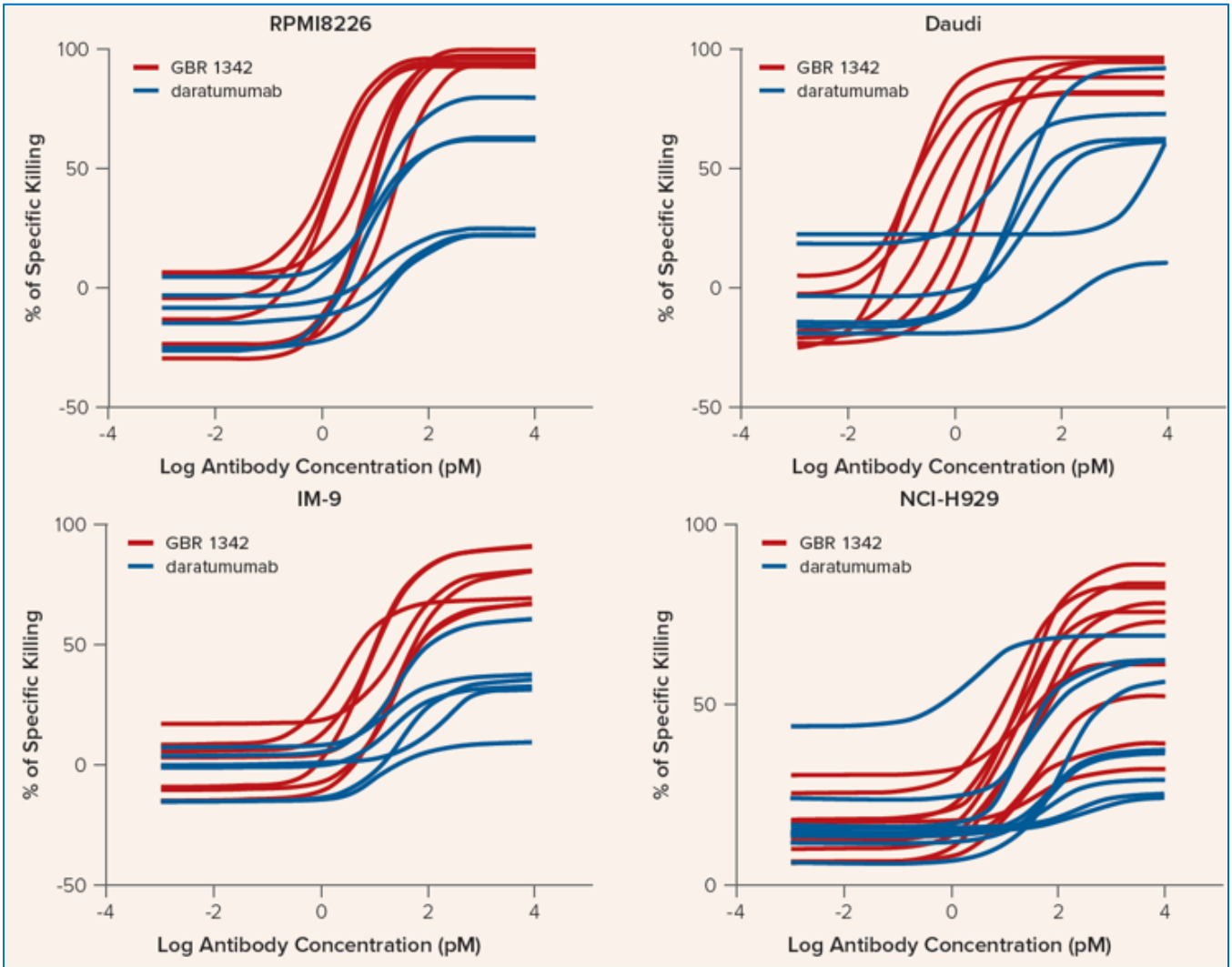
**Figure 2. GBR 1342 Killing of Target Cells Correlates with CD38 Expression**



## KEY FINDINGS

- In redirected lysis (RDL) assays, GBR 1342 demonstrated greater potency versus daratumumab on all cell lines tested, suggesting the redirecting ability of GBR 1342 affords more rapid and efficient T cell cytotoxic activity (**Figure 3**)
  - These data suggest that the unique mechanism of action of GBR 1342 may afford superior anti-tumor activity to patients with multiple myeloma compared with conventional CD38-targeting therapies (eg, daratumumab[1])

**Figure 3. Comparison of GBR 1342 and Daratumumab Potency in RDL Assays**




Graphs show non-linear curve fitting from each PBMC donor with the indicated target cell lines; the results represent at least 2 independent experiments per cell line
PBMC, peripheral blood mononuclear cell; RDL, redirected lysis

## PHASE I STUDY IN SUBJECTS WITH PREVIOUSLY TREATED MULTIPLE MYELOMA

- To evaluate the safety profile and maximum tolerable dose (MTD) of GBR 1342 monotherapy in subjects with relapsed/refractory multiple myeloma
- To further elucidate the safety, tolerability, and preliminary clinical activity (objective response, PK, immunogenicity) of GBR 1342 at the MTD
- To characterize the immunomodulatory effects triggered by GBR 1342

# KEY FINDINGS

## Dosing Schedule (Part 1)

- Intravenous GBR 1342 is administered on Day 1 and Day 15 in 28-day treatment cycles at escalating doses (**Table 1**)

### Table 1. GBR 1342 Dose Escalation Scheme

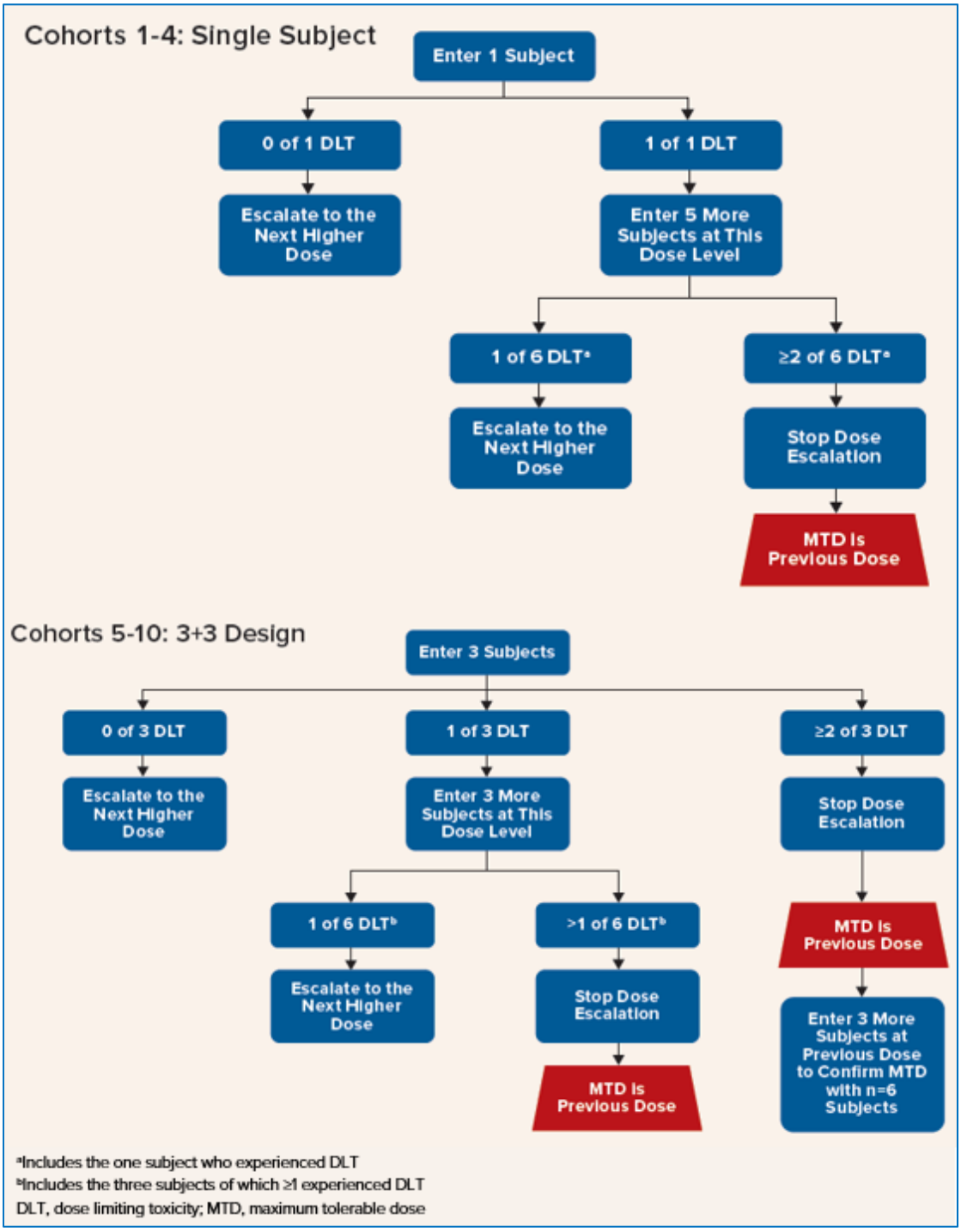
| | | Days of Cycle | | | | | |
|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | Cycle 2 | | Subsequent Cycle(s) | |
| | Cohort | Day 1 | Day 15 | Day 1 | Day 15 | Day 1 | Day 15 |
| Single Subject | 1 | 1 | 3 | 3 | 3 | 3 | 3 |
| | 2 | 3 | 10 | 10 | 10 | 10 | 10 |
| | 3 | 10 | 30 | 30 | 30 | 30 | 30 |
| | 4 | 30 | 60 | 60 | 60 | 60 | 60 |
| 3+3 | 5 | 60 | 100 | 100 | 100 | 100 | 100 |
| | 6 | 100 | 200 | 200 | 200 | 200 | 200 |
| | 7 | 200 | 400 | 400 | 400 | 400 | 400 |
| | 8 | 400 | 600 | 600 | 600 | 600 | 600 |
| | 9 | 600 | 800 | 800 | 800 | 800 | 800 |
| | 10 | 800 | 1000 | 1000 | 1000 | 1000 | 1000 |

Doses are in ng/kg

## Determination of Maximum Tolerable Dose (MTD)

- Dose escalation follows an accelerated design initially with 4 single subject cohorts (Cohorts 1-4) and switches to a classical 3+3 design with intra-subject dose escalation (**Figure 4**)
- Adverse events (AEs) constitute a dose limiting toxicity (DLT) if one of the following conditions applies:
  - Non-hematologic toxicity CTCAE Grade ≥3, except for:
    - Alopecia of any CTCAE grade
    - Any other CTCAE Grade ≥3 skin toxicity recovered to Grade ≤1 within 2 weeks after last dose
    - CTCAE Grade 3 fatigue recovered to Grade ≤2 within 2 weeks after last dose
  - ≥1 hematologic toxicities: CTCAE Grade 3 hemolytic anemia; CTCAE Grade 4 anemia; CTCAE Grade 4 neutropenia lasting 7 days; CTCAE Grade 3 or 4 febrile neutropenia; CTCAE Grade 3 thrombocytopenia lasting more than 7 days
  - Any other AE that in the opinion of the Data Safety Monitoring Committee constitutes a safety threat to the subject
- The observation period for DLT is the 28 days following the first administration of study drug (Day 1 of Cycle 1)
- Subjects will receive GBR 1342 treatment until either disease progression or unacceptable toxicity occurs

**Figure 4. Schematic for Determination of MTD**



# KEY FINDINGS

## STUDY ENDPOINTS

### *Primary*

- Frequency and severity of AEs
- Number of DLTs during the first 28 days after the first administration of study drug (ie, Cycle 1) (Part 1 only)
- Objective response to GBR 1342 according to International Myeloma Working Group (IMWG) response criteria[2] (Part 2 only)

### *Secondary*

- PK endpoints estimated after each dose administration
- Objective response to GBR 1342 according to IMWG response criteria (Part 1 only)
- Anti-tumor activity of GBR 1342 (Part 2), including: progression free survival (PFS); time to treatment failure (TTF); time to disease progression (TTP); overall survival (OS); duration of response; disease control rate (DCR); and duration of disease control compared with prior therapy
- Immunogenicity by anti-drug antibody (ADA) formation assessed from baseline until end of treatment (EOT)

### *Exploratory*

- Changes in pharmacodynamic (PD) biomarkers from baseline as surrogate markers for GBR 1342 activity, including:
  - Cellular biomarkers (CD3, CD4, CD8, CD25, CD38, CD69, and CD127) assessed by fluorescence-activated cell sorting (FACS) analysis of peripheral blood leukocytes
  - Cytokines (interleukin [IL]-2, IL-6, IL-10, interferon [IFN]-γ, tumor necrosis factor [TNF]) assessed in peripheral blood

## STUDY STATUS

- As of January 2018, the first clinical study of GBR 1342 (GBR 1342-101; NCT03309111) is currently recruiting and enrolling patients in the United States

## REFERENCES


1. Larocca A, Mina R, et al. *Oncotarget*. 2017;8(36):60656-72.
2. Rajkumar SV, Harousseau JL, et al. *Blood*. 2011;117(18):4691-5.