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

Therapeutic advances have improved outcomes in multiple myeloma but patients eventually relapse, requiring treatment with agents that are active in refractory disease. CD38, a transmembrane glycoprotein upregulated on myeloma cells, is a validated disease target as evidenced by the anti-myeloma activity of daratumumab, an anti-CD38 human IgG1κ monoclonal antibody. However, not all patients respond and many eventually develop progressive disease to daratumumab monotherapy.[1] GBR 1342, a CD3xCD38 bispecific antibody engineered (using Glenmark's BEAT® platform) to direct T cells to CD38-expressing myeloma cells, has the potential to overcome the limitations of existing therapies. 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 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.

Methods

In Part 1, intravenous GBR 1342 is administered on Days 1 and 15 in 28-day treatment cycles at escalating doses. The first 4 cohorts consist of a single subject. Subsequent cohorts use a 3+3 enrollment 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 AEs (frequency, severity), number of dose-limiting toxicities during Cycle 1 (Part 1), and objective response to GBR 1342 (Part 2). Secondary endpoints include pharmacokinetics and anti-tumor activity of GBR 1342 (progression-free and overall survival).

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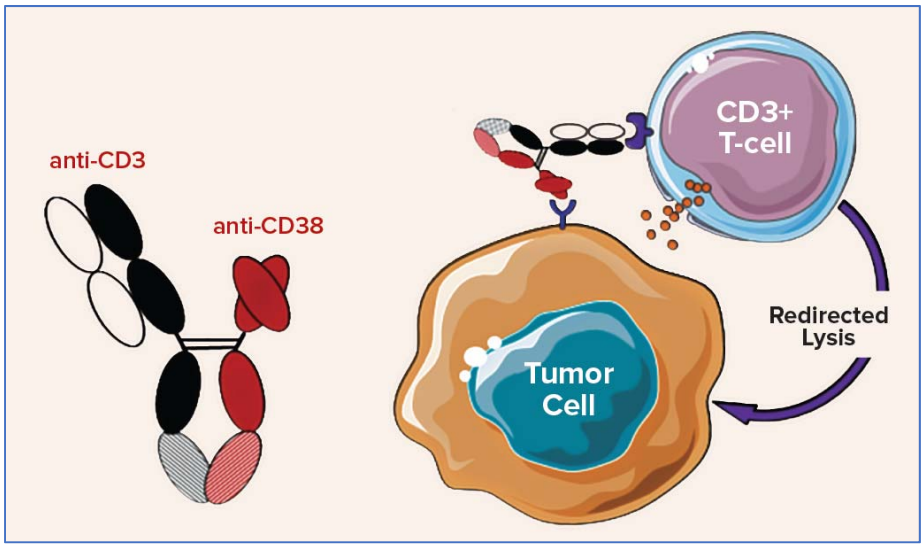
KEY FINDINGS

GBR 1342 OVERVIEW

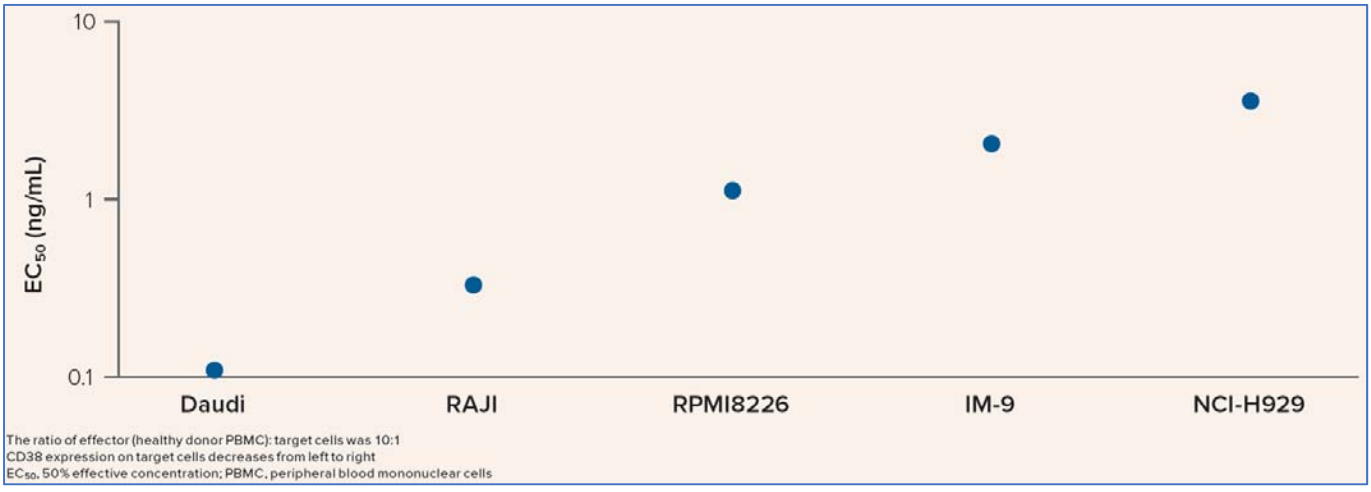
- GBR 1342 is a novel CD3xCD38 bispecific antibody engineered (using the Glenmark Bispecific Engagement by Antibodies based on the T cell receptor [BEAT®] platform) to direct T cells to CD38-expressing myeloma cells by engaging the CD3 molecule on T lymphocytes and the CD38 antigen on tumor cells, thereby 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

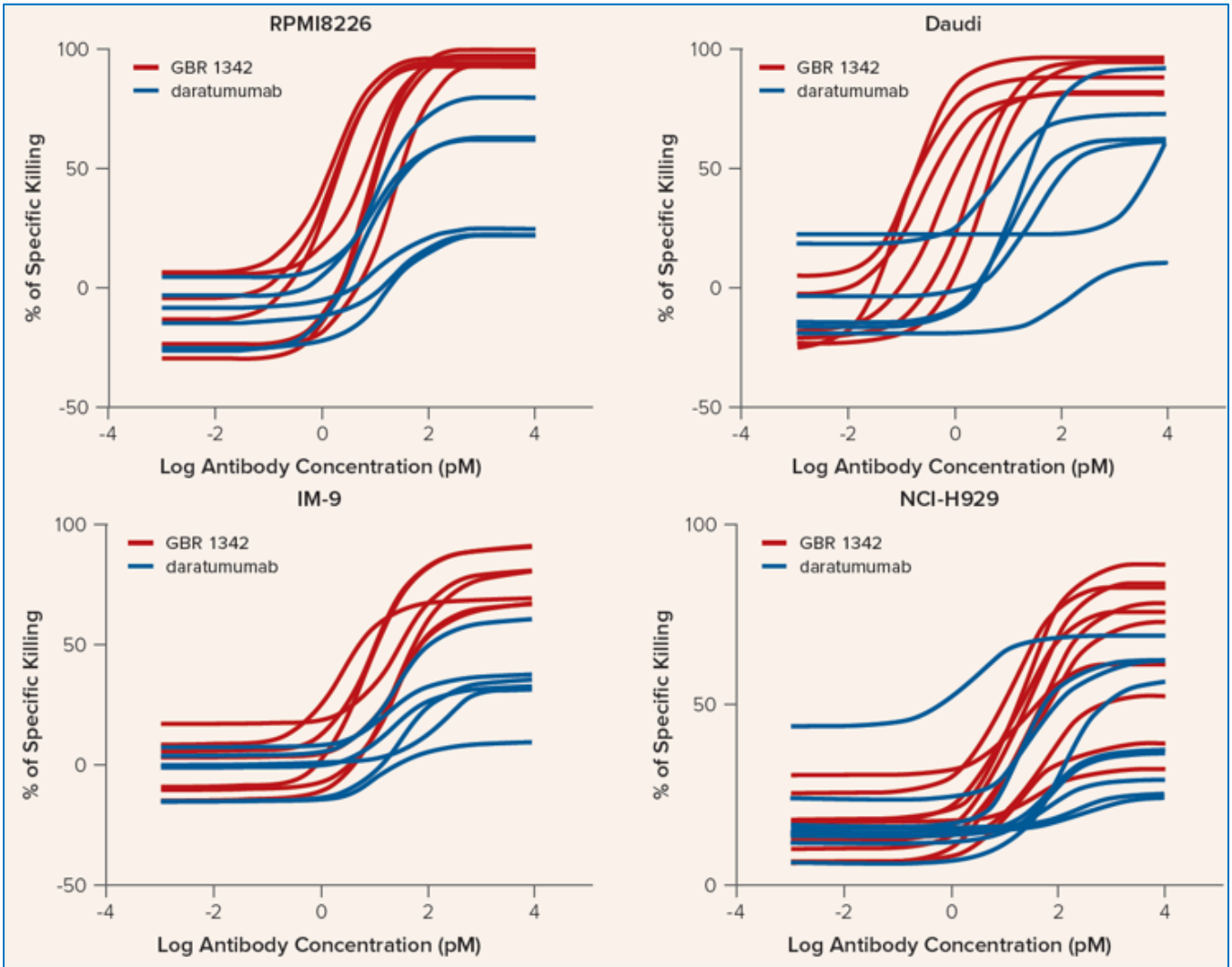
Figure 2. GBR 1342 Killing of Target Cells Correlates with CD38 Expression



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[2])

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

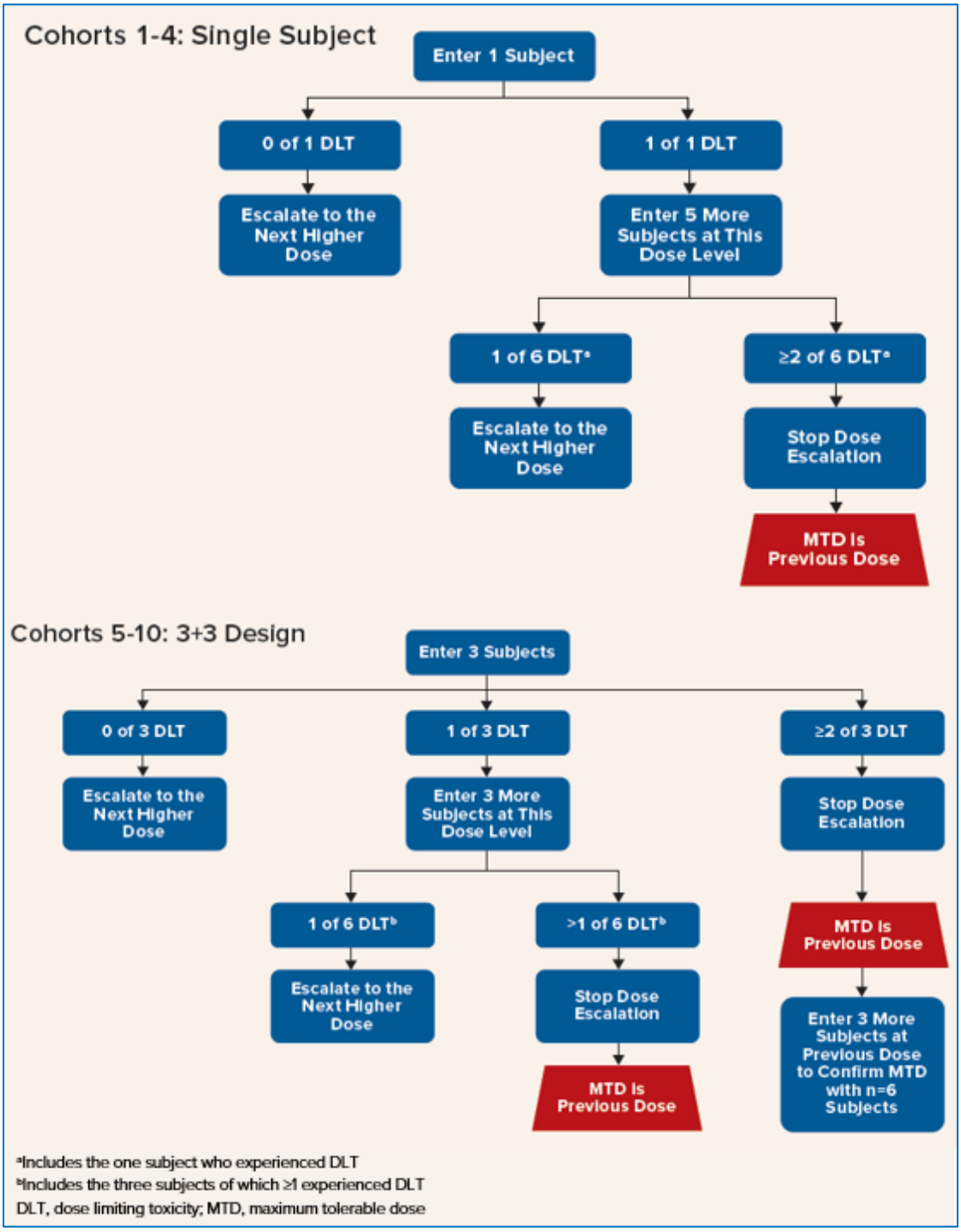
		Days of Cycle					
		Cycle 1		Cycle 2		Subsequent Cycle(s)	
	Cohort	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
Single Subject	1	1	3	3	3	3	3
	2	3	10	10	10	10	10
	3	10	30	30	30	30	30
	4	30	60	60	60	60	60
3+3	5	60	100	100	100	100	100
	6	100	200	200	200	200	200
	7	200	400	400	400	400	400
	8	400	600	600	600	600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

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

REFERENCES

1. Nijhof IS et al. Blood 2016; doi.org/10.1182.
2. Larocca A, Mina R, et al. *Oncotarget*. 2017;8(36):60656-72.
3. Rajkumar SV, Harousseau JL, et al. *Blood*. 2011;117(18):4691-5.