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).
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

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 1. GBR 1342 Design**

**Figure 2. GBR 1342 Killing of Target Cells Correlates with CD38 Expression**
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, daratumumab2).

**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

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**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
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

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Days of Cycle</th>
<th>Subsequent Cycle(s)</th>
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<tbody>
<tr>
<td></td>
<td>Cycle 1</td>
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<td>Day 1</td>
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</tbody>
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Doses are in mg/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

KEY FINDINGS
Figure 4. Schematic for Determination of MTD

Cohorts 1-4: Single Subject

- Enter 1 Subject
  - 0 of 1 DLT
    - Escalate to the Next Higher Dose
  - 1 of 1 DLT
    - Enter 5 More Subjects at This Dose Level
      - 1 of 6 DLT*
        - Escalate to the Next Higher Dose
      - ≥2 of 6 DLT
        - Stop Dose Escalation
          - MTD is Previous Dose

Cohorts 5-10: 3+3 Design

- Enter 3 Subjects
  - 0 of 3 DLT
    - Escalate to the Next Higher Dose
  - 1 of 3 DLT
    - Enter 3 More Subjects at This Dose Level
      - 1 of 6 DLT*
        - Escalate to the Next Higher Dose
      - >1 of 6 DLT*
        - Stop Dose Escalation
          - MTD is Previous Dose
  - ≥2 of 3 DLT
    - Stop Dose Escalation
      - MTD is Previous Dose

*Includes the one subject who experienced DLT
*Includes the three subjects of which ≥1 experienced DLT
DLT, dose limiting toxicity; MTD, maximum tolerable dose
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 criteria3
  (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