

PRELIMINARY BIOMARKER AND PHARMACODYNAMIC DATA FROM A PHASE 1 STUDY OF SINGLE-AGENT BISPECIFIC ANTIBODY T CELL ENGAGER GBR 1302 IN SUBJECTS WITH HER2-POSITIVE CANCERS

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ABSTRACT

Background

HER2 is overexpressed in many solid tumors and is a validated therapeutic target. GBR 1302 is a HER2xCD3 bispecific antibody engineered (using Glenmark's BEAT[®] platform) to direct T cells to HER2 expressing tumor cells. GBR 1302-101 (NCT02829372) is an ongoing, multicenter, open-label, first in human study of GBR 1302 in subjects with HER2 positive cancers to evaluate the safety, tolerability, and preliminary efficacy of GBR 1302, and to elucidate the mechanism(s) by which it redirects T cells to tumor and enhances cytolytic activity of cytotoxic T cells.

Methods

Adults with progressive HER2-positive solid tumors with no available standard or curative treatment receive intravenous GBR 1302 on Day 1 and Day 15 in 28-day treatment cycles at escalating dose levels, starting at 1 ng/kg. The first 4 cohorts consist of a single subject; subsequent cohorts enroll using a 3+3 design. The primary and secondary efficacy and safety endpoints of this trial will be reported at the end of the study. Preliminary pharmacodynamic (PD) data are reported for cellular biomarkers and cytokines as assessed by FACS and ELISA in peripheral blood.

Results

Beginning at 30 ng/kg dosing of GBR 1302 (Cohort 4), numbers of peripheral blood CD3, CD4, and CD8 positive T cell populations decreased within 6 hours of initiating administration, but recovered to levels at or above baseline by 48 hours. A parallel, transient increase was observed in peripheral blood cytokines (IL-2, IL-6, IL-10, IFN- γ , TNF- α). At doses greater than 30 ng/kg, more pronounced cytokine increases were observed, which normalized at 12 hours. At the highest dose level for which data are available (n=8 subjects; Cohort 5), changes from baseline in cytokine expression at ~340 hours were greater by ~60-fold for IL-6, ~30-fold for IL-2, ~3-fold for IFN- γ , ~5-fold for TNF- α , and ~18-fold for IL-10. Two subjects treated at 100 ng/kg experienced Grade 1 cytokine release syndrome, evidenced by short-lived fever spikes. Dose escalation is ongoing.

Conclusions

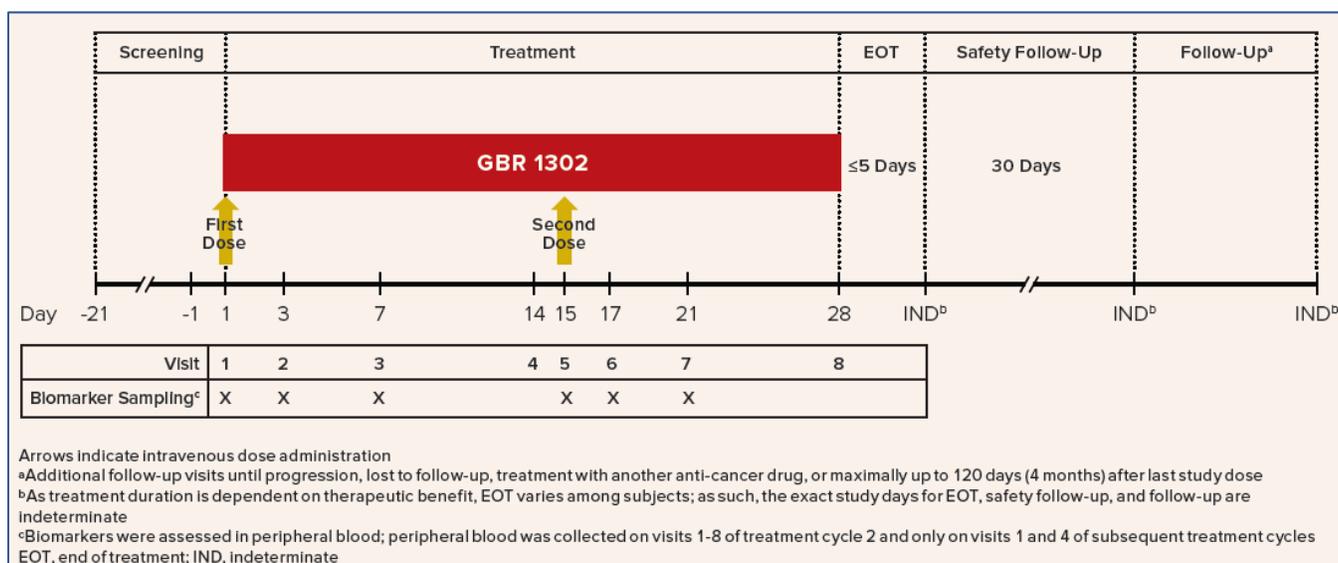
Preliminary PD data indicate changes in peripheral T cell populations and inflammatory cytokines following GBR 1302 treatment.

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STUDY DESIGN/STATUS

- A phase 1, multicenter, open-label, first-in-human study of GBR 1302 (NCT02829372) is currently ongoing and designed to evaluate the safety, tolerability, and preliminary efficacy of GBR 1302 in patients with HER2 positive cancers; the study additionally aims to characterize the immunomodulatory (or immunostimulatory) effects triggered by GBR 1302
- This ongoing study consists of two parts (**Figure 1**)
 - Part 1 Dose-Finding: currently enrolling 30 to 60 adult patients with progressive HER2-positive solid tumors (IHC positive), for which no standard or curative treatment is available, to determine the maximum tolerated dose (MTD) of GBR 1302
 - Part 2 Expansion: plans to enroll multiple patient cohorts to further evaluate the anti-tumor activity, safety profile, and pharmacokinetics of GBR 1302 administered at the MTD

Figure 1. GBR 1302-101 Study Design



Dosing Schedule (Part 1)

- GBR 1302 is administered intravenously on Day 1 and Day 15 in 28-day treatment cycles at escalating dose levels, starting at 1 ng/kg to planned maximum of 1000 ng/kg
- Cohorts 1-4 each consist of a single subject; subsequent cohorts enroll using a standard 3+3 design
- First administration of GBR 1302 is at the safe dose from the previous cohort; second and subsequent doses are at the designated higher dose
- Dose escalation is ongoing with enrollment of Cohort 8 (300 ng/kg first dose followed by 500 ng/kg every 2 weeks)

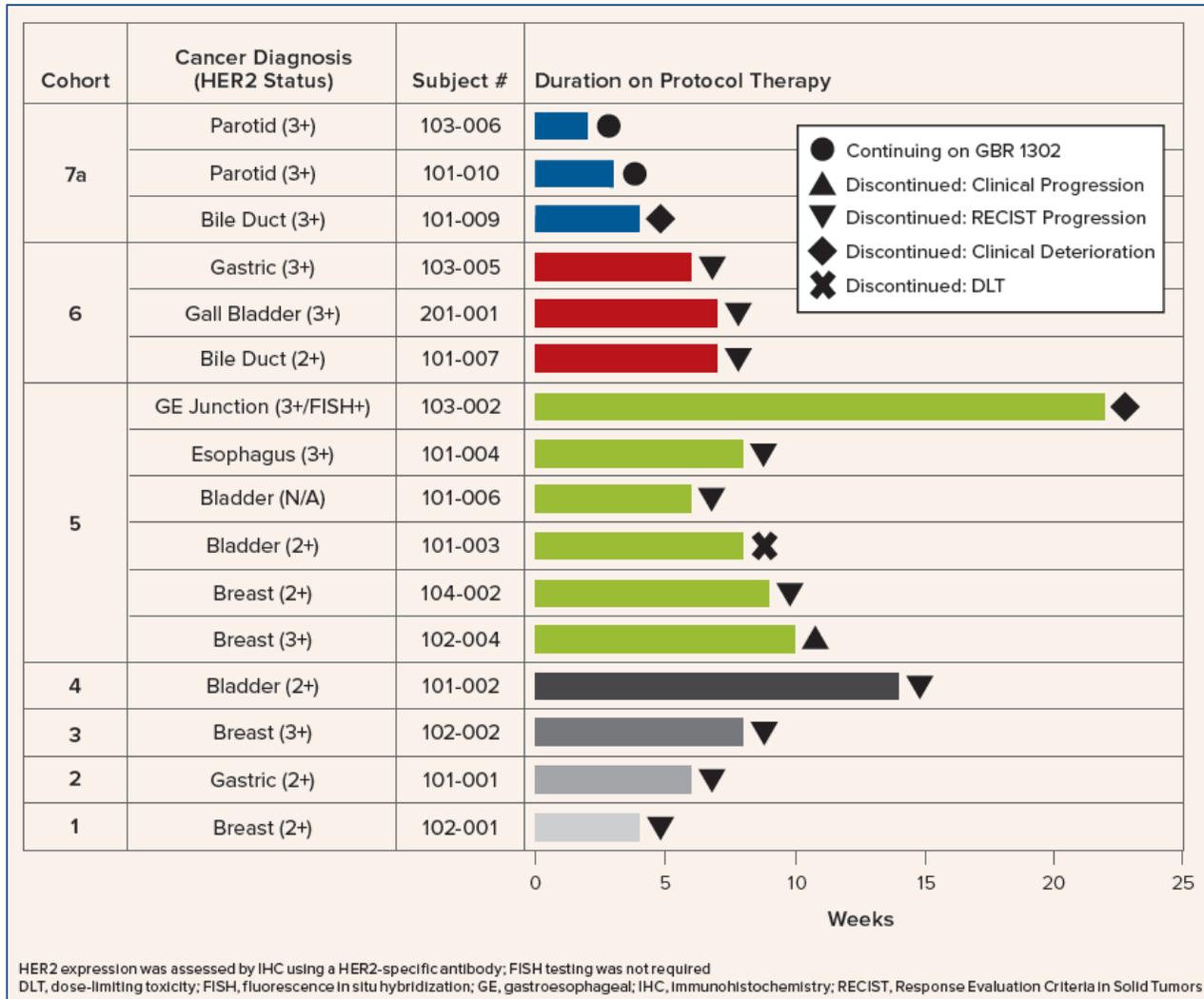
KEY FINDINGS

RESULTS

Duration on Protocol Therapy

- As of December 19, 2017, Cohorts 1-7 have completed the study
- Duration on protocol therapy varied among cohorts and between cancer diagnosis types (**Figure 2**)
 - Of interest, subject 103-002 remained on therapy for 20+ weeks; the subject had gastroesophageal cancer with 3+/FISH+ HER2 status

Figure 2. Duration on Protocol Therapy

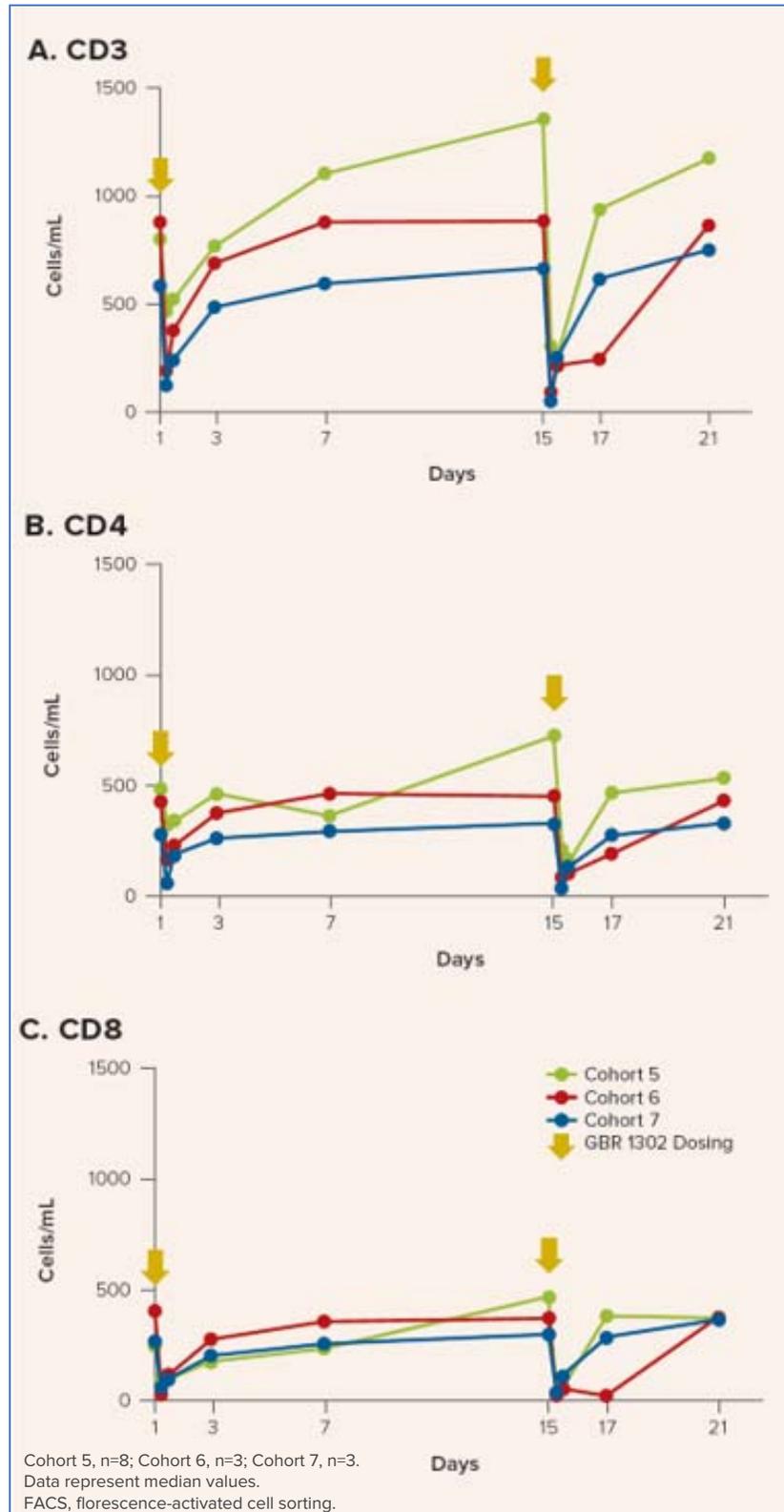


KEY FINDINGS

Cellular Biomarkers

- Beginning at 30 ng/kg dosing of GBR 1302 (Cohort 4), populations of peripheral blood CD3, CD4, and CD8 positive T cells decreased within 6 hours of initiating drug administration, but recovered to levels at or above baseline by 48 hours (**Figure 3**)

Figure 3. FACS Analysis of T Cell Markers Through Approximately 500 Hours

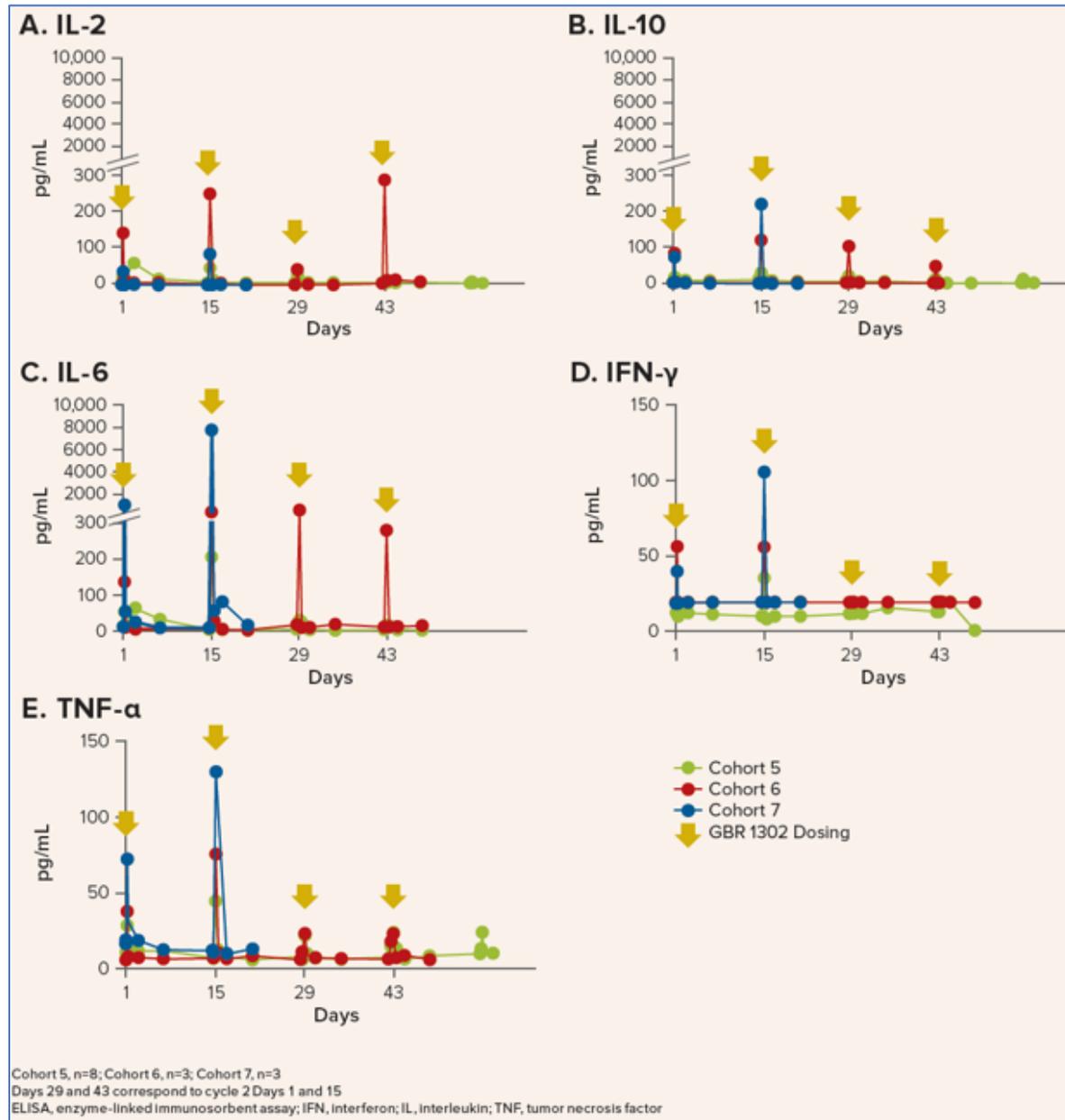


KEY FINDINGS

Cytokine Biomarkers

- A parallel, transient increase in peripheral blood cytokines was observed (**Figure 4**)
- At doses ≥ 30 ng/kg (Cohorts 3 and beyond), successively more pronounced cytokine peaks were observed with each higher dose, which normalized at 12 hours

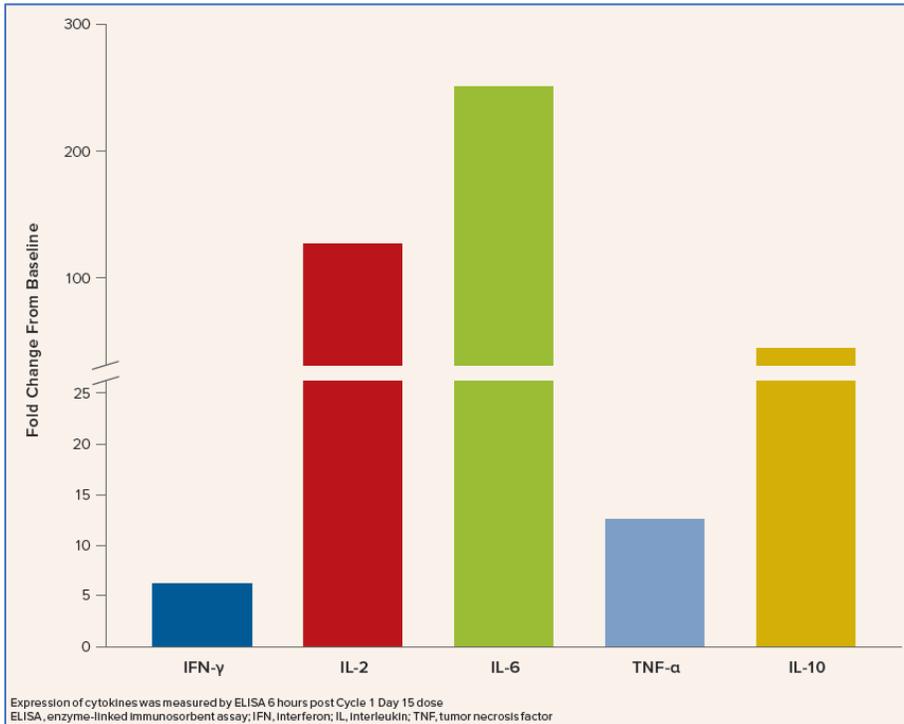
Figure 4. ELISA Analysis of Cytokines Through 1150 Hours



KEY FINDINGS

- Subject 103-002 (Cohort 5), who remained on therapy for the longest duration, demonstrated a distinct cytokine profile (**Figure 5**)
- Future subjects will be closely monitored to determine the relevance of this profile

Figure 5. Subject 103-002 Cytokine Profile



CONCLUSIONS

- Preliminary biomarker data indicate pharmacodynamic changes in peripheral T cell populations and inflammatory cytokines following GBR 1302 treatment
- Changes in T cell subsets and cytokines were generally transient
- The relationship between efficacy, safety, and pharmacodynamic biomarker changes is currently under investigation