A PHASE 1 STUDY OF GBR 1302 IN SUBJECTS WITH HER2-POSITIVE CANCERS

MARTIN WERMKE[1]; HELMUTH SCHMIDT[2]; SEBASTIAN OCHSENREITHER[3];
JONATHAN BACK[4]; YACINE SALHI[5]; ELIEL BAYEVER[6]

[1]UNIVERSITY HOSPITAL CARL-GUSTAV-CARUS, DRESDEN, GERMANY; [2]CELLEX GMBH, COLOGNE, GERMANY; [3]CHARITÉ UNIVERSITY OF MEDICINE, BERLIN, GERMANY; [4]GLENMARK PHARMACEUTICALS SA, LA CHAUX-DE-FONDS, SWITZERLAND;
[5]GLENMARK PHARMACEUTICALS EUROPE LTD, HERTFORDSHIRE, UNITED KINGDOM;
[6]GLENMARK PHARMACEUTICALS INC., MAHWAH, NEW JERSEY, UNITED STATES

ABSTRACT

Background

GBR 1302 is a bispecific antibody targeting human CD3ε and human epidermal growth factor receptor 2 (HER2), which is overexpressed in tumors. GBR 1302 was built using the Glenmark BEAT® platform and designed to recruit cytotoxic T lymphocytes against HER2-positive cancer cells. Preclinically, GBR 1302 has demonstrated potent killing of HER2-overexpressing human cancer cells (HER2 3+ or 2+ by IHC HercepTest), as well as growth suppression of the trastuzumab-resistant cell line JIMT-1. In contrast, the GBR 1302 concentration required to kill primary cardiomyocytes with normal HER2 levels was up to 1000 times greater than the amount needed to kill HER2 3+ tumor cell lines. This study aims to determine the safety and tolerability of GBR 1302 monotherapy in subjects with HER2-positive cancers.

Trial Design

Part 1 (dose-escalation) of this ongoing phase 1 study (NCT02829372) is enrolling adults with progressing HER2-positive solid tumors for which no standard or curative treatment is available. Intravenous GBR 1302 is given every 2 weeks in 28-day cycles at escalating doses. Each of the first 4 cohorts includes a single subject; subsequent cohorts will enroll subjects using a standard 3+3 design. Primary endpoints are maximum tolerated dose (MTD) of GBR 1302, and the relationship of GBR 1302 dose with the incidence, nature, and intensity of adverse events (AEs). After Cycle 1, subjects continue GBR 1302 treatment until disease progression or unacceptable toxicity. Part 2 (expansion) of this study will enroll subjects at the MTD to further evaluate anti-tumor activity of GBR 1302, as well as safety and pharmacokinetics. Due to the known cardiotoxic potential of classic HER2-targeting strategies, this study incorporates a rigorous serological and echocardiographic surveillance schedule. The effects of GBR 1302 on the adaptive immune system will also be studied at a cellular and serological level in a translational research program.

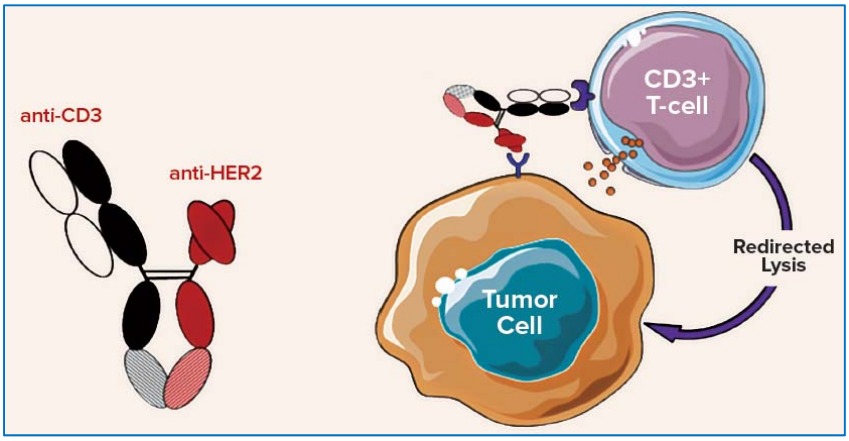
PRESENTED AT THE 4TH ANNUAL ESMO SYMPOSIUM ON IMMUNO-ONCOLOGY
NOVEMBER 4-6, 2016 | LAUSANNE, SWITZERLAND

KEY FINDINGS

GBR 1302 OVERVIEW

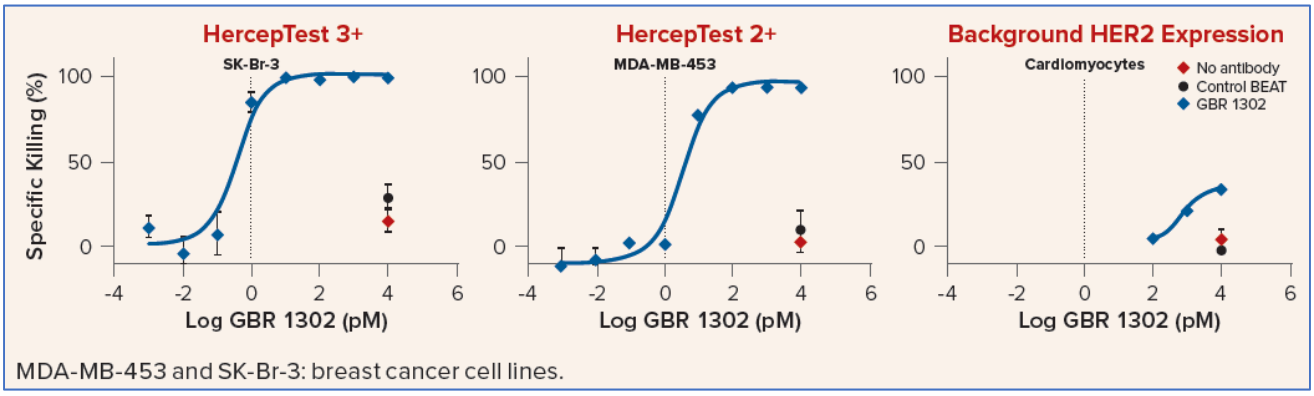
- GBR 1302 is a HER2xCD3 bispecific antibody, engineered using the Glenmark Bispecific Engagement by Antibodies based on the T-cell receptor (BEAT®) platform (**Figure 1**)
  - Includes a single chain variable fragment arm with anti-HER2 specificity (based on trastuzumab) and a fragment antigen binding (Fab) arm with anti-CD3ε specificity
  - GBR 1302 is designed to simultaneously engage the CD3 molecule on T lymphocytes and the HER2 antigen on tumor cells (HER2 3+ or 2+ overexpression), bridging cytotoxic T lymphocytes to tumor cells and thereby killing the bound target cells through redirected lysis
  - Compared to other bispecific T lymphocyte retargeting molecules, GBR 1302 has antibody-like pharmacokinetics with a long elimination half-life of approximately 138 hours (in rat and mouse), similar to IgG

Figure 1. GBR 1302 Design



- Preclinically, GBR 1302 has demonstrated potent and preferential killing of HER2-overexpressing cancer cells at low concentrations (**Figure 2**), as well as suppression of the growth of JIMT-1, a trastuzumab-resistant cell line (data not shown)

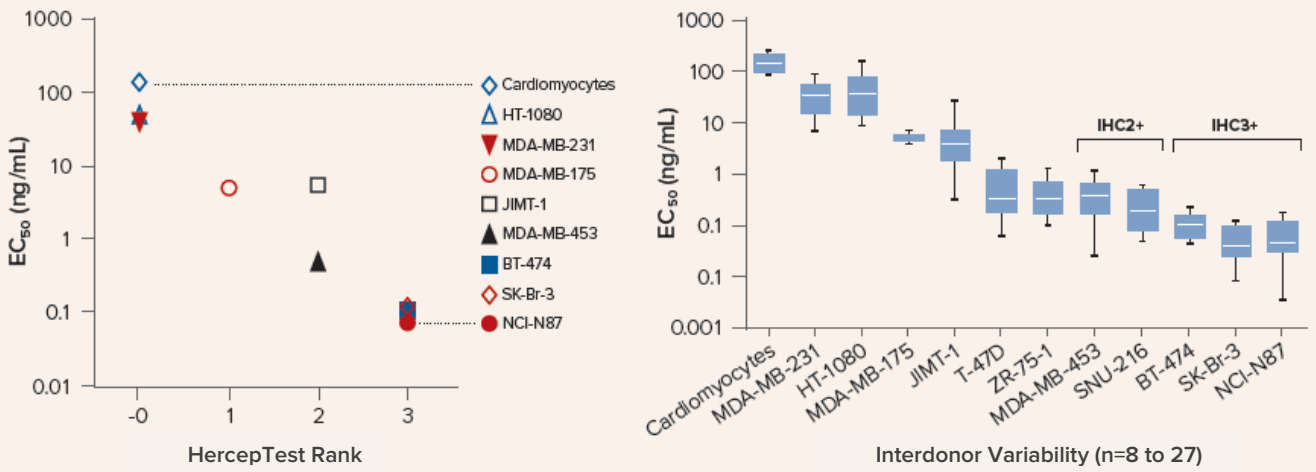
Figure 2. GBR 1302 Killing of Target Cells Correlates with IHC Rank/HER2 Expression



MDA-MB-453 and SK-Br-3: breast cancer cell lines.

- The concentration needed to kill primary cardiomyocytes with normal HER2 levels was approximately up to 1000 times greater than the concentration needed to kill HER2-overexpressing cell lines (**Figure 3**)
  - 2.5 to 3 log difference in killing potency between immunohistochemistry (IHC) 2+/3+ tumor cell lines and normal tissue (primary cardiomyocytes)
  - Interdonor variability of therapeutic window was small
  - Killing activity towards IHC2+ cell lines overlapped with killing activity against IHC3+ cell lines depending on T lymphocyte donor

Figure 3. Therapeutic Window of GBR 1302: HercepTest Rank



HercepTest rank for primary cardiomyocytes was set arbitrarily as 0.

PHASE I STUDY IN HER2-POSITIVE CANCERS (NCT02829372)

- To identify the maximum tolerated dose (MTD) and safety profile of GBR 1302 in subjects with HER2 positive cancers
- To characterize the anti-tumor activity, pharmacokinetics, and immunogenicity of GBR 1302

Dosing Schedule

- Intravenous GBR 1302 will be administered every 2 weeks in 28-day cycles at escalating doses (**Table 1**)

Table 1. Study Cohorts and Dose Escalation Schedule

Cohort	Cycle 1 (28 days)		Subsequent Cycles (28 days per cycle)	
	Day 1 Dose, ng/kg	Day 15 Dose, ng/kg	Day 1 Dose, ng/kg	Day 15 Dose, ng/kg
1 (single subject)	1	3	3	3
2 (single subject)	3	10	10	10
3 (single subject)	10	30	30	30
4 (single subject)	30	60	60	60
5 (3+3 design)	60	100	100	100
6 (3+3 design)	100	200	200	200
7 (3+3 design)	200	400	400	400
8 (3+3 design)	400	600	600	600
9 (3+3 design)	600	800	800	800
10 (3+3 design)	800	1000	1000	1000

KEY FINDINGS

Determination of Maximum Tolerated Dose

- Dose escalation follows a classical 3+3 design with accelerated escalation in the 4 lowest dose levels
- The observation period for dose-limiting toxicity (DLT) is the 28 days following the first administration of study drug in the subject (Day 1 of Cycle 1)
- DLT was defined as any of the following events:
  - Non-hematologic treatment-emergent adverse event (AE), Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher
  - Hematologic toxicity of CTCAE Grade 3 or higher lasting 7 days
  - Any new electrocardiogram abnormality
- After Cycle 1, subjects will continue GBR 1302 treatment until either disease progression or unacceptable toxicity takes place

Study Endpoints

Primary

- Maximum tolerated dose of GBR 1302, based on the number of DLTs during the first 28 days after the first administration of study drug (i.e., Cycle 1) in each cohort
- The relationship of GBR 1302 dose with the incidence, nature, and intensity of AEs, based on CTCAE grading

Secondary

- Objective Response Rate (ORR) - Complete Response (CR) or Partial Response (PR) for selected solid tumors
- Disease Control Rate (DCR) - CR or PR or Stable Disease (SD)
- Duration of disease control - Drug start date to the date of disease progression or death for subjects who had CR, PR, or SD during treatment
- Pharmacokinetics of GBR 1302
- Immunogenicity of GBR 1302 in terms of anti-drug antibody (ADA) formation assessed from baseline until end of treatment (EOT)

Exploratory

- Changes in pharmacodynamic biomarkers from baseline
- Difference in time on previous line of cancer treatment compared to GBR 1302
- Difference in time to disease progression on previous line of cancer treatment compared to GBR 1302

STUDY STATUS

- As of November 2016, currently recruiting participants at 4 centers in Germany