GBR 1302: EFFECT OF CD3-HER2, A BISPECIFIC T CELL ENGAGER ANTIBODY, IN TRASTUZUMAB-RESISTANT CANCERS

JONATHAN BACK[1]; MARTIN WERMKE[2]; JULIE MACOIN[1]; AMELIE CROSET[1]; JOHN KAUH[3]; VENKATESHWAR REDDY[3]

[1]GLENMARK PHARMACEUTICALS SA, LA CHAUX-DE-FONDS, SWITZERLAND; [2]UNIVERSITY HOSPITAL CARL-GUSTAV-CARUS, DRESDEN, GERMANY; [3]GLENMARK PHARMACEUTICALS INC, PARAMUS, NEW JERSEY, USA

ABSTRACT

Background

Current therapies targeting HER2 overexpressing cancers, such as Herceptin (trastuzumab) and Kadcyla (T-DM1), have proven beneficial but therapeutic benefit is limited by many resistance mechanisms. Checkpoint inhibition therapies demonstrate the potential of mobilizing T cell activities to elicit anti-tumor responses, but these T cell tumor-specific immune responses are highly immune contexture-dependent. Using Glenmark's BEAT® platform, we developed GBR 1302, a T cell redirecting antibody targeting CD3 and HER2, as an alternative way of leveraging T cell potency against tumor cells, independently of existing tumor immune response.

Methods

In vitro cytotoxic assays. In vivo tumor models. Ex vivo assay recreating native TME, including immune compartment, stroma and vasculature.

Results

Preclinical pharmacology studies demonstrated that GBR 1302 can trigger a potent killing of HER2 positive (IHC3+) as well as HER2 equivocal (IHC2+) cancer cells while maintaining an acceptable therapeutic window on cells expressing normal levels of HER2. In vitro assays, as well as in vivo tumor models comparing the potency of GBR 1302 to trastuzumab or T-DM1 demonstrated a superior cytotoxic potential for GBR 1302 against a variety of tumor cells and that GBR 1302 is effective in trastuzumab-resistant tumors in vitro and in vivo. To further translate these observations into a clinically relevant human context, we studied the effects of GBR 1302, as a single agent and combination partner, in a patient derived tumor microenvironment matched ex vivo assay with co-culture of autologous immune system and tumor tissue from 50 subjects with varying levels of HER2 expression ranging from 3+ to 1+. GBR 1302 treatment arm was compared to trastuzumab and to a combination of GBR 1302 + a PD-1 inhibitor on metastatic breast, gastric and gastro-esophageal cancers. GBR 1302 is currently in a phase 1 dose escalation clinical trial in HER2 positive and equivocal cancers. Preliminary data from peripheral blood biomarkers indicate that GBR 1302 triggers relevant T cell activation and cytokine production.

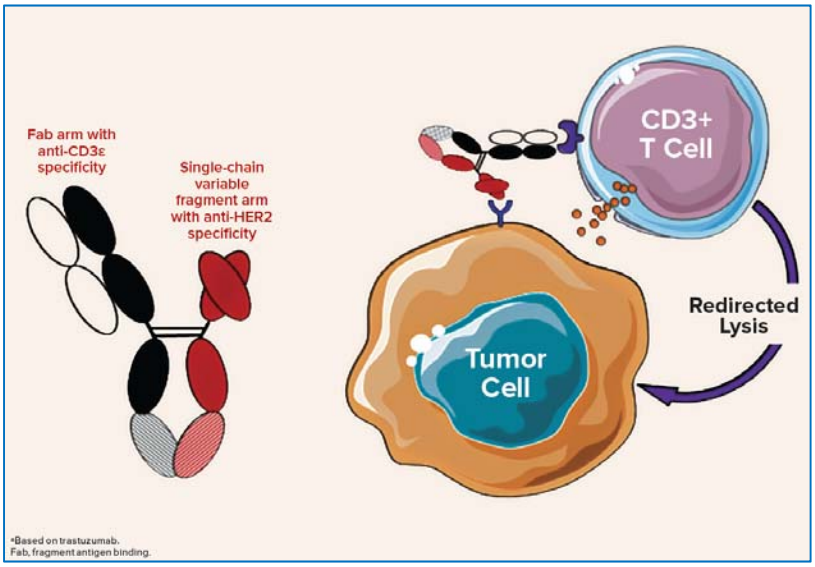
Conclusions

N/A

PRESENTED AT:
THE 54TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY
JUNE 1-5, 2018 | CHICAGO, IL

INTRODUCTION

Figure 1. GBR 1302 Design

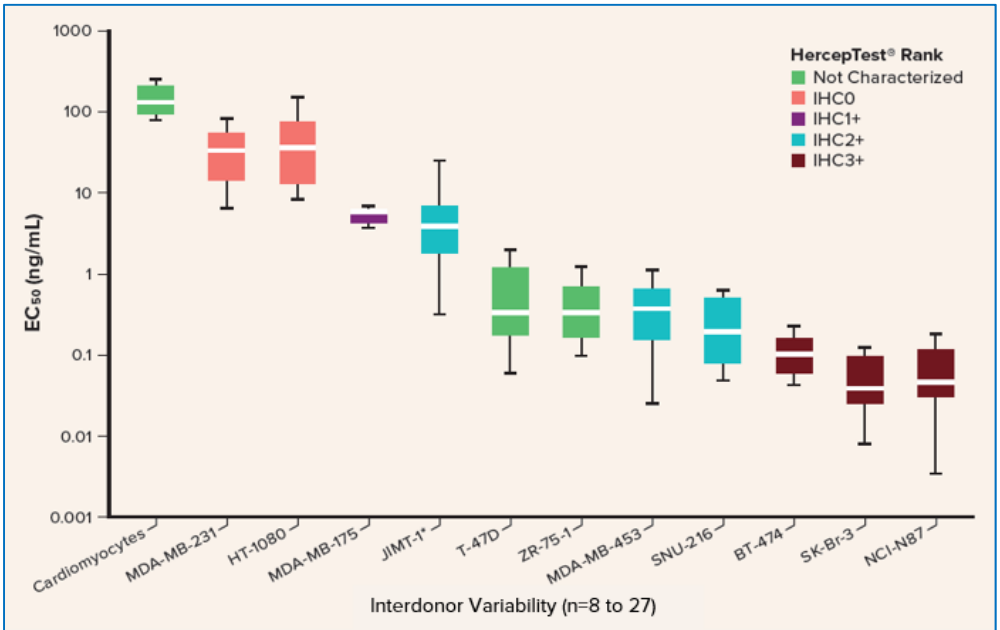


METHODS/RESULTS

Therapeutic Window of GBR 1302

- GBR 1302 triggers potent killing of HER2 positive (IHC3+) and HER2 equivocal (IHC2+) cancer cells, including the trastuzumab-resistant JIMT-1 cell line, while maintaining an acceptable therapeutic window (up to 1000-fold greater) on cells expressing normal levels of HER2 (**Figure 2**)
  - Interdonor variability of the therapeutic window was small
  - Potency on IHC3+ and IHC2+ overlapped

Figure 2. Therapeutic Window of GBR 1302



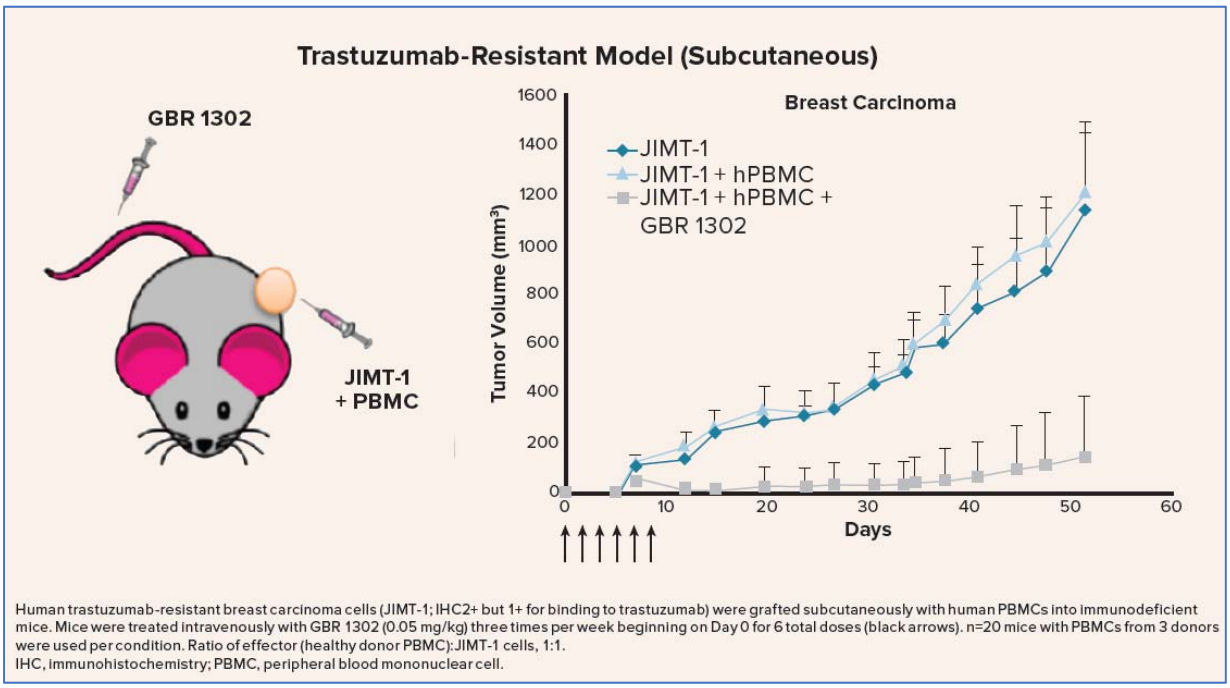
Cell lines were characterized using the HercepTest®. Cardiomyocytes, T-47D cells, and ZR-75-1 cells were not characterized by HercepTest. HercepTest rank for primary cardiomyocytes was set arbitrarily as zero. Ratio of effector (healthy donor PBMC): target cells, 10:1.T-47D and ZR-75-1 cells had HER2 levels by flow cytometry (specific antibody binding capacity) corresponding to IHC1/2+ and IHC2+, respectively.
*JIMT-1 cells are IHC2+ but due to masking of HER2 epitope are equivalent to IHC1+ for binding to trastuzumab.
IHC, immunohistochemistry; PBMC, peripheral blood mononuclear cell.

KEY FINDINGS

Cytotoxic Potential of GBR 1302 Versus Standard-of-Care Therapies

- In a trastuzumab-resistant model, GBR 1302 demonstrated potent tumor growth inhibition (**Figure 3**)

Figure 3. Cytotoxic Potential of GBR 1302: In Vivo Tumor Model

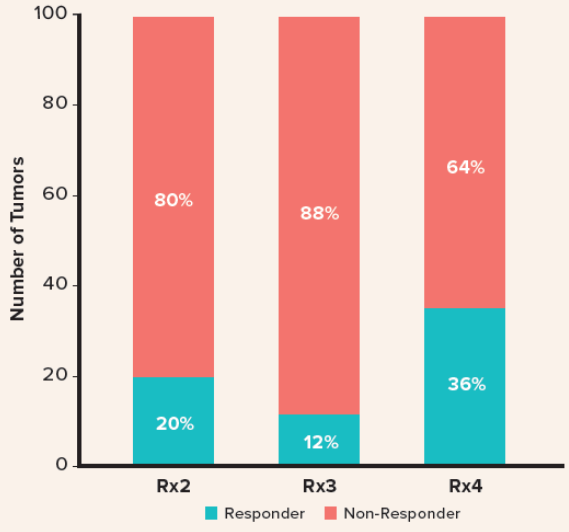


Human trastuzumab-resistant breast carcinoma cells (JIMT-1; IHC2+ but 1+ for binding to trastuzumab) were grafted subcutaneously with human PBMCs into immunodeficient mice. Mice were treated intravenously with GBR 1302 (0.05 mg/kg) three times per week beginning on Day 0 for 6 total doses (black arrows). n=20 mice with PBMCs from 3 donors were used per condition. Ratio of effector (healthy donor PBMC):JIMT-1 cells, 1:1.
IHC, immunohistochemistry; PBMC, peripheral blood mononuclear cell.

Response Rates by HER2 Status in Metastatic Breast and Gastric Cancer

- Metastatic breast cancer patients with IHC2+ and 3+ responded favorably to single-agent GBR 1302 and to combination with anti-PD1, compared with trastuzumab (**Figure 4**)
  - There was an overall predictive response rate of 20% to single-agent GBR 1302 and 36% to combination therapy of GBR 1302 with anti-PD1 in metastatic breast and gastric cancer patients

Figure 4. Primary Human Ex Vivo (CANscript) Studies to Identify Responders



Predictive responders (treatment outcome) are based on M-score that takes into account multiple input parameters for the given tumor specimen. Positive prediction of response: M-score >15; negative prediction of response: M-score <25.
Rx2, GBR 1302; Rx3, trastuzumab; Rx4, GBR 1302 + anti-PD1.

HER2 Status	Number of Samples	Number of Responders (% Responders)		
		GBR 1302	Trastuzumab	GBR 1302 + anti-PD1
Negative	4	0	0	1 (25%)
1+	6	0	0	1 (16.7%)
2+	8	**3 (37.5%)**	**1 (12.5%)**	**5 (62.5%)**
3+	7	2 (28.5%)	1 (14.3%)	3 (42.8%)
Total	**25**	**5 (20%)**	**2 (8%)**	**10 (40%)**

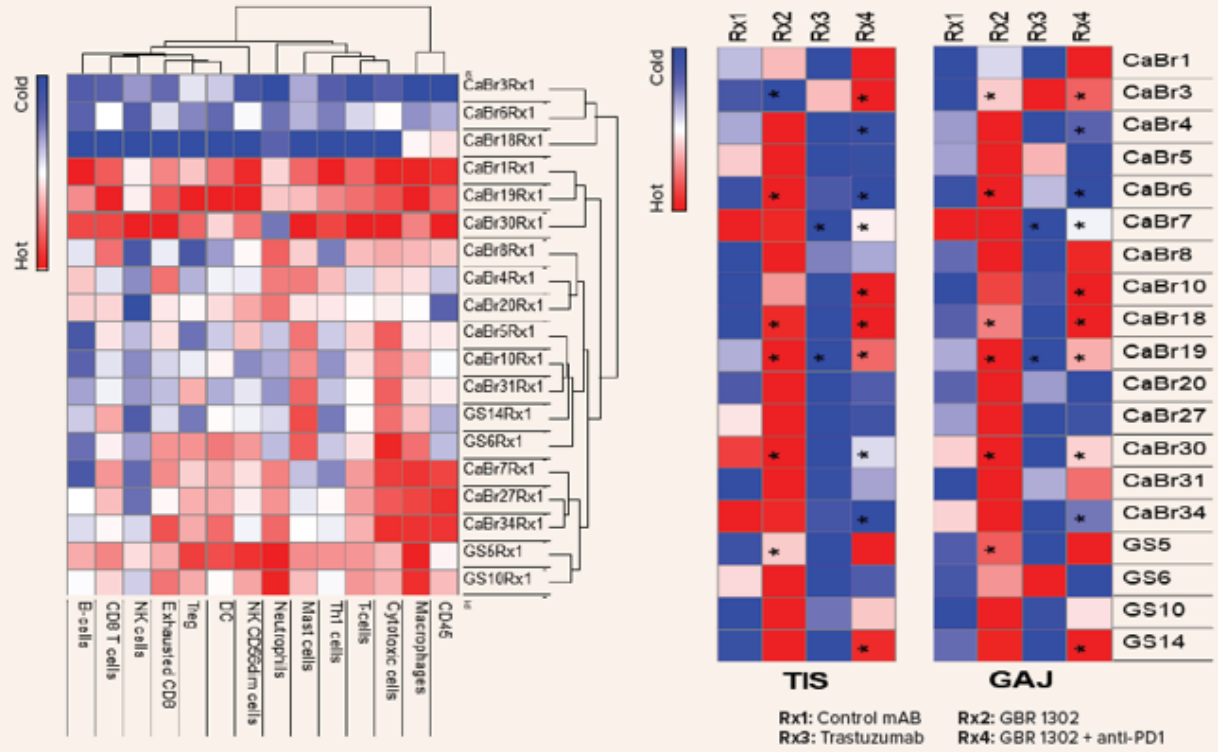
HER2 Status	Number of Samples	Number of Responders (% Responders)		
		GBR 1302	Trastuzumab	GBR 1302 + anti-PD1
Negative	14	2 (14.3%)	2 (14.3%)	5 (35.7%)
1+	4	1 (25%)	1 (25%)	1 (25%)
2+	3	0	0	0
3+	4	2 (50%)	1 (25%)	2 (50%)
Total	**25**	**5 (20%)**	**4 (16%)**	**8 (32%)**

KEY FINDINGS

Immune Cell Signatures of Tumors

- Immune signatures of breast cancers differed from gastric cancers (**Figure 5**)
  - In some instances, HER2 status tumors clustered together or close to each other
  - Diverse relative abundance of immune cells was observed at a subset level between samples
  - Relative to control mAb (Rx1), these signatures increased under the pressure of GBR 1302 (Rx2) and GBR 1302 + anti-PD1 (Rx4) compared with trastuzumab (Rx3)
  - The overall immune signature of the tumors changed from cold (blue) to hot (red) when treated with GBR 1302

Figure 5. Immune Cell Signatures of Metastatic Breast Cancer and Gastric Cancer



TIS and GAJ are two published RNA-based signatures with relevance to clinical response to anti-PD1 in melanoma and head and neck squamous cell carcinoma.

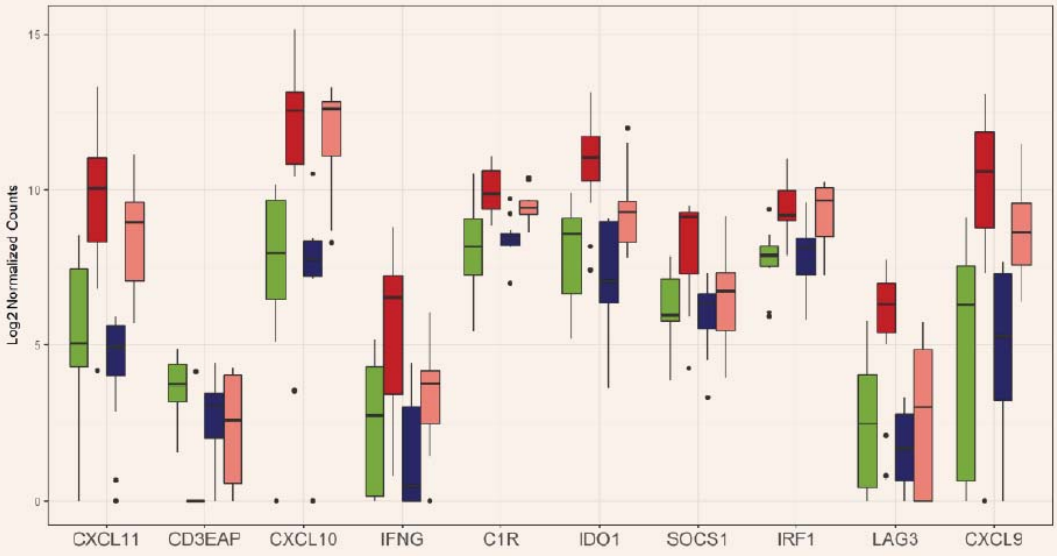
CaBr, breast cancer; DC, dendritic cell; GS, gastric cancer; mAb, monoclonal antibody.

KEY FINDINGS

Difference in Immune Signatures with GBR 1302

- CXCL9, 10, and 11 genes were regulated by IFNγ and DE genes in GBR 1302 predictive responders (**Figure 6**)
- Expression of potential immune resistance mechanism genes (eg, LAG3, IDO, CTLA4) was observed

Figure 6. GBR 1302 Versus Control Immune Signatures



mAb, monoclonal antibody; Rx1, control mAB; Rx2, GBR 1302; Rx3, trastuzumab; Rx4, GBR 1302 + anti-PD1; trt, treatment.

CONCLUSIONS

- GBR 1302 demonstrates potent killing of HER2 positive (IHC3+) and HER2 equivocal (IHC2+) cancer cells
- GBR 1302 displays superior cytotoxic potential versus standard-of-care therapies in multiple in vitro assays and in vivo tumor models, including in trastuzumab-resistant cells
- Translational studies identify predictive responders to GBR 1302 and to the combination of GBR 1302 with anti-PD1
  - Expansion of effector and memory T cells was observed in predictive responders in CANscript studies
  - Pro-inflammatory, IFNγ responsive genes are upregulated in predictive responders
- GBR 1302 is currently in a phase 1 dose escalation clinical trial in HER2 positive and equivocal cancers (NCT02829372)
  - Preliminary data from peripheral blood biomarkers indicate that GBR 1302 triggers relevant T cell activation and cytokine production[1]

REFERENCE

1. Wermke M, Alt J, Kauh J, et al. Poster presented at: ASCO-SITC Clinical Immuno-Oncology Symposium; January 25-27, 2018; San Francisco, CA.