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

INTRODUCTION

Although current therapies targeting HER2-overexpressing cancers have proven beneficial, including trastuzumab (Herceptin®) and ado-trastuzumab emtansine (T-DM1; Kadcyla®), patients often progress on therapy due to primary and/or acquired resistance mechanisms. Immune checkpoint inhibitors have demonstrated the potential of mobilizing T cells to elicit anti-tumor responses, but these tumor-specific immune responses are highly context-dependent.

GBR 1302 is a novel HER2xCD3 bispecific antibody engineered (using the Glenmark Bispecific Engagement by Antibodies based on the T cell receptor [BEAT®] platform) as an alternative way to leverage T cell potency against tumor cells independent of existing tumor immune response.

- GBR 1302 directs T cells to HER2-expressing tumor cells by simultaneously engaging the CD3 molecule on T lymphocytes and the HER2 antigen on tumor cells (HER2 2+ or 3+ overexpression), thereby killing the bound target cells through redirected lysis.

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.

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

- GBR 1302 displayed consistently superior killing of HER2-overexpressing target cells versus trastuzumab or T-DM1 independent of cell cycle, proliferation, and antibody-dependent cellular cytotoxicity.
- In a trastuzumab-resistant model, GBR 1302 demonstrated potent tumor growth inhibition (Figure 3).

Response Rates by HER2 Status in Metastatic Breast and Gastrointestinal Cancer

- Metastatic breast cancer patients with IHC2+ and IHC3+ 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.

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 (Rx3).
- The overall immune signature of the tumors changed from cold (blue) to hot (red) when treated with GBR 1302.

Difference in Immune Signatures with GBR 1302

- CXL19, 10, and 11 genes were regulated by IFNγ and DE genes in GBR 1302 predictive responders (Figure 6).
- Expression of potential immune mechanism genes (eg, LAG3, IDO, CTLA4) was observed.

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.

REFERENCES


DISCLOSURES

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