Enhanced HER2-dependent Immune Activation by Margetuximab, an Investigational Fc-engineered anti-HER2 mAb, Supports Combination with Checkpoint Blockade

Zhang, X., Li, H., Yang, Y., Xu, Q., Kaufman, T., Smith, D., Nordstrom, J., Bonvini, E., Moore, P.A.
MacroGenics Inc, Rockville MD and Brisbane CA

Abstract

Background: Margetuximab (M) has demonstrated anti-tumor activity in patients with advanced HER2+ gastric cancer and PFS superiority to trastuzumab (T) in pre-treated metastatic HER2+ breast cancer patients1. Similar to T, M inhibits HER2 signaling; additionally, M enhances engagement with the activating Fcy receptor (FcyRIIA), while diminishing interaction with the inhibitory FcγRIIB. Given the role of FcγR in coupling innate and adaptive immune responses, clinical studies of M in combination with PD-1 or PD-1+LAG-3 blockade have been initiated1. The combination of M with tebotelimab, an investigational bispecific DART molecule blocking PD-1 and LAG-3, has demonstrated encouraging early evidence of anti-tumor activity in patients with advanced HER2+ malignancies, including those with PD-1 negativity2,3. Here we present data supporting the potential mechanisms underlying the anti-tumor activity elicited by M and tebotelimab combination therapy.

Methods: PBMCs were challenged with HER2-expressing tumor cell lines in the presence of HER2-expressing tumor cells, demonstrating enhanced cytolytic activity against M-opsonized HER2-positive tumor cells. PBMCs, pre-treated with a combination of M and tebotelimab, had increased expression of both the canonical NK cell target, K562, or M-opsonized HER2-positive tumor cells.

Results:

Exposure to the combination of M with tebotelimab was evaluated.

- Induced greater upregulation relative to T of both the canonical NK cell target, K562, or M-opsonized HER2-positive tumor cells.
- Increased expression of both the canonical NK cell target, K562, or M-opsonized HER2-positive tumor cells.
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Conclusions: M, through its immune-stimulatory mechanism, can upregulate checkpoint molecules on myeloid, T- and NK cells in vitro, thereby sensitizing them to immune checkpoint inhibition. These effects were not observed with an FcγRIIIA null version of M or were inhibited by the addition of full length Aβ for dependence of FcγRIIIA interactions.

Introduction

Margetuximab: Fc-engineered anti-HER2 therapeutic mAb

- Engineering:
  - Fab: Same specificity and comparable affinity as trastuzumab
  - Increased affinity for both wild-type and variants of the HER2 extracellular domain (ECD) compared to Trastuzumab
  - Engagement of HER2+ tumor cells with margetuximab induces:
    - Engagement of HER2+ tumor cells with margetuximab induces:
      - Engagement of HER2+ tumor cells with margetuximab induces:
        - Engagement of HER2+ tumor cells with margetuximab induces:
          - Engagement of HER2+ tumor cells with margetuximab induces:

Margetuximab-mediated Engagement with HER-Positive Tumor Cells in Vitro

- Co-stimulation of Monocytes

- Induction of both checkpoint (PD-1 and LAG-3) and co-stimulatory (CD137) pathways

- Margetuximab Induces Enhanced PD-1 and MHC Class I Expression on Tumor Cells via an IFN-dependent Mechanism

- Margetuximab Induces Co-stimulation of Monocytes

Conclusions

- Engagement of HER2+ tumor cells with margetuximab:
  - Engagement of HER2+ tumor cells with margetuximab:
    - Engagement of HER2+ tumor cells with margetuximab:
      - Engagement of HER2+ tumor cells with margetuximab:

Acknowledgements

1. Patel et al., 2020 SITC poster presentation.
2. Patel et al., 2020 JAMA oncology.
3. Patel et al., 2020 JAMA oncology.
4. Patel et al., 2020 JAMA oncology.

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