Margetuximab Mediates Greater Fc-dependent Anti-tumor Activities than Trastuzumab or Pertuzumab In Vitro

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Comparative Inhibition of HER2 Extracellular Domain (ECD) Shedding by Margetuximab and Trastuzumab

Margetuximab (M) Mediates ADCC with Greater Potency than Trastuzumab (T) or Pertuzumab (P)

Margetuximab (M) Induces Greater Activation and Proliferation of NK Cells than Trastuzumab (T)

Conclusions

1. Binding Properties

2. Comparative Binding to HER2 by Margetuximab (M) and Trastuzumab (T)

3. Comparative Binding to SKBR-3 (HER2+) Cells by Margetuximab (M), Trastuzumab (T) and Pertuzumab (P)

4. Anti-proliferative Activities of Margetuximab and Trastuzumab Are Improved by Combination with Pertuzumab

5. Fc-dependent Activities

6. HER2 pathogens

7. ADC/C values obtained with NK cells of different CD16A genotypes

8. Potential implications of the results

Abstract

Introduction: Margetuximab (M), an investigational Fc engineered anti-HER2 monoclonal antibody (mAb), is being developed for the treatment of HER2-positive (HER2+) breast cancer and other solid tumors. M is a fully human IgG1 mAb engineered to express a higher Fc affinity to FcγRIII than that of Trastuzumab (T) or Pertuzumab (P).

Purpose: We compared in vitro properties of M, T and P and combinations of M+P and T+P to evaluate Fc domain contributions to receptor-mediated effects.

Methods: We used a recombinant HER2-His protein for Fc binding studies. HER2+ target cell shedding was measured using a HER2/HER2 antibody sandwich ELISA. NK cells were isolated from healthy donors and activated using anti-CD16A antibodies and anti-CD3/CD28 microbeads. NK cell viability and activation was measured using a viability dye and intracellular expression of CD107a and Granzyme B.

Results: Binding affinity of M and T were unchanged if P was pre-bound, indicating lack of interaction. M, T and P were generally more active than M + T alone. Margetuximab (M) is an investigational Fc-engineered anti-HER2 monoclonal antibody (mAb) in development for the treatment of HER2+ breast cancer and other solid tumors. Margetuximab (M) is a fully human IgG1 mAb engineered to express a higher Fc affinity to FcγRIII than that of Trastuzumab (T) or Pertuzumab (P).

Comparison of Fc-dependent Activities

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ADC/C values obtained with NK cells of different CD16A genotypes

- For each NK cell donor:
  - M is always more potent (lower Emax) than T and is always more potent than P
  - Combination of M + P is always more potent than combination of T + P
  - Similar results obtained with HER2 G1/A and HER2 G1/B target cells