**TrasGEX**, a novel glyco-optimized anti-HER2 monoclonal antibody with improved ADCC activity: A Phase I clinical study in patients with HER2 positive tumors

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1Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; 2Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; 3Instituto Nazionale Tumori, Milan, Italy; 4Hubertus-Wald University Cancer Center, Hamburg, Germany; 5Department of Internal Medicine V (Hematology and Oncology), Innsbruck Medical University (IMU), Innsbruck, Austria; 6Glycotope GmbH, Berlin, Germany (ClinicalTrials.gov: NCT01409343)

**BACKGROUND**

- **TrasGEX** is a humanized and glycooptimized antibody against HER2 featuring fully human glycosylation
- Features optimized Fucosylation, BisecGlcNAc and fully human glycosylation
- Targets lower HER2 expressing tumors
- Polymorphism at position 158 with V for the high affinity FcγRIIIa allotypes
- Reduced / Elimination of core fucose leads to highly improved ADCC activity
- Additional indications
- Strong increase of anti-tumor ADCC (up to 140-fold)
- Active in tumors with lower HER2 expression pattern

**METHODS**

**Study Design:**
- Phase I, multicenter single agent inter-patient dose escalation, cohort of 3+3, followed by an extension group of 16 patients at the dose level deemed RP2D

**Primary Study Objective:**
- To determine the optimal dose and regimen of TrasGEX in patients with locally advanced and/or metastatic HER2-positive cancer

**Secondary Study Objectives:**
- To assess the pharmacokinetic profile of TrasGEX to determine the intrinsic activity of activity
- To assess the safety and tolerability of TrasGEX

**Study Population:**
- Adults (male and female) after failure of standard therapy
- HER2-positive in immunohistochemistry (at least +1) or ERBB2 gene amplification measured by FISH

- All FcγRIIIa allotypes
- All but two patients with grade 1 or 2 toxicity

- Non-linear PK is dose dependent

**Study Drug Administration:**
- Dose: 15 mg, 65 mg, 125 mg, 240 mg, 480 mg, 720 mg
- IV infusion over 90 min duration, every 3 weeks

- Steady state might be reached after 4 infusions (need to be confirmed)

**Results:**

- **Patients disposition:**
  - 21 patients were treated in 6 cohorts. Additionally 16 patients were treated in an extension group at the highest dose level.
  - 28 patients were treated more than 8 weeks and received at least one post-dose CT

- **Safety:**
  - Infusion Related Reactions: 51.4%, all but two of grade 1 or 2
  - After introduction of premedication with steroids and paracetamol:
    - 33% (9/27) developed IRFs during 1st infusion
  - Grade 3: 2 patients
  - 0% (0/27) showed IRFs in one or two following infusions

- **Dosage Escalation:**
  - Final dosing scheme: premedication restricted to 1st infusion only (but repeated if a WFV occur), in order to avoid negative effect of premedication on ADCC effector cells
  - Typical symptoms for IRFs: chills, cold sensation, hypotension, fever, circulatory shock, diarrhea, dyspnea, anemia

- **Adverse events (listed only if greater than 10%):**

  - Grade 1: 3 patients, grade 2: 6 patients

  - Infusion Related Reactions: 9% (3/27) showed IRFs in one or two following infusions

  - Majority of patients showed dose-independent cytokine release

  - Infusion Related Reactions: mostly restricted to first infusion

  - Steady state might be reached after 4 infusions (need to be confirmed)

**Conclusions:**

- **TrasGEX** shows a clinical effect in nearly all cases
- Majority of patients showed dose-independent cytokine release of IL-6, IL-8, IP-10 and TNF-α in two (IL-10) which decreased within 24 h and was restricted to 1st infusion in nearly all cases
- Activity shown already at low dose levels

- **Infusion Related Reactions:**
  - Parotid gland: male patient (39 yrs), CR (RECIST 1.1) after 9 cycles of TrasGEX (720 mg ongoing >280 days at database lock, still under treatment with ongoing CR after 12 cycles of TrasGEX) (no IL-1β, no IFN-γ), Rapidly progressing tumor and skin lesions. No benefit from trastuzumab. Strong effect with TrasGEX (340 mg): full repair of skin lesion after 2 infusions. 72% reduction in sum of target lesion lesions (Hormone breast) at first CT scan at 8 weeks; strong reduction of lymph node infestation. FcγRIIIa status F (low binding affinity)

- **Additional indications:**
  - Breast: Female patient (44 yrs) with invasive ductal cancer since 2008, BR-β (Her2++), Rapidly progressing tumor and skin lesions. No benefit from trastuzumab. Strong effect with TrasGEX (340 mg): full repair of skin lesion after 2 infusions. 72% reduction in sum of target lesion lesions (Hormone breast) at first CT scan at 8 weeks; strong reduction of lymph node infestation. FcγRIIIa status F

**TrasGEX is active in patients with low HER2 expression

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- Non-linear PK is dose dependent

- Fully comparable with trastuzumab

- Infusion Related Reactions are mostly restricted to first infusion

- Strong activity observed on primary tumor, metastases, and others

- Very long half-life allowing 3-weekly dosage regimen

- *TrasGEX* is well tolerated up to 720 mg every three weekly dose

- *TrasGEX* is active in patients with low HER2 expression

- *TrasGEX* shows a clinical effect in nearly all cases

- Activity shown already at low dose levels

- Active in patients with lower HER2 expression (2+ and 1+)

- Active independent of FcγRIIIa polymorphism (ADCC)

- Strong activity observed on primary tumor, metastases, lymph node and skin lesions, and others

**RESULTS**

- **Patients disposition:**
  - Patients (Table A): Tumoral HER2 status (HER2+ = 4, HER2++ = 3, HER2+++ = 5)

<table>
<thead>
<tr>
<th>Tumor HER2 status</th>
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<tbody>
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<tr>
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</tr>
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- **Pharmacokinetics:**

  - No dose-limiting toxicity (DLT) and no maximum tolerated dose (MTD, to highest 720 mg dose)

- **Immunogenicity:**

  - No anti-drug antibodies were observed

**Pharmacokinetics:**

- Non-linear PK is dose dependent

- Fully comparable with trastuzumab

- PK profile after 1st infusion underestimates real terminal t1/2

- (as known for trastuzumab)

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**CONCLUSIONS**

- **TrasGEX** is well tolerated up to 720 mg every three weekly dose

- Infusion Related Reactions are mostly restricted to first infusion with low severity and good handling with premedication

- Very long half-life allowing 3-weekly dosage regimen

- Active in trastuzumab-resistant and refractory patients

- Activity shown already at low dose levels

- Active in patients with lower HER2 expression (2+ and 1+)

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