#2522: Activity results of the GATTO study, a phase Ib study combining the anti-TA-MUC1 antibody Gatipotuzumab with the anti-EGFR Tomuzotuximab or Panitumumab in patients with refractory solid tumors

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Abstract

Background The phase I GATTO study explored the feasibility, tolerability and preliminary activity of combining Gatipotuzumab (GAT), a novel humanized monoclonal antibody binding to the tumor-associated epitope of mucin-1 (TA-MUC1), and an anti-EGFR antibody. Preclinical evidence suggests a complex interaction between TA-MUC1 and EGFR on the cell surface of epithelial tumors and synergistic antibody dependent cell cytotoxicity activity with the double targeting

Methods Initially 20 patients with refractory metastatic disease were treated with GAT administered at 1400 mg Q2W in combination with the glyco-optimized anti-EGFR antibody Tomuzotuximab (TOM) at 1200 mg Q2W. Due to the risk of infusion related reactions, three cycles of TOM were given before start of combined treatment with GAT. After this regimen was proven safe and no DLT was observed, 30 additional patients including colorectal cancer (CRC) already treated with anti-EGFR antibodies, non-small cell lung cancer (NSCLC), head and neck and breast cancers received TOM and GAT administered at the same doses, with GAT treatment starting already one week after the first dose of the anti-EGFR antibody. As allowed in the study expansion, Panitumumab (PAN) was used in place of TOM in 9 CRC patients at investigator's choice

Results By the time of the final analysis in January 2021, 52 patients were enrolled, and 50 received at least one dose of both GAT and anti-EGFR antibodies. Safety was overall good and results are reported in a separate abstract. Because of the difference in treatment schedule, activity results of the two parts of the study are summarized separately. There were 2 and 4 RECIST partial responses in the first and second part of the study, all in CRC patients. In the expansion phase, the median Progression Free Survival (PFS) of CRC patients who received TOM (10) and PAN (9) was 1.9 and 5.5 months, respectively. There were 2 responses in each subgroup and the duration of response was 3.8 and 7.2 months in patients receiving TOM and PAN, respectively. The PFS for NSCLC was 5.3 months and 2 heavily pretreated patients achieved a prolonged control of disease of 10.6 and 9.4 months. The trial was accompanied by a comprehensive translational research program for identification of biomarkers, including soluble TA-MUC1 in serum. In the extension phase patients with baseline values above median appeared to have improved PFS and overall survival; this was not the case for patients of the first part of the study who received GAT only after 3 doses of TOM

Conclusions Combination of TA-MUC1 and EGFR targeting antibody is safe and feasible. Interesting anti-tumor activity was observed in heavily pretreated CRC and NSCLC patients. Levels of soluble TA-MUC1 may have predictive value and potentially be a companion biomarker for further development of the combination

rationale and methods

Gatipotuzumab (GAT) is a novel humanized monoclonal antibody, recognizing the tumor-associated epitope of mucin-1 (TA-MUC1), an aberrantly glycosylated Mucin 1 overexpressed in epithelial cancers. Tomuzotuximab (TO) is a second-generation anti-EGFR antibody.

As the complex interaction between EGFR and TA-MUC1 expressed on the tumor cell surface has been demonstrated to drive carcinogenesis [1-6], a Phase 1b trial combining Gatipotuzumab and an anti-EGFR antibody has been conducted in patients with refractory solid tumors.

1. Nath S and Mukherjee P, Trends Mol. Med., 2014; 20(6): 332-4;
2: Dharmaraj N *et al.* J Cell Biochem 2013; 114(10):2314-22;
3: Jin C, *et al.*)Oncogene 2013; 32(17): 2179-88;
4. Engel BJ *et al.* Oncotarget 2016; 7(22): 32796-809;
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Phase 1b, open label, multicenter (5 centers in Germany,Spain and Italy)

Primary phase:
GAT treatment (1400 mg/dose) started after 3 doses of TO (1200 mg/dose)

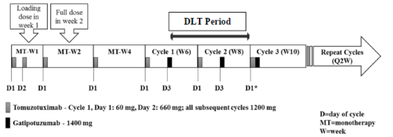


Figure 1: Treatment scheme in the 20 patients of the primary phase

Extension phase:
GAT treatment (1400 mg/dose) started 1 week after TO (1200mg/dose) or another anti EGFR

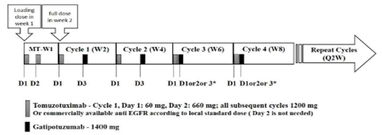


Figure 2: Treatment scheme in the 30 patients of the extension phase

Refractory metastatic cancer patients with measurable disease
EGFR IHC expression ≥25% of tumor cells locally assessed
Date of histology not older than 18 months from screening

Refractory metastatic cancer patients with measurable disease
25% EGFR IHC expression and histology < 18 months not required

The primary population for safety and efficacy analyses was the combined treatment population including all patients who received treatment at least once with both antibodies (Tomuzotuximab / Panitumumab and Gatipotuzumab).

Activity results by study phase

Primary phase: 20 patients
6 mCRC, 5 other GI, 4 pancreas, 3 H&N, 1GYN, 1 UK primary

Extension phase: 30 patients
19 mCRC, 4H&N, 5 NSCLC, 2BC
mCRC: 10 received Tomuzotuximab, 9 received Panitumumab

Figure 3: Kaplan-Meier curves for progression-free survival during the primary phase

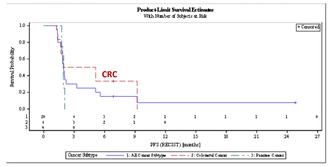


Figure 4: Kaplan-Meier curves for progression-free survival during the extension phase

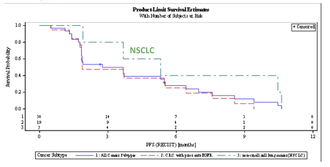


Figure 5: Kaplan-Meier curves for overall survival during the primary phase

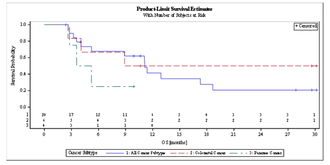
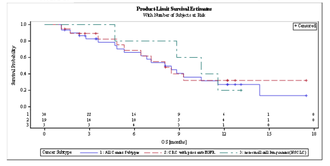


Figure 6: Kaplan-Meier curves for overall survival during the extension phase



Primary phase:
mPFS : 2.0 months
mOS 11.1 months

2 PR in a small subgroup of 4 mCRC patients who received prior anti-EGFR treatment

Extension phase:
mPFS : 2.8months ; mOS : 8.0 months
OS potentially affected by early censoring in S (16.7%) patients who withdrew IC shortly after PD
4 PR in mCRC patients who received prior anti-EGFR
Prolonged disease control in NSCLC patients (mPFS 5.3 months , mOS 10.5 months)

Activity results by soluble TA-MUC1

- **In a comprehensive translational program, several parameters including TA-MUC1, CA15-3, CA125, and EGFR were investigated against safety and efficacy outcomes, as IHC expression and/or in serum before and after Tomuzotuximab and Gatipotuzumab infusions**
- **A possible predictive role was observed only for baseline serum TA-MUC1 levels**
- **Baseline values of sTA-MUC1 above median (61.42 U/mL) appear a potential negative prognostic factor in primary phase patients (who received only 1 dose of combined treatment before first CT assessment) and possibly a positive factor in extension phase patients (who received 3 doses of combined treatment before first CT assessment)**

Primary Phase
sTA-MUC1 above median potentially a negative factor for OS

Figure 7: Kaplan-Meier Curves for Progression-free Survival (RECIST) by sTA-MUC1 Result at Baseline (<global median vs. >=g) (Combined Treatment Population, Primary Subjects)

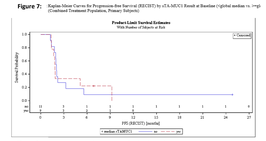
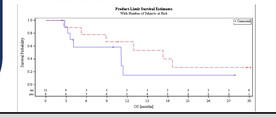


Figure 9: Kaplan-Meier Curves for Overall Survival by sTA-MUC1 Result at Baseline (<global median vs. >=global median) for all Can Treatment Population, Primary Subjects)



Extension Phase
sTA-MUC1 above median potentially a positive factor for PFS and OS

Figure 8: 1.1 Kaplan-Meier Curves for Progression-free Survival (RECIST) by sTA-MUC1 Result at Baseline (<global median vs. >=g (Combined Treatment Population, Extension Subjects)

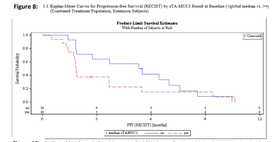
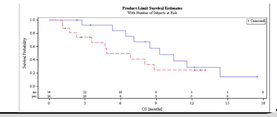


Figure 10: 2. Kaplan-Meier Curves for Overall Survival by sTA-MUC1 Result at Baseline (<global median vs. >=global median) for all Can Treatment Population, Extension Subjects)

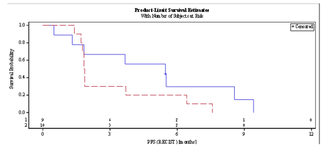


results in extension phase mCRC patients

- Taking into account the signal from the primary phase, in the extension phase all recruited mCRC patients had received prior anti-EGFR treatment (as a surrogate for RAS WT)
- Overall 19 mCRC patients were treated with Tomuzotuximab and Gatipotuzumab (10) or Panitumumab and Gatipotuzumab (9)
- Four RECIST PR were observed, 2 each in patients treated in combination with Tomuzotuximab or Panitumumab
- DOR, mPFS and mOS were numerically superior in the Panitumab group compared to the Tomuzotuximab group.
- Preliminary serum TA-MUC1 data look promising for predicting PFS and OS also in this subgroup of patients.

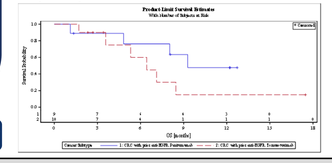
Numerically superior results with Panitumumab and GAT

Figure 11: Kaplan-Meier curves for progression-free survival during the extension phase in mCRC patients with prior anti-EGFR



- **Tomuxotuximab (N=10)**
  mPFS = 1.9 months
  PFSR at 3mo = 30.0%
  PFSR at 6mo = 20.0%
- **Panitumumab (N=9)**
  mPFS = 5.5 months
  PFSR at 3mo = 66.7%
  PFSR at 6mo = 29.6%

Figure 12: Kaplan-Meier curves for overall survival during the extension phase in mCRC patients with prior anti-EGFR



- **Tomuxotuximab (N=10)**
  mOS = 6.4 months
  OS at 3mo = 60.0%
  OS at 6mo = 15.0%
- **Panitumumab (N=9)**
  mOS = 9.3 months
  OS at 3mo = 76.2%
  OS at 6mo = 43.6%

Conclusions

- **Combination of TA-MUC1 and EGFR targeting antibody is safe and feasible.**
- **Interesting anti-tumor activity was observed in heavily pretreated CRC and NSCLC patients.**
- **The good safety profile is also expected to allow combination in future studies with established chemotherapy treatments such as Irinotecan, Docetaxel or Pemetrexed, potentially broadening treatment options for late-stage mCRC or NSCLC patients.**
- **Baseline sTA-MUC1 levels show promise as a predictive biomarker for efficacy outcome.**