#2524: Safety and tolerability 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 driving carcinogenesis processes, and synergistic antibody dependent cell cytotoxicity activity with the dual targeting.

Methods: Initially the study enrolled in a primary phase (PP) 20 patients with EGFR positive metastatic solid tumors, for whom no standard treatment was available. The first 6 patients were enrolled into a safety run-in phase and the number of dose-limiting toxicities (DLTs) was evaluated, in order to de-escalate the doses if needed. Patients received 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 (IRR), the first dose of TOM was reduced to 720 mg split over 2 consecutive days and three cycles of TOM monotherapy were given before start of treatment with GAT. As this regimen was proven safe, no DLT was observed and the initial dose remained unchanged, the study was amended to enroll in an expansion phase (EP) 30 additional patients with refractory colorectal cancer (CRC), non-small cell lung cancer (NSCLC), head and neck and breast cancers. TOM and GAT were given at the same doses and GAT treatment started already one week after the first dose of the anti-EGFR antibody. Additionally investigator had the choice to use a commercial anti-EGFR antibody in place of TOM .

Results: By the time of the final analysis in January 2021, 52 refractory patients were enrolled and 50 received at least one dose of both GAT and anti-EGFR antibodies. Panitumumab (PAN) was used in 9 CRC patients. Because of the difference in treatment schedule, results are summarized separately for the 20 and 30 patients in PP and EP. Overall, the combined treatment was well tolerated and no DLT was observed in the whole study, nor related SAE or death. There were no Treatment Emergent Adverse Events (TEAEs) leading to dose interruptions or reductions in the PP and 2/30 (6.7%) patients in EP stopped both TOM and GAT. 16 IRRs were reported in 8/20 (40%) PP patients, and 40 IRRs in 10 (33.3%) EP patients. Only one event of chills was severe and only 6 events were related to GAT in the EP, all others to TOM. Other frequent TEAEs were those commonly observed with anti-EGFR treatment such as skin toxicity in 17 (85%) PP and 26 (86.7%) EP patients and hypomagnesemia in 10 (50%) PP and 7 (23.3%) EP patients.

Conclusion: Combination of TA-MUC1 and EGFR targeting antibody is safe and feasible. Future studies should test this combination together with chemotherapy. (ClinicalTrials.gov Identifier: NCT03360734).

Rationale

MUC1 (also known as episialin, PEM, H23Ag, EMA, CA15-3 and MCA) is a transmembrane protein with a heavily glycosylated extracellular domain that extends up to 200-500 nm from the cell surface. Tumor Associated Mucin 1 (TA-MUC1) is aberrantly glycosylated and has gained attention as an oncogenic molecule, being commonly overexpressed in most human epithelial cancers cells (1). The loss of normal cell polarity causes TA-MUC1 to be redistributed over the cell surface and within the cytoplasm. TA-MUC1 expressing tumor cells become poorly adherent and metastatic. The barrier function of TA- MUC1 also potentially protects tumor cells from killing by the effector immune cells and a variety of cytotoxic drugs (1,2).

The well-known epidermal growth factor receptor (EGFR) pathway is often hyperactivated through overexpression of somatic mutation in multiple cancer types. The two main pathways activated by EGFR are the RAS–RAF–MAP kinase pathway and the PI3K–PTEN–Akt pathway. These pathways are involved in transmitting mitogenic signaling into the nucleus by regulating several transcription factors, which in turn control the expression of genes relevant for several cellular responses, such as cell proliferation, migration, differentiation, and apoptosis. (3)

Preclinical evidence suggests a complex interaction between TA-MUC1 and the EGFR pathway (4,5). The cytoplasmic domain of the MUC1 protein contains binding motifs for many signaling proteins including EGFR and its ligands, and also forms complexes with EGFR at cell membrane. An association of TA-MUC1 with EGFR has been demonstrated in several carcinomas and several reports have shown that expression of MUC1 inhibits EGFR degradation (3). TA-MUC1 also promotes the nuclear accumulation of EGFR independent of the addition of exogenous ligand. MUC1 has also been found to be specifically upregulated in response to EGFR-directed treatments in breast and lung cancer cell lines (6). MUC1 also increases expression and signaling of EGFR in cell lines of endometrial cancer, resulting in increased cellular proliferation, spheroid formation and survival. MUC1 knockout sensitizes cells to the EGFR inhibitor lapatinib. Finally MUC1-EGFR co-expression has been associated with increased cellular proliferation in human tumors (7).

Based on this complex preclinical interaction between EGFR and TA-MUC1 expressed on tumor cell surface in driving carcinogenesis, in this study we aimed to assess the tolerability, safety and preliminary activity of targeting both EGFR and TA-MUC1 with antibodies. The safety and tolerability results of the study are presented in this poster (#2524) whereas the activity results are presented in poster # 2522.

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Methods

STUDY DESIGN

The GATTO study was a single arm phase Ib study with the purpose to evaluate the safety and efficacy of combined therapy with Tomuzotuximab (TO) and Gatipotuzumab (GAT) in patients with metastatic solid tumors. Treatment started with the administration of TO, since this antibody is more glyco-engineered than GAT and is known to induce more frequent and severe infusion related reactions, whose occurrence tends to decrease after repeated administrations. Thus enrolled patients received an initial dose of 720 mg i.v. of TO followed after one week by subsequent doses of 1200 mg every 2 weeks (Q2W). Additionally, the initial loading dose of TO was split over two days with 60 mg on day 1 and 660 mg on day 2 as prevention of IRRs.

The study was conducted in 2 parts.

In the first part of the study, starting from week 6, GAT was administered at a dose of 1400 mg i.v. Q2W; TO was given on day 1 of the cycle and GAT 48 hours later. From week 10 this interval could be avoided if no infusion related reactions occurred in the preceding weeks. The first 20 patients were allocated to five cohorts: Non-Small Cell Lung cancer (NSCLC), Gastrointestinal cancer (GI), Breast cancer (BC), Gynecological cancers (GYN), and miscellaneous tumors (limited to 20% of the total sample size).

Since there were no safety concerns after enrollment of the first 20 patients, an extension cohort of 30 patients was added as pre-planned in the original study protocol, with a focus on refractory CRC and other tumors with known anti-EGFR treatment sensitivity. The 30 additional patients of the extension cohort were allocated to the four cohorts: (i) refractory metastatic colorectal cancer (mCRC), who failed prior treatment with standard chemotherapeutics and both anti-vascular endothelial growth factor (VEGF) and anti-EGFR antibodies; (ii) recurrent and/or metastatic head and neck cancers who failed prior treatment with a checkpoint inhibitor and at least one line of chemotherapy as appropriate; (iii) refractory metastatic NSCLC who failed all standard treatment options; (iv) refractory metastatic BC who failed all standard treatment options. EGFR expression was not an inclusion criterion in the extension phase and it was possible to use a commercially available anti-EGFR at the physician's choice in the place of Tomuzotuximab.

In this study extension, patients started treatment with GAT already one week after first TO infusion. Furthermore, physicians had the possibility to replace TO with a commercial anti-EGFR antibody of their choice.

Treatment Scheme

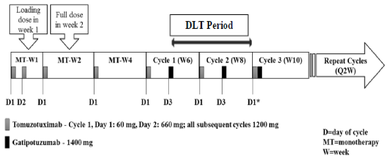

Figure 1: Treatment scheme in the 20 patients of the primary phase

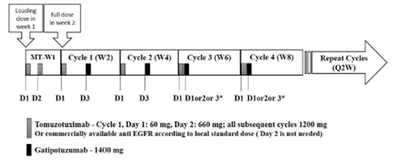

Figure 2: Treatment scheme in the 30 patients of the extension phase

PRIMARY STUDY ENDPOINT

- Incidence and severity of adverse events and infusion related reactions
- Overall tolerability (standard safety assessments – laboratory evaluations, vital signs, ECG, physical examination)

SECONDARY STUDY ENPOINTS

- Investigator assessed efficacy (ORR, DCR, DOR, PFS) based on RECIST 1.1 and irRECIST criteria
- Overall survival
- Immunogenicity

Results

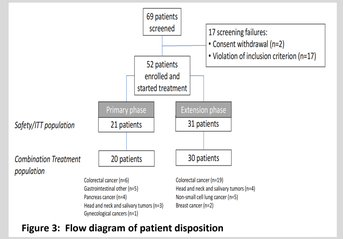

Figure 3: Flow diagram of patient disposition

Patients Disposition

- The Combined Treatment Population was the primary population for safety analyses. This included all patients who received treatment at least once with both antibodies (Tomuzotuximab or Panitumumab and Gatipotuzumab).
- Two patients in the Safety/ITT population (one in each study phase) received treatment at least once with Tomuzotuximab and interrupted treatment before starting Gatipotuzumab. Both patients stopped study treatment before receiving Gatipotuzumab because of disease progression
- Tomuzotuximab was administered in 20 patients in the primary phase and in 21 patients in the extension phase
- 9 mCRC patients in the extension phase received Panitumumab

Safety Results-Primary phase

Related TEAEs, n (%) Obs	Primary Patients (N=20)
Related Treatment Emergent Adverse Event	19 (95.0) 74
Skin and subcutaneous tissue disorders	**17 (85.0) 31**
Rash	14 (70.0) 21
Dermatitis acneiform	2 (10.0) 3
Dry skin	3 (15.0) 3
Skin toxicity	2 (10.0) 2
Metabolism and nutrition disorders	**12 (60.0) 16**
Hypomagnesaemia	10 (50.0) 11
Hypocalcaemia	3 (15.0) 3
Infections and infestations	**5 (25.0) 9**
Paronychia	4 (20.0) 8
Gastrointestinal disorders	**2 (10.0) 3**
Diarrhoea	2 (10.0) 3
General disorders and administration site conditions	**6 (30.0) 9**
Asthenia	3 (15.0) 3
Fatigue	2 (10.0) 4
Oedema peripheral	1 (5.0) 2

Table 1: **Related treatment-emergent adverse events (excluding IRRs) during the primary phase with >2% frequency**
n: number of patients, percentages are based on *n*, *Obs*: number of events

Safety Results- Extension phase

Related Treatment Emergent Adverse Event, n (%) Obs	Extension Patients (N=30)
Related Treatment Emergent Adverse Event	**27 (90.0) 75**
Rash	18 (60.0) 19
Hypomagnesaemia	7 (23.3) 9
Dermatitis acneiform	6 (20.0) 8
Pyrexia	1 (3.3) 6
Dry skin	3 (10.0) 3
Folliculitis	3 (10.0) 3
Nausea	3 (10.0) 3
Palmar-plantar erythrodysaesthesia syndrome	2 (6.7) 2
Paronychia	2 (6.7) 2
Diarrhoea	2 (6.7) 2

Table 2: **Related treatment-emergent adverse events (excluding IRRs) during the extension phase with >2% frequency**
n: number of patients, percentages are based on *n*, *Obs*: number of events

All 20 patients experienced 186 TEAEs overall

- The vast majority of reported TEAEs were mild to moderate (83.9%), while 26 events (14.0%) were severe, 3 (1.6%) were assessed as life-threatening, and 1 (0.5%) was fatal (unrelated pneumonia
- Nine TEAEs in 5 patients were reported as serious, none related to treatment drugs
- Of the 186 reported TEAEs, 90 (48.4%) were considered related to treatment, and 71 (38.2%) were considered TEAEs of special interest.
- All 90 TEAEs were considered related to Tomuzotuximab, including 16 IRRs observed in 8 patients. Twenty-two TEAEs were also considered related also to Gatipotuzumab

All 30 patients experienced 256 TEAEs overall

- The vast majority of reported TEAEs were mild to moderate (95.7%), while 10 events (3.9%) were severe, and 1 (0.4%) was assessed as life-threatening
- Five TEAEs in 5 patients were reported as serious, none related to treatment drugs.
- Of the 256 reported TEAEs, 115 (44.9%) were considered related to treatment, and 105 (41.0%) were considered TEAEs of special interest
- In total, 104 (40.6%) TEAEs were considered related to Tomuzotuximab or Panitumumab, including 35 IRRs reported in 10 patients treated with Tomuzotuximab. Thirty-one (12.1%) TEAEs were considered related to Gatipotuzumab, including 6 IRRs reported in 1 patient; 25 TEAEs in 16 patients were considered related to both antibodies

Conclusions safety results

- In both study phases, at the explored doses and with different treatment schedules and different anti-EGFR antibody, no DLTs were observed, nor was there any need to de-escalate.
- The safety profile of Gatipotuzumab and Tomuzotuximab in this study was consistent with the known safety profile of these drugs to date from prior studies
- Related adverse effects were mainly IRRs expected with Tomozutuximab and skin and metabolic toxicity commonly linked to anti-EGFR treatment
  Tomuzotuximab related IRRs were manageable, not requiring treatment discontinuation and mainly observed at first dosing
- Gatipotuzumab confirmed a favorable safety profile when administered in combination with either Tomuzotuximab or Panitumumab, also when treatment was started in close proximity to anti-EGFR treatment in the extension phase
- Overall, the safety data suggest that the combination therapy of Gatipotuzumab and Tomuzotuximab or an approved anti-EGFR antibody is feasible and tolerable, so that this doublet could potentially also be combined with chemotherapy in future studies