Tucatinib, a HER2 selective kinase inhibitor, is active in patient derived xenograft (PDX) models of HER2-amplified colorectal, esophageal and gastric cancers

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Background

- Tucatinib is a highly potent, orally bioavailable, HER2 selective receptor tyrosine kinase inhibitor
  - More than 1000-fold selective for HER2 compared with EGFR: HER2 IC_{50} 8 nM vs. EGFR IC_{50} >10,000 nM using a cellular signal transduction assay
  - HER2 selectivity may result in improved tolerability compared with dual HER2/EGFR inhibitors (anti-EGFR-related toxicities include high grade diarrhea and skin rash)
- Tucatinib is active in murine HER2+ cancer models
  - Active as a single agent and synergistic in combination with trastuzumab in breast tumor models [1]
  - Improved outcome compared to lapatinib or neratinib in preclinical HER2+ breast and gastric intracranial models[1, 2]
- An ongoing phase 1b study shows tucatinib, combined with capecitabine and trastuzumab, is active in patients with HER2+ metastatic breast cancer [3]
  - Well tolerated, with low rates of Grade 3 diarrhea at the recommended dose
  - PFS of 7.8 months and an overall response rate of 61%, with a median duration of response of 10 months
  - Responses and prolonged stable disease reported in heavily pre-treated patients with brain metastases
- In this report the activity of tucatinib alone, and in combination with trastuzumab, was evaluated in tumor xenograft models of HER2+ colorectal, esophageal and gastric cancers

Tucatinib is Active in the N87 Gastric Cancer Model

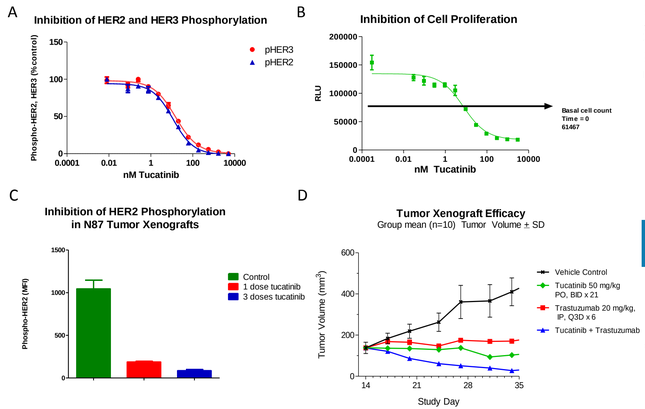

Figure 1. A. Phosphorylated HER2 and HER3 or B, cell proliferation, was measured in N87 tumor cells grown in vitro in the absence or presence of serial half-log dilutions of tucatinib with a starting concentration of 3.0 µM. HER2 and HER3 phosphorylation were measured by Luminex® 2 hrs. after drug administration. Cell proliferation was measured at 72-hours using the CellTiter-Glo® Assay (Promega). C. and D. N87 tumor cells were inoculated subcutaneously in the flank of athymic nude mice. Once tumors reached a volume of ~150 mm^3 mice were randomized into study groups (N=10). Tumors from satellite mice (N=3) were evaluated *ex vivo* for HER2 phosphorylation after 1 or 3 oral doses of 50 mg/kg tucatinib using Luminex®. In the efficacy study, mice were dosed by oral gavage with tucatinib, intraperitoneal trastuzumab or a combination of both drugs, at the dose levels and schedules as indicated.

Tucatinib is Active in HER2+ Gastric PDX Models

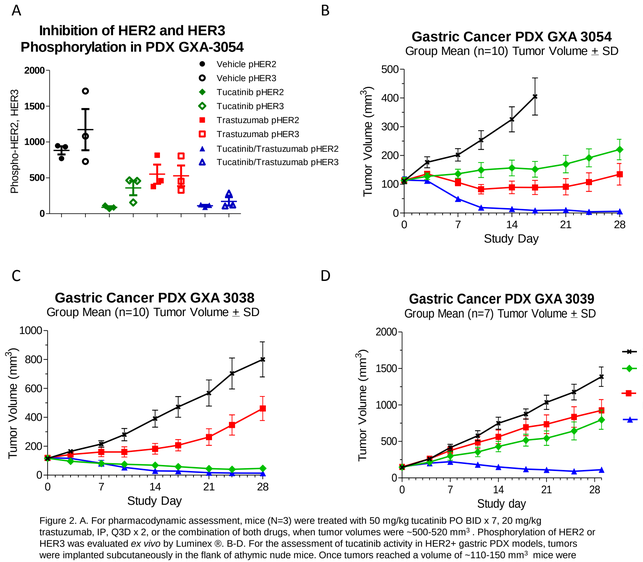

Figure 2. A. For pharmacodynamic assessment, mice (N=3) were treated with 50 mg/kg tucatinib PO BID x 7, 20 mg/kg trastuzumab, IP, Q3D x 2, or the combination of both drugs, when tumor volumes were ~500-520 mm^3. Phosphorylation of HER2 or HER3 was evaluated *ex vivo* by Luminex ®. B-D. For the assessment of tucatinib activity in HER2+ gastric PDX models, tumors were implanted subcutaneously in the flank of athymic nude mice. Once tumors reached a volume of ~110-150 mm^3 mice were randomized into study groups and treated by oral gavage with tucatinib, intraperitoneal trastuzumab or a combination of both drugs, at the dose levels and schedules indicated.

Tucatinib is Active in HER2+ Esophageal PDX Models

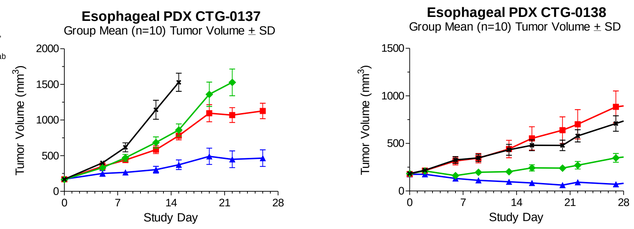

Figure 3. Tucatinib activity in HER2+ esophageal PDX models. Tumors were implanted subcutaneously in the flank of athymic nude mice. Once tumors reached a volume of ~165-185 mm^3 mice were randomized into study groups and treated by oral gavage with tucatinib, intraperitoneal trastuzumab or a combination of both drugs, at the dose levels and schedules indicated.

Tucatinib is Active in HER2+ Colorectal PDX Models

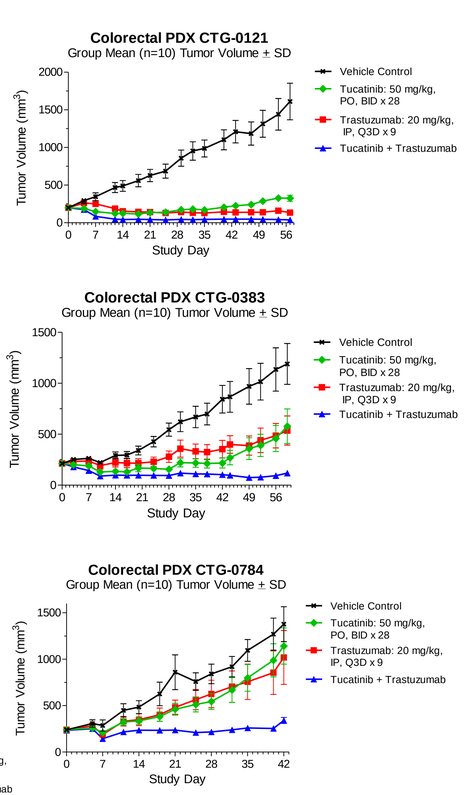

Figure 4. Tucatinib activity in HER2+ colorectal PDX models. Tumors were implanted subcutaneously in the flank of athymic nude mice. Once tumors reached a volume of ~200-240 mm^3 mice were randomized into study groups and treated by oral gavage with tucatinib, intraperitoneal trastuzumab or a combination of both drugs, at the dose levels indicated.

Summary of Activity in Tumor Xenograft Models

		TGI (%)			Tumor Response		
Tumor name	Cancer Type	Tucatinib	Trastuzumab	Tucatinib + Trastuzumab	Tucatinib	Trastuzumab	Tucatinib + Trastuzumab
CTG-0121	Colorectal	104	109	124	1/10 PR, 8/10 SD, 1/10 PD	4/10 PR, 6/10 SD	10/10 PR
CTG-0784	Colorectal	50	36	103	1/10 SD, 9/10 PD	1/10 SD, 9/10 PD	8/10 SD, 1/10 PD
CTG-0383	Colorectal	117	80	137	3/9 PR, 5/9 SD	6/10 SD, 4/10 PD	10/10 PR
CTG-0137	Esophageal	49	55	85	9/9 PD	10/10 PD	10/10 PD
CTG-0138	Esophageal	69	-34	120.1	2/9 SD, 7/9 PD	10/10 PD	7/10 PR, 1/10 SD
CTG-0927	Cholangiocarcinoma	48	63	86	10/10 PD	10/10 PD	2/10 SD, 7/10 PD
GXA-3038	Gastric carcinoma (Asian)	110	50	116	6/10 PR, 3/10 CR, 1/10 SD	10/10 PD	6/10 PR, 4/10 CR
GXA-3039	Gastric carcinoma (Asian)	48	38	103	7/7 PD	7/7 PD	3/7 PR, 4/7 SD
GXA-3054	Gastric carcinoma (Asian)	65	93	136	4/10 SD, 6/10 PD	3/10 CR, 1/10 SD, 6/10 PD	2/9 PR, 7/9 CR
NCI-N87	Gastric carcinoma	113	88	140	4/10 PR, 6/10 SD	6/10 SD, 4/10 PD	8/10 PR, 1/10 CR

%TGI calculated 0-2 days after the last day of Tucatinib dosing, except in CTG-0137 were TGI was calculated on day 15 due to rapid growth of tumors in the vehicle control group.
PR (partial regression) >30% reduction in tumor volume at time of first treatment for at least 2 consecutive measurements, CR (complete regression): no detectable tumor for at least 2 consecutive measurements, SD (stable disease): tumor volume between 70 and 120% of tumor volume at time of first treatment, PD (Progressive disease): tumor volume greater than 120% of tumor volume at time of first treatment

Conclusions

- The data presented in this poster show tucatinib is active in non-clinical models of HER2+ gastrointestinal malignancies, including colorectal, esophageal and gastric cancers
  - Tucatinib inhibits HER2 and HER3 phosphorylation and cell proliferation in the N87 gastric cancer cell line with single digit IC50s *in vitro* and blocks HER2 and HER3 phosphorylation *in vivo* in cell line and patient derived gastric cancer xenograft models
  - As a single agent, tucatinib was active in all HER2+ tumor models tested, with TGI ranging from 48-117%
  - The combination of tucatinib with trastuzumab displayed superior anti-tumor activity compared with either single agent, producing a higher proportion of partial and complete tumor regressions
- These data, together with clinical data in HER2+ breast cancer, support the evaluation of tucatinib in the clinical setting for the treatment of HER2+ gastrointestinal malignancies
  - An open label phase II clinical study combining tucatinib with trastuzumab in HER2+/RAS wild type metastatic colorectal cancer (MOUNTAINEER:NCT03043313) has recently been initiated

[1] Koch et al. AACR 2011; [2] Dinkel et al. AACR 2012 ; [3] Hamilton et al. ASCO 2015;

CASCADIAN THERAPEUTICS

Poster available at http://www.cascadianrx.com/product_pipeline/presentations.html