Randomized Phase 2 Study of Paclitaxel (PTX), Trastuzumab (T) with or without MM-111 in HER2 Expressing Gastroesophageal Cancers (GEC) #4043

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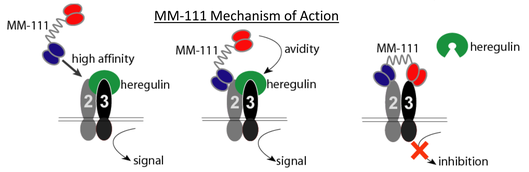
Introduction

BACKGROUND: HER2 overexpression occurs in ≤ 20% of GEC, and T-based front-line therapy improves survival. HER3 is overexpressed in ≤ 87% of GEC and is associated with poor prognosis. HER3 is activated by its ligand heregulin (HRG) to form a potent signaling heterodimer with HER2 and is emerging as a key tumorigenic node. MM-111, a bispecific antibody designed to inhibit HRG-activated HER3 signaling in HER2+ tumors, was evaluated in second-line treatment of advanced HER2+ GEC in combination with weekly PTX and T.

MM-111 Mechanism of Action



METHODS: Patients (pts) who progressed following fluoropyrimidine/platinum-based therapy +/- T for advanced disease or within 6 months of neoadjuvant/adjuvant therapy were randomized 1:1 to 80 mg/m^2 PTX on days 1, 8 and 15 of a 28 day cycle; T at 4 mg/kg load/2 mg/kg/weekly; with (Arm A) or without (Arm B) MM-111 at 20 mg/kg/weekly. Primary endpoints were progression-free survival (PFS) in the intent-to-treat (ITT) population and HRG-high population (pts with HRG ≥ median). Enrollment of 120 pts was planned with 70 or 38 PFS events required to detect a 67% or 50% PFS improvement in the ITT- or HRG-high population, respectively (80% power, alpha = 0.1).

HER2 Positive
HER2 IHC 3+
OR
HER2 IHC 2+ AND HER2 gene amplified by FISH or CISH

60 → **Experimental (A)**: Paclitaxel + Trastuzumab + MM-111

60 → **Comparator (B)**: Paclitaxel + Trastuzumab

Stratified for prior trastuzumab exposure, geographic region and PS

Disease and Treatment Information

		Experimental (N=44)	Comparator (N=44)
Site of Primary Tumor N(%)	Distal esophagus	8 (19%)	6 (14%)
	Gastroesophageal Junction	14 (33%)	12 (29%)
	Stomach (Intestinal type)	7 (17%)	5 (12%)
	Stomach (Diffuse type)	0	3 (7%)
	Stomach (Mixed type)	1 (2%)	3 (7%)
	Stomach (Other type)	12 (29%)	13 (31%)
Time Since Diagnosis (Months)	Median (Range)	9.87 (3.1-312.2)	10.4 (3.9-32.6)
Metastatic Site N (%)	Liver	23 (55%)	23 (50%)
	Lung	5 (12%)	5 (12%)
	Bone	2	0
Prior Trastuzumab N(%)	Yes	35 (80%)	36 (82%)
	No	9 (20%)	8 (18%)
Prior Therapy for Locally Advanced/Metastatic Disease N (%)	Yes	34 (77%)	40 (91%)
	No	10 (23%)	4 (9%)

Demographics

		Experimental (N=44)	Comparator (N=44)
Age (Years)			
	Median (range)	63.5 (31-78)	62.5 (35-81)
Gender N (%)			
	Male	37 (88%)	40 (95%)
	Female	5 (12%)	2 (5%)
ECOG Performance Status at Screening			
	0	18 (41%)	11 (25%)
	1	22 (50%)	29 (66%)
	2	4 (9%)	4 (9%)
World Region N (%)			
	Asia Pacific	10 (23%)	11 (25%)
	Western Europe	17 (39%)	17 (39%)
	North America	15 (34%)	14 (32%)
	Other	2 (4%)	2 (4%)

Overall Safety

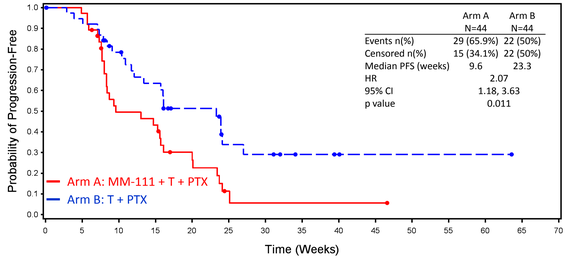
	Experimental (N=44), n (%)	Comparator (N=44), n (%)
Subjects with ≥ Grade 3 treatment-emergent adverse event	26 (61.9%)	24 (57.1%)
Subjects with ≥ Grade 3 study drug-related treatment-emergent adverse event	18 (42.9%)	16 (38.1%)
Subject with ≥ 1 serious treatment-emergent adverse event	19 (45.2%)	16 (38.1%)
Subjects with treatment-emergent adverse event leading to study drug discontinuation	8 (19.0%)	6 (14.3%)
Subject with adverse event leading to death	2 (4.8%)	2 (4.8%)

Treatment Emergent Adverse Events

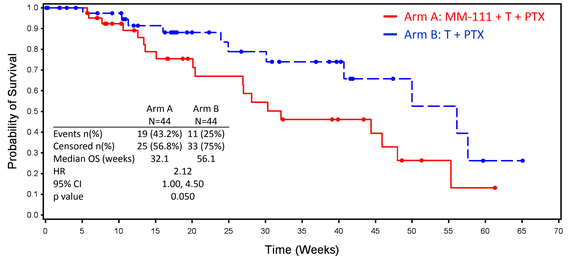
Adverse Event	Experimental (N=44)		Comparator (N=44)	
	All	Grade ≥ 3	All	Grade ≥ 3
Diarrhea	22 (52.4%)	0	12 (28.6%)	0
Nausea	11 (26.2%)	0	11 (26.2%)	0
Constipation	6 (14.3%)	0	7 (16.7%)	0
Vomiting	13 (31.0%)	0	5 (11.9%)	0
Fatigue	14 (33.3%)	0	9 (21.4%)	0
Asthenia	7 (16.7%)	0	8 (19.0%)	0
Peripheral edema	7 (16.7%)	0	1 (2.4%)	0
Alopecia	18 (42.9%)	0	7 (16.7%)	0
Anemia	15 (35.7%)	4 (9.5%)	14 (33.3%)	7 (16.7%)
Neutropenia	7 (16.7%)	6 (14.3%)	7 (16.7%)	4 (9.5%)
Neutrophil count decreased	8 (19.0%)	6 (14.3%)	4 (9.5%)	5 (9.5%)
Decreased appetite	17 (40.5%)	0	10 (23.8%)	0
Cough	7 (16.7%)	0	6 (14.3%)	0

Survival Data

Kaplan Meier Progression-Free Survival (ITT Population)



Kaplan Meier Overall Survival (ITT Population)



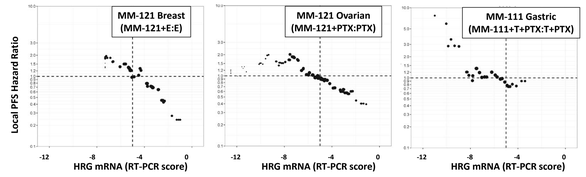
- The study was closed early by the Data Monitoring Committee based on lack of efficacy
- Pharmacokinetic analysis showed expected and similar circulating levels of trastuzumab, paclitaxel and MM-111 in each study arm

Response Rate

Best Overall Response	MM-111 + T + PTX (N=44) n (%)	T + PTX (N=44) n (%)
Complete Response	1 (2.2)	0
Partial Response	4 (9.1)	14 (31.8)
Stable Disease	11 (25.0)	6 (13.6)
Progressive Disease	17 (38.7)	15 (34.1)
Overall Disease Control Rate (CR+PR+SD)	16 (36.3)	20 (45.4)
Missing Scan	11 (25.0)	9 (20.5)

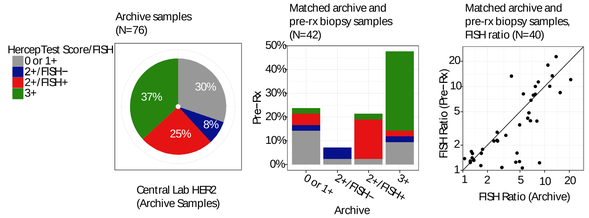
Biomarker Analysis: Heregulin

Local HR Scan of HRG mRNA



- 57 patients had assessable HRG levels measured by quantitative RT-PCR.
- HRG levels were found to be low in the ITT population compared to levels in two previous clinical studies evaluating MM-121, an ErbB3 monoclonal antibody, in combination with exemestane (E) or PTX in breast or ovarian cancer, respectively.
- A negative impact of MM-111 on local HR in patients with low HRG was observed.

Biomarker Analysis: HER2



- 62% of patients had HER2+ status (IHC 3+ or 2+/FISH+) centrally confirmed.
- HER2 IHC in matched archived and pre-treatment biopsy samples showed discordance.
- HER2 FISH amplification was lower in pre-treatment biopsies compared to matched archived samples.

Conclusions

- The addition of MM-111 to paclitaxel and trastuzumab did not improve PFS or OS in HER2+ GECs.
- Overall survival in the paclitaxel/trastuzumab arm was significantly better than historical controls[1,2].
- The addition of MM-111 did not clinically significantly alter the toxicity profile of paclitaxel and trastuzumab.
- Heregulin, a biomarker for MM-111 activity, was lower than anticipated in this patient population.
- Further insight is needed regarding the poor performance of the experimental arm.
- Trastuzumab and paclitaxel appears to be a promising regimen in the second-line treatment of HER2+ GE cancers. Further evaluation is warranted.

1. Hironaka et al, J Clinical Oncology 2013
2. Satoh et al, J Clinical Oncology 2014