Biomarker-Guided Enrichment of the Antitumor Activity of Margetuximab (M) plus Pembrolizumab (P) in Patients with Advanced HER2+ Gastric Adenocarcinoma (GEA)

Abstract #4436

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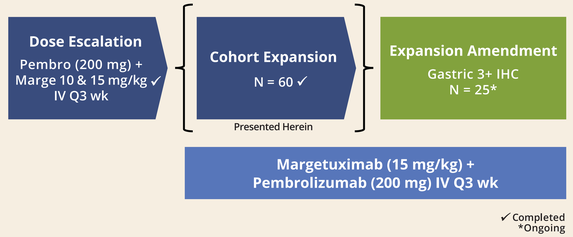
Background

- Trastuzumab + chemotherapy is standard treatment in 1st-line advanced HER2+ gastro-esophageal adenocarcinoma (GEA)
  - No HER2-targeted agents have been shown to be effective in the post-trastuzumab setting in patients with GEA
- Literature reports loss of HER2 expression after trastuzumab in up to 30% of GEA patients; this has potential consequences for subsequent treatment with HER2-targeted agents[1–5]
- Margetuximab is a next generation anti-HER2 monoclonal antibody with an optimized Fc domain designed to mediate activity irrespective of CD16A genotype
- Margetuximab has demonstrated single agent antitumor activity in patients with HER2+ GEA in a Phase 1 study
- Pembrolizumab and nivolumab are approved for 3rd-line treatment of recurrent PD-L1+ gastric cancer (GC)/gastroesophageal (GEJ) cancer (ORR 11.2–13.3%; median PFS 1.6–2 months)[6-7]
- Preclinical studies suggest that coordinated engagement of innate and adaptive immunity with the combination of anti-HER2 antibodies and T-cell checkpoint inhibition could achieve greater antitumor activity than either agent alone[8]

GOAL: Develop chemotherapy-free approach for treatment of gastroesophageal cancer

We report updated results from a Phase 1/2 study of margetuximab in combination with pembrolizumab in 2nd-line verified HER2+ GEA patients (post trastuzumab). Furthermore, we show increased responses in GC over GEJ, presumably due to increased target retention and expression.

Study Design



- Open label, 3+3 dose escalation study
- Escalating margetuximab (marge) doses (10 mg/kg & 15 mg/kg)
- Fixed-dose pembrolizumab (pembro; 200 mg)
- Response assessed by RECIST & irRECIST
- Initial cohort expansions of 30 patients each in North America and Asia
- Protocol expanded to add up to 25 HER2 3+ gastric cancer patients (ongoing)

Methods

- HER2+ (archival), PD-L1-unselected GEA patients 2nd-line post-trastuzumab

Primary Endpoint:
- Safety, tolerability, overall response rate (ORR)

Secondary Endpoints:
- Progression-free survival (PFS) and overall survival (OS); PFS and OS at 6 months

Exploratory Endpoints:
- Disease control rate (DCR) = proportion of patients with complete response (CR) + partial response (PR) + stable disease (SD)

- HER2-expression (post-trastuzumab) was confirmed by NGS of circulating-tumor DNA (ctDNA) for *ERBB2*amp (Guardant360®)
- PD-L1 tested on archival tissue by immunohistochemistry (IHC; Clone 22C3 pharmDx); Combined Positive Score [per standard FDA approved assay]

Results

Demographics

60 patients enrolled in cohort expansion; 30 in North America and 30 in Asia

Characteristic		All Patients (n=60)*
Age	Mean ± SD	59.0 ± 12.73
	Median (Range)	61.0 (19.0, 80.0)
Gender [n (%)]	Male	49 (81.7)
	Female	11 (18.3)
Race [n (%)]	Asian	30 (50.0)
	White	25 (41.7)
	Other	3 (5.1)
	Black or African American	2 (3.3)
ECOG Status [n (%)]	0	26 (43.3)
	1	34 (56.7)
Diagnosis [n (%)]	Gastric Cancer	34 (56.7)
	GEJ Cancer	26 (43.3)

*Data cutoff October 4th, 2018.

Safety — Cohort Expansion

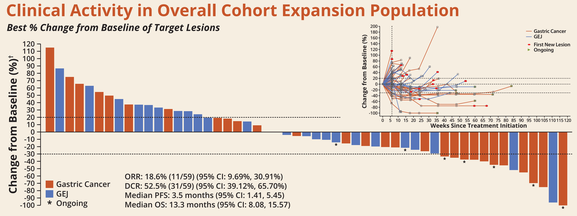
- Treatment with combination of margetuximab and pembrolizumab was well tolerated
- 65% of patients experienced treatment related AE (TRAE), irrespective of grade; 20% of patients with TRAE ≥ Grade 3. Most common TRAE is pruritis in 16.7% of patients
- 5 drug-related serious adverse events reported: autoimmune hepatitis [2], hyponatremia [1], diabetic ketoacidosis [1], and pneumonitis [1]
- 14 adverse events of special interest reported (infusion related reaction [8], autoimmune hepatitis [2], pneumonitis [1], endocrinopathy [1], others [2])

Adverse Event	All Related AE	
	All (N=60)	≥ Gr 3
TOTAL	**39 (65.0)**	**12 (20.0)**
Pruritus	10 (16.7)	–
Infusion related reaction	9 (15.0)	1 (1.7)
Fatigue	8 (13.3)	–
Diarrhoea	8 (13.3)	–
Lipase increased	4 (6.7)	1 (1.7)
Chills	3 (5.0)	–
Rash	3 (5.0)	–
Rash maculo-papular	3 (5.0)	–
Amylase increased	3 (5.0)	2 (3.3)
Aspartate aminotransferase increased	3 (5.0)	1 (1.7)
Pain	2 (3.3)	–
Nausea	2 (3.3)	1 (1.7)
Blood alkaline phosphatase increased	2 (3.3)	1 (1.7)
Alanine aminotransferase increased	2 (3.3)	–
Adrenal insufficiency	2 (3.3)	–
Autoimmune hepatitis	2 (3.3)	2 (3.3)
Pneumonitis	2 (3.3)	1 (1.7)
Anaemia	2 (3.3)	1 (1.7)

Data cut off October 4th, 2018; Events occurring >2% pts.

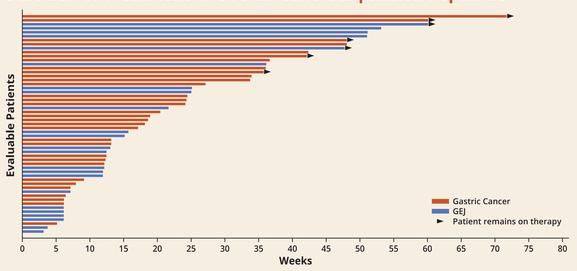
Clinical Activity in Overall Cohort Expansion Population

Best % Change from Baseline of Target Lesions



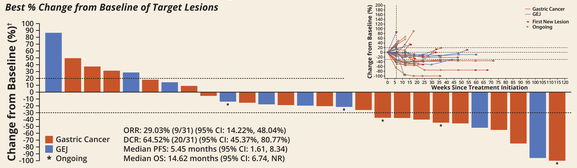
Data Cut-off Oct 4th, 2018. ¹Patients who received at least one marge and pembro dose in expansion phase, and had baseline measurable disease and at least one post-baseline disease assessment.

Duration of Treatment in Overall Cohort Expansion Population



Patient Selection with Prospective ctDNA Confirmation of *ERBB2*amp in Overall Population (Including GC + GEJ)

Best % Change from Baseline of Target Lesions



Data cut-off Oct 4th, 2018. ¹Patients who received at least one marge and pembro dose in expansion phase, and had baseline measurable disease and at least one post-baseline disease assessment.

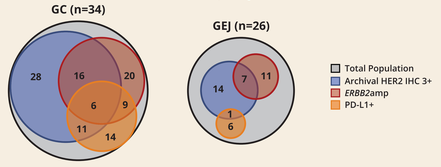
Biomarker Results (Expansion Cohorts)

Biomarker Data			
Positive Biomarker	**All Patients***	**Gastric Cancer**	**GEJ Cancer**
*ERBB2*amp	32/53 (60.4%)	21/32 (65.6%)	11/21 (52.4%)
PD-L1+	24/53 (45.3%)	17/33 (51.5%)	7/20 (35.0%)
*ERBB2*amp/PD-L1+	13/47 (27.7%)	12/31 (38.7%)	0/16 (0%)

- Approximately 60% (32/53) of patients tested had retained HER2 expression post-trastuzumab as determined by *ERBB2*amp using ctDNA
- Approximately 45% (24/53) of patients tested were PD-L1+ by IHC
- For both markers (PD-L1 and *ERBB2*amp), a higher rate of expression was observed in patients with GC

Data cut-off October 10th, 2018. *Includes only patients evaluated per assay.

Biomarker Distribution in GC vs GEJ Populations



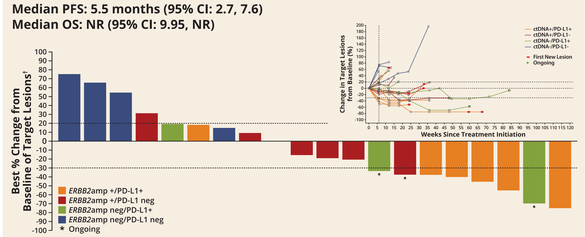
- Higher proportion of GC vs GEJ patients were HER2 IHC3+ at diagnosis
- GC patients, proportionally, had higher level of *ERBB2*amp, PD-L1 expression, and *ERBB2*amp/PD-L1+ post-trastuzumab than GEJ patients

Efficacy Results in Selected Biomarker-Positive Populations

	GC			GEJ Cancer		
	ORR (%)	mPFS (months) (95% CI)	mOS (months) (95% CI)	ORR (%)	mPFS (months) (95% CI)	mOS (months) (95% CI)
HER2 IHC 3+	35.7% (10/28)	5.5 (2.7, 7.6)	NR (10.0, NR)	7.1% (1/14)	3.6 (1.4, 11.2)	13.3 (5.3, 18.0)
*ERBB2*amp	40.0% (8/20)	5.5 (1.7, 8.3)	14.6 (6.7, NR)	9.1% (1/11)	2.5 (1.2, 12.4)	13.3 (3.0, 18.0)
PD-L1+	50.0% (7/14)	4.9 (1.6, 15.5)	NR (6.3, NR)	0% (0/5)	1.4 (1.3, 8.2)	14.0 (0.7, 14.0)
HER2 3+/PD-L1+	63.6% (7/11)	5.6 (1.6, NR)	NR (6.3, NR)	0% (0/1)	1.3 (NR, NR)	N/A
*ERBB2*amp/PD-L1+	55.6% (5/9)	5.5 (1.1, 15.5)	8.4 (1.1, NR)	No Patients	N/A	N/A

Clinical Activity in HER2 3+ GC Population

ORR: 35.7% (10/28) (95% CI: 18.64%, 55.93%)
DCR: 67.9% (19/28) (95% CI: 47.65%, 84.12%)
Median PFS: 5.5 months (95% CI: 2.7, 7.6)
Median OS: NR (95% CI: 9.95, NR)



Data cut-off Oct 4th, 2018. ¹Patients who received at least one marge and pembro dose in expansion phase, and had baseline measurable disease and at least one post-baseline disease assessment.

Conclusions

- Margetuximab + pembrolizumab is a chemotherapy-free combination designed to coordinately engage innate and adaptive immunity
- The combination of margetuximab and pembrolizumab is well tolerated and has demonstrated encouraging preliminary antitumor activity in patients with 2nd line HER2-positive, PD-L1 unselected GEA after treatment with trastuzumab plus chemotherapy
- Consistent with prior tissue-based reports, many GEA patients who progress on or after trastuzumab appear to have tumors that no longer possess HER2 as measured by *ERBB2* amplification
- Results suggest that margetuximab + pembrolizumab activity may be increased in prospectively confirmed HER2+ patients, measured by ctDNA *ERBB2* amplification, as well as PD-L1+ expression
- The antitumor activity of margetuximab plus pembrolizumab is enhanced in patients with IHC3+ HER2+ gastric cancer, likely due to high HER2 retention
- This study is ongoing in patients with HER2 IHC3+ gastric cancer

References

1. J Clin Oncol 35, 2017 (suppl 4S; abstract 12). **2.** J Clin Oncol 34, 2016 (suppl; abstr 4043). **3.** J Clin Oncol 34, 2016 (suppl; abstr 11608). **4.** J Clin Oncol 35, 2017 (suppl 4S; abstract 27). **5.** J Clin Oncol 35, 2017 (suppl 4S; abstract 81). **6.** Keytruda package insert; KEYNOTE-059, ESMO 2017. **7.** ATTRACTION-2 poster ASCO-GI 2017; Kang et al., Lancet, 2017. **8.** Stagg J, et al. Anti–ErbB-2 mAb therapy requires type I and II interferons and synergizes with anti–PD-1 or anti-CD137 mAb therapy. Proc Natl Acad Sci USA. 2011 Apr 26; 108(17): 7142–7147.

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