Antitumor Activity of Margetuximab plus Pembrolizumab in Patients with Advanced HER2+ (IHC3+) Gastric Carcinoma

Abstract #65

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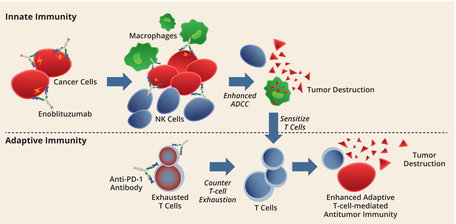
NCT02689284

Background

- Trastuzumab + chemotherapy is standard treatment in 1st line advanced HER2+ gastroesophageal adenocarcinoma (GEA)
  - No HER2-targeted agents have been approved in post-trastuzumab setting in patients with HER2+ GEA
- Loss of HER2 expression after trastuzumab has been reported in up to 70% of GEA patients with potential consequences for subsequent treatment with HER2-targeted agents[1-5]
- Margetuximab is a next generation anti-HER2 monoclonal antibody featuring an optimized Fc domain designed to enhance its Fc-dependent functions, including antibody dependent cell cytotoxicity (ADCC) irrespective of the host's FcγRIIIa (CD16A) genotype

Hypothesis: Coordinate engagement of innate and adaptive immunity with margetuximab and anti-PD-1 mediates greater antitumor activity than either single agent alone

- Coordinate engagement of innate and adaptive immunity with combination of anti-HER2 and anti-PD-1 antibodies achieves greater antitumor activity than either agent alone in murine tumor models[6]
- Margetuximab and pembrolizumab have both demonstrated monotherapy antitumor activity in patients with GEA; and Checkpoint inhibitors (pembrolizumab, nivolumab) are approved for treatment of 3L PD-L1+ patients with GEA
- We reported previously that another Fc-optimized antibody (enoblituzumab, anti-B7H3) combined with pembrolizumab achieved greater antitumor activity than historical experience with checkpoint inhibitors alone in checkpoint-naive patients with SCCHN and NSCLC (PD-L1<1%) (SITC 2018)[7]
- Preliminary data indicates that Fc-modified antibodies (including margetuximab and enoblituzumab monotherapy) can modulate T-cell repertoire in treated patients[8-9]
- NK cells may express PD-1, and PD-1/PD-L1 interaction can impair NK cell function, and PD-1/PD-L1 blockade can enhance NK cell function and preclinical antitumor activity[10]



Goal is to develop chemotherapy-free approach for treatment of GEA

Study Design

✓Enrollment completed. 15 patients ongoing

- Open label, dose escalation study, conventional 3+3 design
- Escalating doses of margetuximab (marge; 10 mg/kg & 15 mg/kg)
- Fixed dose pembrolizumab (pembro; 200 mg)
- Response assessed by RECIST & irRECIST
- 92 Patients treated at recommended Phase 2 dose (RP2D)
  - 61 Gastric cancer (GC)
    - 35 Enrolled in cohort 2 (1), and cohort expansion (34) (HER2 IHC2+/3+)
    - 26 Enrolled in HER2 (IHC3+) GC specific cohort
  - 31 Gastroesophageal junction (GEJ) (HER2 IHC2+/3+)

Methods

- HER2+ (archival), PD-L1-unselected 2nd line GEA pts post trastuzumab
  - Primary endpoints:
    - 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 using a provisional CPS 1 cut point

Results

Demographics

Ninety-two patients have been treated at recommended Phase 2 dose (RP2D); 61 gastric adenocarcinoma (GC) and 31 in gastroesophageal junction adenocarcinoma (GEJ)

Characteristic		GC (n=61)	GEJ (n=31)
Age	Mean ± SD	61.4 ± 13.6	57.9 ± 11.1
	Median (Range)	62.0 (19.0, 85.0)	60.0 (35.0, 79.0)
Gender [n (%)]	Male	48 (78.7)	27 (87.1)
	Female	13 (21.3)	4 (12.9)
Race [n (%)]	Asian	48 (78.7)	3 (9.7)
	White	9 (14.8)	25 (80.6)
	Other	1 (1.6)	3 (9.7)
	Black or African American	3 (4.9)	0
ECOG Status [n (%)]	0	20 (32.8)	13 (41.9)
	1	41 (67.2)	18 (58.1)

*Data cutoff January 8, 2019.

Treatment with Combination of Margetuximab and Pembrolizumab is Well-tolerated

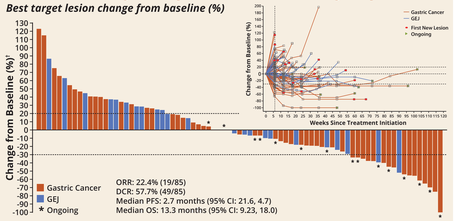
- 64% of patients experienced treatment related AE (TRAE) irrespective of grade
- 18% of patients with TRAE ≥Grade 3
- Most common TRAE: pruritis (16.8%)
- 8 Treatment-related serious adverse events: autoimmune hepatitis [2], hyponatremia [1], diabetic ketoacidosis [1], and pneumonitis [1], hypotension [1], confusional state [1], dizziness [1]
- 17 Adverse events of special interest reported: infusion related reaction [11], autoimmune hepatitis [2], pneumonitis [1], endocrinopathy [1], others [1], LVEF dysfunction [1]

Adverse Event	All Related AE	
	All (N=95)*	≥ Gr 3
TOTAL	**61 (64.2)**	**17 (17.9)**
Pruritus	16 (16.8)	
Diarrhea	14 (14.7)	
Infusion related reaction	13 (13.7)	3 (3.2)
Fatigue	12 (12.6)	
Rash	7 (7.4)	
Rash maculo-papular	5 (5.3)	
Anemia	5 (5.3)	2 (2.1)
Nausea	4 (4.2)	1 (1.1)
Decreased appetite	4 (4.2)	
Lipase increased	4 (4.2)	1 (1.1)
Aspartate aminotransferase increased	4 (4.2)	1 (1.1)
Chills	3 (3.2)	
Alanine aminotransferase increased	3 (3.2)	
Amylase increased	3 (3.2)	2 (2.1)
Hyperthyroidism	3 (3.2)	
Adrenal insufficiency	3 (3.2)	
Vomiting	2 (2.1)	1 (1.1)
Pyrexia	2 (2.1)	
Pain	2 (2.1)	
Ejection fraction decreased	2 (2.1)	
Blood alkaline phosphatase increased	2 (2.1)	1 (1.1)
Pneumonitis	2 (2.1)	1 (1.1)
Hypotension	2 (2.1)	1 (1.1)
Autoimmune hepatitis	2 (2.1)	2 (2.1)

Data cut off January 8, 2019; Events occurring >2% pts; includes all pts treated on study.

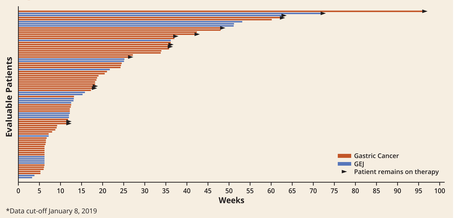
Clinical Activity in Expansion Cohort Only Population

Best target lesion change from baseline (%)



Data cut-off January 8, 2019. [1]Patients 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



*Data cut-off January 8, 2019

Overall Response Rates and Biomarker Incidence (RP2D Cohorts)

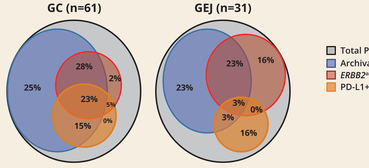
	All Patients*	Gastric Cancer	GEJ Cancer
Objective Response Rate	20/92 (21.7%)	18/61 (29.5%)	2/31 (6.5%)
Biomarker Incidence			
HER2 IHC3+	71/92 (77.2%)	55/61 (90.2%)	16/31 (51.6%)
*ERBB2*amp	48/82 (58.5%)	35/56 (62.5%)	13/26 (50.0%)
PD-L1+	33/76 (43.4%)	26/54 (48.1%)	7/22 (31.8%)
HER2 IHC3+/PD-L1+	25/76 (32.9%)	23/54 (42.6%)	2/22 (9.1%)

Data cut-off January 8, 2019; *Includes only patients evaluated per assay.

- Objective responses in 21.7% (20/92) of HER-2+ GEA patients
  - 15 confirmed/5 unconfirmed responses, 15 patients ongoing
- Responses are higher in GC 29.5% vs GEJ 6.5%
  - Includes initial cohort expansion as well as subsequent IHC-3+ GC cohort expansion
- Approximately 77% of pts were HER2 IHC3+ at baseline (archival) sample
  - Baseline HER2 IHC3+ is higher in GC (90.2%) vs GEJ (51.6%) patients
- Approximately 60% of patients tested retained HER2 expression post-trastuzumab (*ERBB2*amp ctDNA), and 43% of patients tested were PD-L1+ by IHC
  - Higher expression of PD-L1 and *ERBB2*amp was observed in patients with GC (43%) vs GEJ (9%)

Data cut-off January 8, 2019; *Includes only patients evaluated per assay.

Biomarker Distribution in GC vs GEJ Populations



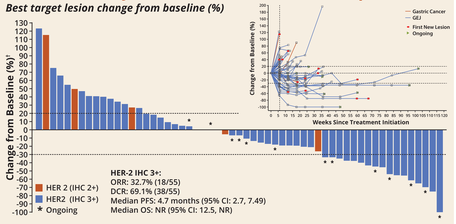
Efficacy Results in Gastric Cancer Population by Biomarker Expression

	n	ORR	DCR	mPFS	mOS
Total	61	29.5% (18/61)	65.6% (40/61)	4.07 (2.30, 5.45)	14.62 (9.07, NR)
IHC3+	**55**	**32.7% (18/55)**	**69.1% (38/55)**	**4.70 (2.66, 7.49)**	**NR (12.48, NR)**
*ERBB2*amp	35	40.0% (14/35)	77.1% (27/35)	4.76 (2.69, 7.59)	14.62 (8.41, NR)
PDL1+	26	46.2% (12/26)	80.8% (21/26)	4.14 (2.60, 7.59)	NR (6.74, NR)
IHC3+/ PDL1+	**23**	**52.2% (12/23)**	**82.6% (12/23)**	**4.14 (2.60, 15.54)**	**NR (6.74, NR)**

ORR=Objective Response Rate; DCR=Disease Control Rate=CR/PR/SD; mPFS=Median Progression Free Survival; mOS=Median Overall Survival

Clinical Activity in Overall Gastric Cancer Population

Best target lesion change from baseline (%)



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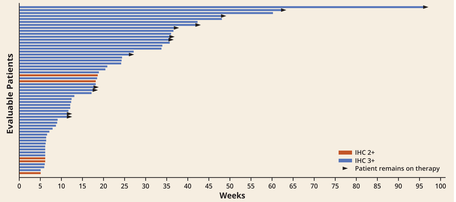
Duration of Treatment in Overall Gastric Cancer Population



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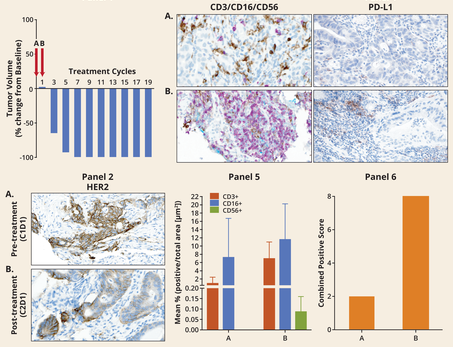
Objective Response Observed Irrespective of Fc Receptor Genotype

- Outcomes for trastuzumab-treated patients who carry lower-affinity CD16A-F allele are worse than those who are homozygous for higher affinity V allele[11]
- Fc receptor genotyping results available in all GC patients
- Objective responses and disease stabilization observed in patient subsets irrespective of Fc receptor genotype

FcγRIII (CD16A) Genotype	Prevalence %(n)	PR	SD	PD	NE
F/F	42.6% (26)	34.6% (9)	34.6% (9)	26.9% (7)	3.8% (1)
V/F	45.9% (28)	25.0% (7)	39.3% (11)	32.1% (9)	3.6% (1)
V/V	11.5% (7)	28.6% (2)	14.3% (1)	57.1% 4	

Enhanced Immune Cell Infiltrate Following Treatment with Margetuximab/Pembrolizumab in a Patient with Subsequent Complete Response



Panel 1: Waterfall plot of percent tumor volume change from baseline through different treatment cycle for patient on study. Red arrow represent timing of tumor biopsy, A (pre-treatment C1D1), B (post-treatment C2D1).

Panel 2–4: IHC staining for samples A and B for HER2, CD3 T-cells, CD16 NK cells, CD56 NK cells and PDL1, respectively.

Panel 5-6: Quantitation of IHC staining for CD3/16/56 and PDL1, respectively, shows increase in immune cell infiltration and activation in TME upon dosing with margetuximab and pembrolizumab.

Conclusions

- Margetuximab + pembrolizumab is a chemotherapy-free combination, designed to coordinately engage innate and adaptive immunity for treatment of GEA
- The investigational combination demonstrated an acceptable safety profile that benchmarked favorably to historical experience with SoC with ramucirumab+/-chemotherapy; ≥Grade 3 TRAEs in 18% of treated patients, and events are consistent with margetuximab or pembrolizumab alone
- Results from the cohort expansion population and ongoing follow-up confirm the anti-tumor activity of the investigational combination of margetuximab and pembrolizumab, and benchmarked favorably to historical experience with single agent checkpoint inhibitors
- Paired biopsy of tissue from a patient with a complete response demonstrates enhanced infiltration of both innate (CD16/CD56 NK cells) and adaptive (CD3 T-cells) immune cell subsets
- Prospective patient selection by HER2 (IHC3+) and/or PD-L1 expression may further enrich for patients more likely to respond to treatment with margetuximab plus pembrolizumab
- Combined administration of Fc-optimized antibodies and checkpoint inhibitors could be an important novel strategy to coordinately engage innate and adaptive immunity, and extend the activity of cancer immunotherapy beyond that achieved with single agent checkpoint inhibition alone

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.** Makiyama et al. Journal of Clinical Oncology 36, no. 15_suppl (May 2018) 4011-4011. **7.** 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. **8.** Data presented at SITC 2018, 4030. **9.** Hsu, et al., J Clin Invest, 2018. **10.** Unpublished. **11.** Presented at SITC 2018, P338. **12.** Musolino A, et al. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER2/neu-positive metastatic breast cancer. J Clin Oncol. 2008;26:1789-96.

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