Margetuximab Plus Pembrolizumab in *ERBB2*-Amplified PD-L1+ Gastroesophageal Adenocarcinoma Post Trastuzumab

ASCO 2018
Abstract #4030

Daniel V.T. Catenacci[1], Haeseong Park[2], Hope Elizabeth Uronis[3], Yoon-Koo Kang[4], Jill Lacy[5], Peter C. Enzinger[6], Se Hoon Park[7], Keun Wook Lee[8], Matthew C.H. Ng[9], Philip Jordan Gold[10], Jennifer Yen[11], Aleksandra Franovic[11], Ronan Joseph Kelly[12], Aisha Wynter-Horton[13], Daner Li[13], John Muth[13], Jan E. Baughman[13], Sam Hong[13], Jan Kenneth Davidson-Moncada[13], Yung-Jue Bang[14]

[1]University of Chicago Pritzker School of Medicine, Chicago, IL; [2]Washington University School of Medicine, St. Louis, MO; [3]Duke University Medical Center, Durham, NC; [4]Department of Oncology, Asan Medical Center, Seoul, Korea; [5]Smilow Cancer Hospital, Yale University, New Haven, CT; [6]Dana-Farber Cancer Institute, Boston, MA; [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [8]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea; [9]National Cancer Center, Singapore, Singapore; [10]Swedish Cancer Institute, Seattle, WA; [11]Guardant Health, Redwood City, CA; [12]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; [13]MacroGenics, Inc., Rockville, MD; [14]Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea

http://ir.macrogenics.com/events.cfm

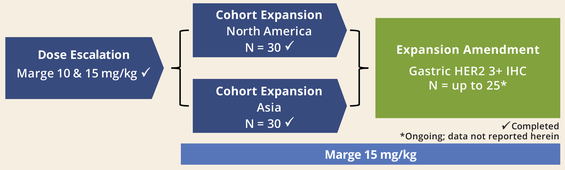
Background

- Trastuzumab + chemotherapy is standard treatment in 1st line advanced HER2+ gastroesophageal adenocarcinoma (GEA)
  - Patients typically progress within 6–8 months
  - No HER2-targeted agents have been shown to be effective in the post-trastuzumab setting in patients with GEA
- Outcomes for trastuzumab-treated breast cancer patients who carry lower-affinity CD16A-F allele may be worse than those who are homozygous for higher affinity V allele[1]
- Margetuximab is a next generation anti-HER2 monoclonal antibody with an optimized Fc domain designed to mediate activity irrespective of CD16A genotype
  - Increased affinity for activating CD16A (FcγR3A) receptor on NK cells/monocytes
  - Decreased affinity for inhibitory CD32B (FcγR2B) receptor
- Loss of HER2 amplification may occur after trastuzumab failure in subset of GEA patients who are initially HER2+
  - Up to 30% demonstrate loss of HER2 positivity post-trastuzumab[2-6]
- In a Phase 1 study, margetuximab has demonstrated single agent antitumor activity in patients with HER2+ GEA
- Pembrolizumab and nivolumab approved for 3rd-line treatment of recurrent PD-L1+ gastric/gastroesophageal (GEJ) cancer
- Preclinical studies suggest that engagement of innate and adaptive immunity with combination of anti-HER2 antibodies and T-cell checkpoint inhibition could achieve greater antitumor activity than either agent alone[7]

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 HER2+ GEA patients (post trastuzumab), and describe potential strategies for biomarker enrichment

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 & irRESIST
- Initial cohort expansions of 30 patients each in North America and Asia
- Protocol expanded to add up to 25 HER2 3+ gastric cancer patients

Methods

- HER2-postive (tested pre-trastuzumab), PD-L1-unselected GEA patients enrolled
  - 2nd-line, post-progression with/after trastuzumab and chemotherapy
  - Checkpoint naïve
  - HER2 3+ or HER 2+/FISH amplified

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:

- *ERBB2* amplification status pre-margetuximab + pembrolizumab; circulating-tumor DNA (ctDNA)
- PD-L1+ on archival tissue by immunohistochemistry (IHC; Clone 22C3 pharmDx, Combined Positive Score [per standard FDA approved assay])
- Disease control rate (DCR) = proportion of patients with complete response (CR) + partial response (PR) + stable disease (SD)

Results

Demographics — Cohort Expansion Phase

Characteristic		All Patients (n=60)*
Age	Mean ± SD	59.0 ± 12.73
	Median (Range)	61.0 (19.0, 80.0)
Gender [n (% 0)]	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 (%)]	GEJ Cancer	34 (56.7)
	Gastric Cancer	26 (43.3)

*Data cut off May 10th, 2018

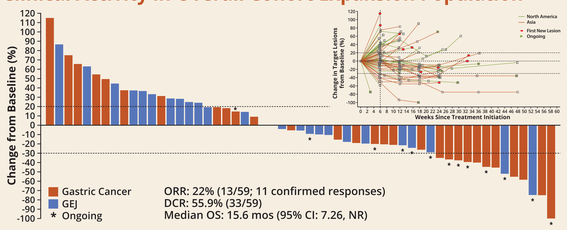
Safety — Dose Escalation and Cohort Expansion

- Treatment with combination of margetuximab and pembrolizumab was well tolerated
- 57% of patients experienced treatment related AE (TRAE), most ≤ Grade 2; 15.6% of patients with ≥ Grade 3. Most common TRAE is fatigue in 14.3% of patients
- 4 Drug-related serious adverse events reported (autoimmune hepatitis [2], infusion related reaction [1], pneumonitis [1])
- 13 Adverse events of special interest reported (infusion related reaction [8], autoimmune hepatitis [2], pneumonitis [1], others [2])

Adverse Event	All Related AE	
	All (N=77)	≥ Gr 3
TOTAL	**44 (57.1)**	**12 (15.6)**
Fatigue	11 (14.3)	
Infusion related reaction	10 (13.0)	2 (2.6)
Pruritus	9 (11.7)	
Diarrhea	7 (9.1)	
Anaemia	3 (3.9)	1 (1.3)
Decreased appetite	3 (3.9)	
Nausea	3 (3.9)	1 (1.3)
Abdominal pain	1 (1.3)	
Back pain	1 (1.3)	
Hypoalbuminaemia	1 (1.3)	
Oedema peripheral	1 (1.3)	

Data cut off May 10th, 2018. Events occurring >10% pts.

Clinical Activity in Overall Cohort Expansion Population†



*Data cut-off May 10th, 2018. ORR, DCR: †Patients who received at least one marge and pembro dose in expansion phase, and had baseline measurable disease. Median OS: Patients who received at least one marge/pembro dose in cohort expansion.

Summary of Updated Activity Data: Cohort Expansion†

	ORR (Response Evaluable)				
	Overall	Gastric Cancer	Asia	GEJ Cancer	North America
	13/59	10/34	11/30	3/25	2/29
	22.0%	29.4%	36.7%	12.0%	6.9%

	Progression-Free Survival				
	Overall	Gastric Cancer	Asia	GEJ Cancer	North America
# of Events / Patients	43/60	24/34	21/30	19/26	22/30
Median (months)	3.61	4.24	5.45	1.49	1.41
95% CI:	(1.41, 5.45)	(1.68, 5.62)	(2.69, 7.49)	(1.38, 4.34)	(1.38, 3.61)

	Overall Survival				
	Overall	Gastric Cancer	Asia	GEJ Cancer	North America
# of Events / Patients	21/60	9/34	7/30	12/26	14/30
Median (months)	15.57	NR	NR	15.57	15.57
95% CI:	(7.26, NR)	(7.52, NR)	(7.52, NR)	(5.26, 15.57)	(5.26, NR)

*Data cut-off May 10th, 2018. ORR: †Patients who received at least one marge and pembro dose in expansion phase, and had baseline measurable disease. PFS and OS: Patients who received at least one marge and pembro dose in cohort expansion. NR: Not Reached

HER2+ Gastric Cancer Therapeutic Landscape (Benchmarks)

	1st Line	2nd Line				3rd Line
	SOC	SOC		Ongoing	Reported			SOC[g]
Agent (Study)	Trastuzumab + Chemo[a] (TOGA)	Ram. + Paclitaxel[b] (RAINBOW)	Ram.[c] (REGARD)	Marge.+ Pembro.[d] (Ongoing Ph.2)	T-DM1[e] (GATSBY)	Pembro.[f] (KEYNOTE-61)	Anti-PD-1: Nivo.[h]/Pembro.[i]
ORR	47%	28%	3%	29% (35% in HER2 3+)	20.6%	15.8%	11.2%[h] – 13.3%[i] PD-L1+ = 15.5%[i] PD-L1– = 5.5%[i]
Median PFS	6.7 mos.	4.4 mos.	2.1 mos.	4.24 mos.	2.7 mos.	1.5 mos.	1.6[h] – 2 mos.[i]
Median OS	13.1 mos.	9.6 mos.	5.2 mos.	Overall 15.57; GC not reached	7.9 mos.	9.1 mos.	5.3[h] – 5.6 mos.[i]
≥ Grade 3 TRAEs	68% (Black Box Warn.)	Overall: N/A 41% Neutropenia 15% Hypertension 12% Fatigue (Black Box Warn.)	Overall: N/A 8% Hypertension (Black Box Warn.)	15.6%	60% (Black Box Warn.)	14.3%	10[h] – 18%[i]
Gastric/GEJ Patient Mix	80/20%	80/20%	75/25%	100% (gastric cohort)	66/34%	Not disclosed	90/10% (excl. 'unknown')

SOC: Standard of Care. [a]Data from Herceptin package insert; Bang, et al., Lancet, 2010; Black box warning: cardiomyopathy, infusion reactions, embryo-fetal toxicity and pulmonary toxicity. [b]Data from Cyramza package insert; Wilkes et al., Lancet Oncology, 2014; Black box warning: hemorrhage, GI perforation, impaired wound healing. [c]Data from Cyramza package insert; Fuchs, et al., Lancet 2014. [d]Data presented at ASCO GI 2018. 15.6% of all patients in dose escalation and cohort expansion (n=77) had ≥ Grade 3 treatment-related AEs. mPFS, mos. and ORR for gastric cancer pts only (n=34). [e]Data from Thuss-Patience, et al., Lancet Oncology, 2017; Black box warning: hepatotoxicity, cardiac toxicity, embryo-fetal toxicity. [f]Merck press release, December 14, 2017; ASCO 2018 Abstract 4062. [g]Note: Avelumab (anti-PD-L1) failed 3L JAVELIN Gastric300 study (Merck KGaA and Pfizer press release, November 28, 2017). [h]ATTRACTION-2 poster ASCO-GI 2017; Kang, et al., Lancet, 2017. [i]Keytruda package insert; KEYNOTE-059, ESMO 2017.

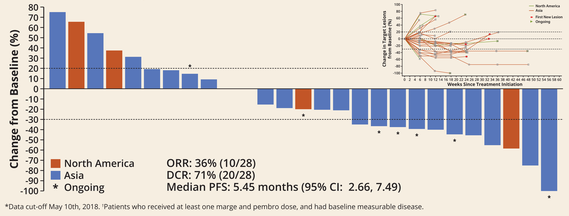
Biomarker Results

	Biomarker Data				
	All Patients*	Gastric Cancer	GEJ Cancer	Asia	North America
HER2 (IHC 3+)	41/60 (68%)	28/34 (82%)	13/26 (50%)	26/30 (87%)	15/30 (50%)
*ERBB2*amp	32/52 (62%)	21/31 (68%)	11/21 (52%)	19/26 (73%)	13/26 (50%)
PD-L1+	20/46 (43%)	14/30 (47%)	6/16 (38%)	13/28 (46%)	7/18 (39%)
*ERBB2*amp/PD-L1+	10/39 (26%)	10/27 (37%)	0/12 (0%)	9/24 (38%)	1/15 (7%)

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

- 68% (41/60) of patients tested were HER2 3+ by IHC staining of tumors
- 62% (32/52) of patients tested had baseline *ERBB2*amp by ctDNA
- 43% (20/46) of patients tested were PD-L1+ by IHC

Clinical Activity in IHC 3+ Gastric Cancer†



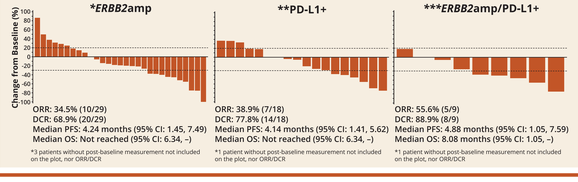
*Data cut-off May 10th, 2018. †Patients who received at least one marge and pembro dose, and had baseline measurable disease.

Summary of Updated Activity Data by Biomarker Subset

	ORR (n(%))	DCR (n(%))	mPFS (mos; 95% CI)	mOS (mos; 95% CI)
All Patients	**13/59 (22.0)**	**33/59 (55.9)**	**3.61 (1.41, 5.45)**	**15.57 (7.26, NR)**
HER2 IHC 3+	12/41 (29.3)	27/41 (65.9)	4.70 (2.66, 7.49)	15.57 (15.57, NR)
*ERBB2*amp*	10/32 (31.3)	21/32 (65.6)	4.24 (1.61, 7.49)	– (6.34, NR)
PD-L1+**	7/19 (36.9)	14/19 (73.7)	4.14 (1.41, 5.62)	– (6.34, NR)
*ERBB2*amp/PD-L1+***	5/10 (50.0)	8/10 (80.0)	4.24 (1.05, 7.59)	8.08 (1.05, NR)
Gastric Cancer Patients	**10/34 (29)**	**22/34 (65)**	**4.24 (1.68, 5.26)**	**– (7.52, NR)**
HER2 IHC 3+	10/28 (35.7)	20/28 (71.4)	5.45 (2.66, 7.49)	– (7.52, NR)
HER2 IHC 3+/*ERBB2*amp	8/17 (47.1)	13/17 (76.5)	5.62 (1.61, 8.34)	– (6.74, NR)
HER2 IHC 3+/PD-L1+	6/11 (54.5)	10/11 (90.9)	5.62 (1.61, NR)	– (6.34, NR)
HER2 IHC 3+/*ERBB2*amp/PD-L1+	5/7 (71.4)	6/7 (85.7)	5.62 (1.41, NR)	– (1.77, NR)

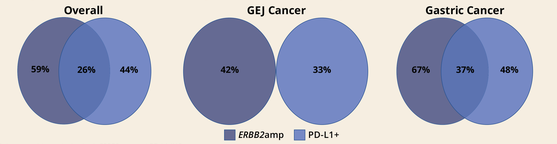
Data cut-off May 10th, 2018. Patients who received at least one marge and pembro dose, and had baseline measurable disease.

- **Response rate in gastric cancer better than overall population**
- **Response rate enriched in overall pop in patients who are HER2 3+, *ERBB2*amp or PD-L1+**
- **Response rate enriched in GC patients who are HER2 3+, HER2 3+/*ERBB2*amp, HER2 3+/PD-L1+**



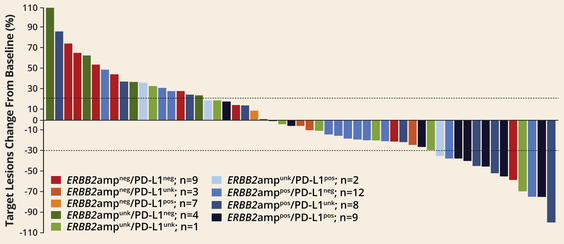
*3 patients without post-baseline measurement not included on the plot, nor ORR/DCR
*1 patient without post-baseline measurement not included on the plot, nor ORR/DCR
*1 patient without post-baseline measurement not included on the plot, nor ORR/DCR

Frequency of *ERBB2*amp and PD-L1 Expression*



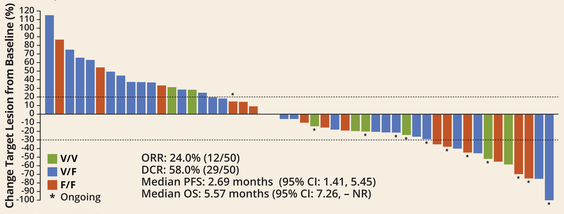
*Subgroup with results for both *ERBB2*amp and PD-L1 IHC.

Clinical Activity by *ERBB2*/PD-L1 Status



Combination is Active Across All Fcγ (CD16) Receptor Genotypes

- Among 50 response-evaluable patients† with available CD16A genotype, responses were independent of FcR genotype; PR: 1 V/V, 6 V/F, 5 F/F with similar allelic distribution among non-responders



Data cut off May 10th, 2018. †Patients with baseline and post-baseline tumor assessments.

Conclusions

- Margetuximab + pembrolizumab is a chemotherapy-free combination designed to coordinately engage innate and adaptive immunity
- Combination of margetuximab and pembrolizumab has demonstrated encouraging preliminary antitumor activity in patients with 2nd-line HER2-positive, PD-L1 unselected GEA after treatment with prior trastuzumab+chemotherapy
- Preliminary antitumor activity of the combination of margetuximab + pembrolizumab benchmarks favorably to prior experience with other agents
- Consistent with prior tissue-based reports, many GEA patients who progress on or after trastuzumab appear to have tumors that no longer possess *ERBB2* amplification
- Preliminary results suggest that margetuximab + pembrolizumab may have enhanced antitumor activity in patients with advanced gastric cancer, and that biomarker selection based on demonstration of baseline *ERBB2* amplification by ctDNA and/or PD-L1 expression by IHC could further enrich for patients more likely to respond to the combination

References

1. 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. **2.** J Clin Oncol 35, 2017 (suppl 4S; abstract 12). **3.** J Clin Oncol 34, 2016 (suppl; abstr 4043). **4.** J Clin Oncol 34, 2016 (suppl; abstr 11608). **5.** J Clin Oncol 35, 2017 (suppl 4S; abstract 27). **6.** J Clin Oncol 35, 2017 (suppl 4S; abstract 81). **7.** Staag 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.