Phase 1b/2 Study of Margetuximab Plus Pembrolizumab in Advanced HER2+ Gastroesophageal Junction or Gastric Adenocarcinoma

Abstract 140

Daniel V.T. Catenacci[1], Haeseong Park[2], A. Craig Lockhart[3], Philip Jordan Gold[4], Peter C. Enzinger[5], Jeffrey L. Nordstrom[6], Sam Hong[6], Howard S. Hochster[7], Ronan Joseph Kelly[8], Hope Elizabeth Uronis[9], Johanna C. Bendell[10], Sang Cheul Oh[11], Se Hoon Park[12], Yeul Hong Kim[13], Yoon-Koo Kang[14], Keun-Wook Lee[15], Matthew CH Ng[16], Jon M. Wigginton[6], Jan Kenneth Davidson-Moncada[6], Yung-Jue Bang[17]

[1]University of Chicago Pritzker School of Medicine, Chicago, IL; [2]Washington University School of Medicine in St. Louis, St. Louis, MO; [3]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; [4]Swedish Cancer Institute, Seattle, WA; [5]Dana-Farber Cancer Institute, Boston, MA; [6]MacroGenics, Inc., Rockville, MD; [7]Yale School of Medicine, Yale University, New Haven, CT; [8]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; [9]Duke University Medical Center, Durham, NC; [10]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [11]Korea University Guro Hospital, Seoul, Korea; [12]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [13]Korea University College of Medicine, Seoul, Korea; [14]Asan Medical Center, University of Ulsan, Seoul, Korea; [15]Seoul National University Bundang Hospital, Seoul, Korea; [16]National Cancer Center, Singapore, Singapore; [17]Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

davidsonj@macrogenics.com

NCT02689284

Background

- Trastuzumab + chemotherapy is standard treatment in 1st line advanced HER2+ gastroesophageal adenocarcinoma (GEA)
- Margetuximab: anti-HER2 monoclonal antibody with an optimized Fc domain that both increases affinity for the activating CD16A (FcγR3A) receptor on NK cells/monocytes and decreases affinity for the inhibitory CD32B (FcγR2B) receptor
  - Designed to mediate activity irrespective of CD16A genotype
- Outcomes for trastuzumab-treated breast cancer patients who carry lower-affinity CD16A-F allele may be worse than those who are homozygous for the higher affinity V allele[1]
- Loss of HER2 amplification may occur after trastuzumab failure in a subset of GEA patients who are initially HER2+
- Margetuximab has demonstrated single agent antitumor activity in patients with HER2+ GEA in a Phase 1 study
- 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 the combination of anti-HER2 antibodies and T-cell checkpoint inhibition could achieve greater antitumor activity than either agent alone[2]
- **Goal: Develop a chemotherapy-free approach for the treatment of gastroesophageal cancer**

Phase 1b/2 Clinical Trial

Open label, dose escalation 3+3 design study of margetuximab (marge) in combination with pembrolizumab (pembro)

Dose Escalation

Dose Level 1
Pembro 200 mg + Marge 10 mg/kg

Dose Level 2
Pembro 200 mg + Marge 15 mg/kg

Cohort Expansion

North America Cohort
Pembro 200 mg + Marge MTD/MAD
n = 30

Asia Cohort
Pembro 200 mg + Marge MTD/MAD
n = 30

Primary Objective

- Characterize safety, tolerability and maximum tolerated dose (MTD) of combination
- Investigate preliminary anti-tumor activity by objective response rate (ORR) & response duration

Secondary Objectives

- Investigate preliminary overall survival (OS) and progression-free survival (PFS)
- Characterize pharmcodynamic activity of the combination
- Characterize pharmacokinetics and immunogenicity of combination

Patient Population

- Relapsed/refractory advanced HER2+ PD-L1-unselected patients with gastroesophageal junction or gastric cancer (GC) post trastuzumab failure

Methods

- Dose escalation evaluated marge 10 and 15 mg/kg and 200 mg pembro q3weeks for 2nd line or higher patients
- Cohort expansion evaluated safety and ORR by RECIST v1.1 in 2nd line patients
- Disease control rate (DCR) = proportion of patients with complete response (CR) + partial response (PR) + stable disease (SD)
- Combination given every 21 days; response assessed every 6 weeks
- HER2 amplification status assessed in a subset of patients by plasma circulating tumor (ct) DNA analysis prior to Cycle 1

Results

Demographics

Characteristic		All Patients (n=67)*
Age	Mean ± SD	58.4 ± 12.70
	Median (Range)	60.0 (19.0, 79.0)
Gender [n (%)]	Male	56 (83.6)
	Female	11 (16.4)
Race [n (%)]	Asian	28 (41.8)
	Black or African American	2 (3.0)
	Other	4 (6.0)
	White	33 (49.3)
ECOG Status [n (%)]	0	26 (38.8)
	1	41 (61.2)
Diagnosis [n (%)]	Gastric Cancer	35 (52.2)
	GEJ Cancer	32 (47.8)

*Data cut off December 4th, 2017.

Safety

- Treatment with the combination of margetuximab and pembrolizumab was well-tolerated overall

Adverse Event	All Related AE		All AE	
	All (N=67)	>Gr 3	All (N=67)	>Gr 3
TOTAL	**37 (55.2)**	**8 (11.9)**	60 (89.6)	31 (46.3)
Fatigue	**10 (14.9)**		18 (26.9)	
Diarrhoea	**6 (9.0)**		14 (20.9)	
Anaemia	**2 (3.0)**		14 (20.9)	9 (13.4)
Nausea	**3 (4.5)**	**1 (1.5)**	13 (19.4)	1 (1.5)
Abdominal pain	**1 (1.5)**		11 (16.4)	3 (4.5)
Decreased appetite	**3 (4.5)**		11 (16.4)	
Vomiting	**1 (1.5)**	**1 (1.5)**	10 (14.9)	3 (4.5)
Pruritus	**7 (10.4)**		10 (14.9)	
Infusion related reaction	**8 (11.9)**	**1 (1.5)**	8 (11.9)	1 (1.5)
Insomnia			8 (11.9)	
Constipation			7 (10.4)	
Hypoalbuminaemia			7 (10.4)	1 (1.5)

* Data cut off December 4th, 2017. Events occurring >10% pts.

- 55% of patients experienced a treatment related AE (TRAE), most ≤ Grade 2; 11.9% of patients with ≥ Grade 3. Most common TRAE is fatigue in 14.9% of patients
- 3 drug-related serious adverse events reported (autoimmune hepatitis [2] and pneumonitis [1])
- 11 adverse events of special interest reported (infusion related reactions [8], autoimmune hepatitis [2], pneumonitis [1])

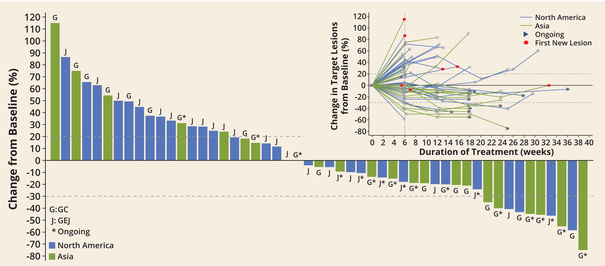
Preliminary Clinical Activity

	Margetuximab (15mg/kg) + Pembolizumab (200 mg) q3weeks (Evaluable Patients[†])				
	Gastric Cancer (n=25)	GEJ Cancer (n=26)	Asia (n=22)	North America (n=29)	Overall
Patient Population	2nd line HER2+				
ORR (all PR[‡])	**32%**	4%	**32%**	7%	18%
DCR (PR+SD)	**72%**	38%	**77%**	38%	55%
Median PFS	**5.5 months**	1.4 months	**5.5 months**	1.4 months	1.6 months
Median OS	**Not Reached**	Not Reached	**Not Reached**	Not Reached	Not Reached

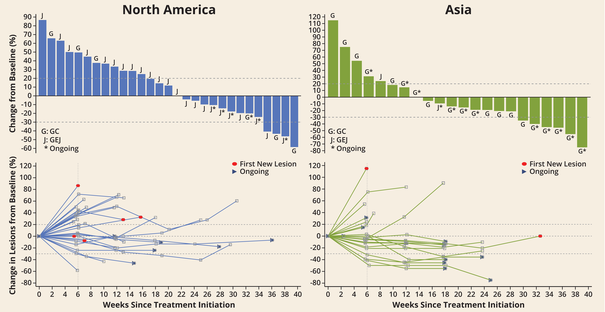
[†]Patients who have received at least one dose and have baseline and at least one post-baseline assessment. [‡]Confirmed + unconfirmed.
*Data cut off December 4th, 2017.

Clinical activity (Marge 15 mg/kg + Pembro 200 mg – All Patients)

- 51 evaluable patients to date at dose of 15 mg/kg marge and 200 mg pembro (29 North America/22 Asia)
- 53% (27/51) with tumor regression (target lesions)
- Best overall responses include 9 patients (18%) with PR (6 confirmed) and 19 (37%) with SD; ORR 18%, DCR 55%



*Data cut off December 4th, 2017.



*Data cut off December 4th, 2017.

Circulating Tumor DNA Results

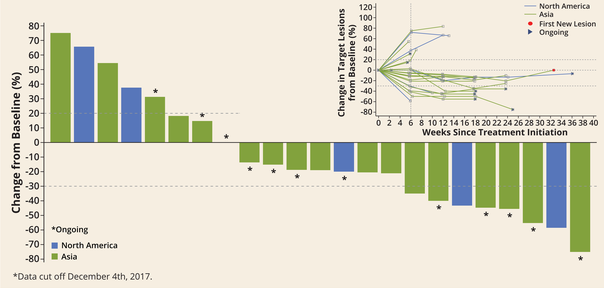
- 45 patients evaluated, 51% (23/45 , MAF>1%) were positive for *ERBB2* amplification by ctDNA post trastuzumab
- Response rate in the ctDNA positive post-trastuzumab population was 26% (6/23), while in the ctDNA negative population was 0% (0/22)
- Rates of *ERBB2* amplification were higher in gastric cancer vs. GEJ cancer

Cancer Type	# Samples (All)	# Samples (MAF >1%)	*ERBB2* CNV positive (All)		*ERBB2* CNV positive (MAF>1%)	
			#	%	#	%
Gastric Cancer	23	19	16	69.5	15	**78.9**
GEJ Cancer	22	15	9	40.9	8	**53.3**

CNV, copy number variant; MAF, mutant allele fraction; ctDNA, circulating tumor DNA
*Data cut off December 4th, 2017.

HER2+ Gastric Cancer Patients (IHC 3+)

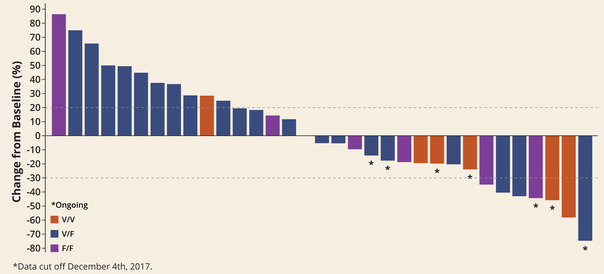
ORR 8/23 (35%), and DCR 18/23 (78%)



*Data cut off December 4th, 2017.

Results by Genotype

Among 33 patients with available CD16A genotype, responses were independent of FcR genotype; PR: 2 V/V, 3 V/F, 2 F/F with similar allelic distribution among patients with anti-tumor activity



*Data cut off December 4th, 2017.

Conclusions

- Margetuximab + pembrolizumab is a well-tolerated, chemotherapy-free combination that has shown preliminary antitumor activity in 2nd line patients with advanced/metastatic gastroesophageal cancer
- Response rate higher and PFS longer in gastric vs GEJ cancer, particularly in patients HER2 3+ at time of diagnosis
- Gastric cancer compared to GEJ tumors has a higher rate of retention of *ERBB2* amplification post-trastuzumab as determined by plasma ctDNA
  - Retained *ERBB2* amplification by ctDNA post-trastuzumab may enrich for treatment benefit
- No clear association between response and CD16A genotype observed
- Higher response rate observed in Asia vs North America
  - May be due to higher percent of gastric cancer in Asia cohort

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.** 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 U S A. 2011 Apr 26; 108(17): 7142–7147.

Presented at The 2018 Gastrointestinal Cancers Symposium, January 18–20, 2018, San Francisco, CA