# Margetuximab plus Pembrolizumab for Treatment of Patients with HER2-Positive Gastroesophageal Adenocarcinoma (GEA) Post-Trastuzumab: Survival Analysis



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NCT02689284

## Background

- Trastuzumab + chemotherapy is standard treatment in 1<sup>st</sup> line advanced HER2+ gastroesophageal adenocarcinoma (GEA); however, patients tend to progress in 6−8 months
- Consistent with previous literature, we have noted ~40% of patients have a loss of HER2 expression post trastuzumab (abstract #2794), likely underlying the lack of efficacy anti-HER2 agents in prior 2<sup>nd</sup> line studies
- Margetuximab is an investigational next generation anti-HER2 monoclonal antibody with an engineered Fc domain that confers enhanced Fc-dependent antitumor activities across all FcyRIIIA (CD16A) genotypes
- Margetuximab has demonstrated single agent antitumor activity in patients with HER2+ GEA in a Phase 1 study
- Current standard of care in 2<sup>nd</sup> line GEA, ramucirumab + taxane, has median progression-free survival (mPFS) of 4.4 months and median overall survival (mOS) of 9.6 months
- Chemotherapy-backbone HER2-targeted agents tested in 2<sup>nd</sup> line HER2+ GEA TyTAN and GATSBY studies showed mPFS and mOS ranged 2.4–5.4 months, and 7.1–11.2 months, respectively
- Pembrolizumab, in 2<sup>nd</sup> line KN061 study, showed mPFS and mOS of 1.5 months and 9.1 months in GEA patients with PD-L1 CPS >1, and both were lower for PD-L1 all comers
- Herein we present survival analysis of an ongoing study in patients receiving margetuximab plus pembrolizumab at the recommended Phase 2 dose (RP2D), 15 mg/kg of margetuximab and 200 mg of pembrolizumab q3wk, a chemotherapy-free treatment, in HER2+ GEA patients post trastuzumab

## Methods

- HER2-positive (archival IHC3+, or ICH2+/FISH positive), PD-L1 unselected GEA patients (data cut 10 July 2019)
- Median PFS and OS analysis performed on patients post progression on trastuzumab-based therapy
- 92 patients treated at RP2D of 15 mg/kg margetuximab + 200 mg pembrolizumab included in analysis (data cut 10 July 2019)
- Biomarker subgroups including archival PD-L1 and HER2 IHC, ERRB2 ctDNA (prior to 2nd line therapy), and tumor site (GC vs GEJ)

#### Margetuximab: Fc-engineered to Activate Immune Responses

### Trastuzumab Fab:

FcyRIIIA (CD16A)

■ ↓ Affinity for inh

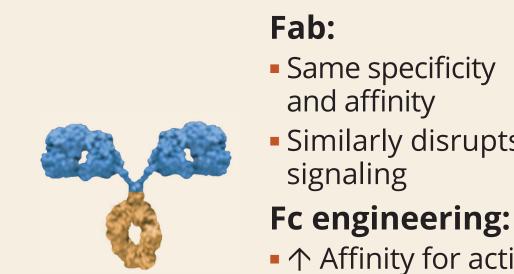
Binds HER2 with high specificityDisrupts signaling that drives cell proliferation and survival

Binds and activates immune cells

Fc:

Wild-type immunoglobulin G1 (IgG1) immune effector domains

#### Margetuximab<sup>1,2</sup>



Anti-HER2 mAb (ng/mL)

	Margetuximab Binding to FcyR Variants						
ts	Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change		
		CD16A	158F	Lower	6.6 x ↑		
•	Activating	CD16A 158V Higher	4.7 x ↑				
tivating	Activating		131R	Lower	6.1 x ↓		
) aibitary			131H	Higher	$\leftrightarrow$		
nibitory	Inhibitory	CD32B	232I/T	Equivalent	8.4 x ↓		

FcγRIIB (CD32B)

Inhibitory CD32B 232I/T Equivalent of the content of the conten

Margetuximab Enhances Innate Immunity In Vitro

## 

## Preclinical Assay of Antibody-Dependent Cellular Cytotoxicity (ADCC)<sup>1</sup>

- Effector Cells: Human NK cells from donors with CD16A genotypes 158VV, 158FV,
- Target Cells: JIMT-1 HER2+ breast cancer cell line resistant to trastuzumab antiproliferative activity
- Cellular Assay: 3:1 Effector: Target ratio; 24-hour incubation time; endpoint:
   % lactate dehydrogenase release
- ¹Nordstrom JL, et al. Breast Cancer Res. 2011;13(6):R123. mAb: monoclonal antibody; NK: natural killer.

Anti-PD-1 Enhances Margetuximab-mediated NK Cell Cytolytic Potential In Vitro

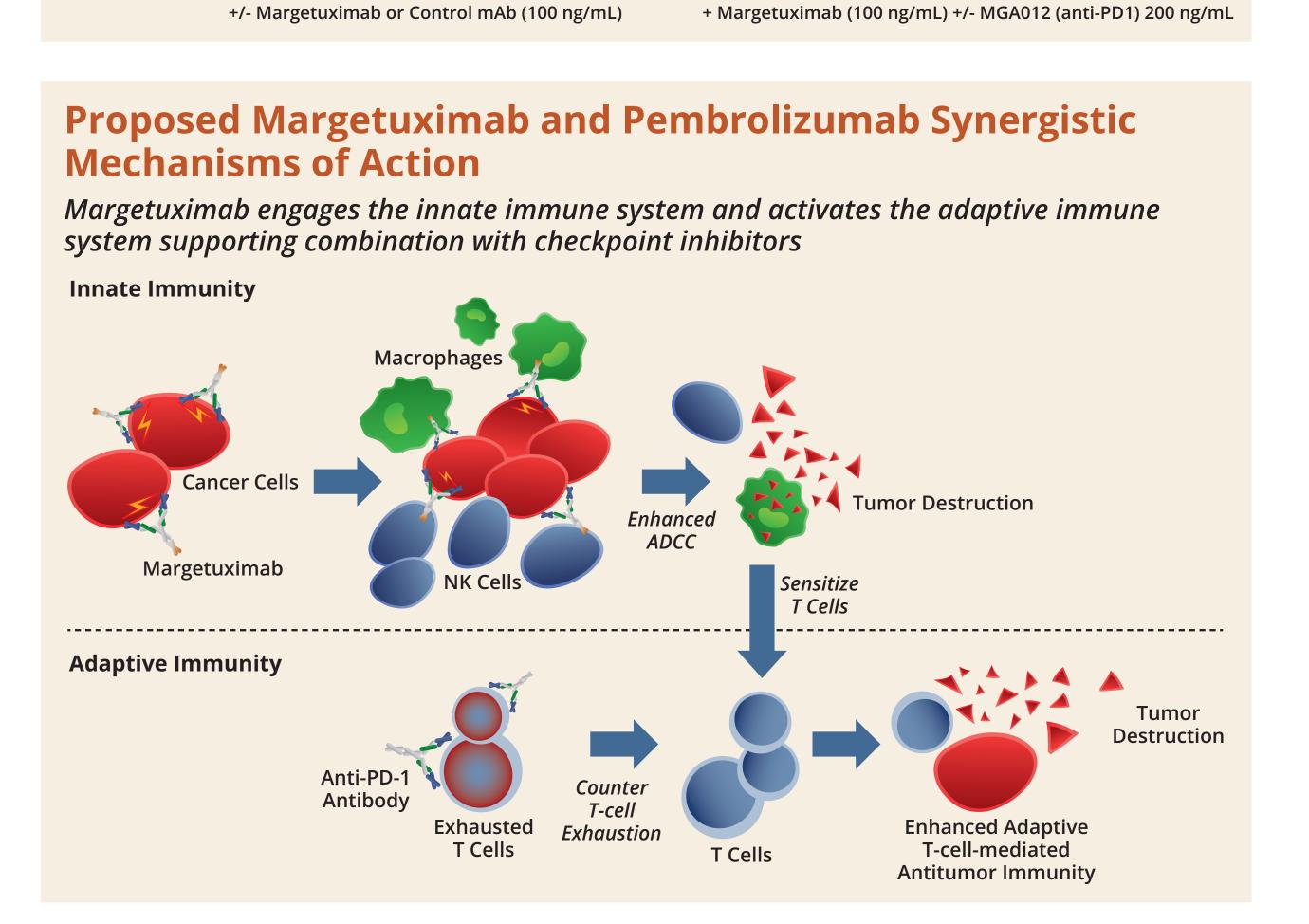
Margetuximab Induces PD-1 Expression on NK and NKT Cells

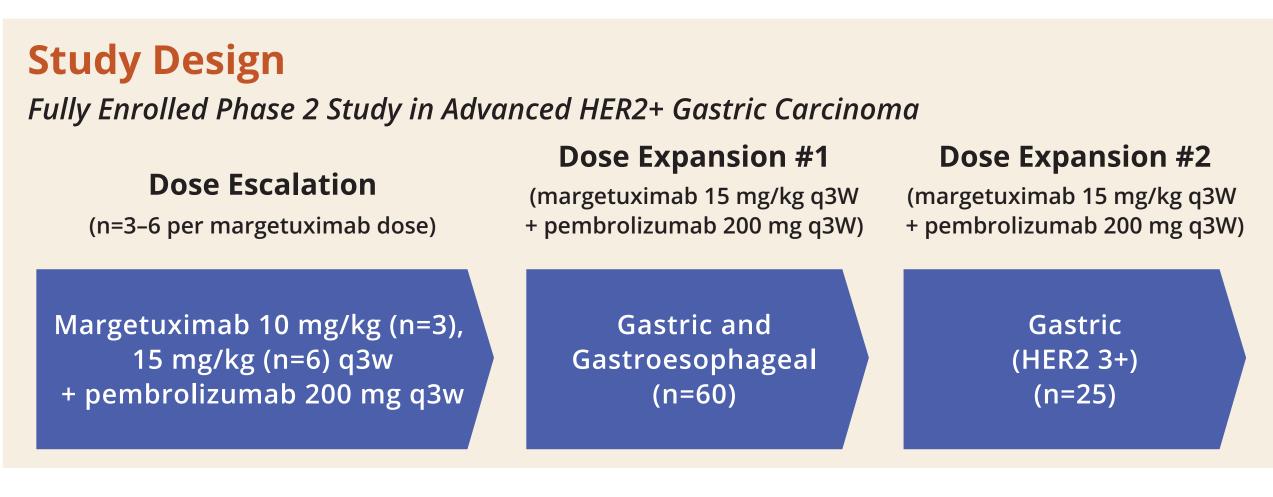
Anti-PD-1 Enhances Margetuximab-mediated NK Cell Proliferation and Expression of Granzyme B/Perforin

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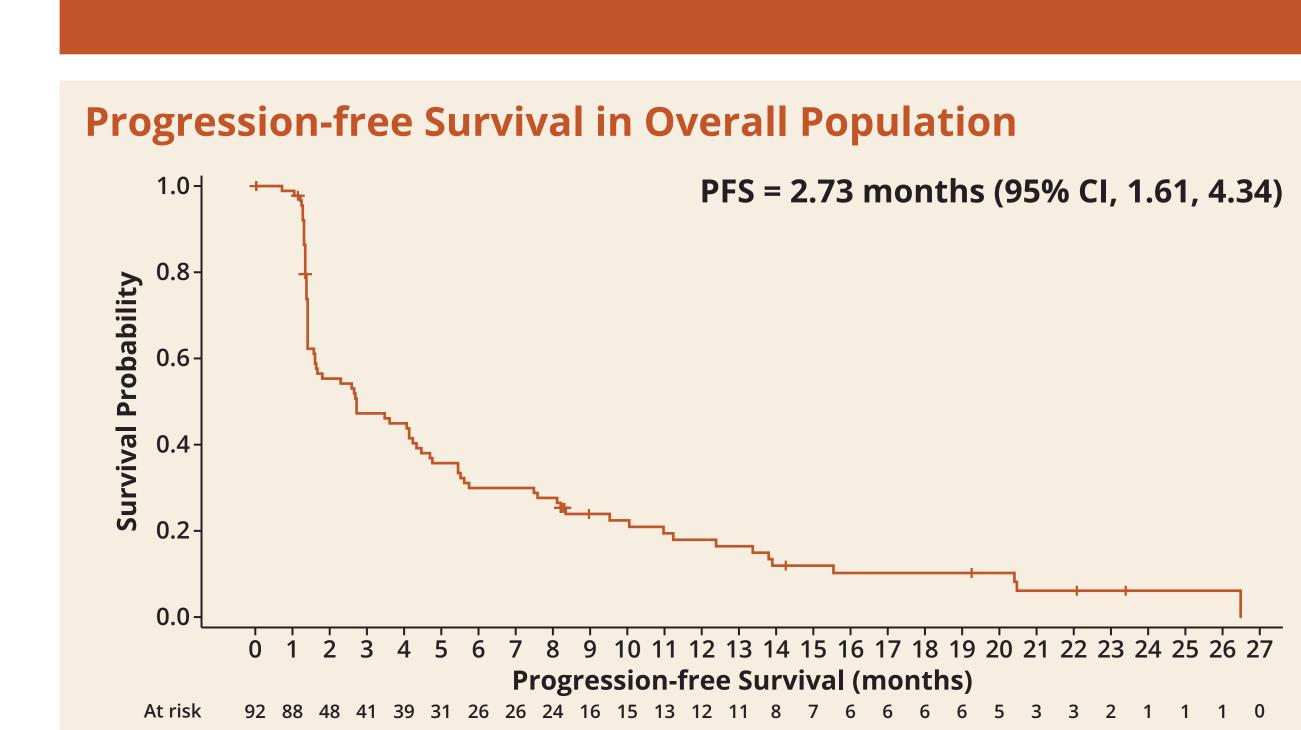
Margetuximab

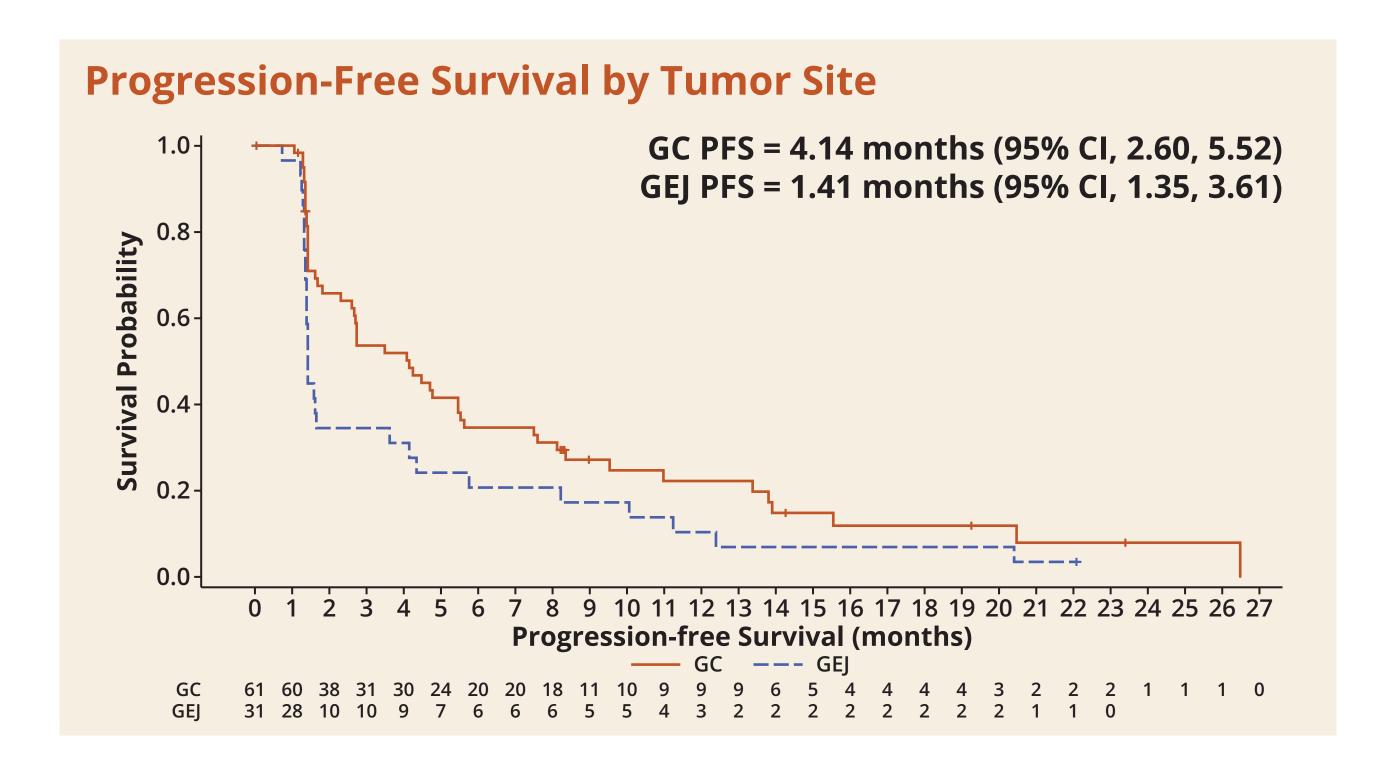
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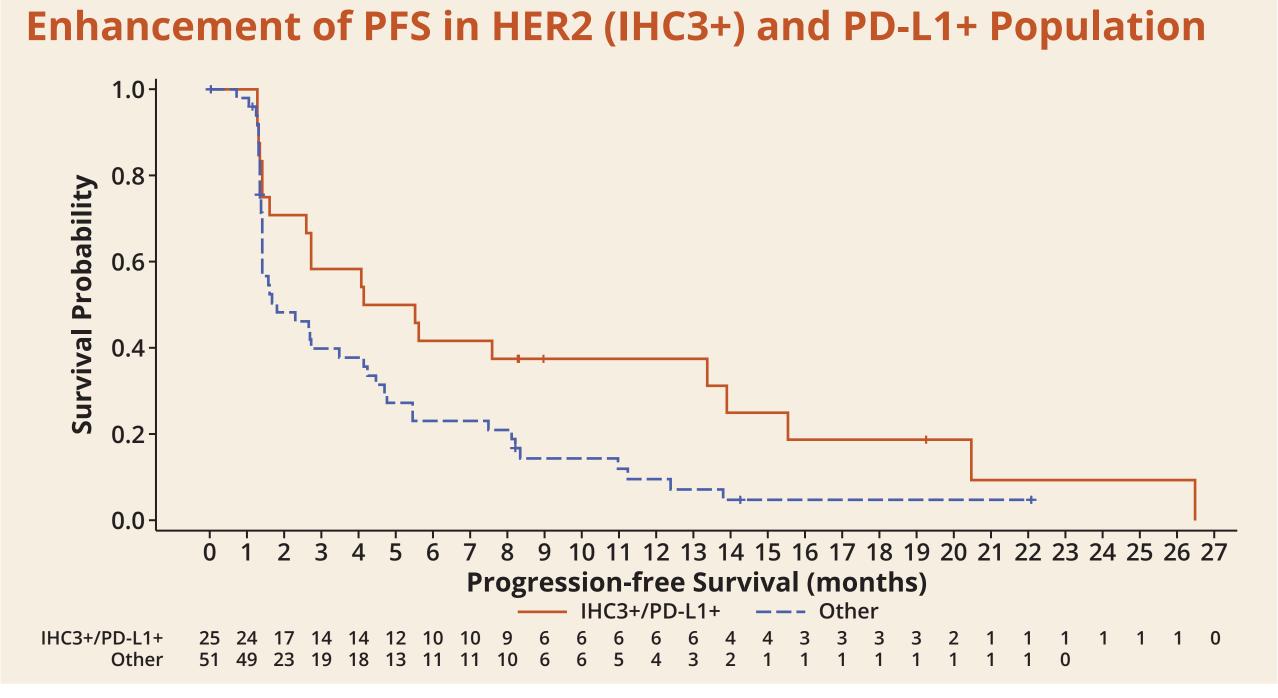


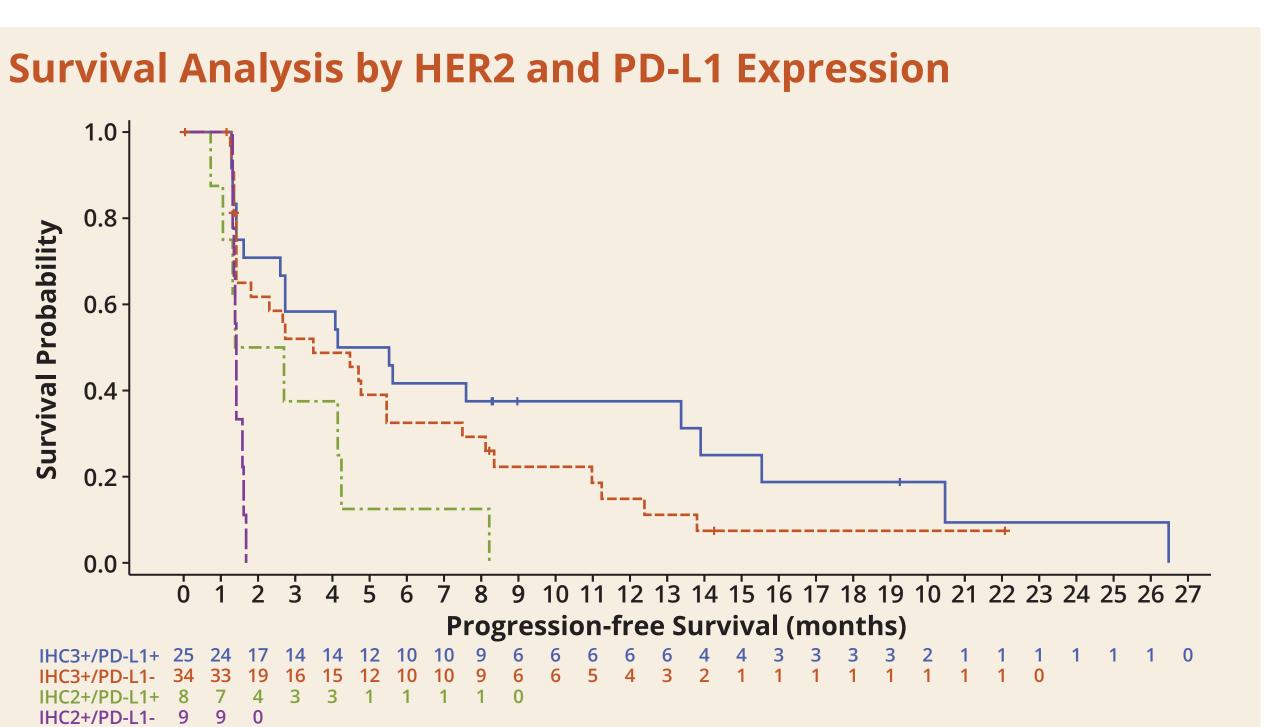


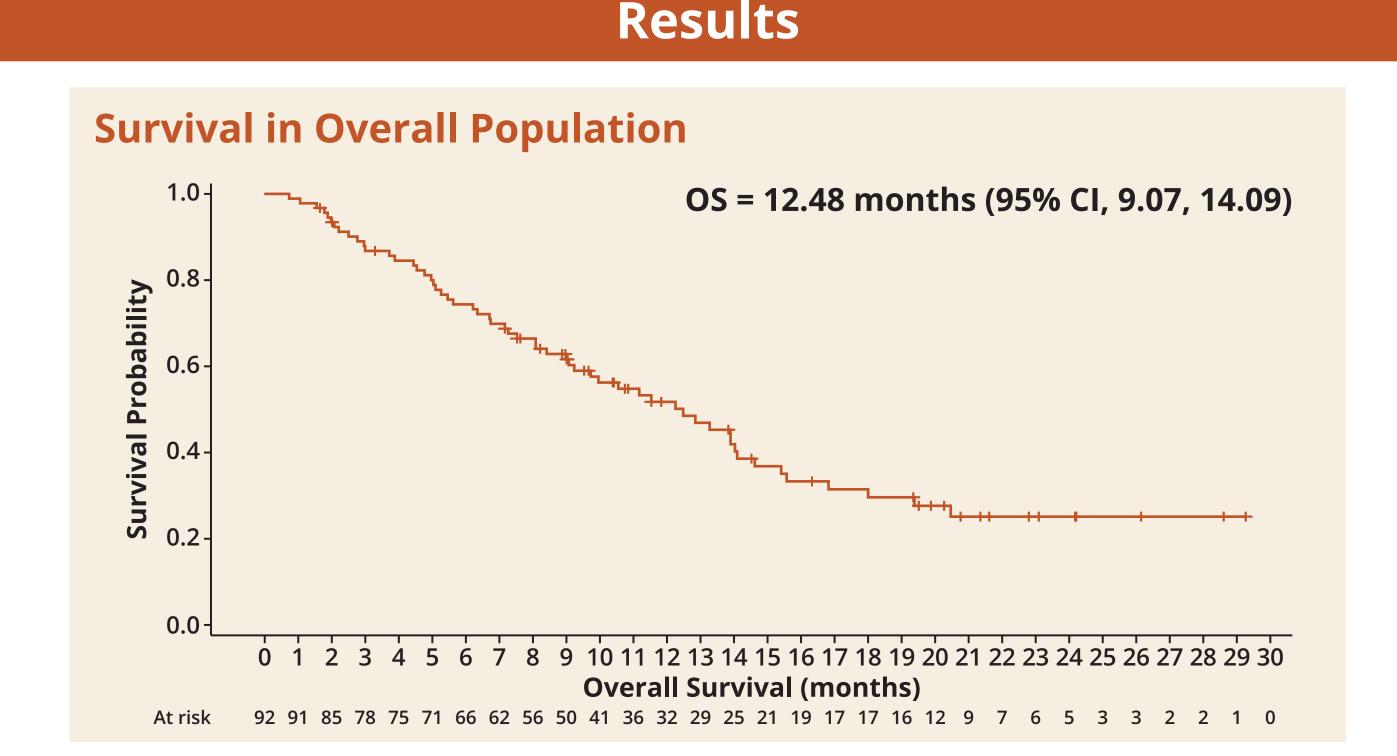
Patient Characteristics						
Charac	All Patients (n=92)					
Λσο	Mean ± SD	60.2 ± 12.83				
Age	Median (Range)	61.0 (19, 85)				
Gandar [n (%)]	Male	75 (81.5)				
Gender [n (%)]	Female	17 (18.5)				
	Asian	51 (55.4)				
Paco [n (06)]	White	34 (37.0)				
Race [n (%)]	Other	4 (4.3)				
	Black or African American	3 (3.3)				
ECOC Status In (06)]	0	33 (35.9)				
ECOG Status [n (%)]	1	59 (64.1)				
Diagnosis In (04)]	Gastric Cancer	61 (66.3)				
Diagnosis [n (%)]	GEJ Cancer	31 (33.7)				
Microsatellite Stable [n (%)]		84 (91.3)				

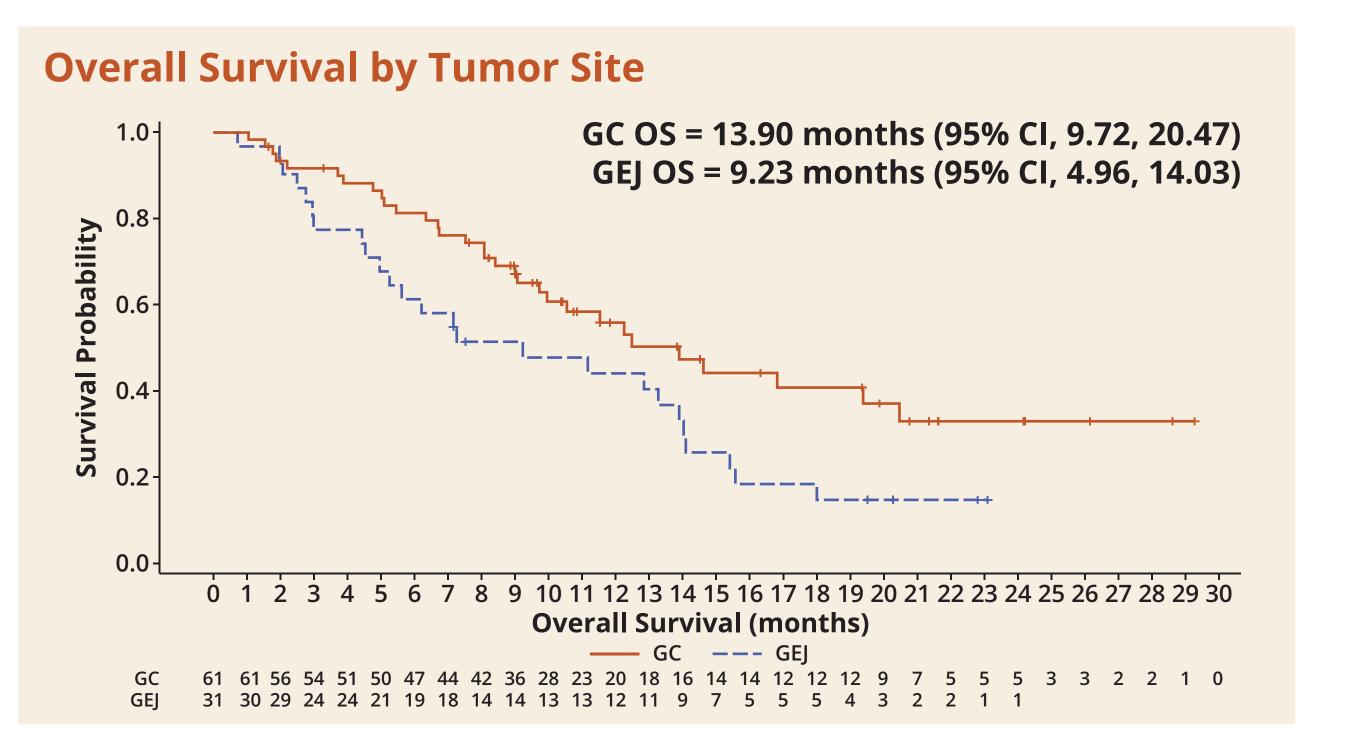


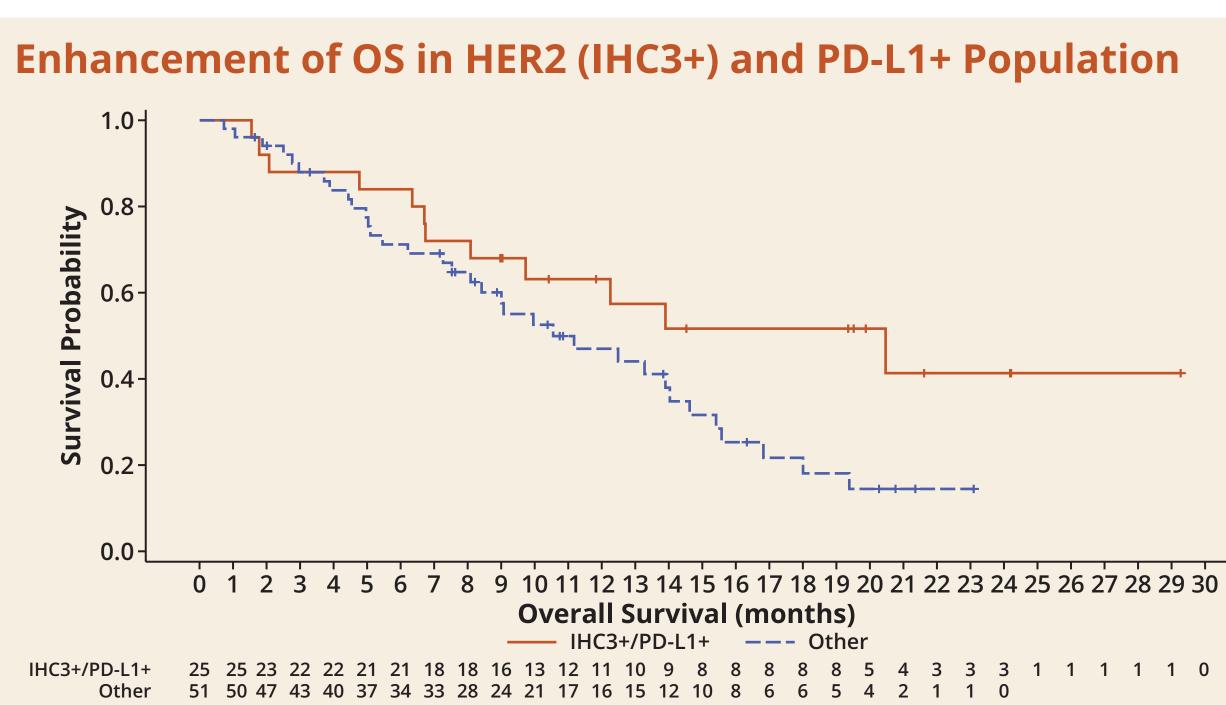


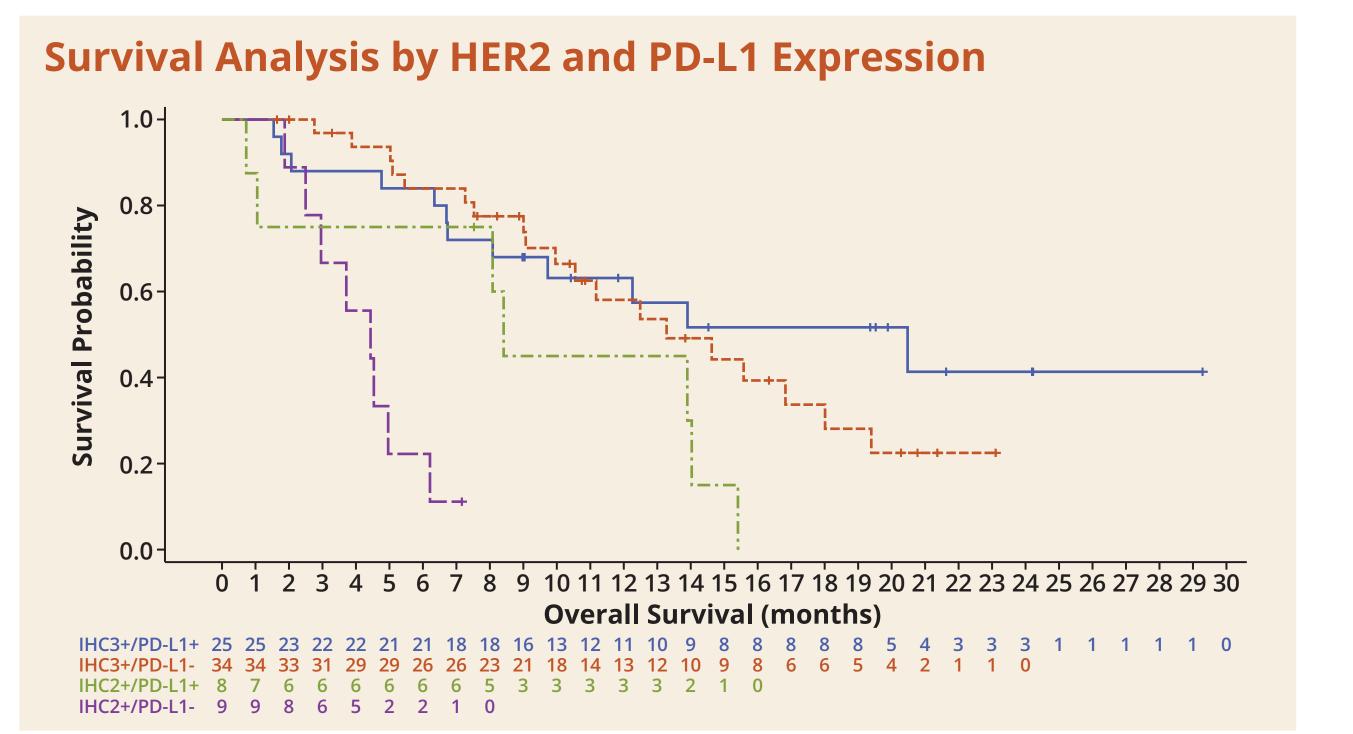












# Efficacy Endpoints in Selected Biomarker Positive Populations by Anatomical Site

	Overall			Gastric Cancer			GEJ Cancer		
	ORR (%, n)* DCR (%, n)	mPFS (months) (95% CI)	mOS (months) (95% CI)	ORR (%, n) DCR (%, n)	mPFS (months) (95% CI)	mOS (months) (95% CI)	ORR (%, n) DCR (%, n)	mPFS (months) (95% CI)	mOS (months) (95% CI)
All Patients	(21.74%) 20/92	2.73	12.48	(29.51%) 18/61	4.14	13.90	(6.45%) 2/31	1.41	9.23
	(54.35%) 50/92	(1.61, 4.34)	(9.07, 14.09)	(65.57%) 40/61	(2.60, 5.52)	(9.72, 20.47)	(32.26%) 10/31	(1.35, 3.61)	(4.96, 14.03)
IHC3+	(28.17%) 20/71	4.34	13.90	(32.73%) 18/55	4.70	14.62	(12.50%) 2/16	2.63	12.01
	(63.38%) 45/71	(2.60, 5.62)	(10.55, 20.47)	(69.09%) 38/55	(2.66, 7.49)	(10.55, NR)	(43.75%) 7/16	(1.35, 11.24)	(5.26, 18.00)
<i>ERBB2</i> amp	(33.33%) 16/48	4.76	13.27	(40.00%) 14/35	5.49	16.82	(15.38%) 2/13	1.41	5.62
	(66.67%) 32/48	(2.60, 8.11)	(8.08, 19.38)	(77.14%) 27/35	(2.69, 8.34)	(9.07, NR)	(38.46%) 5/13	(1.31, 12.39)	(2.96, 13.27)
PD-L1+	(36.36%) 12/33	4.11	13.90	(46.15%) 12/26	4.19	13.90	(0.00%) 0/7	1.35	14.03
	(69.70%) 23/33	(1.41, 7.59)	(8.08, NR)	(80.77%) 21/26	(2.60, 13.37)	(8.08, NR)	(28.57%) 2/7	(0.72, 8.21)	(0.72, NR)
IHC3+/PD-L1+	(48.00%) 12/25	4.83	20.47	(52.17%) 12/23	5.52	20.47	(0.00%) 0/2	1.28	NR
	(76.00%) 19/25	(1.61, 13.90)	(8.08, NR)	(82.61%) 19/23	(2.60, 13.90)	(8.08, NR)	(0.00%) 0/2	(NA)	(2.07, NR)
<i>ERBB2</i> amp/	(55.56%) 10/18	5.52	NR	(58.82%) 10/17	5.52	NR	(0.00%) 0/1	NA	2.07
PD-L1+	(83.33%) 15/18	(1.61, 13.37)	(6.74, NR)	(88.24%) 15/17	(1.61, 13.37)	(6.74, NR)	(0.00%) 0/1		(NA)
<i>ERBB2</i> amp/ IHC3+/PD-L1+	(66.67%) 10/15 (86.67%) 13/15	6.60 (1.61, 15.54)	NR (6.34, NR)	(71.43%) 10/14 (71.43%) 10/14	6.60 (1.61, 15.54)	NR (6.74, NR)	(0.00%) 0/1	NA	2.07 (NA)
*17 confirmed, 3 unconfirmed responses.									

Margetuximab + Anti-PD-1 Data in 2<sup>nd</sup> Line Presents Opportunity to Advance to 1<sup>st</sup> Line

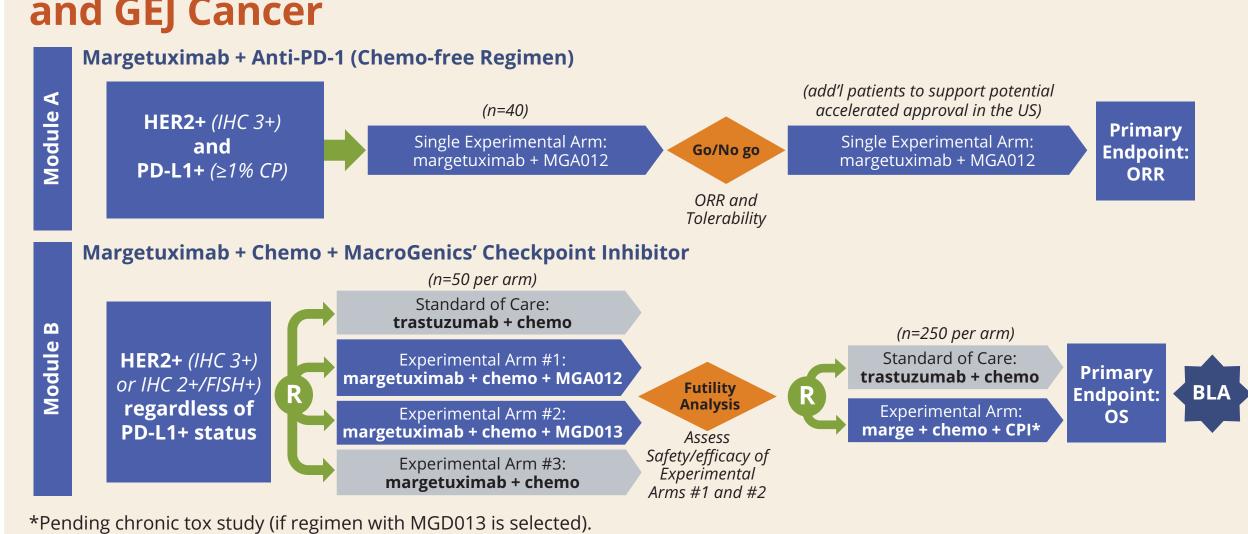
HER2+ gastric cancer benchmarks

	1 <sup>st</sup> Line	2 <sup>nd</sup> Line				
	SOC	SOC Ongoing Phase 2 Study		nase 2 Study	Failed	
Agent (Study)	Trastuzumab +	Ramucirumab + Paclitaxel <sup>b</sup> (RAINBOW)	Margetuximab + Pembrolizumab <sup>c</sup>		Pembrolizumab <sup>d</sup>	
	Chemo <sup>a</sup> (TOGA)		IHC 3+	IHC 3+/PD-L1+	(KEYNOTE-61) 🗶	
ORR	47%	28%	33%	52%	15.8% (PD-L1+)	
Median PFS	6.7 mos.	4.4 mos.	4.7 mos.	5.5 mos.	1.5 mos.	
Median OS	13.1 mos.	9.6 mos.	14.6 mos.	20.5 mos.	9.1 mos	
≥ Grade 3 TRAEs	68%	Overall: N/A 41% Neutropenia 15% Hypertension 12% Fatigue	20%	20%	14.3%	
Gastric/GEJ Patient Mix	80/20%	80/20%	100%/0%	100%/0%	Not disclosed	

## Conclusions

- Margetuximab is an Fc-engineered anti-HER2 antibody that mediates enhanced innate responses and leads to increased HER2-specific adaptive immune responses in patients with HER2+ gastric and breast carcinoma
- In this study, the combination of margetuximab + pembrolizumab, as a chemotherapy-free regimen, in patients with HER-2+ GEA that have progressed/recurred after front-line therapy including trastuzumab has shown:
- An acceptable safety and tolerability
- A prolonged median OS (12.9 mos) compared to historical experience with 2L standard of care (RAINBOW, ramucirimab + taxane, mOS=9.6 mos) or checkpoint inhibitor alone (KN-061, pembrolizumab, mOS=9.1 mos)
- In the HER2 IHC3+/PD-L1+ gastric cancer patients a prolonged median OS (20.5 mos) was noted, which exceeds historical experience with 1L standard of care (TOGA, trastuzumab + chemo, mOS=13.1 mos)
- These results are particularly notable because many patients lose HER2 expression post trastuzumab.
   Dasad on these observations, the combination of margatuvimab, the sheek point inhibitor
- Based on these observations, the combination of margetuximab + a checkpoint inhibitor could provide a potential chemotherapy-free regimen for the treatment of GEA and/or be used with chemotherapy to improve the clinical activity of existing 1L SoC
- A Phase 2/3 study (MAHOGANY) is being initiated to evaluate margetuximab in combination with a checkpoint inhibitor with or without chemotherapy in 1L GEA

## MAHOGANY Phase 2/3 Study: Registration Path in 1L Gastric and GEJ Cancer



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Anti-HER2 mAb (ng/mL)