A Phase 1 Evaluation of Tebotelimab, a Bispecific PD-1 x LAG-3 DART® Molecule, in Combination with Margetuximab in Patients with Advanced HER2+ Neoplasms

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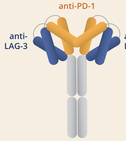
Background

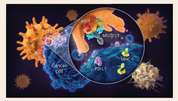
Tebotelimab (MGD013)

- PD-1 and LAG-3 receptors are expressed on "exhausted" T cells
  - Interactions with corresponding ligands negates anti-tumor T-cell activity
- Tebotelimab, an investigational DART protein, targets PD-1 and LAG-3 with a single molecule
  - Tetravalent (bivalent for each target) structure with IgG4 Fc
  - Greater synergistic T-cell activation (IFN-γ) in vitro with tebotelimab compared with combination of individual constituents
- Ongoing tebotelimab Phase 1 study demonstrated safety up to 1200 mg Q2W, with evidence of monotherapy antitumor activity in various advanced solid tumors[1]
  - Objective responses associated with increased baseline LAG-3 expression and IFN-γ gene signature
  - Monotherapy RP2D defined as 600 mg

Tebotelimab



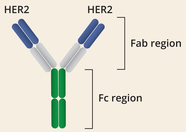
PD-1 x LAG-3 Tetravalent Bispecific DART Molecule



Margetuximab

Investigational Fc-engineered anti-HER2 mAb

- Similar anti-HER2 properties as trastuzumab
- Enhanced Fc-mediated effector function[2]
- Superior PFS to trastuzumab in Phase 3 SOPHIA study in mBC[3]
- Anti-tumor activity in advanced gastric cancer
  - In combination with anti-PD-1[4]



Trastuzumab

- Fab:
  - Binds HER2 with high specificity
  - Disrupts signaling that drives cell proliferation and survival
- Fc:
  - Wild-type immunoglobulin G1 (IgG1) immune effector domains
  - Binds and activates immune cells

Margetuximab[5,6]

- Fab:
  - Same specificity and affinity
  - Similarly disrupts signaling
- Fc engineering:
  - ↑ Affinity for activating FcγRIIIA (CD16A)
  - ↓ Affinity for inhibitory FcγRIIB (CD32B)

Margetuximab Binding to FcγR Variants:

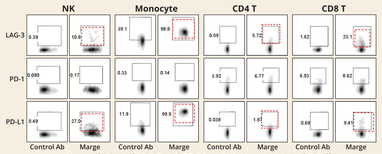
Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6x ↑
		158V	Higher	4.7x ↑
	CD32A	131R	Lower	6.1x ↓
		131H	Higher	↔
Inhibitory	CD32B	232I/T	Equivalent	8.4x ↓

CD16A Genotype May Predict Anti-HER2 Antibody Benefit

- Improved responses to trastuzumab observed in patients with HER2+ breast cancer[7] or gastric cancer[8] who are homozygous for CD16A-158V (V/V), which encodes the higher-affinity Fcγ receptor when compared to CD16A-158F carriers (V/F, F/F)
  - V/V present in approximately 15% of Caucasian, African American, and Asian populations
  - Lower affinity F/F and intermediate affinity V/F carriers comprise the remainder of the population (~85%)
- **Hypothesis:** Greater margetuximab benefit in lower-affinity CD16A-158F carriers (e.g. V/F, F/F)
  - Increased affinity of margetuximab for CD16A-158F over trastuzumab (wild-type IgG1)

Tebotelimab Plus Margetuximab: Combinatorial Biology

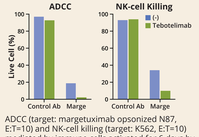
Fc-engineered Margetuximab Upregulates LAG-3/PD-L1 Expression



Upregulation of LAG-3 and PD-L1 on NK, Monocytes and T Cells

Human PBMC (Donor # 731) + N87 (HER2+) gastric cancer cells; E:T = 15:1 +/- margetuximab (no supplementary IL-2)

Tebotelimab Enhances Lytic Activity of Immune Cells Primed by Margetuximab



ADCC (target: margetuximab opsonized N87, E:T=10) and NK-cell killing (target: K562, E:T=10) mediated by immune cells activated for 6 days by margetuximab +/- tebotelimab in the presence of N87 tumor cells.

Phase 1 Study Design

3 + 3 Dose Escalation (Complete)
(Advanced HER2+ solid tumors)

Tebotelimab 600 mg + Margetuximab 15 mg/kg

Tebotelimab 300 mg + Margetuximab 15 mg/kg

MAD/MTD

Cohort Expansion (Ongoing)

- HER2+ Breast Cancer
- HER2+ GC/GEJ Cancer
- Other HER2+ Cancers

Both study drugs administered Q3W.

Study Objectives

Primary

- Characterize safety of combination in patients with HER2+ locally advanced or metastatic cancers

Secondary

- Characterize PK and immunogenicity of combination administered Q3W
- Assess preliminary antitumor activity of combination using RECIST v1.1 and irRECIST

Exploratory

- Explore relationships between PK/PD, patient safety, and antitumor activity of combination
- Determine relationship between clinical response and expression of PD-L1, HER2, and/or LAG-3 on tumor cells and immune cell infiltrates
- Investigate immune-regulatory activity of combination in vivo, including various measures of T-cell activation in peripheral blood and/or tumor biopsy specimens
- Explore relationships among Fcγ receptor allelic variation in CD16A, CD32A, and CD32B and clinical response

Key Entry Criteria

- Age ≥ 18 years
- ECOG performance status 0 or 1
- Life expectancy ≥ 12 weeks
- Measurable disease per RECIST v1.1
- Acceptable laboratory parameters
- Cancer must have progressed following standard therapy, or during/after HER2-directed therapy if approved and available for patients with HER2+ gastric, GEJ, or breast cancer
- History of HER2 positivity defined as (1) IHC 3+ or IHC 2+ with ISH positivity or (2) HER2 amplification by NGS

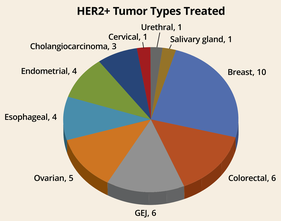
Patient Demographics and Disposition

Demographics

	Tebotelimab + Margetuximab (n=41)
Median age (range), years	63 (29, 86)
Gender, n (%)	
Male	17 (41.5)
Female	24 (58.5)
ECOG PS, n (%)	
0	19 (46.3)
1	22 (53.7)
Median prior lines of therapy (range)	2 (1, 7)
Prior Checkpoint Inhibitor	
Yes	9 (22.0)
No	32 (78.0)
Prior HER2-directed therapy	
Yes	28 (68.3)
No	13 (31.7)

Data cut-off: 05Oct2020

HER2+ Tumor Types Treated

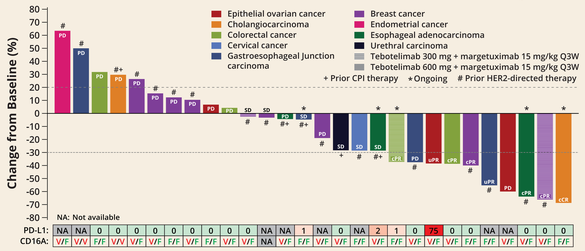


End of Treatment Disposition

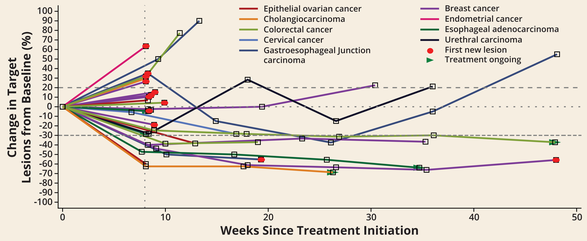
	Tebotelimab + Margetuximab
Patients treated	41
Response-evaluable patients	28 (68.3)
Median duration of therapy, weeks (min, max)	9.8 (1.7, 64.4)
Continuing treatment, n (%)	11 (26.2)
Treatment discontinuation, n (%)	30 (73.2)
Reasons for discontinuation, n (%)	
Disease progression	21 (51.2)
Adverse event	6 (14.3)
Patient/physician decision/withdrawal	2 (4.9)
Unknown	1 (2.4)

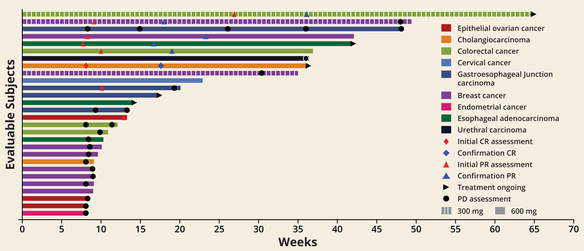
Preliminary Results

Preliminary Evidence of Anti-tumor Activity



PD-L1 Combined Positive Score (CPS) calculated as follows: Number of PD-L1+ cells (tumor cells, lymphocytes and macrophages)/total number of viable tumor cells x 100.





	Breast	GEJ/Esophageal	Colorectal	Other	Total
Evaluable patients	9	7	4	8	28
ORR (confirmed)	22.2% (2/9)	14.3% (1/7)	50% (2/4)	12.5% (1/8)	21.4% (6/28)
ORR (confirmed + unconfirmed)	22.2% (2/9)	28.6% (2/7)	50% (2/4)	25% (2/8)	28.6% (8/28)
Disease control rate	44.4% (4/9)	57.1% (4/7)	50% (2/4)	50% (4/8)	50% (14/28)

Benchmark data from PANACEA study[4]

11.5% ORR (n=52) in a single arm, multicenter Ph. 1b/2 trial of pembrolizumab + trastuzumab in HER2+ mBC

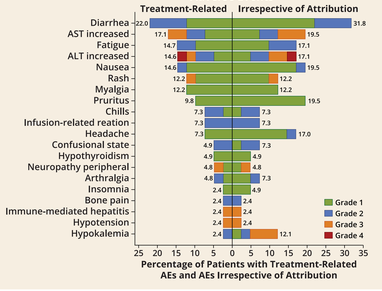
- 15% ORR in PD-L1 positive (n=6/40)
- 0% ORR in PD-L1 negative (n=0/12)

Safety Overview

Overall AE Totals	No. (%) of Patients	
	All Grades (N=41)	≥ Grade 3 (N=41)
AE (irrespective of causality)	37 (90.2)	17 (41.5)
Treatment-related AE	30 (73.2)	8 (19.5)
SAE (irrespective of causality)	7 (17.1)	6 (14.6)
Treatment-related SAE	2 (4.9)	2 (4.9)
AE leading to treatment discontinuation	6 (14.6)	4 (9.8)
Adverse Events of Special Interest (AESIs)		
Infusion-related reaction	3 (7.3)	0 (0)
Arthralgia	2 (4.9)	0 (0)
Immune-mediated hepatitis	1 (2.4)	1 (2.4)
Left ventricular dysfunction	1 (2.4)	1 (2.4)
Pancreatitis	1 (2.4)	1 (2.4)
Hyperthyroidism	1(2.4)	0 (0)

- Dose escalation levels cleared with no DLTs
- Combination generally well-tolerated with safety profile consistent with tebotelimab monotherapy
- Diarrhea is most common TRAE — all Grade 1 or 2 events with no evidence of colitis
- Immune-related adverse events recovered with immunosuppression, hormonal treatment, and/or treatment interruption or discontinuation

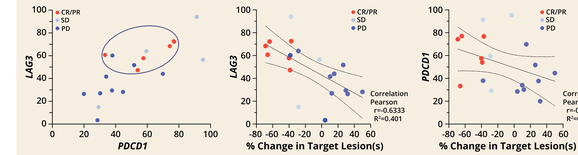
Adverse Events



Association of Baseline LAG-3/PD-1 Expression with Clinical Response

Dual *LAG3/PDCD1* Expression at Baseline Associates with Objective Response

Baseline LAG-3 and PD-1 Levels Inversely Correlate with Best % Change in Target Lesions



- Patients demonstrating objective responses exhibit higher expression of both LAG-3 and PD-1 (*PDCD1*) mRNA in baseline biopsy samples
- Expression of *LAG3* and *PDCD1* mRNA in baseline tumor biopsy inversely correlates with best change in tumor lesion
  - Highest correlation observed with LAG-3 expression
- ROC analyses of LAG-3 expression and objective responses (confirmed and unconfirmed) indicate a 75% response rate in LAG-3 biomarker high patients vs 9% in biomarker low patients
  - Further analyses ongoing and will be extended to additional patients to further define potential enrichment biomarker component(s)

The NanoString PanCancer IO 360™ assay was used to interrogate gene expression, including the abundance of 14 immune cell types and 32 immuno-oncology signatures, from archival biopsies of 19 HER2+ advanced solid tumor cohorts treated with margetuximab and tebotelimab. **Left:** Normalized expression scores (standardized 0-100) for *LAG3* were plotted against *PDCD1*. **Right:** Correlation of standardized *LAG3* and *PDCD1* expression levels to best percent change in tumor lesions from baseline, respectively. Receiver Operating Characteristic (ROC) analyses were performed on the 19 patient data set using Youden Index and Distance methods.

Conclusions

- Tebotelimab + margetuximab combination generally well tolerated
  - Safety profile consistent with tebotelimab monotherapy
- Evidence of antitumor activity observed among refractory patients with various HER2+ tumor types
  - Objective responses (n=8; 6 confirmed) observed in multiple advanced HER2+ tumor types
  - ORR (including unconfirmed responses) = 28.6% (Compares favorably to benchmark mBC data from PANACEA study)
  - 64.3% of response-evaluable population with decrease of target lesion tumor burden
  - Duration of response (n=6 confirmed responders): 4.21–8.97 months (3 patients ongoing)
- Majority of responding patients with baseline PD-L1 expression of ≤ 1
- All responding patients carry less favorable CD16A-158F allotype (i.e. V/F or F/F)
- Baseline LAG-3 and PD-1 mRNA expression associated with clinical response
  - Analyses ongoing to define patient enrichment biomarker
- Enrollment in HER2+ tumor-specific cohorts ongoing

References

1. Luke JJ, et al. ASCO 2020. **2.** Nordstrom, et al., 2011 *Breast Cancer Research*, 13: R123. **3.** Rugo, et al., ASCO 2019, Chicago, IL. **4.** Catenacci, et al., ASCO GI 2019, San Francisco, CA / Catenacci et al. 2020 *Lancet Oncology*, in press. **5.** Nordstrom JL, et al. *Breast Cancer Res.* 2011;13(6):R123. **6.** Stavenhagen JB, et al. *Cancer Res.* 2007;67(18):8882-8890. **7.** Musolino A, et al. *J Clin Oncol.* 2008;26(11):1789-1796. **8.** Wang DS, et al. Onco Targets Ther. 2017;10:5065-5076.