Evaluation of Tumor Microenvironment Identifies Immune Correlates of Response to Combination Immunotherapy with Margetuximab (M) and Pembrolizumab (P) in HER2+ Gastroesophageal Adenocarcinoma (GEA)

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Abstract #2547

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Background

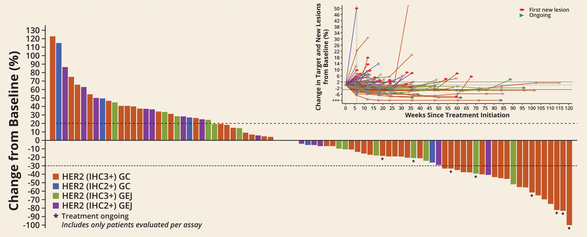
- Gastric cancer is the fifth most common cancer and the third most common cause of cancer deaths worldwide
- Despite improvements in treatment, the 5-year survival of patients with GEA is disappointing
- Individual molecular subtypes of GEA display preferential responses to PD-1 blockade
- Margetuximab is an investigational Fc-optimized anti-HER2 monoclonal antibody being tested in combination with pembrolizumab in HER2+ GEA post trastuzumab

Materials and Methods

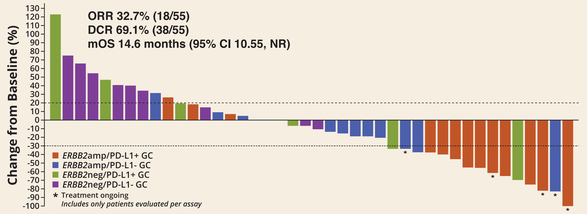
- 92 patients with advanced, relapsed/refractory HER2+ gastric cancer (GC) and gastroesophageal junction (GEJ) cancer were treated with margetuximab + pembrolizumab in the CP-MGAH22-05 study
- 55 pre-treatment tumor samples were assessed by NanoString's PanCancer IO360™ (IO360) gene expression assay (for research use only)[1]
  - IO360 signature scores were calculated and are presented as fold changes (FC) and analyzed by unpaired t test
- Associations examined include:
  - Overall inflamed tumor microenvironment (TME)
  - Complete response (CR) n=1, partial response (PR) n=13, stable disease (SD) n=23, progressive disease (PD) n=18
  - Immunohistochemistry (IHC) status for PD-L1 (positive n=25, versus negative n=27) and HER2 (IHC3+ n=45, versus IHC2+ n=10)
  - Tumor location (GC n=46, versus GEJ cancer, n=9)

Results

Best Response by HER2 Expression and Tumor Site

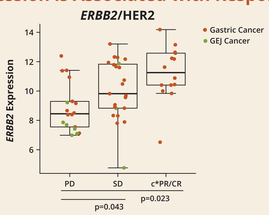


HER2 (IHC3+) Gastric Cancer



- Increased response rate in patients with *ERBB2*amp, a surrogate for HER2 expression, post trastuzumab
- Double positive population (*ERBB2*amp/PD-L1+) most sensitive population to combination therapy

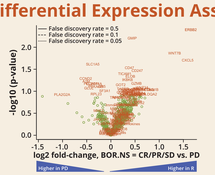
ERBB2/HER2 Expression is Associated with Response



- *ERBB2* mRNA expression significantly correlated with response, being 5.13 times higher in patients achieving CR/PR compared with patients with PD

*c: Confirmed

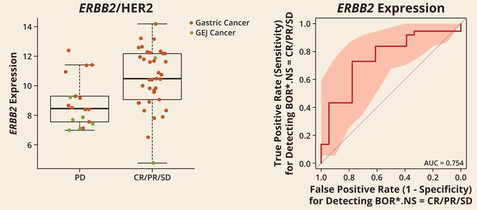
Differential Expression Associated with Anti-Tumor Activity



Gene	Fold Change	SE	p-value
ERBB2	3.145	0.549	0.004
GMIP	1.357	0.155	0.006
WNT7B	2.493	0.516	0.014
CXCL5	3.006	0.660	0.020
SLC1A5	0.771	0.162	0.024
CD47	1.305	0.171	0.029
CD247	1.459	0.250	0.034
TICAM1	1.220	0.136	0.040
ELOB	1.321	0.197	0.046
CCND2	0.697	0.262	0.051

- *ERBB2* mRNA expression significantly correlated with anti-tumor activity, being 3.1 times higher (p=0.004) in patients achieving CR/PR/SD compared with patients with PD

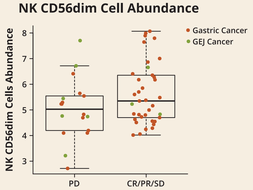
ERBB2/HER2 Expression is Associated with Anti-Tumor Activity



- *ERBB2* expression was associated with anti-tumor activity of margetuximab + pembrolizumab with an AUC of 0.754

*Best overall response

NK CD56dim Cell Abundance Trends Higher with Anti-Tumor Activity



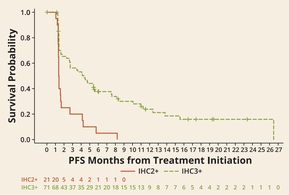
NK CD56dim Genes
IL21R
KIR2DL3
KIR3DL1
KIR3DL2

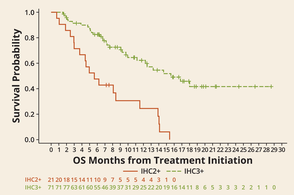
- Tumor control was associated with a modest increase in CD56dim NK cells (p=0.092)

Baseline HER2 Immunohistochemistry

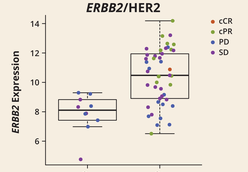
HER2 IHC PFS	HER2 IHC2+ (n=21)	HER2 IHC3+ (n=71)
# of events	21	57
Median PFS (95% CI)	1.38 months (1.31–1.61)	4.34 months (2.60–5.62)
HR by Cox model, 0.32; 95% CI, 0.17–0.53; Log-rank P<0.0001		
6-month PFS rate (95% CI)	4.8% (0.3–19.7)	38% (26.4–49.5)
12-month PFS rate (95% CI)	NA	24% (13.8–35.0)

HER2 IHC OS	HER2 IHC2+ (n=21)	HER2 IHC3+ (n=71)
# of events	19	37
Median OS (95% CI)	5.6 months (2.99–11.53)	13.9 months (10.55–20.47)
HR by Cox model, 0.30; 95% CI, 0.17–0.53; Log-rank P<0.0001		
12-month OS rate (95% CI)	24.4% (8.2–45.3)	59.8% (44.6–70.8)



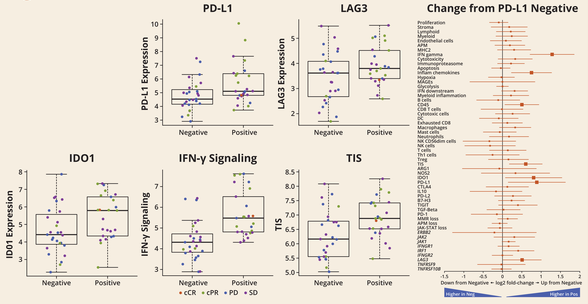


ERBB2/HER2 Expression is Associated with HER2 3+ IHC



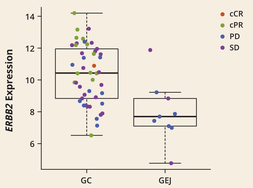
- *ERBB2* mRNA expression was 5.6 times higher in patients with HER2 IHC3+ compared with IHC2+ tumors

PD-L1 Positive IHC Is Associated with Interferon-related Signatures



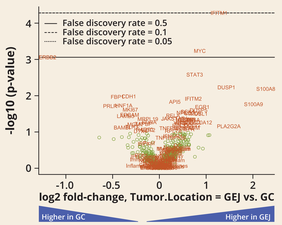
- PD-L1-positive tumors had higher expression of PD-L1, IFN-γ signaling, LAG3, IDO1, inflammatory chemokine and tumor inflammation signature (TIS) scores

ERBB2/HER2 Expression is Associated with Gastric Tumors



- Gastric tumors xpressed higher levels of *ERBB2* (5.25 FC, p<0.001) compared with GEJ tumors

Differential Gene Expression in Gastric vs. GEJ Tumors



Gene/Signature	Fold Change	p-value
IFITM1	2.420	0.0001
MYC	1.820	0.0006
ERBB2	5.252	0.0009
STAT3	1.687	0.0026
DUSP1	2.699	0.0059
S100A8	4.841	0.0065
CDH1	1.574	0.0105
FBP1	1.863	0.0108
IFITM2	1.653	0.0121
API5	1.257	0.0148
S100A9	4.036	0.0172
HNF1A	1.695	0.0187
PRLR	2.073	0.0193
EGR1	1.888	0.0205
MKI67	1.538	0.0244
DUSP5	1.787	0.0251
SGK1	1.522	0.0277
NFIL3	1.435	0.0295
CD209	1.632	0.0307
FOSL1	1.804	0.0316
EPCAM	1.554	0.0337
RELA	1.224	0.0355
LAMB3	1.651	0.0365
MRPL19	1.187	0.0441
EDN1	1.501	0.0452
NFKBIA	1.473	0.0462
CDKN1A	1.554	0.0464

- GEJ tumors had lower expression of *ERBB2* and higher expression of *IFITM1*, *MYC* and *STAT3*, and less clinical responses

Discussion

- We show for the first time that GEA with high *ERBB2* expression have an inflamed TME
- Our initial data describe potential immunologic differences between GC and GEJ tumors

Reference

1.

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