Clinical, biologic, and immunogenic characteristics of gastro-esophageal cancers (GEC) harboring *CLDN18::ARHGAP* fusions

#496

A. Grothey[1], A. Fifield[2], K. Sweeney[2], H-J. Lenz[3], M. Oberley[2], S. Goel[4], S. Wei[5], B. Somer[1]

[1]West Cancer Center and Research Institute, [2]Caris Life Sciences, [3]USC Norris Comprehensive Cancer Center, [4]Rutgers Cancer Institute of New Jersey, [5]Fox Chase Cancer Center

INTRODUCTION

- Claudin 18.2 (CLDN18.2) is a tight junction protein which is specifically expressed in normal stomach and GEC tissue
- CLDN18.2 overexpression has recently emerged as a therapeutic target in advanced GEC
- *CLDN18::ARHGAP* fusions are pathognomonic for GEC, but their biologic relevance in this malignancy is poorly understood

METHODS

- DNA and RNA (whole transcriptome) sequencing was performed for 4430 GEC tumor samples submitted to Caris Life Sciences
- *CLDN18::ARHGAP* fusions were identified from RNA transcripts
- CLDN18 (43-14A) and PD-L1 (28-8) protein levels were determined by immunohistochemistry (IHC)
- TMB-High (TMB-H) was defined as ≥10 mutations/MB
- Mismatch repair deficiency/microsatellite instability-high (dMMR/MSI-H) status was determined by a combination of IHC and NGS
- Only pathogenic or likely pathogenic (P/LP) mutations were considered when calculating gene mutation frequencies
- Tumor microenvironment (TME) immune cell fractions were estimated by RNA deconvolution using quanTIseq
- Significance was tested using Mann-Whitney, Fisher's Exact, or Chi-squared tests with multiple comparisons correction as appropriate; stars denote p-values or q-values as follows: **** < 0.0001, *** < 0.001, ** < 0.01, * < 0.05
- Real-world overall survival (OS) and nivolumab time on treatment (ToT) were obtained from insurance claims data and calculated from collection date to time of last clinical contact and first of nivolumab to last of nivolumab, respectively; associated hazard ratios (HR) and p-values were calculated using the Cox proportional hazard model.

Fusion	Prevalance
None	93.95% (4068/4330)
CLDN18:ARHGAP26	5.22% (226/4330)
CLDN18:ARHGAP6	0.72% (31/4330)
CLDN18:ARHGAP42	0.09% (4/4330)
CLDN18:ARHGAP18	0.02% (1/4330)

Table 1: *CLDN18::ARHGAP* fusions
Prevalence of *CLDN18::ARHGAP* fusion isoforms in GEC

	Fusion- N=4068	Fusion+ N=262	p-value
Age			
Median age (range)	66 (19-90+)	58 (19-90+)	<0.0001
Sex			
Female	41.08% (1671/4068)	64.12% (168/262)	<0.0001
Male	58.92% (2397/4068)	35.88% (94/262)	
Histology			
Adenocarcinoma/Carcinoma	79.99% (3254/4068)	73.28% (192/262)	0.0006
Signet Ring Cell Adenocarcinoma	8.95% (364/4068)	15.65% (41/262)	
Adenocarcinoma, Diffuse Type	3.49% (142/4068)	6.11% (16/262)	
Adenocarcinoma, Intestinal Type	3.81% (155/4068)	1.53% (4/262)	
Mucinous Adenocarcinoma	1.18% (48/4068)	0.76% (2/262)	
Other/Unclear	2.58% (105/4068)	2.67% (7/262)	

Table 2: Patient characteristics
Patient characteristics for *CLDN18::ARHGAP* fusion+ vs fusion- cohorts

Threshold	Cohort	IHC+	IHC-	test	p-value
≥2+, ≥75%	Fusion+	**79.5% (35/44)**	20.5% (9/44)	chi-square	<0.0001
	Fusion-	47.9% (430/898)	52.1% (468/898)		
≥2+, ≥40%	Fusion+	**86.4% (38/44)**	13.6% (6/44)	chi-square	<0.0001
	Fusion-	54.5% (489/898)	45.5% (409/898)		

Table 3: CLDN18 protein levels
CLDN18 IHC positivity by fusion status when using either standard (≥2+, ≥75%, intensity, percentage positive cells) or reduced (≥2+, ≥40%) thresholds

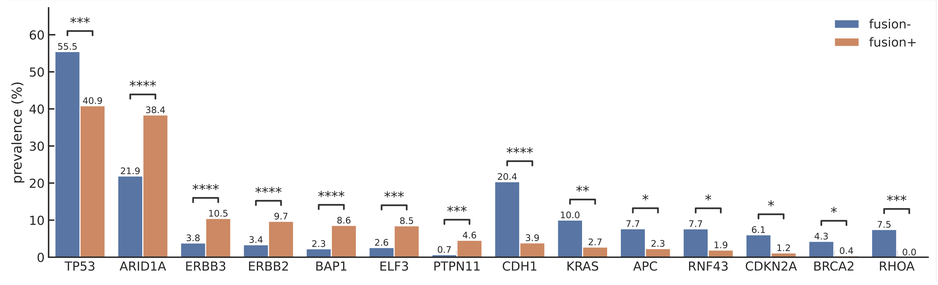

Figure 1: Mutations
Differentially enriched P/LP mutations for fusion+ vs fusion- cohorts. Stars denote q-values

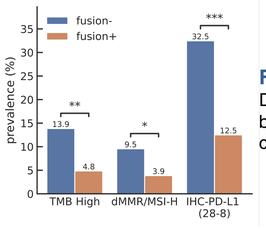

Figure 2: IO biomarkers
Differentially enriched IO biomarkers for fusion+ vs fusion- cohorts. Stars denote q-values

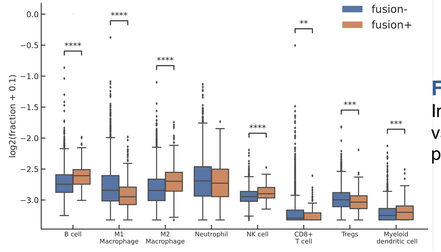

Figure 3: TME
Immune cell fractions for fusion+ vs fusion- cohorts. Stars denote p-values

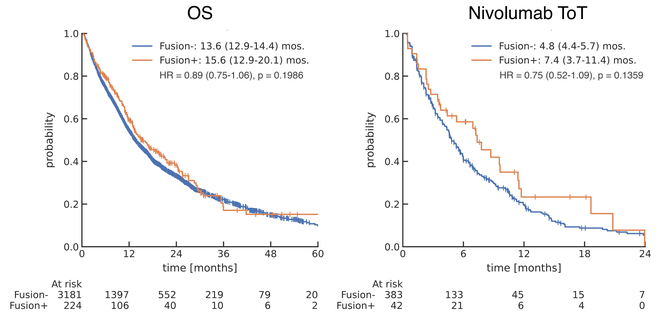

Figure 4: Patient outcomes
OS and nivolumab ToT by fusion status. Legend shows median OS or ToT with 95% confidence interval and HR with 95% confidence interval

STUDY HIGHLIGHTS

- Patients with fusion+ tumors were younger, more likely to be female, and had an increased prevalence of diffuse type and signet ring cell adenocarcinomas
- Fusion+ tumors had a higher prevalence of *ERBB2/3* mutations and a lower prevalence of *CDH1*, *KRAS*, and *RHOA* mutations and IO-related biomarkers (TMB High, dMMR/MSI-H, and PD-L1+)
- Fusion+ tumors had higher CLDN18.2 IHC positivity
- Fusion+ tumors had decreased infiltration of CD8+ T cells and M1 macrophages and increased infiltration of M2 macrophages
- There was no significant difference in OS or nivolumab ToT by fusion status, but a numeric trend for better outcomes for fusions in spite of more aggressive histology and lower prevalence of IO biomarkers

CONCLUSIONS

- *CLDN18::ARHGAP* fusions characterize GECs with distinct clinical and biologic features that suggest lower immunogenicity
- Fusions were positively correlated with a higher CLDN18 protein expression

Contact: agrothey@WESTCLINIC.com

COI: A. Grothey has no conflicts of interest to declare