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ANNUAL MEETING
2024 • SAN DIEGO
APRIL 5-10
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Comprehensive molecular and immunological characterization of early-onset esophagogastric cancer

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COLUMBIA | COLUMBIA UNIVERSITY HERBERT IRVING COMPREHENSIVE CANCER CENTER

NewYork-Presbyterian

Disclosure Information

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Lawrence Wu

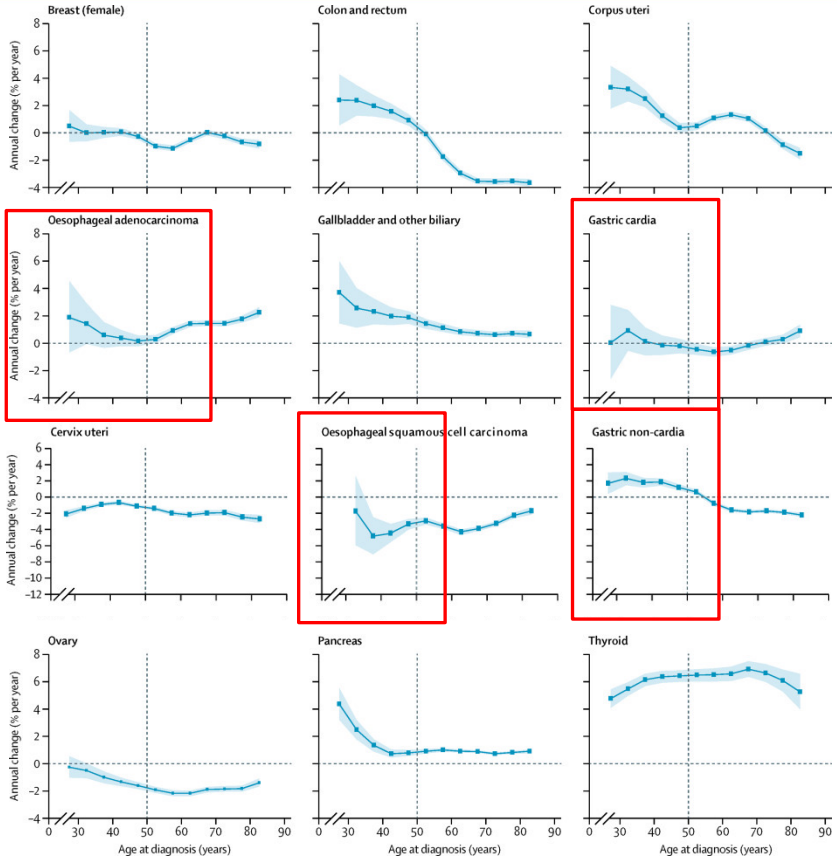
I have no financial relationships to disclose.

Introduction

- Esophagogastric cancer (EGC) is a highly prevalent cancer globally with annual incidence of over 1.5 million[1,2]
- In the United States, the incident of early-onset esophagogastric cancer (EOEGC), defined as age of diagnosis <50, has increased over 30% in recent decades[3-5]

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394-424
2. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144(8):1941-53
3. Islami F, DeSantis CE, Jemal A. Incidence Trends of Esophageal and Gastric Cancer Subtypes by Race, Ethnicity, and Age in the United States, 1997-2014. Clin Gastroenterol Hepatol 2019;17(3):429-39
4. Bergquist JR, Leiting JL, Habermann EB, et al. Early-onset gastric cancer is a distinct disease with worrisome trends and oncogenic features. Surgery 2019;166(4):547-55
5. Codipilly DC, Sawas T, Dhaliwal L, et al. Epidemiology and Outcomes of Young-Onset Esophageal Adenocarcinoma: An Analysis from a Population-Based Database. Cancer Epidemiol Biomarkers Prev 2021;30(1):142-9

Introduction



- Rising incidence of esophagogastric cancers in the United States from 1995 to 2014[6]
  - Increasing along with several other gastrointestinal malignancies

6. Sung H, Siegel RL, Rosenberg PS, Jemal A. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. Lancet Public Health. 2019;4(3):e137-e147

Introduction

- Risk factors for EGC[7-8]
  - Smoking
  - Alcohol
  - Obesity
  - Helicobacter pylori infection
- Single center study at Memorial Sloan Kettering found that EOEGC patients were more likely to be genomically stable, have diffuse histology, and are less likely to be microsatellite-instability-high[9]
- Prior studies limited by single center or small multi-institutional cohort analyses

7. Domper Arnal MJ, Ferrandez Arenas A, Lanas Arbeloa A. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol 2015;21(26):7933-43
8. Karimi P, Islami F, Anandasabapathy S, et al. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014;23(5):700-13
9. Lumish MA, Walch H, Maron SB, et al. Clinical and Molecular Characteristics of Early-Onset versus Average-Onset Esophagogastric Cancer. J Natl Cancer Inst 2023

Objectives

1. Provide a detailed analysis of the molecular characteristics of early versus average-onset esophagogastric cancer in a large real-world database
2. Define immune microenvironment characteristics of early versus average-onset esophagogastric cancer
3. Evaluate response to immune checkpoint inhibitors in patients with early versus average-onset esophagogastric cancer

Methods

- **Patient Samples:** 5,175 esophagogastric cancer patients in Caris Life Sciences database
- **Comprehensive molecular analysis**
  - Next generation sequencing (NGS)
  - Tumor mutation burden (TMB)
  - Deficient mismatch repair (dMMR)/microsatellite-instability (MSI)
  - HER-2 and PD-L1 IHC
  - Whole transcriptomic sequencing (WTS)
    - Gene fusions
    - MAPK Pathway activation score
    - Immune checkpoint gene expression
    - Gene set enrichment analysis
    - Immune cell infiltrate fractions

Methods

- **Real-world overall survival (OS) data:** Obtained from insurance claims data and calculated from date of tissue collection/treatment start until date of last contact
- **Statistical analysis:** Chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q<0.05$)

Results – EGC is predominantly male and adenocarcinoma histology

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	Age<50	Age≥50
Number of patients	530	4645
Male	350 (66.0%)	3445 (74.1%)
Female	180 (34.0%)	1200 (25.8%)
Adenocarcinoma histology	405 (76.4%)	3502 (75.4%)
Other histology	125 (23.6%)	1143 (24.6%)

Results – Mutational analysis with increased frequency of *CDH1* mutations in EOEGC.

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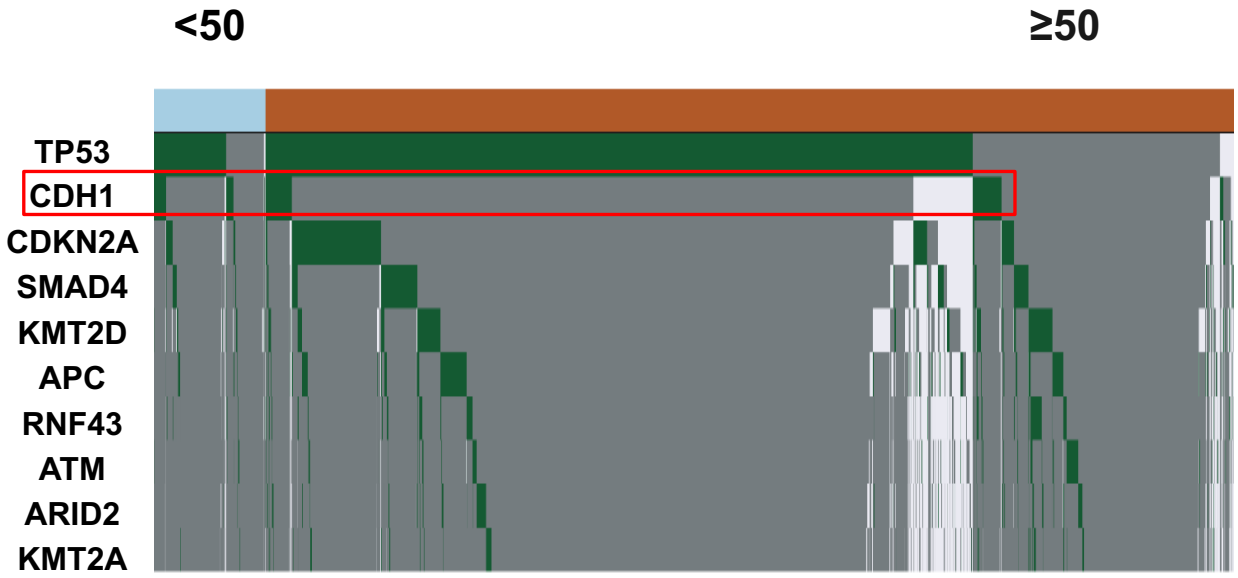

Features	% <50	% ≥50	%	p-value	q-value
TP53	65.90	**74.44**	-8.54	2.78E-05	0.002
CDH1	**18.88**	6.49	12.39	3.85E-23	2.19E-20
CDKN2A	8.84	**13.54**	-4.70	0.003	0.10
SMAD4	5.00	**8.18**	-3.18	0.011	0.26
KMT2D	4.61	8.50	-3.89	0.003	0.09
APC	3.47	7.66	-4.19	0.000	0.02
RNF43	1.93	4.48	-2.55	0.006	0.17
ATM	1.72	3.48	-1.76	0.034	0.52
ARID2	0.58	3.67	-3.09	0.000	0.01
KMT2A	0.39	2.40	-2.02	0.003	0.10

Results – Copy number alteration and fusion analysis with increased frequency of *CCNE1*, *MYC*, *FGFR2* amplifications and increased *ARHGAP26* fusion frequency in EOEGC.

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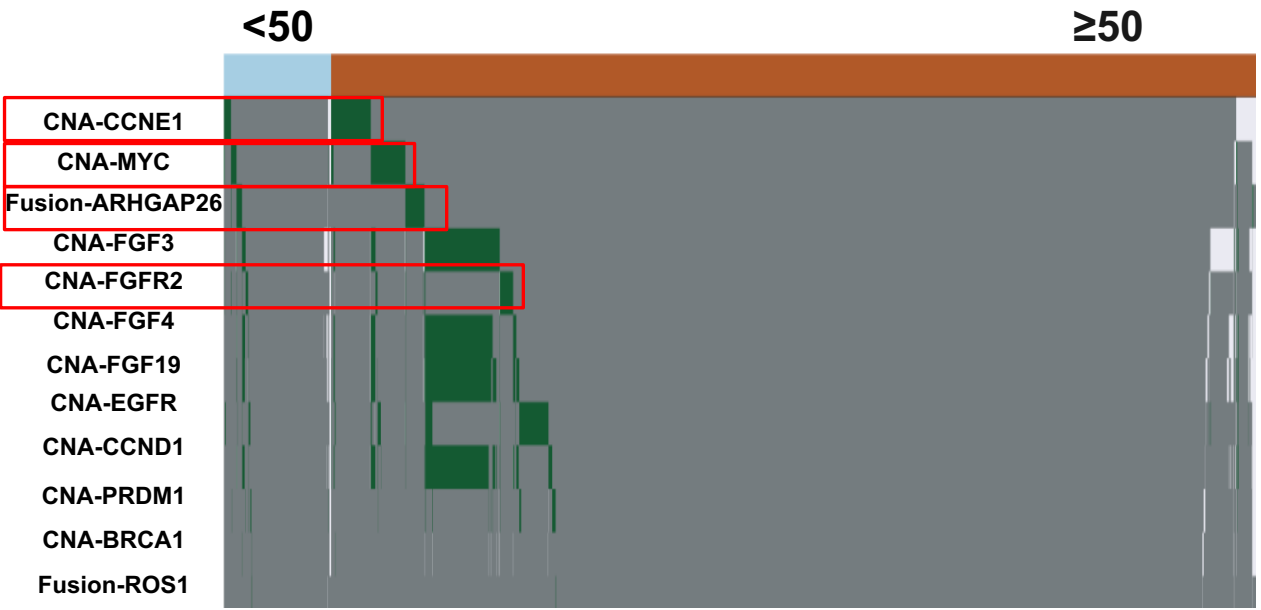

Features	% <50	% ≥50	%	p-value	q-value
CNA-CCNE1	**6.81**	4.38	**2.43**	0.01	0.27
CNA-MYC	**6.13**	4.14	1.99	0.03	0.52
Fusion-ARHGAP26	**5.67**	2.20	**3.47**	1.59E-06	0.0002
CNA-FGF3	4.01	**9.37**	-5.36	6.35E-05	0.003
CNA-FGFR2	**3.45**	1.87	1.58	0.02	0.29
CNA-FGF4	3.32	**8.62**	-5.30	3.06E-05	0.002
CNA-FGF19	2.91	**9.15**	-6.24	1.54E-06	0.0002
CNA-EGFR	2.87	**4.79**	-1.92	0.04	0.59
CNA-CCND1	2.70	**8.92**	-6.22	1.16E-06	0.0002
CNA-PRDM1	1.72	0.79	0.93	0.04	0.56
CNA-BRCA1	0.38	0.02	0.36	0.03	0.47
Fusion-ROS1	0.38	0.04	0.33	0.05	0.63

Results – Trend towards decreased HER2 expression in EOEGC.

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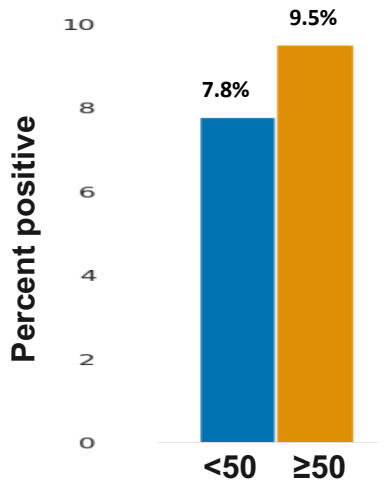
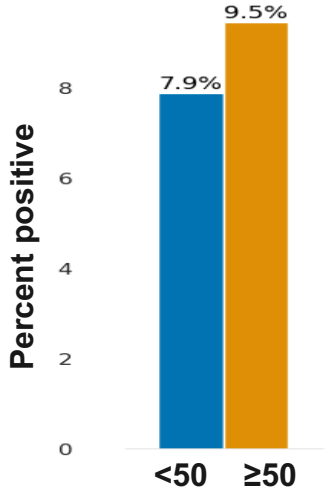


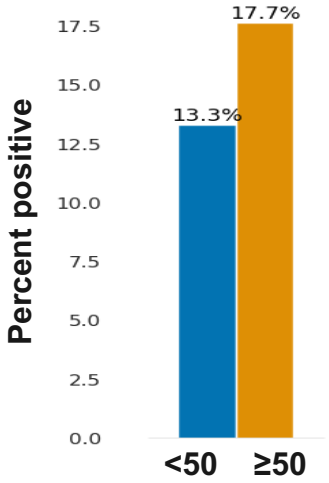
	N Pos (%)	p-value	q-value
<50	36 (7.8)	0.25	1.0
≥50	386 (9.5)		

CNA



	N Pos (%)	p-value	q-value
<50	41 (7.9)	0.24	1.0
≥50	430 (9.5)		

CISH



	N Pos (%)	p-value	q-value
<50	38 (13.3)	0.06	0.66
≥50	413 (17.7)		

Results – Decreased TMB-high and dMMR/MSI-H in EOEGC.

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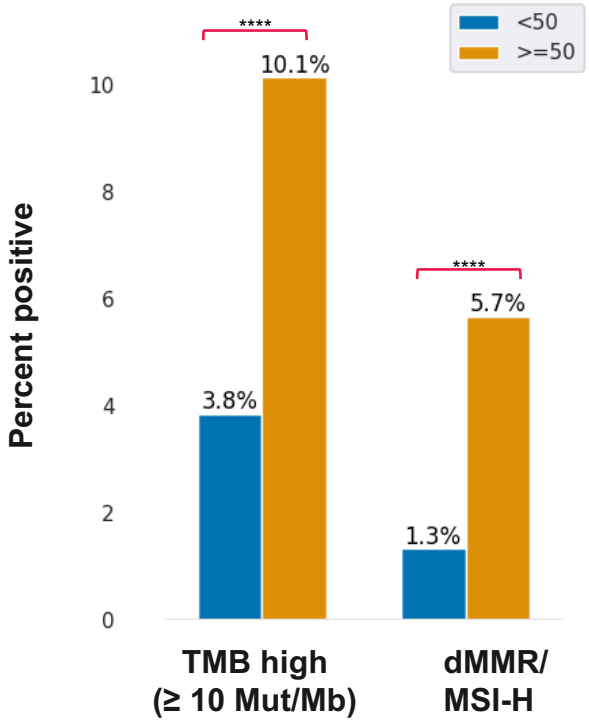

	TMB high			dMMR/MSI-H		
	N Pos (%)	p-value	q-value	N Pos (%)	p-value	q-value
<50	20 (3.8)	0.000003	0.0003	7 (1.3)	0.00002	0.001
≥50	464 (10.1)			262 (5.7)		

Results – Trend towards decreased PD-L1 positivity in EOEGC.

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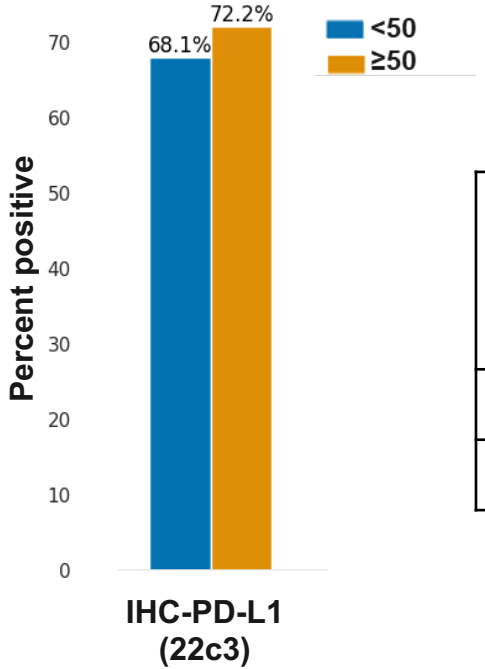

	IHC-PD-L1 (22c3)		
	N Pos (%)	p-value	q-value
<50	329 (68.1)	0.06	0.64
≥50	3050 (72.2)		

Results – Decreased MAPK pathway activity score in EOEGC.

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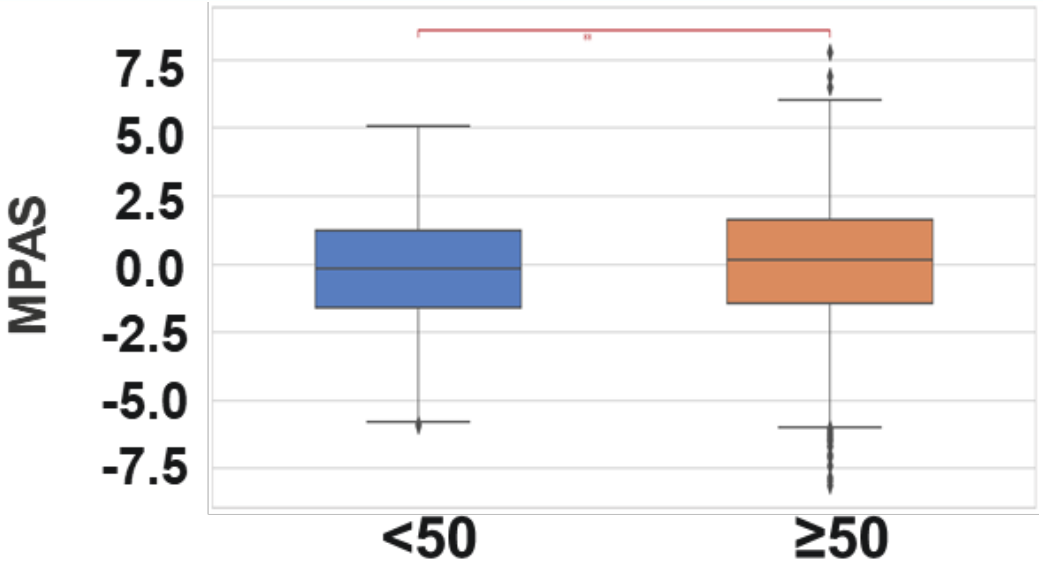

	Median	p-value	q-value
<50	-0.16	0.003	0.003
≥50	0.13		

Results – Immune gene expression analysis with increased *HAVCR2* (*TIM-3*) expression in EOEGC. Decreased *PD-L1* expression in EOEGC. No difference in *LAG-3*, *CTLA-4*, *IDO-1* expression.

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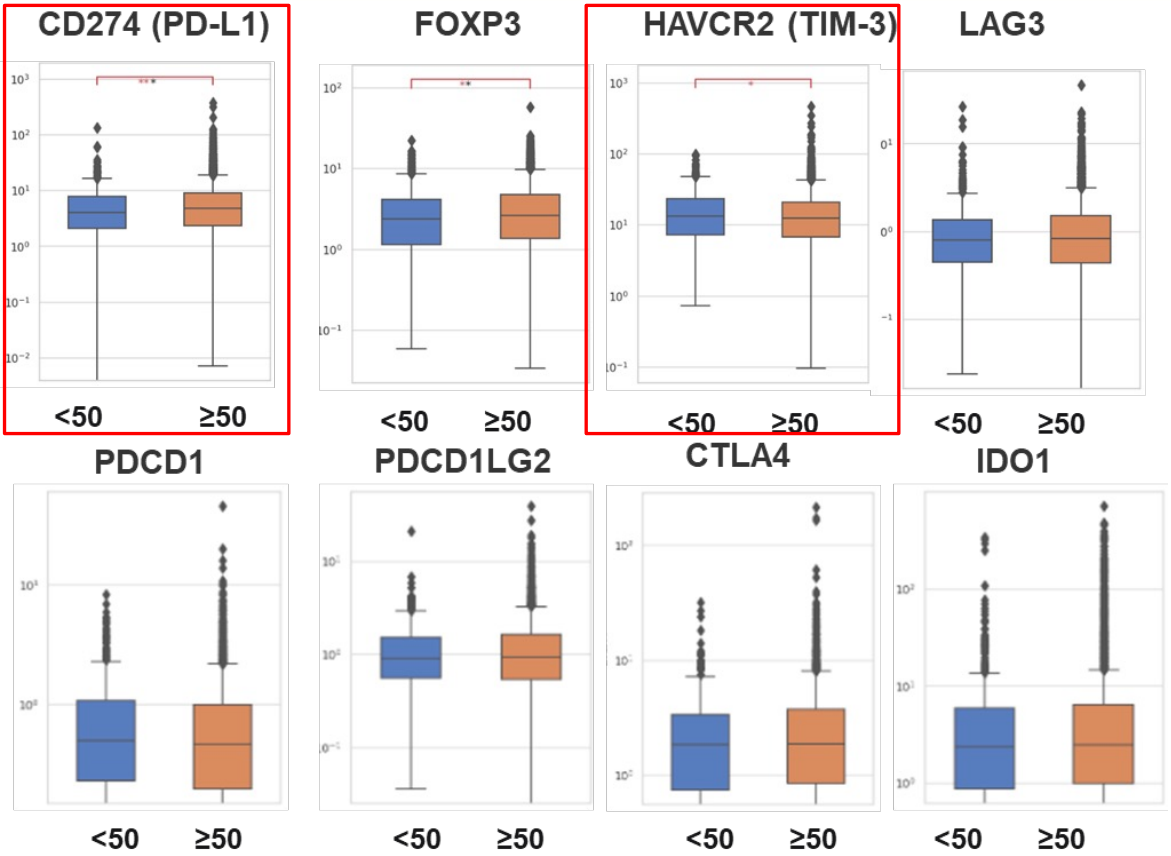

Gene	Median		Fold change	p-value	q-value
	<50	>=50)			
CD274	3.99	4.74	0.84	0.0007	0.006
FOXP3	2.39	2.60	0.92	0.004	0.02
HAVCR2	13.34	12.27	1.09	0.02	0.05
LAG3	0.79	0.83	0.96	0.11	0.19
PDCD1	0.49	0.46	1.07	0.23	0.23
PDCD1LG2	0.90	0.94	0.96	0.22	0.23
CTLA4	1.84	1.89	0.98	0.12	0.19
IDO1	2.36	2.46	0.96	0.16	0.21

Results – Increased B cell and M2 macrophages in EOEGC. Decreased M1 macrophages in EOEGC.

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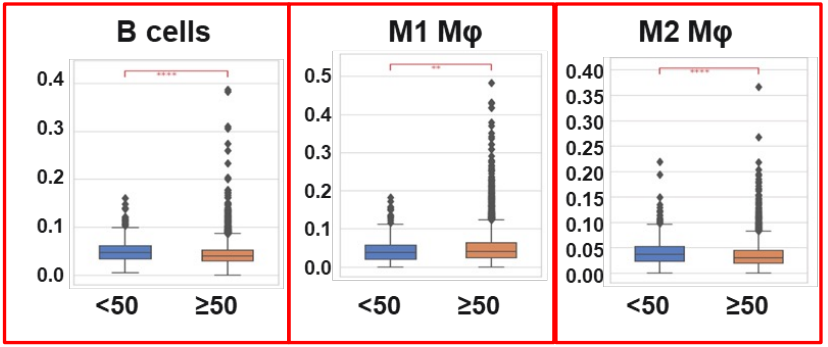

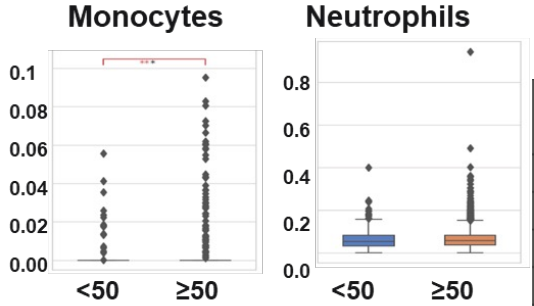

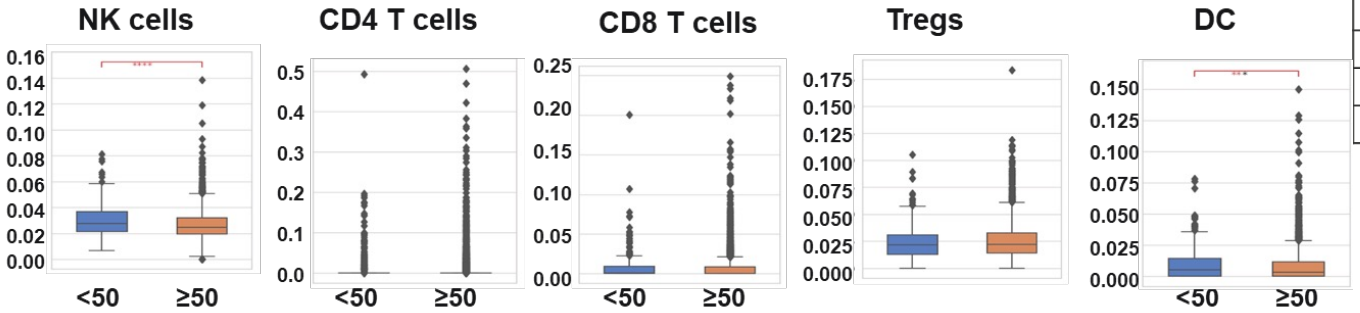

Cells	Median %		p-value	q-value
	<50	>=50		
B cells	**4.71**	3.92	7.85E-11	8.64E-10
Mφ M1	3.74	**4.00**	0.001	0.002
Mφ M2	**3.63**	3.02	1.54E-09	8.48E-09
Monocytes	0.00	0.00	0.001	0.002
Neutrophils	5.38	5.83	0.36	0.40
NK cells	**2.76**	2.47	2.13E-08	7.81E-08
T cells CD4	0.00	0.00	0.06	0.08
T cells CD8	0.06	0.05	0.72	0.72
Tregs	2.19	2.23	0.17	0.20
DC	0.52	0.32	0.0007	0.002

Results – Gene set enrichment analysis with increased enrichment of epithelial-mesenchymal transition and angiogenesis genes in EOEGC

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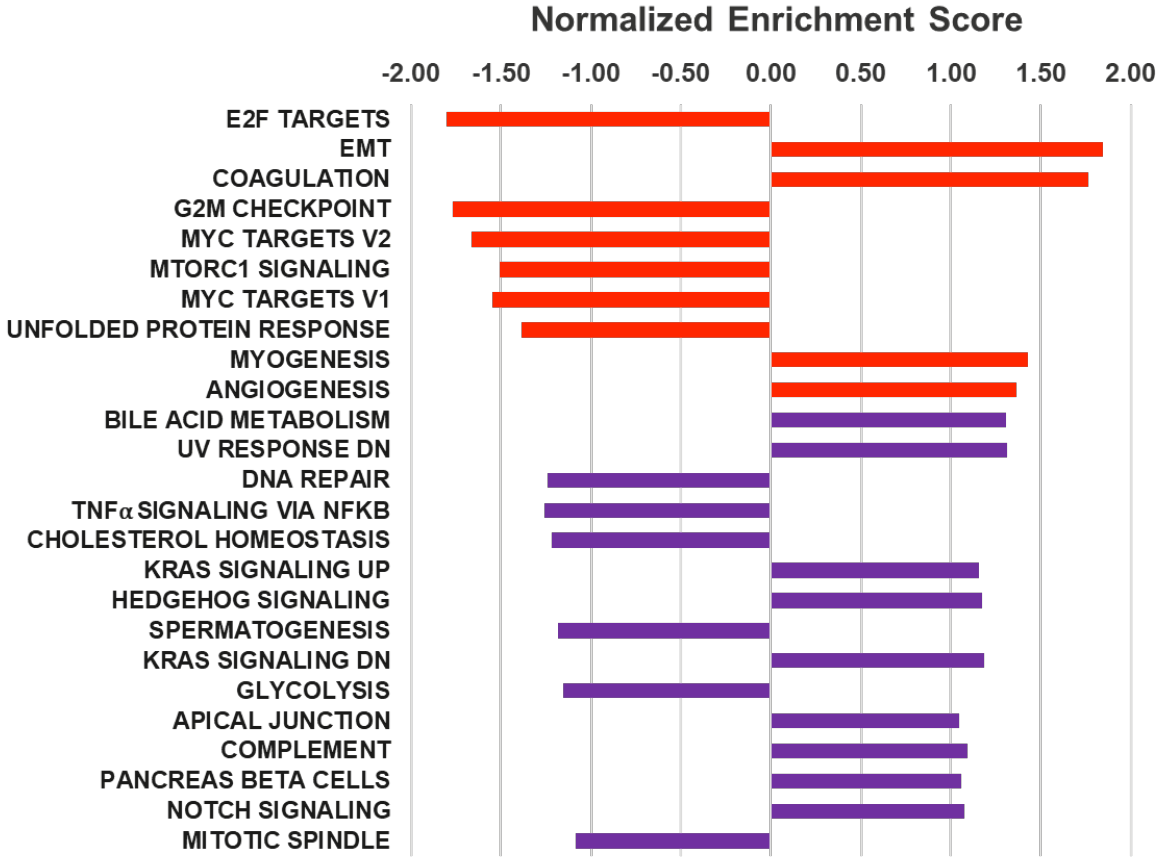

Term	NES	FDR
E2F TARGETS	-1.80	0.00
EMT	1.85	0.00
COAGULATION	1.76	0.01
G2M CHECKPOINT	-1.77	0.01
MYC TARGETS V2	-1.66	0.02
MTORC1 SIGNALING	-1.51	0.05
MYC TARGETS V1	-1.55	0.05
UNFOLDED PROTEIN RESPONSE	-1.38	0.16
MYOGENESIS	1.43	0.17
ANGIOGENESIS	1.37	0.24
BILE ACID METABOLISM	1.30	0.31
UV RESPONSE DN	1.31	0.34
DNA REPAIR	-1.24	0.51
TNFα SIGNALING VIA NFKB	-1.26	0.54
CHOLESTEROL HOMEOSTASIS	-1.22	0.56
KRAS SIGNALING UP	1.16	0.63
HEDGEHOG SIGNALING	1.18	0.65
SPERMATOGENESIS	-1.18	0.66
KRAS SIGNALING DN	1.19	0.70
GLYCOLYSIS	-1.15	0.74
APICAL JUNCTION	1.05	0.81
COMPLEMENT	1.10	0.82
PANCREAS BETA CELLS	1.06	0.85
NOTCH SIGNALING	1.07	0.85
MITOTIC SPINDLE	-1.09	0.86

Results – Trend towards decreased overall survival in EOEGC patients treated with immune checkpoint inhibitors.

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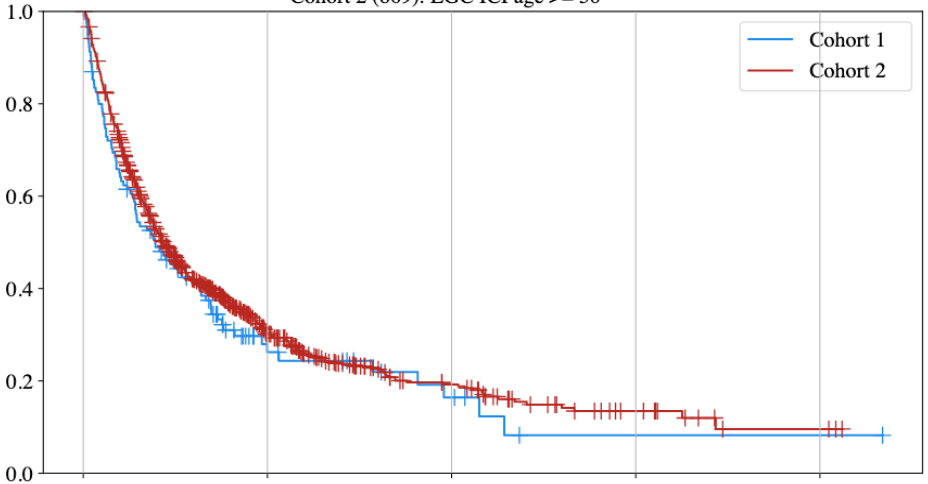
Immune Checkpoint Inhibitors

Performance : First of Atezolizumab, Ipilimumab, Nivolumab, Pembrolizumab -> Last Contact
HR = 1.138 (95% CI: 0.907 - 1.429) p = 0.262
Cohort 1 Median = 195 days (95% CI: 138 days-310 days)
Cohort 2 Median = 219 days (95% CI: 193 days-252 days)
Median Difference = -24 days (-11.0%)
Cohort 1 (115): EGC ICI age < 50
Cohort 2 (869): EGC ICI age >= 50



Cohort 1 115	15	6	1	1
Cohort 2 869	149	47	13	3

Results – Trend towards decreased overall survival in EOEGC patients treated with immune checkpoint inhibitors.

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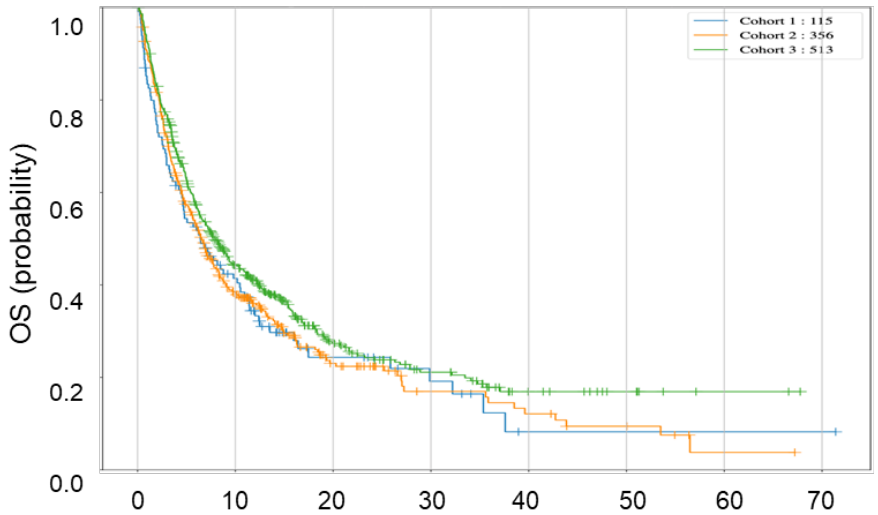
Immune Checkpoint Inhibitors

Performance : First of Atezolizumab, Ipilimumab, Nivolumab, Pembrolizumab -> Last Contact
p = 0.08249
Cohort 1(EGC Age<50 ICI) Median = 6.416 m (95% CI: 4.54 m-10.199 m)
Cohort 2(EGC 50<=Age<65 ICI) Median = 6.58 m (95% CI: 5.494 m-7.699 m)
Cohort 3(EGC Age>=65 ICI) Median = 7.929 m (95% CI: 6.547 m-9.377 m)



Cohort 1 : 115 115	42	13	7	1	1	1	1
Cohort 2 : 356 356	112	36	14	10	6	0	0
Cohort 3 : 1290 1290	187	67	36	14	7	2	0

Conclusion

- EOEGC is characterized by:
  - Increased *CDH1* mutational frequency
  - Increased frequency of *CCNE1, MYC, FGFR2* amplifications and increased *ARHGAP26* fusion
  - Decreased MAPK pathway activity
  - Enrichment of genes associated with epithelial-mesenchymal transition and angiogenesis
  - Decreased markers of immunotherapy response
- These characteristics demonstrate the limitations of currently approved therapies and potential therapeutic opportunities in the EOEGC population

Conclusion

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9. Lumish MA, Walch H, Maron SB, Chatila W, Kemel Y, Maio A, et al. Clinical and Molecular Characteristics of Early-Onset versus Average-Onset Esophagogastric Cancer. J Natl Cancer Inst 2023

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