Coupling Tumor Genomics, Whole Transcriptome Sequencing, and Patient Outcomes to Define the Tumor Microenvironment in Receptor Tyrosine Amplified Gastrointestinal Cancers: Analysis from 24,598 Cases

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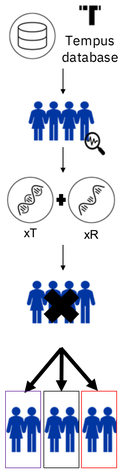
ASCO Gastrointestinal Cancers Symposium
#427

INTRODUCTION

The tumor microenvironment (TME) is increasingly appreciated as a modulator of response to standard chemotherapy and biologic agents. Prior studies have suggested that receptor tyrosine kinase amplifications (RTK amp) in *ERBB2, EGFR, MET*, and *FGFR2* may be associated with an immunosuppressive TME. As RTKs are among the most common oncologic targets, we sought to map TME features to tumor genomics across RTK amp and RTK non-amplified GI cancers.

METHODS



Tempus Lens was used to identify 24,598 patients with gastroesophageal adenocarcinoma, colorectal carcinoma, or cholangiocarcinoma who underwent xT and xR testing. Embedded with in Lens is Workspaces, a computational platform that enables quick insight extraction from select cohorts of Tempus data using a rich library of tools.

Squamous cell histology, MSI-H, and known MMR deficiency were excluded.

Patients were classified as RTK amp if they had *a ERBB2, MET, EGFR, or FGFR2* copy number ≥8.

Analysis:

- Wilcoxon rank sum, Fisher's exact, and Pearson's Chi-squared tests were used to compare groups.
- Somatic alterations were examined, along with RNA expression data for relevant receptor genes, and biomarkers including PD-L1 and tumor mutational burden (TMB).
- Immune cell proportions were estimated using quanTIseq.
- Real-world overall survival (rwOS) was measured as time from first-line therapy start to death or censoring and was analyzed using the Kaplan-Meier method and log-rank tests.

SUMMARY

- In our study cohort, RTK amplifications were seen in approximately 10% of all samples and aligned with known tumor specific prevalences.
- RTK amplifications were enriched for *MYC* and *CCNE1* genomic alterations and associated with modified expression of immunosuppressive regulatory genes *IDO1, TIM-3*, and *LAG3*.
- By bulk RNA sequencing the differences in immune cell type abundance were modest and higher resolution approaches are needed to dissect cell state distribution.
- Across all cancer types, RTK amp was associated with shorter median rwOS (16.3 vs 20.8 months, p = 0.001), though this was reversed for gastroesophageal patients (13.6 vs 11.0 months, p = 0.009).

RESULTS

Table 1. Cohort Characteristics

Characteristic	Overall N = 24,597[1]	RTK Amplified N = 2,086[1]	RTK Non-Amplified N = 22,511[1]	p-value[2]
Age at Diagnosis				<0.001
Mean (SD)	61 (13)	62 (13)	61 (13)	
Sex				<0.001
Male	15,009 (61%)	1,489 (71%)	13,520 (60%)	
Female	9,588 (39%)	597 (29%)	8,991 (40%)	
Race				0.062
White	11,730 (78%)	1,016 (81%)	10,714 (77%)	
Black or African American	1,658 (11%)	113 (9.0%)	1,545 (11%)	
Other Race	1,076 (7.1%)	83 (6.6%)	993 (7.2%)	
Asian	634 (4.2%)	50 (4.0%)	584 (4.2%)	
Unknown	9,499	824	8,675	
Ethnicity				0.8
Not Hispanic or Latino	9,398 (85%)	812 (85%)	8,586 (85%)	
Hispanic or Latino	1,637 (15%)	138 (15%)	1,499 (15%)	
Unknown	13,562	1,136	12,426	
Smoking Status				<0.001
Never smoker	9,441 (49%)	704 (43%)	8,737 (50%)	
Ex-smoker	7,194 (37%)	715 (43%)	6,479 (37%)	
Current smoker	2,614 (14%)	230 (14%)	2,384 (14%)	
Unknown	5,348	437	4,911	
Stage				<0.001
Stage 1	227 (1.2%)	14 (0.9%)	213 (1.2%)	
Stage 2	871 (4.6%)	44 (2.7%)	827 (4.8%)	
Stage 3	2,433 (13%)	155 (9.7%)	2,278 (13%)	
Stage 4	15,322 (81%)	1,390 (87%)	13,932 (81%)	
Unknown	5,742	483	5,259	
Metastatic Status at Biopsy				<0.001
Metastatic	15,748 (80%)	1,404 (85%)	14,344 (80%)	
Pre-metastatic	3,930 (20%)	250 (15%)	3,680 (20%)	
Unknown	4,919	432	4,487	
Diagnosis				<0.001
Colorectal cancer	16,292 (66%)	585 (28%)	15,707 (70%)	
Cholangiocarcinoma	2,650 (11%)	139 (6.7%)	2,511 (11%)	
Esophageal cancer	2,478 (10%)	681 (33%)	1,797 (8.0%)	
Gastric cancer	1,766 (7.2%)	345 (17%)	1,421 (6.3%)	
Gastroesophageal junction cancer	1,411 (5.7%)	336 (16%)	1,075 (4.8%)	

1 n (%)
2 Pearson's Chi-squared test

Table 2. Somatic mutations stratified by RTK amplification status

Characteristic	Overall N = 24,598[1]	RTK Amplified N = 2,088[1]	RTK Non-Amplified N = 22,510[1]	p-value[2]	q-value[3]
TP53	18,408 (74.8%)	1,900 (91.0%)	16,508 (73.3%)	<0.001	<0.001
ERBB2	1,677 (6.8%)	1,225 (58.7%)	452 (2.0%)	<0.001	<0.001
APC	13,565 (55.1%)	522 (25.0%)	13,043 (57.9%)	<0.001	<0.001
KRAS	8,359 (34.0%)	195 (9.3%)	8,164 (36.3%)	<0.001	<0.001
EGFR	591 (2.4%)	527 (25.2%)	64 (0.3%)	<0.001	<0.001
TOP2A	454 (1.8%)	403 (19.3%)	51 (0.2%)	<0.001	<0.001
CDKN2A	2,267 (9.2%)	386 (18.5%)	1,881 (8.4%)	<0.001	<0.001
RARA	388 (1.6%)	371 (17.8%)	17 (0.1%)	<0.001	<0.001
SMAD4	3,728 (15.2%)	240 (11.5%)	3,488 (15.5%)	<0.001	<0.001
MET	285 (1.2%)	276 (13.2%)	9 (0.0%)	<0.001	<0.001
PIK3CA	3,049 (12.4%)	110 (5.3%)	2,939 (13.1%)	<0.001	<0.001
ARID1A	2,036 (8.3%)	172 (8.2%)	1,864 (8.3%)	>0.9	>0.9
FGFR2	273 (1.1%)	172 (8.2%)	101 (0.4%)	<0.001	<0.001
CDKN2B	1,501 (6.1%)	166 (8.0%)	1,335 (5.9%)	<0.001	<0.001
MYC	781 (3.2%)	157 (7.5%)	624 (2.8%)	<0.001	<0.001
FBXW7	1,755 (7.1%)	88 (4.2%)	1,667 (7.4%)	<0.001	<0.001
BRAF	1,535 (6.2%)	10 (0.5%)	1,525 (6.8%)	<0.001	<0.001
HNF1B	206 (0.8%)	132 (6.3%)	74 (0.3%)	<0.001	<0.001
PTEN	1,418 (5.8%)	26 (1.2%)	1,392 (6.2%)	<0.001	<0.001
LRP1B	1,297 (5.3%)	127 (6.1%)	1,170 (5.2%)	0.084	0.087
MTAP	967 (3.9%)	126 (6.0%)	841 (3.7%)	<0.001	<0.001
CCNE1	474 (1.9%)	119 (5.7%)	355 (1.6%)	<0.001	<0.001
CCND1	469 (1.9%)	109 (5.2%)	360 (1.6%)	<0.001	<0.001

1 n (%); 2 Pearson's Chi-squared test; 3 False discovery rate correction for multiple testing

ERBB2 was the most amplified RTK. *TP53, MYC, MTAP, and CCNE1* alterations were enriched among RTK amp (p<0.001). *KRAS, APC, PIK3CA*, *PTEN* and BRAF alterations were enriched among RTK non-amp (p < 0.001).

Table 3. TMB and PD-L1 Status stratified by RTK amplification

Characteristic	Overall N =24,598	RTK Amplified N = 2,088[1]	RTK Non-Amplified N = 22,510[1]	P-value[2]
TMB Status				>0.9
Low	22,296 (95%)	1,913 (95%)	20,383 (95%)	
High	1,227 (5.2%)	106 (5.3%)	1,121 (5.2%)	
Unknown	1,075	69	1,006	
PD-L1 IHC Status				<0.001
Negative	8,272 (53%)	596 (39%)	7,676 (55%)	
Positive	7,327 (47%)	935 (61%)	6,392 (45%)	
Unknown	8,999	557	8,442	

1 n (%); 2 Pearson's Chi-squared test

RTK amps were more commonly PD-L1 positive (61% vs 45%, p < 0.001), though no difference in TMB was seen.

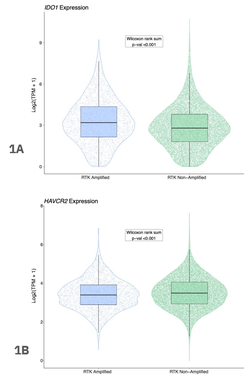


Figure 1. A. RTK amp showed higher expression of *IDO1* and **B.** *HAVCR2* (TIM-3) expression.

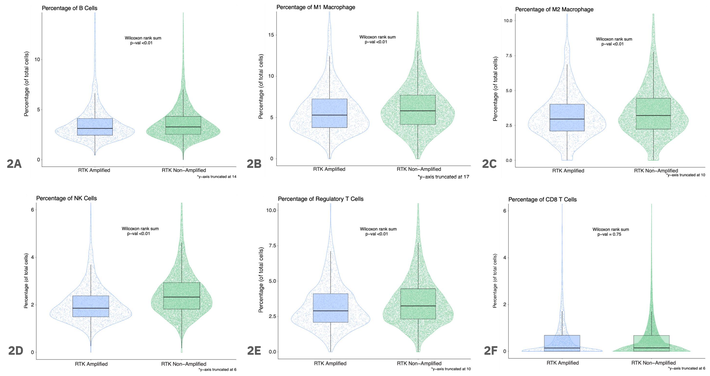


Fig 2A-E. Enrichment of immune cells stratified by RTK amplification status. **A.** B cells; **B.** M1 macrophages; **C.** M2 macrophages, **D.** NK cells; **E.** Reg T cells; **F.** CD8 T cells. Although absolute differences were small, statistically significant enrichment among RTK non-amps was seen in B-cells, macrophages, T regulatory cells, and NK cells (p < 0.001), but not CD8 T-cells (p = 0.8).

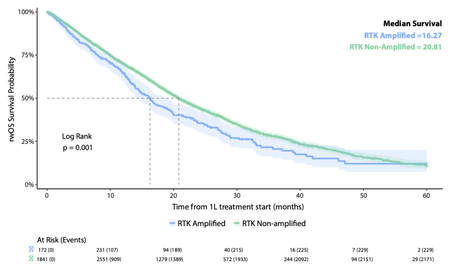


Figure 3. rwOS of entire cohort of patients. In the entire cohort, RTK amp was associated with shorter median rwOS.

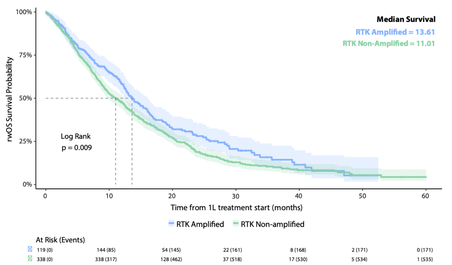


Figure 5. In patients with gastroesophageal patients, RTK amp was associated with a longer median rwOS.

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Conference-specific guidelines

Poster presentation Instructions

Internal due dates

- **24th November 2025, Monday:** Posters due for SciComm review
- **1st December 2025, Monday:** Posters submitted for legal/exec leadership review
- **22nd December 2025, Monday:** Poster printing deadline
- **22nd December 2025, Monday:** E-poster deadline
- **January 8 - 10, 2026:** ASCO GI 2026, San Francisco

Poster Presenters: All final presentation files (including optional recordings and/or slides) are due December 22, 2025.

Data Visualization Guidelines

Tempus Color palettes

Qualitative

SciComm preferred palette
This is a minor update to the default palette recommended by graphic design (see below) chosen to minimize the grouping of similar colors.

['#5993F7', '#D97C4F', '#62B882', '#CC78A7', '#774D9A', '#515CBE', '#E9C74E', '#B8E382', '#A54A72', '#C8B1F6']

Graphic design recommendation
For cases where data are paired or grouped in a logical way, we recommend using this ordering (or any re-ordering) that results in the clearest presentation of the data

['#5993F7', '#515CBE', '#D97C4F', '#E9C74E', '#774D9A', '#C8B1F6', '#A54A72', '#CC78A7', '#62B882', '#B8E382']

Graphic design variant
In the event that a slightly lighter look is preferred, this palette (or a logical re-ordering of colors to fit the application) is acceptable

['#86B2FF', '#738AFF', '#F99B6D', '#FCE285', '#AD6CE4', '#CCB2FF', '#E777A8', '#FFC0E3', '#89D3A5', '#D1ECAF']

Continuous

(Note: while these palettes are meant to be used in continuous applications, they are ultimately constructed from discrete color palettes with code examples showing how to properly extrapolate and create a continuous palette for applications such as heatmaps. However, these palettes may also be used in their discrete form [depending on the application], much the same as the qualitative palettes listed above.)

Sequential

['#29293C', '#384162', '#485889', '#5770AF', '#6687D6', '#779BEB', '#8BACED', '#9EBDF0', '#B3CCF3', '#C7DDF6']

Diverging

['#384162', '#475889', '#5770AF', '#6687D6', '#8BACED', '#FFFFFF', '#DDC2CD', '#C99EAD', '#B47A8F', '#9F5773', '#893157']

1. SciComms Data Visualization Best Practices

1. Figure Sizing and Exporting