Prevalence of genomic alterations in Xerna tumor microenvironment subtypes in colorectal cancer patients

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Introduction

In advanced colorectal cancer (CRC), analysis of the tumor microenvironment (TME) may be useful as a predictive biomarker, supporting use of immunotherapies and anti-angiogenic therapies. [1]

The Xerna TME™ Panel utilizes RNA sequencing data and machine learning to analyze the angiogenic and immunogenic biology of the TME and classifies tumors into four subtypes (*Figure 1*).

We investigated the distribution of TME subtypes and associated genomic alterations in CRC for their potential use in therapy selection.

Methods

336 CRC patient samples underwent testing with the OncoExTra™ test.

OncoExTra utilizes whole-exome, whole-transcriptome sequencing to identify actionable alterations (i.e., those with FDA-approved matched therapies in any cancer, with matched clinical trials, or with evidence in cancer guidelines or the literature for possible matched therapies).

Expression data from whole-transcriptome sequencing were analyzed with the Xerna TME Panel to assign each sample to one of four subtypes:

- **Immune Active (IA),**
- **Immune Suppressed (IS),**
- **Immune Desert (ID), and**
- **Angiogenic (A).**

Results

The characteristics of the patient cohort and the distribution of Xerna subtypes are shown in *Table 1*. More patient samples were in the ID (n=107, 31.8%) and IS (n=101, 30.1%) subtype groups than in the A (63, 18.8%) and IA (65, 19.3%) subtype groups.

Combining subtypes to focus on the immune environment axis, approximately half of the patient samples (49.4%) had high (IA+IS) vs. low (ID+A) immune subtypes (*Table 1*).

247 (73.5%) patient samples harbored targetable alterations associated with an FDA-approved therapy.

21 biomarkers were significantly associated with Xerna subtypes (*Table 2*).

- 19 were over-represented in high immune subtypes.
- 13 were indicative of defective DNA repair.

Microsatellite instability (MSI-high) and high tumor mutational burden (TMB-high) were detected in 30 (8.9%) and 37 (11.0%) patient samples; most but not all occurred in the high immune subtypes (*Table 2*).

Some MSI-high and TMB-high samples occurred in low immune subtypes (ID+A), perhaps indicating a lower propensity for response to ICI therapy (*Table 2*).

138 of 306 (45.1%) MSI-low and 133 of 299 (44.5%) TMB-low samples were in the high immune subtypes, suggestive of possible sensitivity to ICI therapy.

Actionable *KRAS/NRAS*, and *BRAF* alterations were detected in 162 (48.2%) and 23 (6.8%) patients respectively; none were significantly associated with TME subtypes.

Conclusions

- **The Xerna TME Panel classified 49.4% of CRC patients to IA or IS subtypes. These patients may benefit from ICI therapy despite many of them lacking biomarkers currently used for the therapy decision.**
- **Most (73.5%) patients harbored alterations associated with FDA-approved therapies, providing the potential for novel combination therapies [3].**
- **These findings warrant further study and clinical validation in CRC patients treated with ICI therapy.**

Questions?

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References

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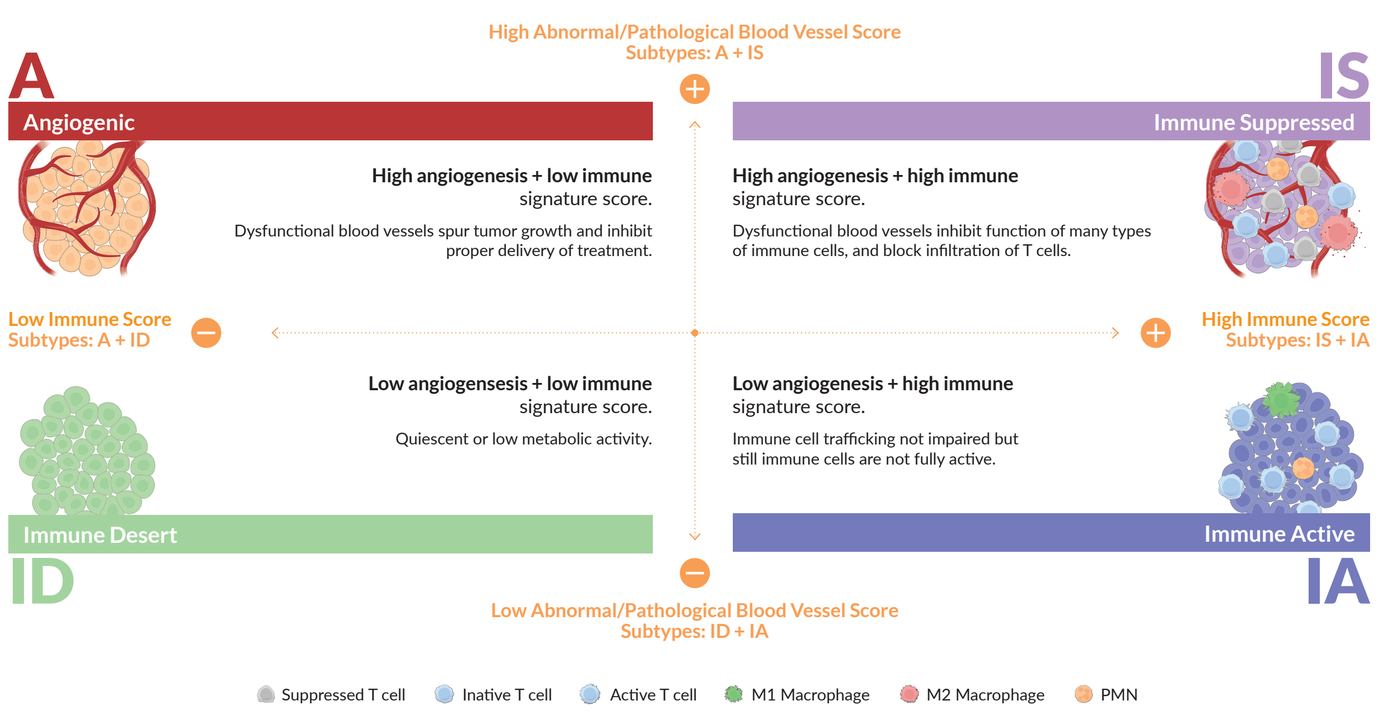
▼ ***Figure 1.***

The machine learning-based Xerna score is obtained from RNA gene expression levels of ~100 genes. The score reflects the dominant cellular micro-environment of the tumor, along immune and angiogenic axes, and may be useful for predicting response to particular therapies, thus informing therapy decisions. [2]



▼ ***Table 1.***

Patient characteristics and Xerna tumor microenvironment subtype / immune group.

		Xerna subtype				Immune group	
Variable	**All Samples**	**A**	**IA**	**ID**	**IS**	**High (IA/IS)**	**Low (A/ID)**
N	**336**	**63 (18.8%)**	**65(19.3%)**	**107(31.8%)**	**101 (30.1%)**	**166 (49.4%)**	**170 (50.6%)**
Age (years)							
Mean (SD)	57.0 (13.16)	56.0 (12.73)	57.3 (14.36)	58.5 (14.00)	55.9 (11.66)	56.5 (12.76)	57.6 (13.56)
Sex							
Female	172 (51.2%)	34 (54.0%)	32 (49.2%)	58 (54.2%)	48 (47.5%)	80 (48.2%)	92 (54.1%)
Male	164 (48.8%)	29 (46.0%)	33 (50.8%)	49 (45.8%)	53 (52.5%)	86 (51.8%)	78 (45.9%)
Actionable Alterations per Sample							
Mean (SD)	5.1 (4.97)	3.6 (1.81)	7.6 (7.33)	4.3 (3.41)	5.5 (5.28)	6.3 (6.23)	4.0 (2.93)
Median	4.0	3.0	4.0	4.0	4.0	4.0	3.5
Q1-Q3	3-5	2-5	3-10	3-4	3-5	3-6	3-5
Min, Max	0, 36	0, 10	1, 36	1, 31	1, 27	1, 36	0, 31

▼ ***Table 2.***

Frequency of the 21 actionable biomarkers that exhibited a significant association across the Xerna Panel immune subtypes (IA+IS vs A+ID; Fisher's Exact Test) out of 54 actionable biomarkers present in 5 or more patient samples. No correction for multiple comparisons was employed. N is the number of patient samples.

** Biomarkers indicative of defective DNA repair*

		Xerna subtype				Immune group		
Biomarker	**Total** (n=336)	**A** (n=63)	**IA** (n=65)	**ID** (n=107)	**IS** (n=101)	**High (IA/IS)** (N=166)	**Low (A/ID)** (N=170)	**p-value**
TMB-high*	37 (11.0%)	0 (0.0%)	19 (29.2%)	4 (3.7%)	14 (13.9%)	33 (19.9%)	4 (2.4%)	<0.001
MSI-high*	30 (8.9%)	0 (0.0%)	17 (26.2%)	2 (1.9%)	11 (10.9%)	28 (16.9%)	2 (1.2%)	<0.001
*RNF43**	27 (8.0%)	0 (0.0%)	12 (18.5%)	3 (2.8%)	12 (11.9%)	24 (14.5%)	3 (1.8%)	<0.001
*MSH6**	17 (5.1%)	0 (0.0%)	10 (15.4%)	1 (0.9%)	6 (5.9%)	16 (9.6%)	1 (0.6%)	<0.001
ASXL1	23 (6.8%)	2 (3.2%)	10 (15.4%)	1 (0.9%)	10 (9.9%)	20 (12.0%)	3 (1.8%)	<0.001
ARID1A	35 (10.4%)	2 (3.2%)	11 (16.9%)	6 (5.6%)	16 (15.8%)	27 (16.3%)	8 (4.7%)	<0.001
APC	253 (75.3%)	52 (82.5%)	42 (64.6%)	89 (83.2%)	70 (69.3%)	112 (67.5%)	141 (82.9%)	<0.01
*MSH3**	19 (5.7%)	0 (0.0%)	10 (15.4%)	3 (2.8%)	6 (5.9%)	16 (9.6%)	3 (1.8%)	<0.01
*PRKDC**	15 (4.5%)	0 (0.0%)	7 (10.8%)	2 (1.9%)	6 (5.9%)	13 (7.8%)	2 (1.2%)	<0.01
FBXW7	30 (8.9%)	3 (4.8%)	10 (15.4%)	5 (4.7%)	12 (11.9%)	22 (13.3%)	8 (4.7%)	<0.01
*POLD1**	6 (1.8%)	0 (0.0%)	3 (4.6%)	0 (0.0%)	3 (3.0%)	6 (3.6%)	0 (0.0%)	<0.05
PTCH1	9 (2.7%)	0 (0.0%)	4 (6.2%)	1 (0.9%)	4 (4.0%)	8 (4.8%)	1 (0.6%)	<0.05
*FANCM**	5 (1.5%)	0 (0.0%)	2 (3.1%)	0 (0.0%)	3 (3.0%)	5 (3.0%)	0 (0.0%)	<0.05
*MLH1**	5 (1.5%)	0 (0.0%)	3 (4.6%)	0 (0.0%)	2 (2.0%)	5 (3.0%)	0 (0.0%)	<0.05
*NBN**	5 (1.5%)	0 (0.0%)	4 (6.2%)	0 (0.0%)	1 (1.0%)	5 (3.0%)	0 (0.0%)	<0.05
TP53	241 (71.7%)	46 (73.0%)	40 (61.5%)	85 (79.4%)	70 (69.3%)	110 (66.3%)	131 (77.1%)	<0.05
PIK3CA	72 (21.4%)	12 (19.0%)	23 (35.4%)	16 (15.0%)	21 (20.8%)	44 (26.5%)	28 (16.5%)	<0.05
CTNNB1	11 (3.3%)	1 (1.6%)	5 (7.7%)	1 (0.9%)	4 (4.0%)	9 (5.4%)	2 (1.2%)	<0.05
*ERCC5**	8 (2.4%)	0 (0.0%)	5 (7.7%)	1 (0.9%)	2 (2.0%)	7 (4.2%)	1 (0.6%)	<0.05
*MLH3**	8 (2.4%)	0 (0.0%)	5 (7.7%)	1 (0.9%)	2 (2.0%)	7 (4.2%)	1 (0.6%)	<0.05
*RAD50**	8 (2.4%)	0 (0.0%)	4 (6.2%)	1 (0.9%)	3 (3.0%)	7 (4.2%)	1 (0.6%)	<0.05