219 PREVALENCE OF GENOMIC ALTERATIONS IN XERNA™ TUMOR MICROENVIRONMENT SUBTYPES IN COLORECTAL CANCER PATIENTS

[1]Gargi D Basu*, [1]Janine LoBello, [1]Snehal G Thakkar, [2]Jessica Aldrich, [2]Matthew Halbert, [2]Patrick Eimerman, [3]Cynthia A Flannery, [3]Nishitha Therala, [1]David W Hall, [5]Daniel Pointing, [5]Lea Vohar, [5]Roman Lustrik, [5]Luka Ausec, [6]Mark Uhlik, [7]Seema Iyer, [6]Laura Benjamin, [3]Frederick L Baehner. *[1]Exact Sciences, Phoenix, AZ, USA; [2]Exact Sciences, Madison, WI, USA; [3]Exact Sciences, Redwood City, CA, USA; [5]Genialis Inc., Boston, MA, USA; [6]OncXerna Therapeutics, Waltham, MA, USA; [7]OncXerna Therapeutics, Bloomfield, NJ, USA*

Background In advanced colorectal cancer (CRC), analysis of the tumor microenvironment (TME) may be useful as a predictive biomarker, particularly supporting the 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 to classify tumors into four TME subtypes.[2] In this study, we investigated the distribution of Xerna TME subtypes and associated genomic alterations in CRC for their potential use in therapy selection.

Methods A total of 336 CRC patient samples underwent testing with the OncoExTra™ assay. This assay utilizes whole-exome, whole-transcriptome sequencing to identify actionable alterations, defined as 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. The whole-transcriptome expression data were analyzed using 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). Biomarker associations were explored.

Results Approximately half (49.4%) of the patient samples had high (IA+IS) versus low (ID+A) immune subtypes, and 247 (73.5%) harbored targetable alterations associated with an FDA-approved therapy. Several biomarkers were significantly associated ($p<0.05$) with Xerna subtypes, most of which were over-represented in high immune subtypes (19 of 21), with 13 indicative of defective DNA repair (table 1). Microsatellite instability (MSI-high) and high tumor mutational burden (TMB-high) were detected in 30 (8.9%) and 37 (11.0%) patient samples, with 28 (16.9%) and 33 (19.9%) occurring within high immune subtypes (IA+IS), respectively. Some MSI-high and TMB-high samples occurred in low immune subtypes (ID+A), perhaps indicating a lower propensity for response to ICI therapy. Of note, 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, though none were significantly associated with TME subtypes.

Conclusions The Xerna TME Panel classified 49.4% of CRC patients to IA or IS subtypes who may benefit from ICI therapy, including many lacking biomarkers currently used for this 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.

REFERENCES

1. Huyghe N, Benidovskaya E, Stevens P, Van den Eynde M. Biomarkers of Response and Resistance to Immunotherapy in Microsatellite Stable Colorectal Cancer: Toward a New Personalized Medicine. *Cancers (Basel)*. 2022 Apr 29;**14**(9):2241. doi: 10.3390/cancers14092241. PMID: 35565369; PMCID: PMC9105843.
2. Uhlik M, Pointing D, Iyer S, Ausec L, Štajdohar M, Cvitkovič R, Žganec M, Culm K, Santos VC, Pytowski B, Malafa M, Liu H, Krieg AM, Lee J, Rosengarten R, Benjamin L. Xerna™ TME Panel is a machine learning-based transcriptomic biomarker designed to predict therapeutic response in multiple cancers. *Front Oncol*. 2023 May 12;**13**:1158345. doi: 10.3389/fonc.2023.1158345. PMID: 37251949; PMCID: PMC10213262.
3. Yang Z, Wu G, Zhang X, Gao J, Meng C, Liu Y, Wei Q, Sun L, Wei P, Bai Z, Yao H, Zhang Z. Current progress and future perspectives of neoadjuvant anti-PD-1/PD-L1 therapy for colorectal cancer. *Front Immunol*. 2022 Sep 9;**13**:1001444. doi: 10.3389/fimmu.2022.1001444. PMID: 36159842; PMCID: PMC9501688.

Ethics Approval The study was approved by WCG IRB Ethics Board, approval number 20181863.

Abstract 219 Table 1 Frequency of actionable biomarkers that exhibited a significant association across the Xerna Panel immune subtypes (IA+IS vs A+ID; Fisher's Exact Test). No correction for multiple comparisons was employed.

Biomarker	Total (%) (N=336)	A (N=63, 18.8%)	IA (N=65, 19.3%)	ID (N=107, 31.8%)	IS (N=101, 30.1%)	High Immune Score (IA+IS) (N=166, 49.4%)	Low Immune Score (A+ID) (N=170, 50.6%)	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
PRDM1	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
MAX	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
MAX	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

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0219