PREVALENCE OF GENOMIC ALTERATIONS IN XERNATM TUMOR MICROENVIRONMENT SUBTYPES IN COLORECTAL CANCER PATIENTS

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Abstracts

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); 13 indicative of defective DNA repair (table 4). 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 (IA+IS) versus low immune subtypes (ID+A), perhaps indicating a lower propensity for response 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 into 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

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