The Xerna™ TME Panel potentially predicts response to a combination of the TLR9 agonist vidutolimod and PD-1 inhibitor pembrolizumab in metastatic melanoma patients with anti-PD-1 treatment.

**ABSTRACT**

**Background:** Few therapeutic options exist for anti-PD-1 refractory, metastatic melanoma patients, and today’s biomarkers are insufficient in aiding who should receive potential combination modalities. We report a Phase II clinical trial of the Xerna™ TME Panel in metastatic melanoma patients. A multi-center study (NCT02601684) showed that in combination with anti-PD-1 pembrolizumab, the Xerna™ TME Panel outperformed a simple baseline classifier in distinguishing the potential therapeutic benefit in 12% of patients (p-value = 0.022). The Xerna™ TME Panel consists of an artificial neural net that uses gene expression data (SAMPLE) to analyze the relevant hallmark signatures to each cohort (i.e. angiogenesis and immunogenic properties of stromal biology, and the metastatic melanoma patients, and today’s biomarkers are insufficient in aiding who should receive potential combination modalities. We report a Phase II clinical trial of the Xerna™ TME Panel in metastatic melanoma patients. A multi-center study (NCT02601684) showed that in combination with anti-PD-1 pembrolizumab, the Xerna™ TME Panel outperformed a simple baseline classifier in distinguishing the potential therapeutic benefit in 12% of patients (p-value = 0.022).

**Methods:** Total RNASeq was performed on formalin-fixed paraffin-embedded (FFPE) biopsy specimens collected from a subset of patients prior to therapy (N=38) and 2 weeks post initiation of therapy (N=10). Gene expression data was analyzed using the Xerna TME Panel algorithm to assign a TME subtype. Correlations analysis between TME subtypes, response to therapy, and other genomic signatures were performed.

**Results:** Overall response rate in the pretreatment cohort available for biomarker analysis was 20%, comparable to the entire validated pembrolizumab arm. The cohort a showed clear distinction of TME subtypes with high prevalences of IS (34%) and ID (30%), indicative of therapy refractory/inflammatory biology. An overall response rate of 34% was observed in the IS subtype, compared with 12% in the other subtypes combined. Comparison with other “halo” gene signatures confirmed enrichment of inflammatory and immunogenic biology in the Xerna TME Panel.

**Conclusions:** The Xerna TME Panel performed superior classification performance across all biomarker metastatic melanoma patient groups and the most relevant hallmarks associated with high response rates were identified, including Apoptosis (IS), Immune Activity (IS), Immune Desert (ID), and Immune Suppression (IS). Gene expression data (SAMPLE) is analyzed through a machine learning-based artificial neural net algorithm (MODEL) which provides a single signature score. The Xerna TME Panel Workflow shows the best overall responses sorted by Xerna TME subtype and patient ID numbers.

**METHODS**

**Overview of Xerna TME Panel**

- **Gene expression data (SAMPLE) is analyzed through a machine learning-based artificial neural net algorithm (MODEL) which provides a single signature score.**
- **The Xerna TME Panel can be used to classify a patient’s tumor microenvironment along an immune and angiogenic axis, resulting in one of four TME phenotypes (Angiogenesis – A, Immune Activity – IA, Immune Desert – ID, Immune Suppression – IS).**
- **Each class or combination of classes can be predictive of treatment outcome with various targeted therapies, including angiogenic and immunogenic properties of stromal biology, and the most relevant hallmark signatures to each cohort (i.e. angiogenesis and immunogenic properties of stromal biology, and the metastatic melanoma patients, and today’s biomarkers are insufficient in aiding who should receive potential combination modalities. We report a Phase II clinical trial of the Xerna™ TME Panel in metastatic melanoma patients. A multi-center study (NCT02601684) showed that in combination with anti-PD-1 pembrolizumab, the Xerna™ TME Panel outperformed a simple baseline classifier in distinguishing the potential therapeutic benefit in 12% of patients (p-value = 0.022). 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