PREDICTION OF CANCER IMMUNOTHERAPY RESPONSE USING ULTRASOUND IMAGING OF TUMOR STIFFNESS AND PERFUSION

Chrysovalantis Voutour", 1Triantafyllos Stylianopoulos, 1Fotis Mpekris, 1Myrofora Panagi, 1Christina Michael, 1John Martin. 1University of Cyprus, Aglantzia, Nicosia, Cyprus; 2Materina Therapeutics, Las Vegas, Nevada, , Las Vegas, NV, USA

Background Solid tumors are highly heterogeneous tissues that might differ considerably between different types or even among tumors of the same type. As a result, while in some patients (responders) a particular treatment may be very effective, in other patients (non-responders) the same treatment may not be beneficial and in many cases. Emerging technologies have been used towards the development of new biomarkers mainly through analyzing the human genome or biological markers, such as the expression of PD-L1/PD-1, but so far most of them have failed to translate into clinical tools and only a limited number has managed to be approved for cancer prediction. Here, we hypothesize that aspects of the tumor microenvironment, and particularly the tumor stiffness and perfusion can be used as biomarkers predictive of response to immune checkpoint inhibition in desmoplastic (i.e., rich in extracellular fibers) murine tumor models.

To modulate tumor stiffness and improve perfusion, strategies based on the use of drugs that inhibit CAF-stimulating signaling factors to normalize the levels of intratumor extracellular matrix have been developed. These therapeutic are known as mechanotherapeutics, because they normalize mechanical abnormalities in the TME, i.e., stiffness and blood flow. Towards the development of this novel therapeutic class, several generic drugs with decades of safe use in other diseases have been repurposed to act as cancer mechanotherapeutics, including the anti-hypertensives losartan and bosentan, the corticosteroid dexamethasone, the antihistamine tranilast and the antibiotic pirfenidone.

Methods In this study, we employed clinically-applied ultrasound shear wave elastography (SWE) and contrast-enhanced ultrasound (CEUS) to demonstrate in four orthotopic murine tumor models of breast cancer (4T1 and E0771), sarcoma (MCA205) and melanoma (B16F10) that specific measures of stiffness and perfusion can predict the efficacy of immune checkpoint inhibition.

Results Interestingly, we further show that these correlations between tumor stiffness/perfusion and therapeutic efficacy are valid even when data from all tumor models are considered together (figure 1). SWE and CEUS are non-invasive imaging modalities that are employed for diagnostic purposes in the clinical practice in oncology, cardiology and other diseases.

Conclusions Furthermore, SWE has been investigated in patients with breast cancer as a marker of response to chemotherapy. Therefore, the results of our study are highly transferable to the clinic.

Acknowledgements This project received funding from the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation programme (grant agreement nos. 863955 and 101069207 to T.S.).

REFERENCES

Abstract 108 Figure 1 Tumor stiffness strongly correlates to perfusion markers independently of heterogeneities among tumor types. Plots of the stiffness (in terms of elastic modulus) of 4T1, E0771, MCA205 and B16F10 tumors as a function of the values of the perfusion measures of mean transit time and rise time demonstrate the strong linear correlation even when data from all tumor types are considered together. The Pearson’s r value and the R2 value of the best linear fit to the experimental data is shown to quantify the strength of the correlations. A Pearson’s r value>0.8 denotes a very strong correlation.