BEYOND PD-L1: UNRAVELING THE ENIGMA OF IMMUNOTHERAPY RESPONSE IN PD-L1 NEGATIVE (<1%) NSCLC PATIENTS THROUGH QUANTIFICATION OF PD-1/PD-L1 ENGAGEMENT IN THE TUMOR MICROENVIRONMENT

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Background Profound advances in cancer patient treatments have come with the advent of immunotherapies directed at blocking immune-suppressive ligand-receptor interactions. However, while there has been success with these immune checkpoint interventions, there has been limited success in stratifying patients for these interventions with response rates at approximately 14%.

Methods To address this, we have determined the extent of the molecular target, intercellular PD-1/PD-L1 interaction state, in formalin-fixed paraffin embedded tumor samples from non-small cell lung carcinoma patients, using a high-throughput automated quantitative imaging platform (QF-Pro®). QF-Pro® is a FRET/FLIM based assay which can be used to quantify the distance between this receptor ligand pair directly within FFPE samples.

Results The multi-site blinded analysis across a cohort of 188 IO-treated patients (treated with nivolumab, pembrolizumab, atezolizumab or durvalumab) demonstrated the intra- and inter-tumoral heterogeneity of the PD-1/PD-L1 immune checkpoint engagement and notably showed no correlation between the extent of PD-1/PD-L1 interaction and PD-L1 expression (r=0.05, P=0.55). Importantly, PD-L1 expression scores used clinically to stratify the patients, correlated poorly with overall survival. By contrast, patients showing a high PD-1/PD-L1 interaction had significantly better responses to anti-PD-1/PD-L1 treatments, as evidenced by increased OS (median 31 months vs 10 months). This relationship was particularly strong in the setting of first line treatments. Even more critically, in a subset of patients determined as being PD-L1 negative (PD-L1 TPS <1%), response to treatment was still observed in those patients with PD-1/PD-L1 interactions (median >60 months vs 14 months) (figure 1). This therefore may yield a mechanism to successfully treat those patients who, under current guidelines, are not be considered for these therapies. Moreover, an early insight of this trend has been observed in a small cohort of prospective NSCLC patients whereby higher interaction states remain predictive of improved treatment response.

Conclusions Using the functional read out of this immune checkpoint engagement (PD-1/PD-L1 interaction) as a predictive biomarker for the stratification of NSCLC patients instead of PD-L1 expression should significantly improve response rates to immunotherapy. This would both capture patients excluded from checkpoint immunotherapy (high PD-1/PD-L1 interaction but low PD-L1 expression, 24% of patients), and additionally avoid the treatment of patients resistant to this type of treatment (low PD-1/PD-L1 interaction but high PD-L1 expression) who may benefit from alternative cancer therapeutics, such as other immunotherapies. Even at this early stage, QF-Pro® has set an unbiased quantitative cut-off to be considered for anti-PD-1/PD-L1 therapies which can be deployed directly into clinical practice.

Ethics Approval All patients gave written informed consent. Ethical and Scientific Committees approved the study: CEIm-E PI2020200; CEIm Hospital Clinico San Carlos 21/002; CEIm MD Anderson MD21/002; Institutional Review Board of Institut Bergonié. The Medical Research Ethics Committee (MREC) of the BEBO Foundation for the Assessment of Ethics of Biomedical Research, declared Medical Research involving Human Subjects Act did not apply to this study and no official approval was required by Dutch national law. The MREC of the BEBO Foundation is recognized by the Central Committee on Research Involving Human Subjects (CCMO) and accredited by the Dutch Association of MRECs (NVMETC), San Carlos (Samples and anonymised data from patients included in this study were provided by the BioBank del HCSC B.00000725 (PT20/00074)), Alicante: (‘Samples and data from patients included in this study were provided by the BioBank ISABIAL); Biocruces (‘Samples and data from patients included in this study were provided by the Basque Biobank/Biocruces Bizkaia Node’); and Biodonostia (‘Samples and data from patients included in this study were provided by the Basque Biobank/Biodonostia’).

Abstract 222-G Figure 1 QF-Pro® identifies responders to anti-PD-1/PD-L1 therapies even in PD-L1 negative (<1% PD/L1 TPS) NSCLC patients. QF-Pro® was able to set a threshold of PD-1/PD-L1 interaction state where patients would significantly respond to anti-PD-1/PD-L1 therapies, as evidenced by increased overall survival. This was even observed in PD-L1 negative (<1% PD/L1 TPS) patients, whereby those patients with PD-1/PD-L1 interaction states above this QF-Pro® threshold responded to these therapies (median overall survival >60 months vs 14 months for those patients with low PD-1/PD-L1 interaction).

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