14P Circulating tumor DNA (ctDNA) residual and dynamics of ctDNA clonality indicated therapeutic efficacy of sintilimab plus docetaxel in previously treated advanced non-small cell lung cancer

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Background: Sintilimab + docetaxel showed encouraging efficacy and tolerable safety profile in advanced Chinese NSCLC pts who had failed first-line therapy. This study aims to explore potential circulating biomarker(s), especially dynamics of ctDNA, predicting therapeutic response and long-term outcome.

Methods: Advanced NSCLC pts who had failed standard platinum doublet or EGFR-TKI without receiving any ICIs before would be enrolled in this single-arm phase II study. Docetaxel (75mg/m2, day 1) + Sintilimab (200mg, day 3) every 3 weeks for 4-6 cycles followed by Sintilimab maintenance were prescribed until disease progression, unacceptable toxicity, or up to 2 years. 10 mL blood would be drawn from each patient immediately after enrollment (baseline, C0D0) and after two cycles of treatment. ctDNA was detected via a 448-gene panel. bTMB was calculated as the number of mutations divided by sequence length (1.16Mb). Positivity was defined as $\geq$ 2 somatic variants, $\leq$ 1 somatic variant within a sample was considered negative. Clonality was defined as AF/AFmax $\geq$ 50%.

Results: Pts with positive ctDNA after 2 courses of treatment (at 6th week) displayed inferior prognosis (mPFS, 91d vs NR, ctDNA (+) vs ctDNA (-) after 2 treatment courses respectively, P $<$ 0.0001; mOS, 147d vs 467d, P $=$ 0.0039). Irrespective of driver mutations (EGFR, ERBB2 in this study), ctDNA residual at 6th week was an independent risk factor for progression or death (HR $=$ 100 [4.10-2503.00], P $=$ 0.005, Cox Regression). Furtherly, clearance of clonal mutations and no clonal formation at 6th week were associated with longer PFS (mPFS 89d vs 266d, HR $=$ 4.40 [0.84-23.16], P $=$ 0.003); Clearance of clonal mutations was associated with longer OS (mOS 147d vs 467d, HR $=$ 7.01 [1.30-37.69], P $=$ 0.0048). Baseline bTMB was not associated with the efficacy of Sintilimab+ Docetaxel treatment.

Conclusions: ctDNA residual, as well as dynamics of clonality in ctDNA could predict long-term clinical benefit of sintilimab + docetaxel in pts with previously treated advanced NSCLC, irrespective of driver mutations as well as bTMB. Further validation of ctDNA residual and dynamics of clonality as robust predictive biomarkers is warranted.

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15P Serum immune checkpoint biomarkers as predictors of response to anti-PD-1/PD-L1 treatment in non-small cell lung cancer (NSCLC) patients

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Background: There is limited data on the predictive biomarkers of response to immune checkpoint blockade (ICB) treatment of non-small cell lung cancer (NSCLC) patients. The main aim of this prospective study is to understand the utility of pre-treatment soluble immune checkpoint and tumor markers as early predictors of response in locally advanced/metastatic NSCLC patients treated with ICBs.

Methods: The study was conducted at the National Center for Cancer Care and Research (NCCCR), HMC, Qatar. A total of 26 patients on anti-PD-1/PDL-1 treatment were enrolled, and pre-treatment blood samples were collected. Multiplex Magnetic Bead Panel kits were utilized to measure concentrations of soluble immune checkpoint and tumor markers including BTLA, GITR, HVEM, IDO, LAG-3, PD-1, PDL-1, PDL-2, TIM-3, CD28, CD80, 4-1BB, CD27, CTLA-4, ICOS Ligand, CD276, VISTA, B7-H6; CD47 (IAP), BLAST-1, Galectin-9, TIMD-4; OX40, S100A8/A9, E-cadherin, MICB, Nectin 2, NTSE, PVR, Singlec 7, Singlec 9,CEA, CA-19-9, CA-125 CYFRA21-1 and CA-15-3. Mann-Whitney test was used to evaluate difference in medians in responders and non-responders. Response to treatment was assessed 4 months after initiation of treatment via PET CT imaging data.

Results: Clinical response to ICB treatment was determined based on RECIST criteria and PET CT imaging data. 12/26 (46%) patients showed clinical response to the treatment while 14/26 (54%) were identified as non-responders. Interestingly, in clinically responding patients, significant upregulation of the immune inhibitory soluble programmed death-ligand 1 (sPD-L1) molecule ($<$0.002**) and the immune stimulatory biomarkers glucocorticoid-induced TNFR-related protein (GITR) ($<$0.0005***), and Herpes virus entry mediator (HVEM) ($<$0.006**) were recorded. However, non-responding patients showed significant upregulation of 3 important immune suppressive biomarkers; T-cell immunoglobulin and mucin domain containing 4 (TIMD-4) (p$<$0.0361*), Nectin 2 (p$<$0.0310*) and the carcinoembryonic antigen (CEA) tumor marker (p$<$0.0484*).

Conclusions: The study shows that soluble immune suppressive/stimulatory biomarkers can serve as plausible early biomarkers of response to ICB treatment.

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16P Stromal compartment specific gene signatures dissect immunotherapy response groups in non-small cell lung cancer

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Background: Immunotherapies, such as immune checkpoint inhibitors (ICI) have shown durable benefit in a subset of non-small cell lung cancer (NSCLC) patients. The composition and activation status of the cellular milieu contained within the tumour microenvironment (TME) is becomingly increasingly recognised as a driving factor in treatment-refractory disease.

Methods: Here, we employed multiplex IHC (mIHC), and digital spatial profiling (DSP) to capture the targeted immune proteome and transcriptome of tumour and TME compartments of pre-treatment samples from a 2nd line NSCLC ICI-treated cohort (n=41 patients; n=25 responders, n=16 non-responders).

Results: Patients sensitive to ICI therapy expressed higher levels of IL2 receptor alpha (CD25, p=0.028) within the tumour compartments, which corresponded with the increased expression of IL2 mRNA(p=0.001) within their stroma. IL2 mRNA levels within the stroma positively correlated with the expression of pro-apoptotic markers cleaved caspase 9(p=2e-5) and BAD(p=5.5e-4) and negatively with levels of memory T cells (CD45RO) (p=7e-4). Immuno-inhibitory markers CTLA-4(p=0.021) and IDO-1(p=0.023) were supressed in ICI-responsive patients. Tumour CD44(p=0.02) was depleted in the response group and corresponded inversely with significantly higher stromal expression of its ligand SPP1 (osteopontin,p=0.008). Analysis of differentially expressed transcripts indicated the potential inhibition of stromal interferon-gamma (IFNγ) activity and estrogen-receptor and Wnt-1 signalling activity within the tumour cells of ICI responsive patients. Cox survival analysis indicated tumour CD44 expression was associated with poorer prognosis (HR=1.61, p=0.01), consistent with its depletion in ICI sensitive patients. Interestingly, stromal mRNA for E-selectin (HR=652, p=0.001), CCL17 (HR=70, p=0.006) and MTOR (HR=1065, p=0.008) were highly associated with poorer outcome, indicating pro-tumourigenic features in the tumour microenvironment that may facilitate ICI resistance.

Conclusions: Through multi-modal approaches, we have dissected the characteristics of NSCLC and provide evidence for the role of IL2 and stromal activation by osteopontin in the efficacy of ICI therapy.

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17P Dynamic changes of CT-radiomic and systemic immune-inflammatory features predict the response to immune checkpoint inhibitors in advanced NSCLC patients

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Background: Clinically suitable biomarkers to foresee the response to immune checkpoint inhibitors (ICIs) can be achieved by decoding tumor heterogeneity and its evolution during treatment. Thus, we determine whether the longitudinal assessment