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MHC-II antigen presentation pathway as a predictive biomarker for sintilimab plus chemotherapy in first-line treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (nsq-NSCLC)


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Background
Immunotherapy plus chemotherapy is a promising treatment for first-line nsq-NSCLC. However, predictive biomarkers for this immuno-combination remain to be elucidated.

Methods
In a randomized, double-blind, phase III study evaluating the efficacy of sintilimab, an anti-PD-1 antibody, plus pemetrexed and platinum (Chemo) as first-line treatment (ORIENT-11), 397 patients with locally advanced or metastatic nsq-NSCLC were randomized (2:1 ratio) to receive either sintilimab plus Chemo (Combo) or placebo plus Chemo. The primary endpoint was progression-free survival (PFS). RNA sequencing was conducted on 248 baseline tumor biopsies (168 in Combo and 80 in Chemo).

Results
Combo group showed superiority to Chemo group in PFS (HR=0.48, 95%CI: 0.36-0.64, p<0.0001). Survival analysis showed that top 20 genes (Ranked by P-value) including ITGB2, ADAP2, MPP1, PIK3AP1, GBGT1, RAB27A, CD180, NEK6, RLN3, CD84, CASP8, DRAM1, HLA-DMB, OTULIN, HELZ, VDR, HLA-DPA1, MX2, FOCA1, MKRN1 were significantly associated with good efficacy of Combo treatment (mean HR 0.26, P<0.0001) but not Chemo treatment except for NEK6 (HR, 0.38; 95% CI, 0.14−0.50; P=0.0047). In line with this, we found that the entire signature score of MHC-II antigen presentation pathway was more significantly associated with clinical efficacy of Combo (HR, 0.51; 95% CI, 0.28-0.91; P=0.0230) than that of MHC-I (HR, 0.70; 95% CI, 0.39−1.25; P=0.2230). It was further validated that cells with MHC-II presentation capability also contributed to the longer PFS in the Combo group, e.g. macrophage (HR, 0.48; P=0.0120), activated dendritic cell (HR, 0.46; P=0.0114), immature dendritic cell (HR, 0.47; P=0.0134), or immature B cell (HR, 0.51; P=0.0245). Finally, multiplex immunohistochemistry data from 57 patients demonstrated concordance between RNA and protein expression and that higher level of CD68 protein was associated with good outcome (HR, 0.42; 95% CI, 0.12-1.54; P=0.1930).

Conclusions
Signature of MHC-II antigen presentation was significantly associated with longer PFS in patients receiving immune-combination therapy and could be served as a predictive biomarker.

Clinical trial identification
NCT03607539.

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