ORIGINAL ARTICLE

Updated Overall Survival Data and Predictive Biomarkers of Sintilimab Plus Pemetrexed and Platinum as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC in the Phase 3 ORIENT-11 Study

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Disclosure: Drs. J Sun, H Zhou, S Wang, L Sun, C Mancao, B Peng, and W Xu are full-time employees of Innovent Biologics Inc. Dr. Puig is a full-time employee of Eli Lilly and Company. Dr. Zhang reports receiving grants from AstraZeneca, Bristol-Myers Squibb, and Pfizer. The remaining authors declare no conflict of interest.

A subset of the biomarker data of this study has been presented at the ESMO virtual conference 2020, September 19-21, 2020.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2021.07.015

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Received 8 May 2021; revised 7 July 2021; accepted 12 July 2021
Available online - 3 August 2021

ABSTRACT

Introduction: Sintilimab plus chemotherapy significantly prolonged progression-free survival (PFS) compared with chemotherapy alone in nonsquamous NSCLC in the ORIENT-11 study. Updated overall survival (OS) and PFS data and corresponding biomarker analyses are reported here.

Methods: In this study, a total of 397 patients with previously untreated, locally advanced or metastatic nonsquamous NSCLC were assigned to sintilimab plus chemotherapy combination treatment (combo) group or placebo plus chemotherapy treatment group. The patients were stratified by programmed death-ligand 1 (PD-L1) expression levels. Immune signature profiles from tumor RNA sequencing and PD-L1 immunohistochemistry were correlated with clinical outcome to identify predictive biomarkers.

Results: As of January 2021, with median follow-up of 22.9 months, median OS was significantly improved in the combo group compared with the placebo plus chemotherapy treatment group (not reached versus 16.8 mo; hazard ratio [HR] = 0.60, 95% confidence interval [CI]: 0.45–0.79, $p = 0.0003$). High or medium immune cell infiltration was strongly associated with improved PFS in the combo group, in contrast to absent or low immune cell infiltration, which suggests that chemotherapy could not prime "immune deserts" to obtain benefit from programmed cell death protein-1 inhibition. In particular, high major histocompatibility complex (MHC) class II presentation pathway expression was significantly correlated with prolonged PFS (HR = 0.32, 95% CI: 0.19–0.54, $p < 0.0001$) and OS (HR = 0.36, 95% CI: 0.20–0.64, $p = 0.0005$) in the combo group. Importantly, patients with low or absent PD-L1 but high MHC class II expression could still benefit from the combo treatment. In contrast, MHC class I antigen presentation pathway was less relevant in this combination setting.

Conclusions: The addition of sintilimab to chemotherapy resulted to significantly longer OS in nonsquamous NSCLC. Expression of MHC class II antigen presentation pathway could identify patients benefiting most from this combination.

Keywords: Nonsquamous NSCLC; Sintilimab; RNA sequencing; MHC class-II antigen presentation pathway; Predictive biomarker

Introduction

In recent years, immunotherapy on the basis of programmed cell death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) antibodies in combination with platinum-based doublet chemotherapy has significantly improved progression-free survival (PFS) and overall survival (OS) in patients with previously untreated advanced or metastatic NSCLC.[1,2] Nevertheless, given the overall limited clinical efficacy and increased toxicity from such a combination treatment, identification of biomarkers for selection of patients who might benefit from immunotherapy and chemotherapy combinations is of great interest. Because the predictive power of current biomarker candidates such as PD-L1 expression and tumor mutational burden (TMB) is limited, especially in the combination treatment,[3,4] alternative biomarkers remain in great demand for improved clinical decision making.

Sintilimab is an IgG4 anti–PD-1 antibody with high-affinity blocking interaction of PD-1 and its ligands.[5,6] According to the interim analysis (by November 15, 2019) of the phase 3 study ORIENT-11,[7] sintilimab plus pemetrexed and platinum (sintilimab + chemotherapy combination treatment [combo]) significantly improved PFS assessed by blinded independent radiographic review committee (hazard ratio [HR] = 0.48, $p < 0.0001$) as compared with placebo plus pemetrexed and platinum (chemotherapy treatment [chemo]) in patients with previously untreated locally advanced or metastatic nonsquamous NSCLC. Nevertheless, at the time of the interim analysis, OS data were immature in both groups: only 51 patients (19.2%) in the combo group and 39 patients (29.8%) in the chemo group had death events, respectively. Here, we will report the updated OS and PFS data of this study. In addition, using whole transcriptome sequencing of baseline tumor samples from the ORIENT-11 study, we aimed to evaluate the predictive value of tumor immune cell infiltrations and signatures of immune-related pathways for clinical outcome in patients who received immune-combination treatment.

Materials and Methods

Study Design

ORIENT-11 is a randomized, double-blind, phase 3 study conducted in 47 centers in the People's Republic of China (ClinicalTrials.gov identifier: NCT03607539).[7] Briefly, patients with previously untreated, locally advanced or metastatic nonsquamous NSCLC without sensitizing EGFR or anaplastic lymphoma kinase genomic aberration were randomized (2:1 ratio) to receive either sintilimab or placebo plus pemetrexed and platinum once every 3 weeks for four cycles, followed by sintilimab or placebo plus pemetrexed as maintenance therapy. These patients were stratified by PD-L1 expression (tumor proportion score [TPS] $\geq$ 1% or TPS $<$ 1%). The treatment was continued until disease progression, intolerable toxicity, initiation of new treatment, or withdrawal of consent. Patients in the chemo group were allowed to cross over to receive sintilimab monotherapy if they met all protocol-specified criteria. The primary end point was PFS assessed by blinded independent radiographic review committee. OS was a prespecified secondary end point. The clinical protocol was approved by the respective institutional review boards and ethics committees. All participants provided written informed consent.

PD-L1 Analysis by Immunohistochemistry

PD-L1 protein expression score TPS, which is the percentage of viable tumor cells revealing partial or complete membrane staining at any intensity expression, was assessed on baseline tumor formalin-fixed paraffin-embedded tissue using the 22C3 pharmDx assay (Agilent Technologies) at a central laboratory (Covance, Shanghai, People's Republic of China).

Library Construction and RNA Sequencing

RNA was extracted from formalin-fixed, paraffin-embedded baseline tumor samples using the RNeasy formalin-fixed, paraffin-embedded kit (Qiagen), and ribosomal RNAs were removed using the NEBNext rRNA Depletion Kit (NEB). For the complementary DNA library preparation, the NEBNext Ultra II Directional RNA Library Prep Kit for Illumina was used as per manufacturer's recommendations. Briefly, fragmentation was first carried out using divalent cations, followed by strand-specific construction of RNA-sequencing (RNA-seq) libraries. RNA-seq was carried out on the NovaSeq 6000 system (Illumina). Reads quality control was conducted with FastQC,[8] and raw reads were filtered by Trimmomatic[9] and mapped to the human GRCh38 reference genome using STAR aligner.[10] Only samples with unique reads mapping rate of at least 30% and with reads duplication rate of at most 90% were used for downstream analysis. The HTSeq-count command was used to count reads mapped to each gene.[11] Gene expression level was quantified on the basis of raw read counts using transcripts per million normalization.

Immune Cell Signature and Antigen Presentation Pathway Analysis

Gene expression signatures defining 28 immune cell populations[12] were used to calculate immune cell signature scores using the GSVA algorithm on the basis of gene expression levels of transcripts per million.[13] Unsupervised hierarchical clustering was used to define the overall level of immune cell infiltration (high or medium or low). When analyzing the association between a specific immune cell signature and clinical outcome, the median expression level was used as a cutoff to divide patients into high or low expression group. p values presented are not adjusted for multiple testing.

For antigen presentation pathway analysis, two analysis strategies were used: a smaller gene set including seven major histocompatibility complex (MHC) class I- (HLA-A,-B,-C,-E,-F,-G and B2M) and 15 MHC class II- (HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, HLA-DPA, HLA-DPB1, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB2, HLA-DRA, HLA-DRB1, HLA-DRB3, HLA-DRB4, HLA-DRB5) related genes, respectively, and a larger set including 496 and 126 genes involved in the entire class I and class II antigen presentation pathways were adopted.[14] Each MHC class I or II gene set was first scaled by z-score and then averaged between genes to their expression levels. The gene sets of class I or II antigen presentation pathways were downloaded from the Reactome Pathway Database.[14] Expression levels of antigen presentation pathways were also calculated by the GSVA algorithm.

Functional Enrichment Analysis

For each protein-coding gene, the population was iteratively split into high or low groups by gene-specific median value and then associated with PFS per treatment arm to obtain PFS-associated genes ($p < 0.05$; p values are not adjusted for multiple testing). These genes were then further categorized into three groups (combo-specific, chemo-specific, and overlap). Next, Gene Ontology biological process (GOBP) enrichment analysis of these three gene lists was conducted using the R clusterProfiler package.[15] The functional similarity between two significantly enriched GOBP terms (adjusted p or $p < 0.01$) was calculated on the basis of their gene lists using Jaccard index, in which pairs of GOBP terms with similarity more than 0.1 were used to construct the final functional interaction network. The functional

groups of GOBP terms were summarized on the basis of the GO hierarchy.

Survival Analysis

The previous interim analysis was performed on the basis of data cutoff on November 15, 2019, with 198 events of PFS. This trial continues to accumulate long-term data after the interim analysis. We updated PFS as of data cutoff on May 15, 2020, and OS as of data cutoff on January 15, 2021. The Kaplan-Meier method was used to analyze PFS and OS. The stratified log-rank test was used to evaluate the treatment difference. The HRs and associated 95% confidence intervals (CIs) were calculated on the basis of a stratified Cox proportional-hazards model.

In this study, aiming to identify predictors for the efficacy of immune-combination treatment, the biomarker analysis was mainly based on PFS, which would not be affected by subsequent treatments or crossover. The survival analysis was performed using the R survival package,[16] and *p* value and HR between two groups were calculated with the coxph function. Survival curves were plotted using the R survminer package.[17] All statistical tests were two sided; *p* value less than 0.05 was deemed statistically significant.

Results

Patient Characteristics

A total of 397 patients (intent-to-treat [ITT]) with previously untreated, locally advanced or metastatic nonsquamous NSCLC were enrolled and randomized to receive either sintilimab 200 mg (n = 266) or placebo (n = 131) plus pemetrexed and platinum. In total, tumor samples from 62.5% of the ITT population (168 and 80 samples from the combo and chemo group, respectively) were collected for RNA sequencing (Supplementary

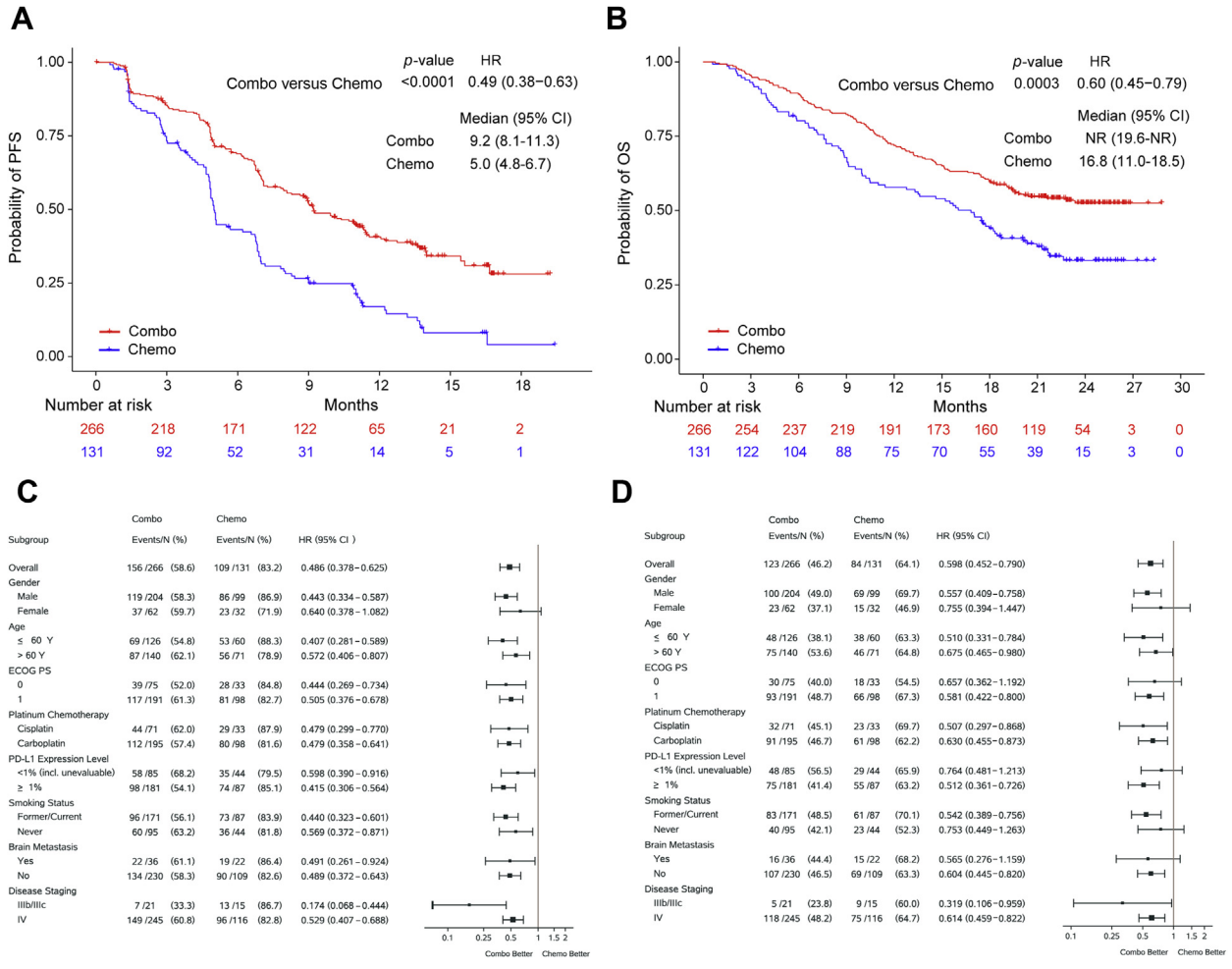

Figure 1. Survival analysis in the intention to treat patients. Kaplan-Meier plots for (*A*) PFS and (*B*) OS and forest plots of HRs in key subgroups for (*C*) PFS and (*D*) OS are illustrated with respective *p* value, HR, 95% CI, and sample size. Chemo, chemotherapy treatment; CI, confidence interval; Combo, sintilimab plus chemotherapy combination treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reached; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

Fig. 1). After stringent quality control, the biomarker evaluable population (BEP) included 113 samples from the combo group and 58 samples from the chemo group (43.1% of the ITT). Baseline clinical characteristics such as age, sex, disease stage, and PD-L1 expression and PFS were well balanced between the BEP and ITT cohorts (Supplementary Table 1 and Supplementary Fig. 2). Therefore, we assumed that the RNA analysis of the BEP could represent the ITT population in this study. Main clinical characteristics were also balanced between the combo and chemo groups.

Updated PFS and OS

As of May 15, 2020, the median follow-up for PFS was 14.8 months. A total of 156 patients (58.6%) in the combo group and 109 patients (83.2%) in the chemo group had a disease progression or death event. The median PFS was significantly prolonged in the combo group (9.2 versus 5.0 mo; HR = 0.49, 95% CI: 0.38–0.63, $p < 0.0001$) (Fig. 1*A*).

We updated OS by cutoff date on January 15, 2021. With a median follow-up of 22.9 months, 123 patients (46.2%) in the combo group and 84 patients (64.1%) in

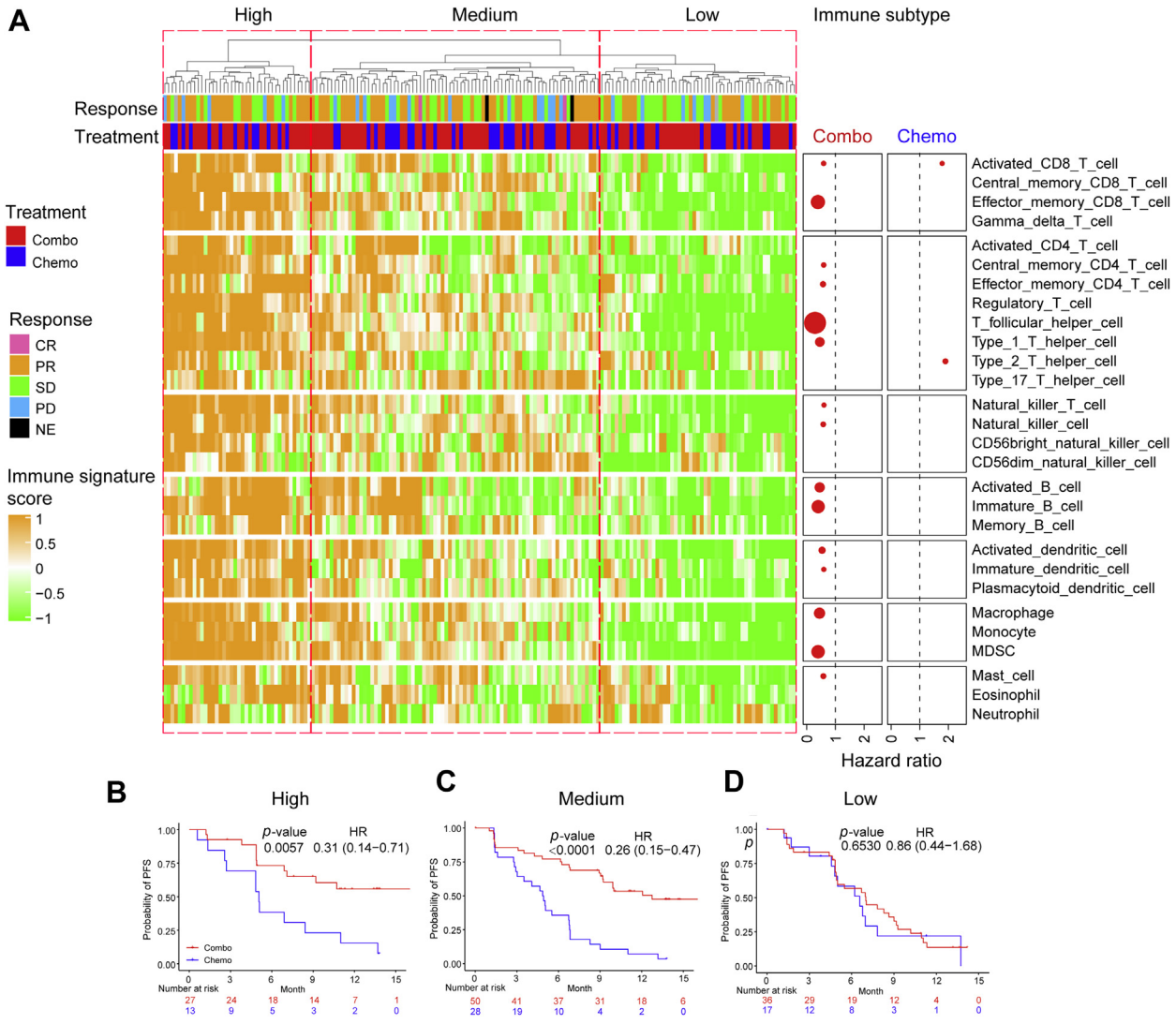

Figure 2. Immune cell signatures in tumor microenvironment and association with PFS. (*A*) Heatmap of immune score of 28 immune cell populations (left panel) and forest plots (right panel) display the correlation of each immune cell population with PFS. Node position reflects HR (<1 for favorable outcome with high immune score on the basis of median expression level per signature in respective treatment). Only significant ($p < 0.05$) correlations are displayed and node size reflects the *p* value (node size reflects significance). Overall, immune cell signatures revealed three immune subtypes (red dashed boxes in left panel) on the basis of unsupervised clustering across the biomarker evaluable population. For the different subtypes, PFS association with treatment is displayed in individual survival plots: (*B*) high immune score, (*C*) medium immune score, and (*D*) low immune score with respective *p* value, HR, 95% confidence interval, and sample size. Chemo, chemotherapy treatment; Combo, sintilimab plus chemotherapy combination treatment; CR, complete response; HR, hazard ratio; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

the chemo group died. Furthermore, 60 patients (45.8%) in the chemo group crossed over to receive sintilimab after disease progression. The median OS of the combo group was still not reached in comparison to that of the chemo group which was 16.8 months (HR = 0.60, 95% CI: 0.45–0.79, $p = 0.0003$) (Fig. 1*B*). Both PFS and OS benefits associated with the addition of sintilimab were observed in all subgroups evaluated (Fig. 1*C* and *D*).

Immune Cell Signatures and Clinical Outcome

On the basis of the overall infiltration of 28 immune cell subpopulations[12] in the tumor microenvironment,

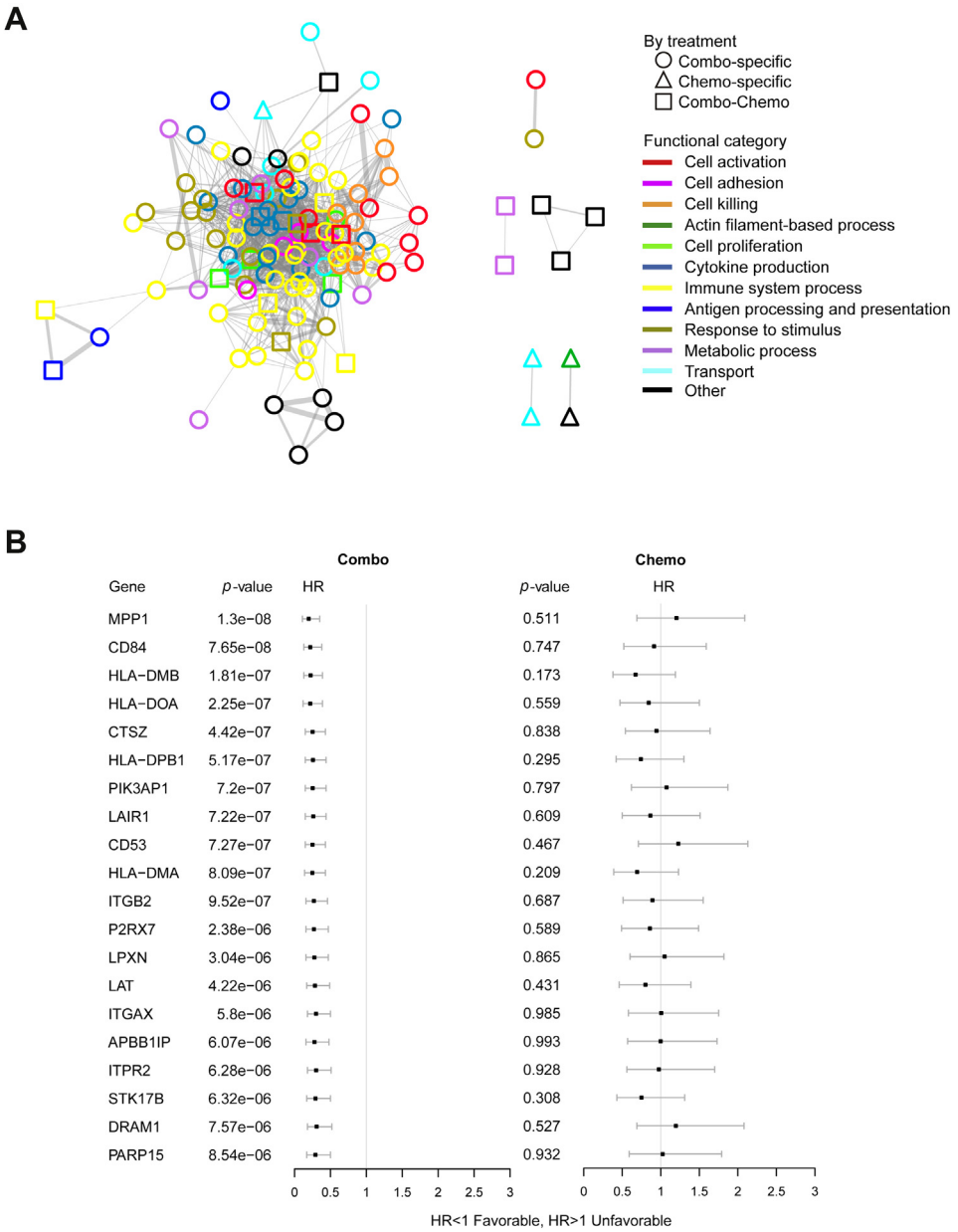

Figure 3. Pathway enrichment analysis and top 20 genes significantly correlated with PFS. (*A*) Differences in enriched pathways of PFS-related genes from combo or chemo treatment group are revealed. Each node represents an enriched pathway. Node shape indicates the specific treatment group, and color indicates functional category of pathway according to Gene Ontology annotation (Supplementary Table 2). Edge width of node connection represents functional similarity between two pathways. Combo-specific, pathways enriched specifically in the sintilimab + chemotherapy combination treatment; chemo-specific, pathways enriched specifically in the chemotherapy treatment; combo-chemo, pathways enriched in both treatment groups. (*B*) Forest plot of 20 genes most significantly correlated with PFS in the combo treatment is revealed. Red colored genes are related to antigen presentation. Chemo, chemotherapy treatment; Combo, sintilimab plus chemotherapy combination treatment; HR, hazard ratio; PFS, progression-free survival.

three patient clusters were observed by unsupervised clustering: one with an overall high infiltration of immune cells, one with medium, and one with low or absent infiltration (Fig. 2*A*). Significantly improved PFS associated with the addition of sintilimab to chemotherapy was observed in patients with both high and medium immune cell infiltrations, with HR of 0.31 (95% CI: 0.14–0.71, $p = 0.0057$) for high infiltration population and 0.26 (95% CI: 0.15–0.47, $p < 0.0001$) for medium infiltration population, respectively (Fig. 2*B* and *C*). Nevertheless, no additional benefit was detected in patients with low or absent immune cell infiltration (HR = 0.86, 95% CI: 0.44–1.68, $p = 0.6530$; Fig. 2*D*).

Next, we evaluated the association between PFS and specific immune cell subsets (Fig. 2*A*, right panel). When splitting the population by median expression levels of respective cell subsets, we found that general CD8 T cell infiltration (Supplementary Fig. 3), especially effector memory and activated CD8 T cells, correlated with improved PFS in the combo group. In addition, the presence of antigen-presenting cells (APCs) including B cells, dendritic cells, and macrophages was also associated with clinical outcome in the combo group. In line with these findings, we also observed that patients with high follicular helper T cell infiltration had longer PFS when receiving combination treatment.

Pathway Enrichment Analysis

We sought to confirm this finding by a different and unbiased pathway enrichment analysis on the basis of PFS-related gene lists (see details in the Materials and Methods section; Fig. 3*A* and Supplementary Table 2). There were 2588 combo-specific PFS-associated genes that were mainly enriched for immune-related pathways. In contrast, a total of 667 chemo-specific, PFS-associated genes were mainly involved in transport and actin filament-based process. There were also 123 PFS-associated genes shared by both the combo and chemo groups which were enriched in metabolic processes and antigen processing and presentation.

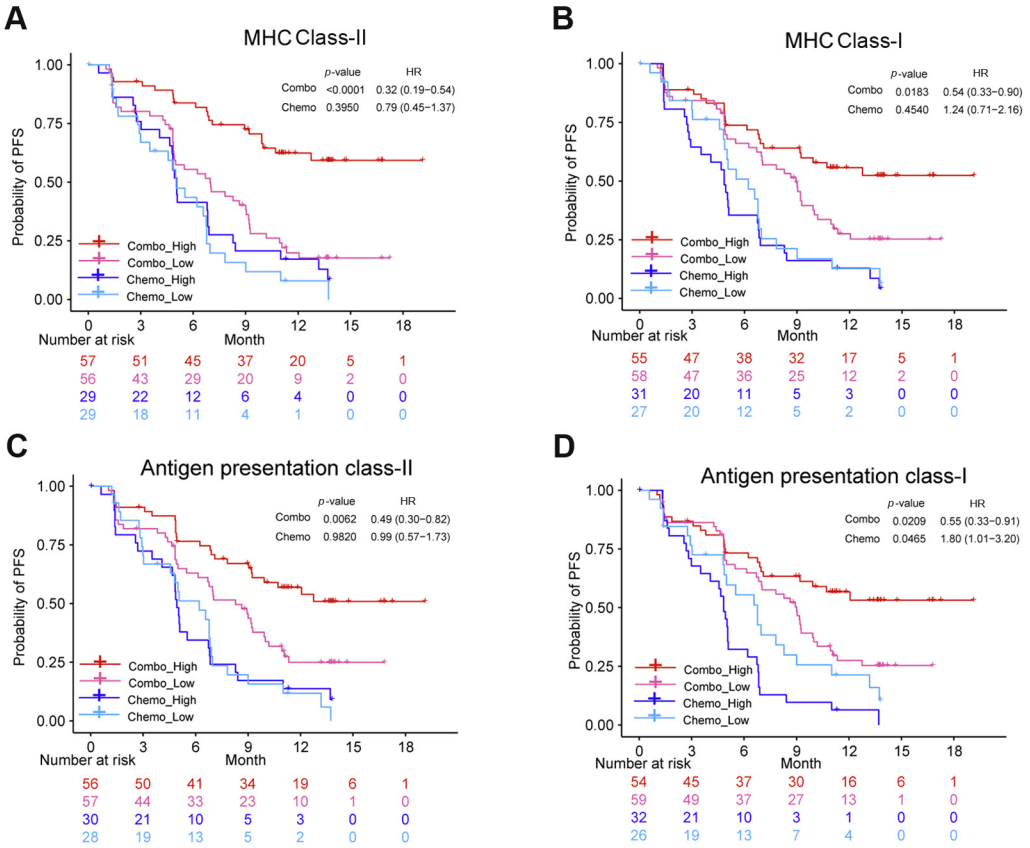

Figure 4. Association between PFS and gene expression of antigen presentation pathways. PFS correlation of high and low (*A*) MHC class II-related gene signatures, (*B*) MHC class I-related gene signature, (*C*) class II antigen presentation pathway signature, and (*D*) class I antigen presentation pathway signature is revealed for the combo and chemo treatment groups with respective *p* value, HR, 95% confidence interval, and sample size. Chemo, chemotherapy treatment; Chemo_high (or Chemo_low), chemotherapy treatment and high (or low) RNA expression level; Combo, sintilimab plus chemotherapy combination treatment; Combo_high (or Combo_low), sintilimab plus chemotherapy combination treatment and high (or low) RNA expression level; HR, hazard ratio; MHC, major histocompatibility complex; PFS, progression-free survival.

Next, genes related to PFS of the combo treatment were ranked by p value and the top 20 genes strongly correlated with PFS are illustrated in Figure 3*B*. Functionally, several genes of these top 20 genes played important roles in immune regulation, such as innate immunity, leukocyte migration, and leukocyte activation. Of note, four genes were closely linked to antigen presentation: as components of the MHC class II complex, HLA-DMB, HLA-DOA, HLA-DPB1, and HLA-DMA play central roles in presentation of the antigen peptides.[18,19] Finally, class II transactivator (CIITA), the master regulator of MHC class II genes, even not among the top 20 genes, also revealed significant association with PFS in the combo treatment (HR = 0.33, $p < 0.0001$) (Supplementary Fig. 4).

Antigen-Presenting Pathway and Clinical Outcome

After identifying APCs and genes coding components of the MHC class II complex as key factors for survival correlation in the combo treatment, we next sought to delineate the association between antigen presentation pathways and clinical outcome. We found that especially patients with high MHC class II-related gene expression had significantly longer PFS than those with low MHC class II-related gene expression in the combo group (HR = 0.32, $p < 0.0001$; Fig. 4*A*). In the chemo group, the PFS of patients with high or low MHC class II-related gene expression was comparable (HR = 0.79, $p = 0.3950$; Fig. 4*A*). In addition, although with lower predictive value, higher MHC class I-related gene expression correlated with longer PFS in patients receiving combo treatment (HR = 0.54, $p = 0.0183$; Fig. 4*B*). Analyzing entire antigen presentation pathway expression by the larger gene sets also highlighted the importance of class II antigen presentation pathway: in the combo group, patients with high class II antigen presentation pathway expression had significantly longer PFS (HR = 0.49, $p = 0.0062$; Fig. 4*C*), whereas the correlation between PFS and class I antigen presentation pathway expression was significant but less strong (Fig. 4*D*). Of note, when analyzing the association between antigen presentation pathways and OS, we observed that only MHC class II-related gene expression was correlated with OS in the combo group (HR = 0.36, $p = 0.0005$; Supplementary Fig. 5), whereas MHC class I-related gene expression was not significantly associated with OS benefit.

Predictive Role of MHC Class II Antigen Presentation in Patients With Different PD-L1 Expression Levels

PD-L1 immunohistochemistry expression levels in the BEP were illustrated in Supplementary Table 1. The association between PD-L1 expression (cutoff value of TPS1 and TPS50) and PFS in both combo and chemo groups by two cutoffs was illustrated in Figure 5*A* and *B*.

As only the expression of MHC class II antigen presentation pathway correlated with both PFS and OS benefit with combo treatment, we then tested the predictive value of its expression in patients with different PD-L1 expression levels. No correlation was observed between PD-L1 immunohistochemistry and MHC class II gene expression (Spearman r = 0.28, $p = 0.0002$; Supplementary Fig. 6). We found a significant correlation

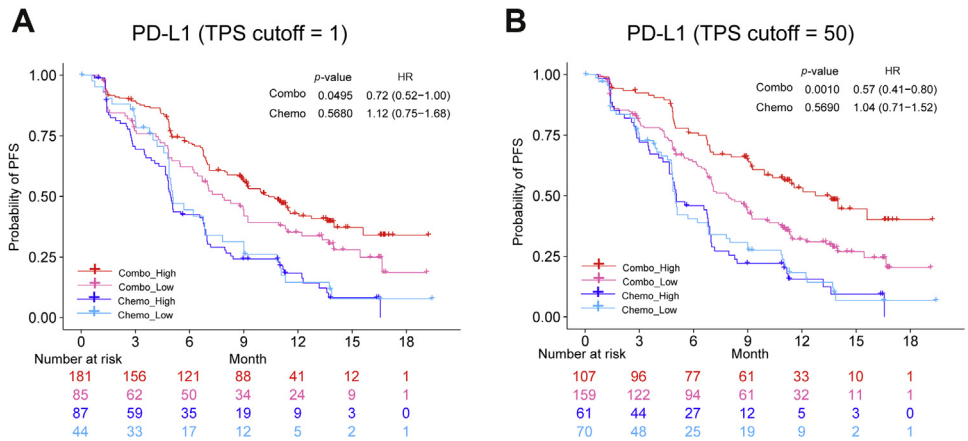

Figure 5. Association between PFS and PD-L1 expression. PFS correlation of high and low PD-L1 protein expression assessed by IHC for ITT at (*A*) TPS1 cutoff and (*B*) TPS50 cutoff is revealed for the combo and chemo treatment groups with respective p value, HR, 95% confidence interval, and sample size. Chemo_high (or Chemo_low), chemotherapy treatment with PD-L1 expression level greater than or equal to 1 (or <1); Combo_high (or Combo_low), sintilimab + chemotherapy combination treatment with PD-L1 expression level greater than or equal to 50 (or <50); Chemo, chemotherapy treatment; Combo, sintilimab plus chemotherapy combination treatment; HR, hazard ratio; IHC, immunohistochemistry; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

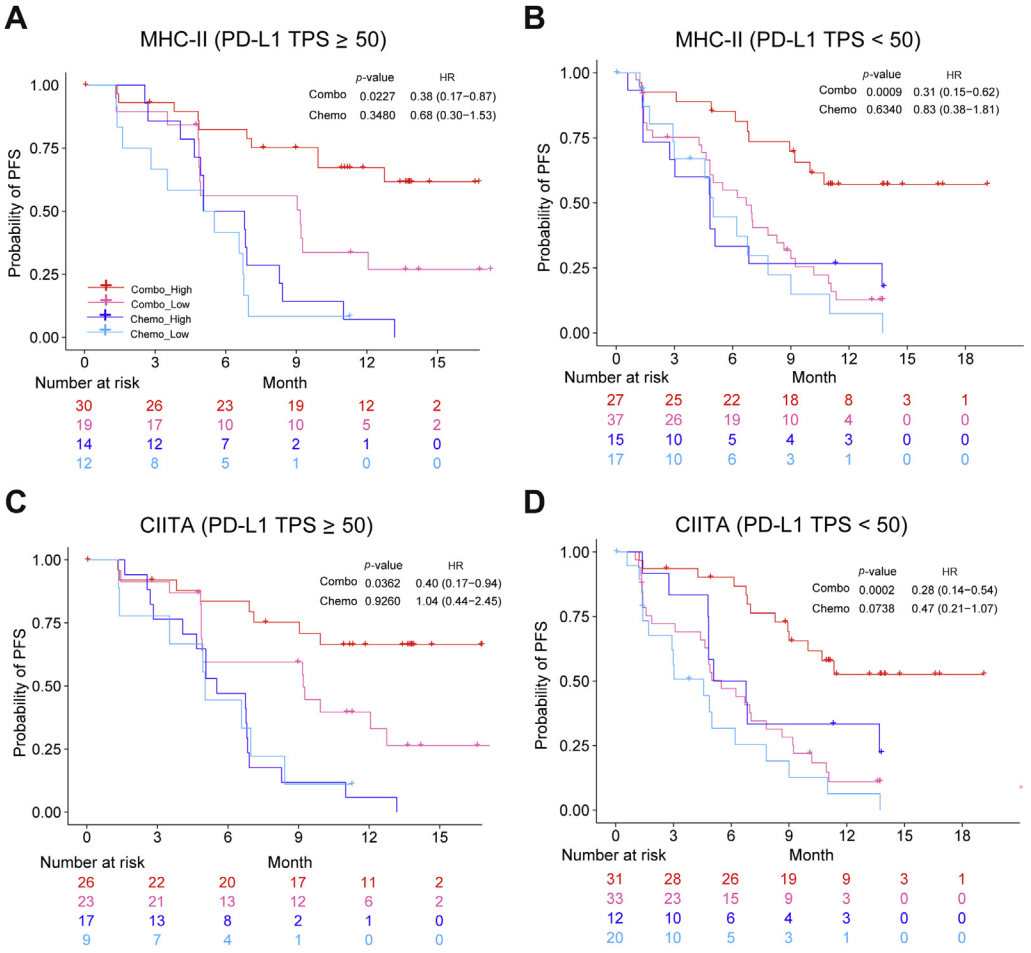

Figure 6. Association between PFS and MHC class II or CIITA expression in patients with different PD-L1 expression levels. PFS correlation of high and low MHC class II-related gene signature (split by median expression) in (*A*) PD-L1 high expression subgroup and (*B*) PD-L1 low expression subgroup is revealed. PFS correlation of high and low CIITA expression (split by median) in (*C*) PD-L1 high expression subgroup and (*D*) PD-L1 low expression subgroup is revealed. Chemo, chemotherapy treatment; Chemo_high (or Chemo_low), chemotherapy treatment and high (or low) expression level of respective marker; CIITA, class II transactivator; Combo, sintilimab plus chemotherapy combination treatment; Combo_high (or Combo_low), sintilimab plus chemotherapy combination treatment and high (or low) expression level of respective marker; MHC, major histocompatibility complex; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

of PFS and MHC class II expression in patients with greater than or equal to 50% PD-L1 expression in the combo treatment (HR = 0.38, $p = 0.0227$; Fig. 6*A*). In addition, in patients with less than 50% PD-L1 expression receiving combo treatment, high MHC class II expression was strongly associated with improved PFS (HR = 0.31, $p = 0.0009$; Fig. 6*B*). Similar results were observed for CIITA expression in predicting clinical outcome for patients receiving combination treatment with different levels of PD-L1 expression (Fig. 6*C* and *D* and Supplementary Fig. 7). Collectively, these findings supported the value of composite biomarker analysis of PD-L1 and MHC class II or CIITA, especially in patients with low or absent PD-L1 expression, who could still benefit from combination treatment in case of high MHC class II or CIITA expression.

Discussion

In this updated OS analysis of ORIENT-11 study, with approximately 14 more months of follow-up than in the interim analysis, the superior efficacy of sintilimab-combination treatment versus that of chemotherapy alone was confirmed. Of note, the OS benefit associated with the addition of sintilimab to chemotherapy occurred despite 45.8% of patients in the chemo group crossed over to receive sintilimab monotherapy after disease progression. These data strongly supported that sintilimab-combination treatment should be considered as front-line therapy for patients with previously untreated, locally advanced or metastatic nonsquamous NSCLC without EGFR or ALK genomic tumor aberrations. In addition, to the best of our knowledge, this is the first biomarker study to explore the association between

gene expression profile in the tumor microenvironment and the efficacy of immune-combination treatment in patients with NSCLC on the basis of a large randomized phase 3 trial. We found that high immune cell infiltration, particularly the infiltration of APCs and high expression of MHC class II antigen presentation pathway, significantly correlated with improved outcome in patients who underwent combination therapy. Compared with MHC class II, MHC class I antigen presentation pathway was less relevant in this combination setting. Collectively, these findings suggest that antigen presentation, particularly MHC class II pathway, is critical to gain clinical benefit from immune-combination treatment. These results might shed light into the mode of action of this combination therapy and highlight the potential value of MHC class II expression to select patients for immune-combination treatment.

It was generally thought that although "cold" tumors did not respond to PD-1 or PD-L1 monotherapy, the addition of chemotherapy could turn "cold" tumors into "hot" ones; thus, patients with "cold" tumors might still benefit from combination treatment.[20] Nevertheless, our data indicated that compared with chemotherapy alone, the clinical benefit from the combination of sintilimab with chemotherapy was only observed in patients with high or medium infiltration of immune cells, but not in those with low or absent infiltration. Chemotherapy could enhance immune response by means of several mechanisms such as induction of immunogenic tumor cell death and increased tumor-antigen release.[21,22] Surrounding APCs, such as dendritic cell and macrophages, may take up the dead cells and present antigens to T cells, that is, through MHC class II to CD4 T cells and cross present the MHC class I peptides to CD8 T cells, respectively. Thus, the benefit of chemotherapy might require the presence of preexisting adaptive immunity too. Our study revealed that chemotherapy in patients with low immune cell infiltration failed to sensitize the nonresponsive "cold" tumor to immunotherapy based. Novel strategies to overcome the absence of preexisting immunity in cold tumors warrant further exploration in future.

The importance of the antigen-processing machinery in immunotherapy has been documented in several cancers, including melanoma, classic Hodgkin's lymphoma, and NSCLC.[23–25] We also found that high infiltration of APCs strongly correlated with improved outcome in patients receiving combination therapy. Of note, although it was generally conceived that MHC class I or CD8-mediated immunity was critical for immunotherapy, our data suggested that MHC class II presentation was also very important in immune-combination therapy. In fact, our finding is in line with recent basic research revealing MHC class II binds a higher diversity of tumor antigens as compared with MHC class I,[26,27] thus tumor neoantigens were largely recognized by CD4+ T cells.[28,29] In addition, maintenance of functional CD8+ T cell memory required both CD4+ T cells and tumor cell expression of MHC class II neoantigen.[30]

To date, effective biomarkers to select patients who can benefit from immune-combination treatment remain lacking.[31] The predictive value of PD-L1 expression and TMB is limited: in both KEYNOTE-189 and KEYNOTE-407 studies, patients with low or absent PD-L1 expression and those with low TMB still derived PFS and OS benefits from immune-combination therapies.[1–4] Similarly, the PFS benefit from the combo treatment in this ORIENT-11 study was observed in patients with low or even negative PD-L1 expression if their MHC class II expression was high. Nevertheless, the combo treatment failed to improve clinical outcome in patients with both low PD-L1 and low MHC class II expression. These findings support the development of composite biomarkers consisting PD-L1 and MHC class II expression to enlarge the patient population that benefits from such a combination treatment but also could potentially spare toxicity from a patient population with limited treatment benefit.

This study had several limitations. First, the BEP population accounted for only approximately 50% of the ITT population. Although the baseline characteristics and prognosis were comparable between these two populations, selection bias could still exist in this study. Second, additional analyses for other important biomarkers such as TMB could not be performed owing to limited tumor samples. Third, the analysis was of retrospective and exploratory nature only; the sample set was not divided into a training and validation set owing to the limited sample size and would require additional validation using an independent data set. Finally, whether MHC class II expression could predict outcome in other patient populations or in patients treated with other combination strategies needs further exploration.

In conclusion, the addition of sintilimab to chemotherapy resulted in significantly longer OS than chemotherapy alone in nonsquamous NSCLC. This study also shed light on the important role of APCs and related pathways in cancer immunotherapy and highlighted the potential value of the MHC class II pathway for identifying patients who might benefit most from immune-combination treatment.

CrediT Authorship Contribution Statement

Yunpeng Yang: Conceptualization, Methodology, Formal analysis, Validation, Writing—Original Draft, Writing—Review and Editing.

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Hui Zhou, Shuyan Wang, Luyao Sun: Methodology, Formal analysis, Data Curation, Writing—Original Draft.

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Acknowledgments

The study was funded by Innovent Biologics, Inc., National Key Research and Development Program of the People's Republic of China (grant numbers 2016YFC0905500, 2016YFC0905503), the Chinese National Natural Science Foundation Project (grant numbers 82072558 and 81772476), and Medical Scientific Research Foundation of Guangdong Province (grant number C2018062). The authors thank all the patients, their families, investigators, and health care professionals who took part in this study.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.07.015.

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