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Five-year follow-up of neoadjuvant PD-1 inhibitor (sintilimab) in non-small cell lung cancer

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ABSTRACT

Background Neoadjuvant anti-programmed cell death protein-1 (PD-1) therapy exhibits potential in treating resectable non-small cell lung cancer (NSCLC). Previously, we have reported the 3-year clinical outcomes of this trial, implying the effectiveness and feasibility of neoadjuvant sintilimab monotherapy. However, the long-term prognosis of patients receiving neoadjuvant mono-immunotherapy has yet to be elucidated.

Methods For patients with stage IA-IIIB NSCLC, two doses of sintilimab (200 mg) were administered intravenously in the neoadjuvant setting. The 5-year event-free survival (EFS), disease-free survival (DFS), and overall survival (OS) were assessed in these updated results. The predictive role of specific biomarkers in neoadjuvant immunotherapy was also explored.

Results With a median follow-up of 61.0 months, 5-year DFS and OS rates of patients who underwent R0 resection were 65.7% and 80.4%, respectively. The 5-year DFS and OS rates of patients with positive programmed death-ligand 1 (PD-L1) expression were 71.9% and 90.9%, respectively. The presence of PD-L1 positivity (tumor proportion score ≥1%) showed a tendency toward the promising prognosis (OS, HR, 0.143; 95% CI: 0.027 to 0.743), especially for those who did not achieve pathological complete response (pCR). In addition, tumor mutation burden was positively correlated with a favorable prognosis. A total of 10 recurrences and 5 subsequent deaths were identified within the 5-year follow-up, with lung metastasis being the predominant.

Conclusions These updated analyses were the first to unveil the 5-year survival benefits of neoadjuvant sintilimab monotherapy, implying the potential value of PD-1 inhibitors in neoadjuvant therapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ For patients with non-small cell lung cancer (NSCLC) treated with neoadjuvant programmed cell death protein-1 inhibitor (sintilimab), 3-year overall survival (OS) and disease-free survival (DFS) rates are 88.5% and 75.0%, respectively. However, the long-term follow-up of these patients remains unknown.

WHAT THIS STUDY ADDS

⇒ The 5-year OS rate is 80.4% and the 5-year DFS rate is 65.7%, implying the long-term survival benefits of neoadjuvant sintilimab monotherapy for NSCLC. In addition, the 5-year OS and DFS rates of patients with positive programmed death-ligand 1 (PD-L1) expression are 90.9% and 71.9%, respectively, suggesting that the presence of PD-L1 positivity tended toward promising prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Our findings provide a novel insight into the survival benefits brought by sintilimab as a neoadjuvant treatment for patients with NSCLC, which may shed light on the clinical use of neoadjuvant mono-immunotherapy and the development of individualized therapeutic strategies.

INTRODUCTION

Over the past few decades, noteworthy advancements have been achieved in the treatment of non-small cell lung cancer (NSCLC).[1–3] However, the 5-year overall survival rates for patients with stage IB-IIIB NSCLC remain quite low (26–68%), highlighting significant room for improving the prognosis of patients.[4] For these patients, surgical excision may be insufficient and lead to a disappointing prognosis, necessitating additional therapeutic interventions.[5 6] Despite the administration of neoadjuvant chemotherapy, the 5-year survival rate for patients with NSCLC remains unsatisfactory.[7] Herein, it is of great importance to identify promising therapeutic regimens in the perioperative setting, which may improve the prognosis of patients with NSCLC.

The administration of immune checkpoint inhibitors (ICIs) has revolutionized the treatment paradigm of NSCLC, especially for patients with expression of immune-related biomarkers.[8] Although ICIs have provided unprecedented survival benefits to patients with NSCLC, numerous ongoing studies are underway to assess and compare the efficacy of various ICIs in a neoadjuvant setting, aiming to identify the most effective regimen.[9–13] The initial trial of the programmed cell death

protein-1 (PD-1) inhibitor, nivolumab, as neoadjuvant therapy demonstrated the safety and efficacy of this treatment approach, offering novel perspectives on perioperative management for NSCLC.[13] Subsequent investigations have explored the use of ICIs with chemotherapy as neoadjuvant treatment for NSCLC, resulting in a notable extension of survival time compared with neoadjuvant chemotherapy alone.[11 14] Since chemotherapy may lead to various adverse events and may be prematurely terminated, researchers have devoted efforts to exploring non-chemotherapy-based treatment strategies, with the goal of minimizing adverse events. However, the long-term prognosis of patients undergoing neoadjuvant mono-immunotherapy remains largely unknown, apart from findings from the CheckMate 159 trial, which poses great challenges for subsequent studies.[15]

Our group has previously revealed findings from the first trial involving neoadjuvant PD-1 inhibitor (sintilimab) for NSCLC in China, including the 3-year follow-up data, implying the feasibility and safety of this therapeutic strategy.[9 16] In the current report, we present long-term (5-year) clinical outcomes of patients, marking the longest follow-up period in China. Additionally, we have demonstrated the enduring predictive significance of biomarkers in patients with NSCLC undergoing neoadjuvant immunotherapy.

MATERIALS AND METHODS

Study design

The study design has been comprehensively described elsewhere (registration number: ChiCTR-OIC-17013726).[9 16] After enrollment, patients received two doses of intravenous sintilimab (200 mg) every 3 weeks as the neoadjuvant treatment. The specific imaging technique was used to evaluate the tumor size and other radiological characteristics at the baseline and after the second dose of the drug. We conducted the surgery for each patient 29–43 days after the second dose of intravenous sintilimab (200 mg). We performed positron-emission tomography plus contrast-enhanced CT to analyze standardized uptake value and tumor size at baseline and within 1 week before operation. Three different adjuvant therapies were available for each patient after the surgery, including conventional chemotherapy or chemoradiation therapy, sintilimab monotherapy, or sintilimab combined with chemotherapy. The choice of adjuvant therapy was discussed by a multidisciplinary board based on clinical conditions following surgery, adverse events (AEs) and response to sintilimab.[9] To evaluate the clinical condition, specific imaging techniques were used for each individual a month after the surgery.

Throughout the neoadjuvant treatment, we tracked the AEs experienced by each patient up to 3 months following the final administration. The multidisciplinary board assessed the AEs of each patient and determined their suitability for further treatment with sintilimab. All patients tolerated the neoadjuvant immunotherapy, and no patients were excluded. During the screening period, tumor samples for epidermal growth factor receptor (EGFR) assay were acquired through tissue biopsy. And tumor biomarkers were assessed by using the remaining samples from eligible patients. The protocol and its amendments underwent thorough review and approval by the Independent Ethics Committee. Before the initiation of any study procedures, all participating patients completed the required written informed consent forms.

Participants

Patients ranging in age from 18 to 75 years old, diagnosed with stage IA-IIIB NSCLC were enrolled. Patients were treatment-naive and had adequate organ function. The Eastern Cooperative Oncology Group (ECOG) performance status of each patient was 0. The diameter of the primary tumor of each eligible patient was more than 2 cm. Exclusion criteria included patients with any existing malignant tumor, history of allogeneic organ transplantation or hemopoietic stem cell transplantation, coagulation disorders necessitating warfarin treatment, active autoimmune diseases, uncontrolled and active infection, uncontrolled hypercalcemia, uncontrolled hypertension, grade III–IV congestive heart failure, EGFR-sensitive mutations, prior antitumor treatment, history of interstitial lung disease, hypersensitivity to monoclonal antibodies, systemic immunosuppressive therapy within 1 month before the treatment in this trial, embolism, ischemia, or artery thrombosis within 6 months before the treatment in this trial.

Assessments and endpoints

The survival status of each patient was consistently followed at 3-month intervals following the cessation of treatment. We used contrast-enhanced CT for postoperative evaluation every 3 months until loss to follow-up, disease progression, metastasis, death or 2 years after surgery. The annual radiographic tumor assessment was performed for each patient 3 years after surgery. AEs were monitored throughout the follow-up periods. Here, we updated the primary analyses of the long-term prognosis of patients in this exploratory trial, including the event-free survival (EFS), disease-free survival (DFS), and overall survival (OS) rates at 12, 36, and 60 months. Moreover, we performed the survival analyses in subgroups determined by the programmed death-ligand 1 (PD-L1) status, tumor mutation burden (TMB), pathological regression rate, tumor stage, and pathological type. We used immunohistochemical staining to detect PD-L1 expression with primary antibodies to PD-L1 (CST13684S), which has been described in previous publications.[9 16] The method for TMB evaluation was described in our previous publication.[17] TMB was measured in mutations per Mb.

Statistical analyses

This study is an exploratory, single-arm investigation for which a formal sample size calculation was not performed. Based on insights from prior exploratory studies, we

enrolled a total of 40 patients. The Kaplan-Meier method was employed to estimate 5-year EFS, DFS, and OS rates. Patients were classified into subgroups defined by specific characteristics, such as PD-L1 expression, pathological regression rates, and TMB. The comparison of EFS, DFS, and OS between different subgroups was performed through the log-rank test. We used the Cox proportional hazard model to determine survival probabilities and calculate HRs for different subgroups. All p values<0.05 were considered statistically significant.

RESULTS

Patients enrollment

From March 6, 2018, to March 8, 2019, a total of 40 eligible patients with NSCLC were finally enrolled in this trial. Among the patients in our trial, 33 patients (82.5%) were men and 7 patients were women (17.5%); 8 patients (20.0%) never smoked; 8 patients (20.0%) had stage I disease, others (80.0%) had stage II and III disease; 36 patients (90.0%) received R0 resection, 1 patient (2.5%) received R2 resection and 3 patients (7.5%) did not undergo the following surgery; 33 patients (82.5%) had lung squamous cell carcinoma, and 7 patients had other pathological subtypes, including lung adenocarcinoma (15.0%) and lung adenosquamous carcinoma (2.5%); lymph node involvement was detected in 25 patients (62.5%) at baseline; data of PD-L1 expression were available in 32 patients (80%), including 10 and 22 patients with negative and positive PD-L1 expression, respectively (online supplemental table S1).

Safety and recurrence

We have identified neoadjuvant treatment-related adverse events (TRAEs) in 21 patients and AEs in 22 patients, which were previously reported in detail.[9 16] Since TRAEs and AEs were reported in our initial publication, no new events were identified during the 5-year follow-up.[9] Among 14 patients, we have observed 22 postoperative complications. Two patients died shortly after the operation due to severe AEs: immune-related pneumonia following the surgery led to the death of one patient, and disturbance of consciousness following the surgery led to the death of the other. Compared with recurrences in the publication reporting clinical outcomes of 3-year follow-up, two more recurrences were identified, including a patient with lung metastasis and a patient with lymph node metastasis.[16] Recurrences were observed in 10 patients (27.8%) during the 5-year follow-up period, comprising 4 patients with lung metastasis, 3 with brain metastasis, 1 with bone metastasis, 1 with lymph node metastasis, and 1 with local recurrence. Among these 10 patients, metastases were observed in 6 patients (60.0%) within 1–3 years after the operation, whereas metastases were observed in 3 patients (30.0%) 3 years after the operation (figure 1).

Survival time

In this trial, 40 patients were enrolled, with a median follow-up time of 61.0 months (range: 1.73–70.8 months), and 36 patients with R0 resection were eligible for the following survival analyses. In the 5-year follow-up, 7 patients died and metastases were identified in 10 patients. The 5-year DFS rate was 65.7% (95% CI: 51.6% to 83.6%)

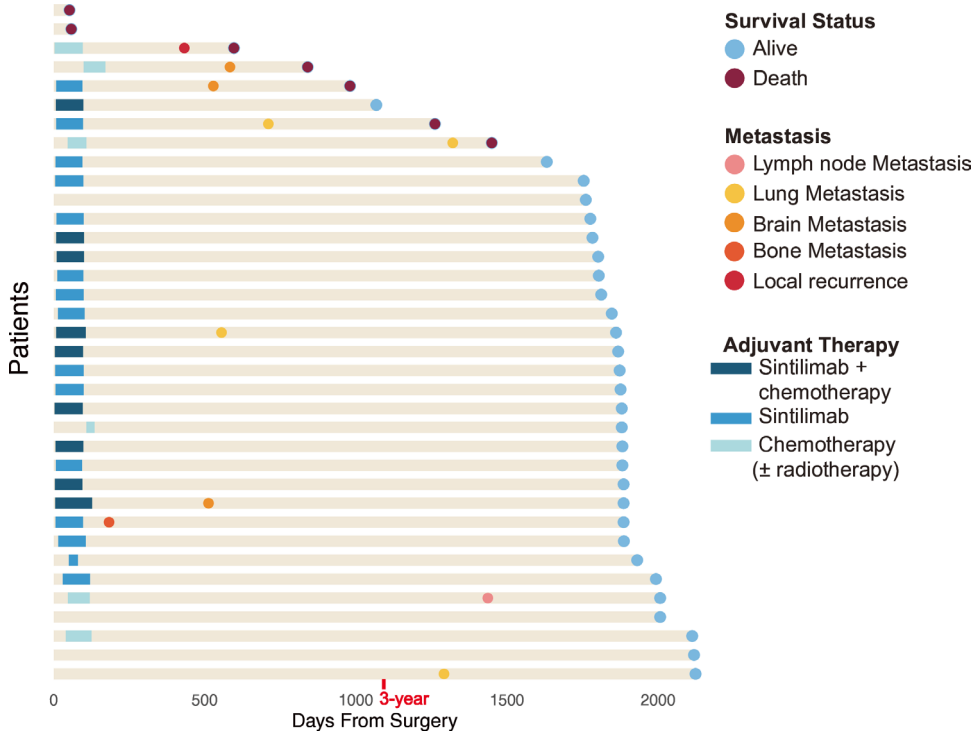

Figure 1 Survival status, metastasis and type of adjuvant therapy of 36 patients with non-small cell lung cancer who received R0 resection after ≥3 years of follow-up.

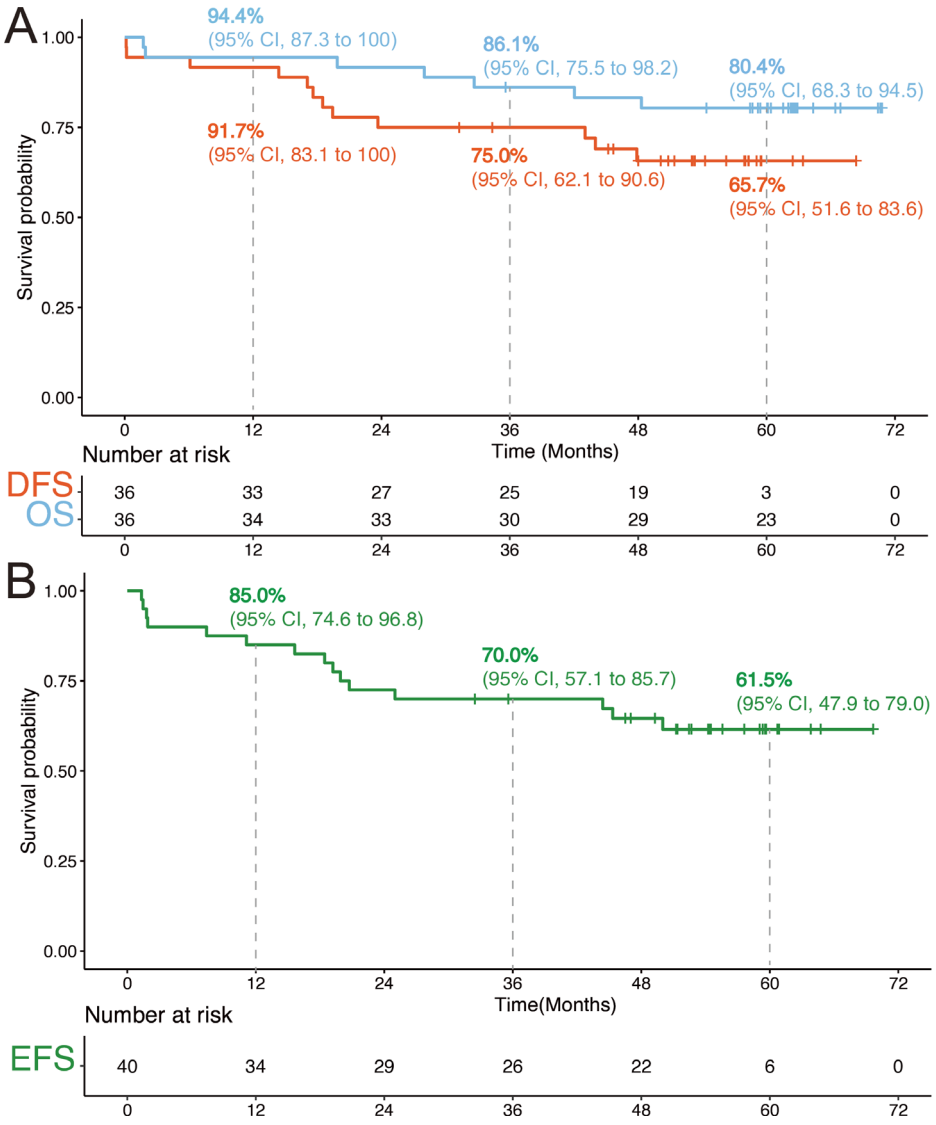

Figure 2 Overall survival, disease-free survival and event-free survival among patients in the study. (A) Overall survival and disease-free survival of 36 patients with R0 resection. (B) Event-free survival of 40 patients in the study. DFS, disease-free survival; EFS, event-free survival; OS, overall survival.

and the 5-year OS rate was 80.4% (95% CI: 68.3% to 94.5%) in the 36 patients with R0 resection (figure 2A). For participants with PD-L1 expression, updated results from the 5-year follow-up revealed one additional patient death and two additional recurrences compared with the results from our previous publication. Among the tumor proportion score (TPS)≥1% population, the 5-year DFS rate was 71.9% (95% CI: 55.0% to 93.9%) and the 5-year OS rate was 90.9% (95% CI: 79.7% to 100%) (online supplemental figure S1A). For EFS of all 40 patients in this trial, the 5-year EFS rate was 61.5% (95% CI: 47.9% to 79.0%) (figure 2B). And in TPS≥1% population, the 5-year EFS rate was 71.5% (95% CI: 54.5% to 93.9%) (online supplemental figure S1B).

Subgroup analysis

The prognostic value of specific biomarkers in different subgroups was analyzed. As the traditional predictive biomarker of immunotherapy, we have classified patients into various subgroups (TPS<1% and ≥1%, TPS<10% and ≥10%, TPS<50% and ≥50%). Consistent with our previous publication, patients with TPS≥1% had a significantly better prognosis than those with TPS<1%.[16] In this updated analysis with the 5-year follow-up, patients with TPS≥1% had relatively longer DFS than those with TPS<1% (HR, 0.364 (95% CI: 0.117 to 1.135); log-rank p=0.069; figure 3A). We have also observed a relatively longer EFS in patients with TPS≥1% (HR, 0.366 (95% CI: 0.117 to 1.141); log-rank p=0.071; figure 3B). Furthermore, our findings revealed that OS was significantly longer in patients with TPS≥1% than in TPS<1% population (HR, 0.143 (95% CI: 0.027 to 0.743); log-rank p=0.0074), suggesting that TPS≥1% may serve as an important indicator for OS benefits (figure 3C). Ricciuti *et al* have revealed that patients with very strong PD-L1 expression (TPS≥90%) experienced the greatest benefit from ICIs in advanced NSCLC.[18] In our cohort,

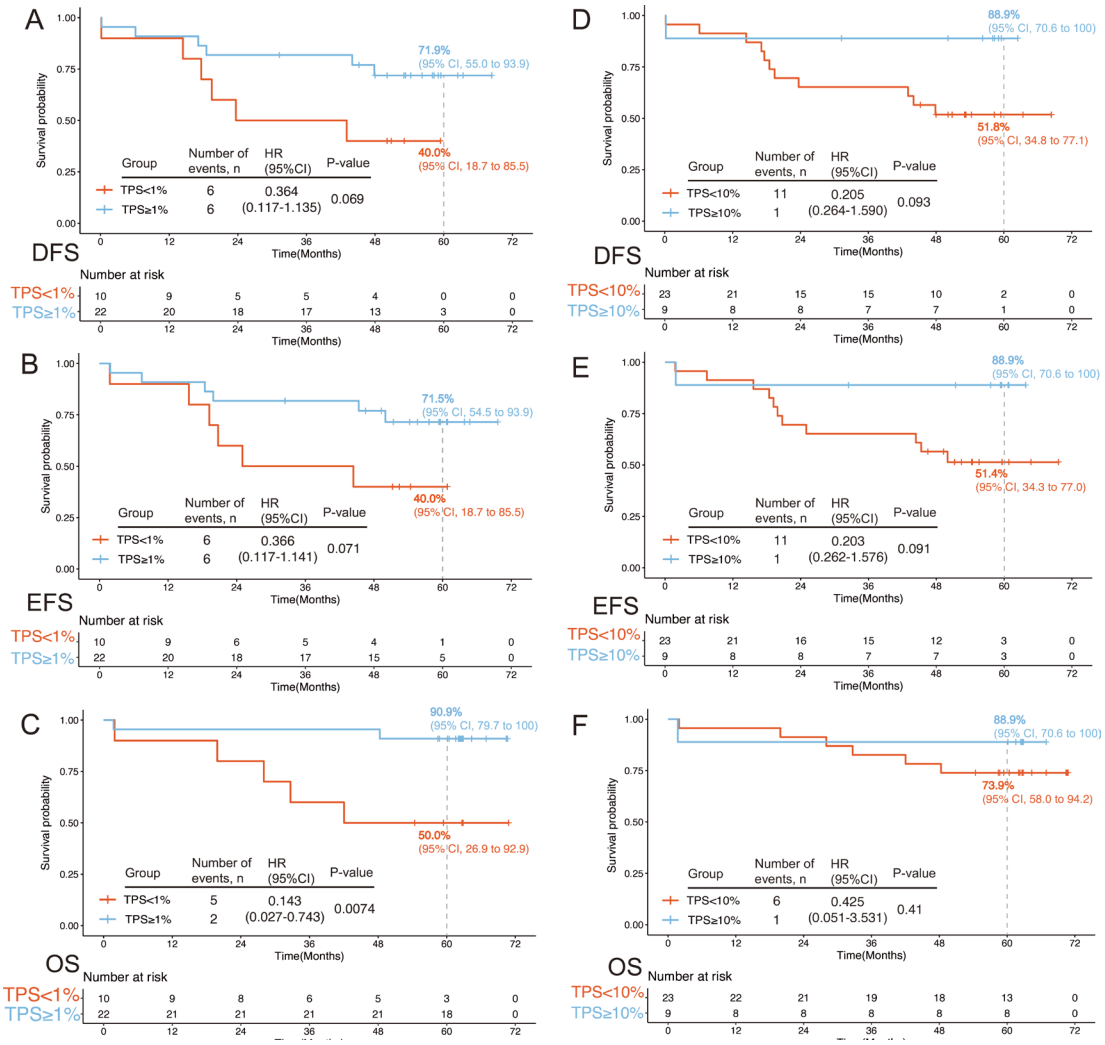

Figure 3 Disease-free survival, event-free survival and overall survival among patients with PD-L1 expression. (A–C) Disease-free survival (A) and event-free survival (B) and overall survival (C) among patients with PD-L1 TPS<1% or ≥1%. (D–F) Disease-free survival (D) and event-free survival (E) and overall survival (F) among patients with PD-L1 TPS<10% or ≥10%. DFS, disease-free survival; EFS, event-free survival; OS, overall survival; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

two patients exhibited very strong PD-L1 expression (TPS≥90%). Next, we compared the prognosis of patients between TPS≥10% and TPS<10% populations. Similar to the findings in the TPS≥1% population, patients with TPS≥10% demonstrated a more favorable prognosis than those with TPS<10% (DFS, HR, 0.205 (95% CI: 0.264 to 1.590); log-rank p=0.093, figure 3D–E). However, no significant OS benefits were observed in the TPS≥10% population (figure 3F). And no significant difference in prognosis was identified between subgroups with a cut-off value of 50% (online supplemental figure S2).

In addition to PD-L1, we evaluated the prognostic value of other biomarkers. For TMB, we have selected a cut-off value of 10 to stratify patients into different subgroups. According to the results, the DFS and EFS of patients in the TMB-high subgroup were relatively longer than those in the other subgroup (online supplemental figure S3A,B), suggesting a potential correlation between high TMB levels and favorable clinical outcomes. Pathological responses may serve as potential indicators for patient prognosis. Our findings revealed that patients who achieved major pathologic responses (MPR) had a longer survival time than those who did not (online supplemental figure S3C,D). The 5-year clinical outcomes suggested that MPR was a better predictor of prognosis compared with the results obtained with a 3-year follow-up. Regarding pathological complete response (pCR), although we did not observe significant differences in clinical outcomes between patients who achieved pCR and those who did not, the 5-year DFS and EFS rates were relatively higher among patients who achieved pCR (online supplemental figure S3E,F).

Except for one patient who achieved pCR and subsequently died because of immune-related pneumonitis shortly after the surgery, no recurrence was observed in the remaining patients of the pCR subgroup, indicating a promising prognosis for patients who achieved pCR. Herein, predictive biomarkers for patients with residual tumors (non-pCR subgroup) may hold greater significance. Among patients in the non-pCR subgroup, those

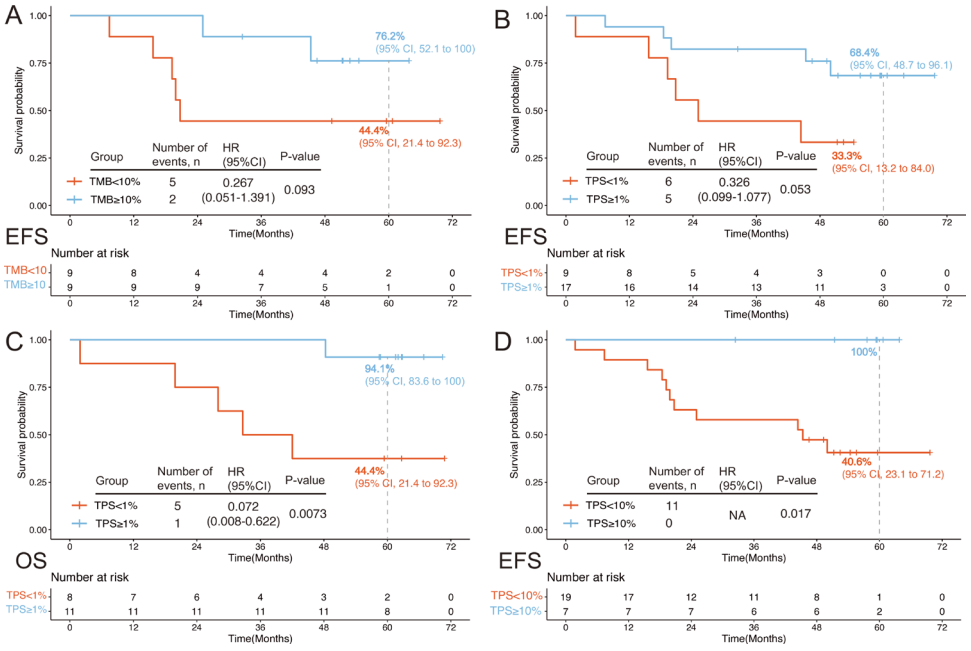

Figure 4 Event-free survival and overall survival among patients who do not achieve pathological complete regression. (A) Event-free survival among patients with TMB<10 or ≥10 in the non-pCR subgroup. (B–C) Event-free survival and overall survival among patients with TPS<1% or ≥1% in the non-pCR subgroup. (D) Event-free survival among patients with TPS<10% or ≥10% in the non-pCR subgroup. EFS, event-free survival; pCR, pathological complete response; TMB, tumor mutation burden; TPS, tumor proportion score.

with high TMB tended to have a more promising prognosis than those with low TMB (figure 4A, online supplemental figure S4A). Furthermore, we found that PD-L1 expression had more predictive value in patients with residual tumors compared with the overall patient population, especially for cut-off values of 1% and 10%. The clinical outcomes of patients with positive PD-L1 expression (TPS≥1%) were more favorable than the other (figure 4B, online supplemental figure S4B), and the OS benefit was statistically significant (HR, 0.072 (95% CI: 0.008 to 0.622); log-rank p=0.0073; figure 4C). No recurrence was observed in TPS≥10% population, highlighting the significant role of PD-L1 in predicting prognosis in the non-pCR population (EFS, log-rank p=0.017, figure 4D; DFS, log-rank p=0.018; online supplemental figure S4C).

Furthermore, we have evaluated the potential of TMB and PD-L1 in predicting the prognosis of non-MPR population. While TMB was not significantly associated with patients' clinical outcomes, PD-L1 demonstrated good predictive performance in this subgroup (online supplemental figure 4D). Subgroups were also categorized based on tumor stage and histological type. Patients with stage III disease tended to have worse clinical outcomes than those with stage I or stage II disease, suggesting that tumor stage may be a prognostic factor for neoadjuvant immunotherapy (online supplemental figure 5A and C). However, statistical significance was not achieved in both analyses based on DFS and OS. And better prognosis was observed in patients with lung squamous cell carcinoma than in those with lung adenocarcinoma (online supplemental figure S5B and D). Similar to the subgroup analyses of the disease stage, the findings indicated no notable differences between the two arms across various histological types.

DISCUSSION

To our knowledge, sintilimab exhibits a favorable long-term survival probability for NSCLC. This study is the inaugural published trial of neoadjuvant mono-immunotherapy with long-term follow-up in China, providing a median follow-up time of 61.0 months. At 5 years, approximately 80.4% of patients were alive and 65.7% were free of disease progression and alive. Furthermore, during the 5-year follow-up, no newly observed TRAEs were observed, indicating sustained long-term safety following the administration of neoadjuvant sintilimab. Our findings suggested that patients expressing PD-L1 may benefit from neoadjuvant mono-immunotherapy, particularly those who did not achieve pCR. This updated report is the first to present the 5-year clinical outcomes of neoadjuvant mono-immunotherapy in China, providing innovative insights into the administration of PD-1 inhibitors in perioperative settings.

Neoadjuvant chemoimmunotherapy has been regarded as the most prevalent perioperative therapeutic strategy for NSCLC, and some clinical trials have revealed the long-term follow-up of patients who underwent the treatment, such as CheckMate 816[12] and KEYNOTE-671.[11] Due to the high incidence of side effects of chemotherapy, the present study was designed to evaluate the efficacy of neoadjuvant mono-immunotherapy for patients with NSCLC. The safety and feasibility of neoadjuvant sintilimab monotherapy have been shown in the first publication of

this trial, with 40.5% and 16.2% of patients achieving MPR and pCR, respectively.[9 16] In the current report, we have noted the 5-year OS rate of 80.4% and 5-year DFS rate of 65.7%, suggesting that neoadjuvant sintilimab treatment may contribute to extending survival time for patients with NSCLC in the long-term observation. The long-term clinical outcomes are probably connected to the unique mechanisms of PD-1 inhibitors, distinguishing them from conventional chemotherapy.[19] According to the latest reports of the CheckMate 159 trial, patients with NSCLC who underwent neoadjuvant nivolumab monotherapy achieved 5-year OS and recurrence-free survival rates of 80% and 60%, respectively.[15] Despite the similar 5-year OS rates, our trial had a higher proportion of patients in advanced stages (stage IIIA and IIIB, 45.0%) compared with CheckMate 159 (stage IIIA, 33.0%), implying the great efficacy of neoadjuvant sintilimab monotherapy. Another study presented the 3-year survival rate of patients receiving neoadjuvant atezolizumab monotherapy, and this rate was comparable to the 5-year OS rate observed in our trial.[20] Felip *et al* have revealed the 3-year OS rate (81.1%) for patients with NSCLC receiving the PD-L1 inhibitor as adjuvant treatment (IMpower010), which was relatively lower than that in our cohort, implying that neoadjuvant treatment may be more efficient.[21] Our updated results revealed that sintilimab as the neoadjuvant treatment could also "lift the tail of the survival curve" of patients with NSCLC, showing its sustained effectiveness for locally advanced NSCLC.

With the increasing prevalence of immunotherapy, the predictive role of various biomarkers has been extensively explored and verified.[17 22–24] PD-L1, as one of the most popular biomarkers, has shown contrasting value in predicting responses and prognosis in patients with NSCLC undergoing immunotherapy.[25–27] These updated results revealed that PD-L1 could serve as a long-term prognostic factor for patients with NSCLC who underwent neoadjuvant mono-immunotherapy.[9 16] For example, clinical outcomes of the TPS≥1% population tended to be more promising compared with those with PD-L1<1%, especially in terms of OS. For subgroups stratified by 10%, the difference between the two subgroups was more significant with the 5-year follow-up than the 3-year follow-up.[16] Besides, survival benefits were shown in individuals with high PD-L1 expression when we stratified patients by 50%. Despite the statistical significance was not achieved, the trends were more obvious in the analyses of the long-term follow-up compared with the short-term follow-up. As demonstrated in our previous publications, the limited size of the cohort and a case of pneumonitis-related death (low-incidence but life-threatening) shortly after surgery in the high PD-L1 expression subgroup might contribute to the lack of statistical significance.[16 28] However, excluding individuals who died of pneumonia, the survival advantage remained noteworthy in patients with high expression of PD-L1.

The role of TMB as a predictive biomarker for immunotherapy remains controversial in NSCLC.[29–31] Our previous findings suggested that TMB≥10 tended to be positively correlated with improved prognosis, particularly in terms of EFS.[16] In the current analyses with the long-term follow-up, patients in the high-TMB subgroup exhibited a higher survival probability than those in the low-TMB subgroup. Interestingly, our findings contrast with the updated results of CheckMate 159 trial, which revealed that TMB was not correlated with improved OS or recurrence-free survival (RFS).[15] The relatively small size of our cohort may have contributed to the biases in the analyses, leading to divergent outcomes between our trial and the CheckMate 159 trial, both of which involved neoadjuvant mono-immunotherapy. In another study investigating neoadjuvant atezolizumab monotherapy for patients with NSCLC, a positive correlation was observed between TMB and pCR, suggesting the potential utility of TMB as a predictor for responses to neoadjuvant mono-immunotherapy in NSCLC.[20]

Pathological regression rates serve as crucial indicators for predicting the prognosis of patients receiving neoadjuvant treatment.[32] Generally, patients who achieve pCR tend to have favorable clinical outcomes, whereas those with residual tumors (non-pCR) have a poorer prognosis.[33] The necessity of adjuvant therapy for patients who achieve pCR after neoadjuvant treatment remains highly controversial. Due to the limited number of patients in this study, we were unable to characterize this subgroup of patients, highlighting the need for further studies with a large number of patients to explore the efficacy of adjuvant therapy. For those with residual tumors, a total of 10 recurrences were identified over the 5-year follow-up period, emphasizing the essential role of biomarkers in predicting recurrences for these patients. As noted in our results, OS benefits were significantly observed in non-pCR patients with PD-L1≥1%, and no recurrence was identified in those with PD-L1≥10%. Herein, we believe that PD-L1 may play a more crucial role in predicting the prognosis of non-pCR patients than that of all patients. Nevertheless, the mechanisms underlying the role of these biomarkers in non-pCR patients remain to be explored.

There are some limitations in the present study that may affect the accuracy of our conclusions. First, the small cohort size of the trial increases the susceptibility to random events, potentially affecting the robustness of our findings. For example, some subgroups consisted of fewer than 10 patients, potentially introducing bias when comparing differences among patients in these subgroups. Second, patients received various adjuvant therapies in this trial, which might result in potential bias in the long-term follow-up. In the future, large-scale and randomized trials are warranted to corroborate the conclusions drawn in this report, offering innovative insights into the administration of neoadjuvant immunotherapy.

CONCLUSIONS

To sum up, these updated results suggest that neoadjuvant mono-immunotherapy results in a favorable long-term prognosis and a low incidence of AEs in patients with NSCLC. Although the effectiveness of ICIs combined with chemotherapy has been demonstrated in the preoperative setting, the administration of single-agent ICIs prior to surgery should also be regarded as a viable option for NSCLC. However, the efficacy of neoadjuvant mono-immunotherapy warrants further investigation and validation through large-scale randomized trials.

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Contributors BZ: Conceptualization, Project administration, Writing—Original Draft, Writing—Review and Editing. FZ: Conceptualization, Supervision, Project administration, Writing—Review and Editing. WG: Investigation, Resources, Data Curation, Writing—Review and Editing. SW: Investigation, Resources, Data Curation. NL: Investigation, Resources, Data Curation. BQ: Term, Methodology, Validation. LZ: Term, Methodology, Validation. JL: Methodology, Software, Visualization. KS: Methodology, Software, Visualization. QX: Methodology, Software, Visualization. FL: Conceptualization, Supervision, Project administration. SG: Conceptualization, Supervision, Project administration, Funding acquisition. SG accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests The authors report no conflict of interest.

Patient consent for publication All authors agree to the publication of this article

Ethics approval This study involves human participants and was approved by Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (17-151/1407). Participants gave informed consent to participate in the study before taking part.

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