Sintilimab with chemotherapy as first-line treatment for locally advanced or metastatic squamous non-small-cell lung cancer: a real-world data study

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Abstract
Purpose The ORIENT-12 study demonstrated the promising results of sintilimab combined with gemcitabine and platinum (GP) therapy in squamous non-small-cell lung cancer (sqNSCLC) patients. However, the efficacy of sintilimab plus paclitaxel/nab-paclitaxel and platinum (TP) in sqNSCLC is not yet known.
Methods Real-life data were retrospectively collected from patients with untreated locally advanced or metastatic sqNSCLC who were treated with sintilimab plus TP (arm A) or sintilimab plus GP (arm B) between January 2019 and January 2021. Baseline characteristics, the efficacy of sintilimab, and adverse events were analyzed.
Results A total of 52 patients were included (arm A, n = 32 and arm B, n = 20). The overall response rate was 59.4% in arm A and 40.0% in arm B. The median progression-free survival was 13.9 months (95% confidence interval [CI], 6.9–21.0) in arm A and 8.5 months (95% CI, 6.9–10.2) in arm B (hazard ratio [HR], 0.61; 95% CI, 0.30 to 1.25; p = 0.18). The median overall survival was 21.3 months (95% CI, 13.4–29.3) in arm A and 13.3 months (95% CI, 9.1–17.5) in arm B (HR, 0.62; 95% CI, 0.28–1.36; p = 0.23). Adverse events of grade 3 or higher occurred in 37.5% of the patients in arm A and 55.0% of the patients in arm B.
Conclusions Sintilimab-TP may have similar clinical benefits compared with sintilimab-GP in patients with untreated advanced or metastatic sqNSCLC. These results require further validation by prospective randomized controlled studies.

Keywords Squamous non-small-cell lung cancer · Sintilimab · Chemotherapy · Real world

Abbreviations
GP Gemcitabine + platinum
sqNSCLC Squamous non-small-cell lung cancer
TP Paclitaxel/nab-paclitaxel and platinum
PFS Progression-free survival
HR Hazard ratio
CI Confidence interval
PD-1 Programmed cell death protein 1
PD-L1 Programmed cell death-ligand 1
ORR Objective response rate
ICIs Immune checkpoint inhibitors
EGFR Epidermal growth factor receptor
ALK Anaplastic Lymphoma Kinase
RECIST Response Evaluation Criteria in Solid Tumors
CR Complete response
PR Partial response
DCR Disease control rate
SD Stable disease
TTR Time to response
OS Overall survival
AEs Adverse Events
irAEs Immune-mediated adverse events

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Introduction

Primary lung cancer is the second most commonly diagnosed cancer with the highest mortality, worldwide (Sung et al. 2021). Squamous non-small cell lung cancer (sqNSCLC) accounts for 20–30% of all lung cancers (Socinski et al. 2016). Antiangiogenesis therapy and targeted therapy can significantly prolong the survival time of non-squamous NSCLC, while they demonstrate moderate benefits for sqNSCLC (Wang and Li 2016). Immune checkpoint inhibitors (ICIs) including programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors significantly improve the outcomes of patients with sqNSCLC (Chen et al. 2019). The phase 3 CheckMate 017 study (Brahmer et al. 2015) demonstrated that nivolumab monotherapy, which was used as a second-line therapy compared with docetaxel treatment, remarkably improved treatment efficacy in patients with advanced sqNSCLC. Subsequently, the KEYNOTE-024 (Reck et al. 2016) and KEYNOTE-042 (Mok et al. 2019) studies confirmed the clinical benefit of ICI monotherapy in the first-line treatment of NSCLC regardless of the histological subgroups. However, the objective response rate (ORR) of ICI monotherapy was unsatisfactory and was related to the expression level of PD-L1. Novel therapies that improve response and long-term efficacy are urgently required. The antitumor efficacy of ICIs with paclitaxel/nab-paclitaxel and platinum as the first-line treatment of sqNSCLC has been confirmed by a series of studies, such as KEYNOTE-407 (Paz-Ares et al. 2018), IMpower131 (Jotte et al. 2020), and RATIONALE 307 (Wang et al. 2021).

Sintilimab is a highly selective, fully human monoclonal antibody that blocks the interactions of PD-1 and its ligands and possesses a strong antitumor response (Zhang et al. 2020). The ORIENT-12 (NCT03629925) was a randomized, double-blind, phase III study, which indicated that sintilimab combined with gemcitabine and platinum (GP) treatment significantly prolonged progression-free survival (PFS) compared with that of GP as the first-line treatment of locally advanced or metastatic sqNSCLC (median PFS: 5.5 months vs. 4.9 months; hazard ratios [HR], 0.536; 95% confidence intervals [CI], 0.422–0.681; \( p < 0.00001 \)) (Zhou et al. 2021). Paclitaxel/nanoparticle albumin-bound [nab]–paclitaxel and platinum (TP) are the standard regimens for first-line treatment of sqNSCLC. However, the efficacy of sintilimab combined with paclitaxel/nab-paclitaxel and platinum in sqNSCLC is not yet known.

The present study aimed to investigate the efficacy and safety of sintilimab with chemotherapy (paclitaxel/nab-paclitaxel + platinum or gemcitabine + platinum) in real-world patients with locally advanced or metastatic sqNSCLC.

Materials and methods

Patients

The present study was a retrospective study conducted at the First Affiliated Hospital of Guangzhou Medical University. The medical records of consecutive patients who received their initiated therapy between January 2019 and January 2021 were reviewed. Records for patients with sqNSCLC (according to the 2015 World Health Organization classification) without sensitizing epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations, incurable stage IIIB-IV tumors [according to the 8th edition AJCC/IASLC classification (Goldstraw et al. 2016)], and at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Eisenhauer et al. 2009) were reviewed. Patients who were treated with sintilimab plus paclitaxel/nab-paclitaxel and platinum (sintilimab-GP, arm A) or sintilimab plus gemcitabine and platinum (sintilimab-GP, arm B) in the first line were included. Patients younger than 18 years old, who had received previous therapies for locally advanced or metastatic disease, or had the active autoimmune disease were excluded.

Data collection and outcome assessment

The patient data were collected retrospectively from medical files and included patient demographics, the Eastern Cooperative Oncology Group (ECOG) performance status (PS), PD-L1 expression levels, tumor response to ICIs, and adverse events (AEs).

The ECOG PS was evaluated prior to treatment initiation. The tumor image was performed every two or three cycles during treatment. The evaluations of the clinical responses were performed by investigators according to the RECIST version 1.1. ORR was defined as the proportion of patients achieving complete response (CR) and partial response (PR). The disease control rate (DCR) corresponds to all cases with CR, PR, and stable disease (SD). The time to response (TTR) was defined as the time from the initiation of sintilimab to the first documented CR or PR. PFS was estimated as the duration from the initiation of sintilimab to disease progression or patient death. The overall survival (OS) was defined as the time from the initiation of sintilimab to patient death. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). PFS was the primary endpoint. OS, ORR, DCR, and TTR were the secondary endpoints. The final follow-up time was October 31, 2021.
Statistical analysis

The clinical and tumor characteristics were summarized as medians and ranges for continuous variables and as frequencies and percentages for categorical variables. An independent-samples t test or the Mann–Whitney U test was used to analyze continuous variables. The differences in the continuous variables were assessed using either the Chi-square (χ²) or Fisher’s exact test. The Kaplan–Meier survival estimates were calculated for PFS and OS with 95% CI and the log-rank test was used to evaluate between-group differences. The follow-up time was estimated using the reverse Kaplan–Meier method. Cox regression was applied to calculate the HR with a 95% CI of factors associated with PFS. All P values were based on the two-sided hypothesis test and a p value < 0.05 was considered to indicate statistically significant differences. All analyses were conducted using IBM SPSS Statistics (Armonk, NY), version 25.

Results

Patients

In total, 52 patients were eligible and enrolled in the present study. The median age of all patients was 61 (range, 46–84) years. The majority of the patients were men (88.5%) and exhibited ECOG PS of 1 (75.0%) (Table 1). At the time of diagnosis, 21 (40.4%) patients were stage IV, and 31 patients (59.6%) had stage IIIB/IIIC disease.

Arm A (sintilimab-TP) included 32 (61.5%) patients and arm B (sintilimab-GP) 20 (38.5%). In arm A, 20 patients received nab-paclitaxel and 12 received paclitaxel. Baseline demographic and disease characteristics exhibited no significant differences between the groups (Table 1). A median of 4 doses (range, 1–20) of arm A and 6 doses (range, 3–34) of arm B was used.

Efficacy

The overall median follow-up for this analysis was 20.4 months. The confirmed ORR was 59.4% (95% CI, 41.4–77.4) in arm A and 40.0% (95% CI, 16.5–63.5) in arm B (p = 0.24; Table 2 and Fig. 1). In addition, 6.4% of the patients who received sintilimab-TP and 5.0% of those who received sintilimab-GP exhibited disease progression (Table 2 and Fig. 1). The DCR was 93.8% in arm A and 95.0% in arm B. The median TTR was 2.0 months (range: 0.8–6.7) with arm A and 1.9 months (range: 0.7–3.0), respectively (Table 2).

A total of 30 events of progression or death were noted and the median PFS was estimated to 13.9 months (95% CI, 6.9–21.0) in arm A and 8.5 months (95% CI, 6.9–10.2) in arm B (HR for PFS, 0.61; 95% CI, 0.30–1.25; p = 0.18; Fig. 2a). The 12-month PFS rate was 50.9% with TP and 31.9% with GP. Across subgroups that were analyzed, the two treatment groups exhibited similar PFS benefits (Fig. 2b). However, male patients (HR, 0.50 [95% CI, 0.24–1.06]; p = 0.071) and patients with PD-L1 expression level of 1–49% (HR, 0.29 [95% CI, 0.08–1.07]; p = 0.062) tended to benefit from arm A over arm B (Fig. 2b).

The median OS was 21.3 months (95% CI, 13.4–29.3) in arm A and 13.3 months (95% CI, 9.1–17.5) in arm B (HR, 0.62; 95% CI, 0.28–1.36; p = 0.23) (Fig. 3a), with a total of 25 events in the treatment population. The OS rate at 1 year was 77.2% in arm A and 68.5% in arm B. Across all subgroups that were analyzed, arm A showed better OS benefits than arm B in the subgroup with PD-L1 expression of 1–49% (HR, 0.15 [95% CI, 0.03–0.83]; p = 0.030) (Fig. 3b).

Table 1 Characteristics of patients at baseline

| Characteristics | Arm A (N=32) | Arm B (N=20) | p value |
|-----------------|--------------|--------------|---------|
| Age (years)     | Median (range) 63(46–84) | 58 (47–77) | 0.62 |
| <60, n (%)      | 11 (34.4) | 11 (55.0) | 0.16 |
| Sex (male/female) | 29/3 | 17/3 | 0.66 |
| Smoking status, n (%) | 16 (50.0) | 14 (70.0) | 0.16 |
| Current/former  | 16 (50.0) | 6 (30.0) | |
| ECOG PS, n (%) | 0 | 8 (25.0) | 5 (25.0) | 1 |
| 1               | 24 (75.0) | 15 (75.0) | |
| Disease status, n (%) | 21 (65.6) | 10 (50.0) | |
| IIIB/IIIC       | 11 (34.4) | 10 (50.0) | |
| PD-L1 TPS, n (%) | 0% | 6 (18.7) | 4 (20.0) | 0.73 |
| <1%             | 12 (37.5) | 10 (50.0) | |
| ≥ 50%           | 7 (21.9) | 4 (20.0) | |
| Unknown         | 7 (21.9) | 2 (10.0) | |
| Neoadjuvant therapy | 0 | 1 (5.0) | 0.39 |
| Adjuvant therapy | 1 (3.1) | 2 (10.0) | 0.55 |
| ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1 TPS, programmed death-ligand 1 tumor proportion score |
Safety

AEs of any cause occurred in all patients in the two treatment groups (Table 3). AEs of grade 3 or higher occurred in 37.5% of the patients in arm A and 55.0% of the patients in the arm B. The AEs led to the discontinuation of all treatment components in 3.1% and 10.0% of arms A and B, respectively, and to the discontinuation of sintilimab in 12.5% and 10.0% of arms A and B, respectively. No toxicity-related deaths occurred. The most common AEs in arm A were anemia (68.8%), decreased white blood cell count (37.5%), increased alanine aminotransferase (31.3%), decreased neutrophil count (25.0%) and peripheral neuropathy (25.0%), whereas the most common AEs in arm B were anemia (75.0%), decreased white blood cell count (40.0%), decreased neutrophil count (30.0%), and decreased platelet count (20.0%).

Immune-mediated adverse events (irAEs) occurred in 12 of 32 patients (37.5%) in arm A and in 9 of 20 patients (45.0%) in arm B; grade 3 or higher irAEs occurred in 3 patients (9.4%) and one patient (5.0%), respectively. A higher number of hematological AEs was noted in arm B than in arm A, while the number of cases with peripheral neuropathy, hyperthyroidism, myositis, and immune-mediated pneumonitis was higher in arm A than that in arm B.

Discussion

To our knowledge, this is the first study of sintilimab combined with TP versus sintilimab plus GP for patients with untreated advanced or metastatic sqNSCLC. We demonstrated that sintilimab-TP had favorable efficacy with acceptable safety, comparable with our results for sintilimab-GP.

In the phase 3 ORIENT-12, sintilimab in combination with GP revealed a significantly prolonged PFS compared with chemotherapy alone in patients with sqNSCLC (Zhou et al. 2021). The results of phase 3 trials suggested that the combination of PD-1 inhibitors and TP had greater efficacy than that of TP monotherapy (Jotte et al. 2020; Paz-Ares et al. 2018; Wang et al. 2021). Sintilimab with
Fig. 2 Kaplan–Meier curves of estimated progression-free survival (PFS) (a) and a Cox proportional hazard regression analysis of PFS in prespecified subgroups (b). CI, confidence interval; HR, hazard ratio; Sint, sintilimab; GP, gemcitabine and platinum; TP, paclitaxel/nab-paclitaxel and platinum; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1 TPS, programmed death-ligand 1 tumor proportion score.
a

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| Arm A (n=32) | Arm B (n=20) |
|-------------|-------------|
| Median OS, months (95% CI) 21.3 (13.4, 29.3) | 13.3 (9.1, 17.5) |
| HR = 0.62 (95% CI, 0.28–1.36), p = 0.23 |
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b

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| Gender    | HR (95% CI) |
|-----------|-------------|
| Male      | 0.51 (0.23-1.17) |
| Female    | 1.23 (0.08-19.86) |
| Age       |             |
| <60       | 0.27 (0.06-1.36) |
| ≥60       | 0.76 (0.28-2.05) |
| Smoking   |             |
| Current/former | 0.57 (0.21-1.55) |
| Never     | 0.62 (0.15-2.47) |
| Disease stage |         |
| IIIB/IIIC | 0.57 (0.16-1.98) |
| IV        | 0.67 (0.30-2.52) |
| ECOG PS   |             |
| 0         | 0.23 (0.04-1.26) |
| 1         | 0.89 (0.36-2.25) |
| PD-L1 TPS |             |
| <1%       | 1.10 (0.22-5.58) |
| ≥1%       | 0.37 (0.10-1.32) |
| 1-49%     | 0.15 (0.03-0.83) |
| ≥50%      | 4.22 (0.35-50.54) |
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Sint-TP better  Sint-GP better
TP may have similar or even improved efficacy than sintilimab combined with GP.

In the present study, the sintilimab-TP group exhibited higher ORR (59.4% vs. 40.0%), 12-month OS rate (77.2% vs. 68.5%), PFS (median, 13.9 vs. 8.5 months; HR = 0.61), and OS (median, 21.3 vs. 13.3 months; HR = 0.62) than the sintilimab-GP group. However, the results were not significantly different. Interestingly, the sintilimab-TP group showed a superior OS benefit than the sintilimab-GP group in the subgroup with PD-L1 expression of 1–49%. The PFS and ORR of arm B were consistent with those of sintilimab-GP in the ORIENT-12 study (median PFS, 5.5 months; ORR, 44.7%) (Zhou et al. 2021). In addition, the outcomes of arm A observed in the present study were comparable to those reported in the KEYNOTE-407 (median PFS, 6.4 months; median OS, 15.9 months) (Paz-Ares et al. 2018), IMPower131 (median PFS, 6.3 months; median OS, 14.2 months) (Jotte et al. 2020), and RATION-ALE 307 (median PFS, 7.6 months) (Wang et al. 2021) studies.

Sintilimab with TP or GP therapy was well tolerated, with a low proportion of grade 3 or higher AEs and discontinuation of treatment due to AEs. In addition, the rate of discontinuation of treatment due to AEs was lower in the sintilimab-TP group than that in the sintilimab-GP group (3.1% vs. 10.0%). The high frequencies of AEs in both groups included anemia, decreased white blood cell count, and decreased neutrophil count. The incidence of these hematological AEs was considered to be related to chemotherapy and was lower in the sintilimab-TP group than in the sintilimab-GP group. However, non-hematological AEs were higher in arm A than arm B. A previous study reported higher number of cases with anemia, neutropenia, and thrombocytopenia in the GP group than that of the TP group. Notably the number of cases with grade 3 or 4 anemia and neutropenia was significantly higher in the GP group compared with that of the TP group (Mudad et al. 2017). The majority of AEs were resolved or improved and were manageable.

The present study exhibits certain limitations. First, it was a retrospective observational study with a small sample size. A large-scale prospective cohort study should be conducted to further explore these findings. Second, the results provided only a narrow time window with limited follow-up for certain patients. Our follow-up results will provide a more comprehensive analysis.

In conclusion, the present study revealed that the effectiveness of sintilimab plus platinum and gemcitabine or paclitaxel/nab-paclitaxel in a real-world setting was comparable to that reported in clinical trials. The treatment groups may exhibited similar efficacy with regard to patients with untreated advanced or metastatic sqNSCLC, with safety profiles. Sintilimab combined with paclitaxel/nab-paclitaxel and platinum may be a novel option for the treatment of sqNSCLC patients.

| Event                                      | Arm A (N=32) | Arm B (N=20) |
|--------------------------------------------|--------------|--------------|
| Event                                      | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| Any event                                  | 32 (100)   | 12 (37.5)    | 20 (100)   | 11 (55.0)    |
| Event leading to discontinuation of all treatment components | 1 (3.1) | 1 (3.1) | 2 (10.0) | 2 (10.0) |
| Event leading to discontinuation of sintilimab | 4 (12.5) | 3 (9.4) | 2 (10.0) | 2 (10.0) |
| Anemia                                      | 22 (68.8)  | 1 (3.1)     | 15 (75.0)  | 4 (20.0)    |
| White blood cell count decreased            | 12 (37.5)  | 1 (3.1)     | 8 (40.0)   | 1 (5.0)     |
| Alanine aminotransferase increased          | 10 (31.3)  | 2 (6.3)     | 2 (10.0)   | 0           |
| Neutrophil count decreased                  | 8 (25.0)   | 2 (6.3)     | 6 (30.0)   | 1 (5.0)     |
| Peripheral neuropathy                       | 8 (25.0)   | 1 (3.1)     | 1 (5.0)    | 0           |
| Platelet count decreased                    | 3 (9.4)    | 1 (3.1)     | 4 (20.0)   | 1 (5.0)     |
| Immune-mediated pneumonitis                 | 3 (9.4)    | 1 (3.1)     | 1 (5.0)    | 0           |
| Rash                                        | 2 (6.3)    | 0           | 3 (15.0)   | 0           |
| Hyperthyroidism                             | 2 (6.3)    | 0           | 0          | 0           |
| Myositis                                    | 2 (6.3)    | 1 (3.1)     | 0          | 0           |
| Hypothyroidism                              | 1 (3.1)    | 0           | 1 (5.0)    | 0           |
| Encephalitis                                | 0          | 0           | 1 (5.0)    | 1 (5.0)     |
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Data availability statement  All datasets presented in this study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Declarations

Conflict of interests  All authors have no conflicts of interest to disclose.

Ethics statement  The studies involving human participants were reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Guangzhou Medical University (Guangzhou, Guangdong, China).

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