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Research Paper

Health-related quality of life and symptoms in patients with previously untreated, locally advanced or metastatic non-squamous non-small cell lung cancer treated with sintilimab or placebo plus pemetrexed and platinum (ORIENT-11): A randomized, double-blind, phase 3 trial

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ABSTRACT

Background: In the phase 3 ORIENT-11 study, sintilimab plus pemetrexed-platinum provided statistically significant longer overall survival and progression-free survival versus placebo plus pemetrexed-platinum as first-line treatment in patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC). Here, we report the patient-reported outcomes (PRO) analysis findings in ORIENT-11.

Methods: PROs were measured using the European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire Core 30 items (EORTC QLQ-C30) and the Lung Cancer Symptom Scale (LCSS) questionnaire. PRO endpoints included evaluation of least square (LS) mean changes from baseline to week 12 (platinum-containing treatment) and week 21 (maintenance treatment), time to true deterioration (TTD), and overall improvement or stability rate for QLQ-C30 and LCSS scales. PRO scores in two groups were compared using the Mann–Whitney test. Least squares (LS) mean changes from baseline to week 12, week 21, and other time points were assessed with mixed-effect model repeated measures analysis. TTD was calculated using the Kaplan-Meier method and compared with the Cox proportional hazards model between groups.

Results: 252 (94.7 %) patients in the sintilimab-combination group and 123 (93.9 %) patients in the placebo-combination group had a baseline and at least one postbaseline PRO assessment. Change from baseline to week 12 or 21 favored the sintilimab-combination group on QLQ-C30 global health status/quality of life (GHS/QoL), most function and symptoms scales, and most LCSS scales. Notably, the QLQ-C30 pain score change gradually deteriorated in the placebo-combination group with increased treatment. At the same time, it improved in the sintilimab-combination group significantly from 6 weeks later, with the improvement sustained in subsequent courses of treatment. Sintilimab plus chemotherapy significantly delayed the TTD in most QLQ-

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C30 and LCSS scales compared with placebo plus chemotherapy, and the overall improvement or stability rates were higher in the former.
Conclusions: The addition of sintilimab to chemotherapy maintained or improved health-related quality of life and symptoms compared with chemotherapy. Along with the previous efficacy and safety results, these data support the addition of sintilimab to standard chemotherapy as first-line therapy in locally advanced or metastatic non-squamous NSCLC.
Clinical trial registration: NCT03607539.

1. Introduction

Non-small cell Lung Cancer (NSCLC) is commonly associated with a series of symptoms, including cough, dyspnea, pain, and fatigue [1–3]. Unfortunately, the symptom burden is particularly severe in advanced or recurrent NSCLC patients [2]. Disease-related symptoms in NSCLC patients have been correlated with decreased health-related quality of life (HRQoL) and poor prognosis [4,5]. In addition to expanding life span, another essential goal of tumor treatment is to maintain or improve HRQoL [6,7]. Therefore, evaluating the tolerability of treatment and its impact on HRQoL is of immense importance and has clinical implications.

Immunotherapy is a noted breakthrough for advanced NSCLC, significantly prolonging disease progression and overall survival [8]. Sintilimab, a recombinant fully humanized IgG4 anti-PD-1 monoclonal antibody, restores antitumor immunity by blocking the PD-1/PD-L1 signaling axis [9]. Sintilimab has also proven effective as an antitumor drug in clinical trials and is approved for the treatment of multiple tumors by the Chinese National Medical Products Administration, including NSCLC [10–16].

In the phase 3 ORIENT-11 study in first-line advanced NSCLC, the addition of sintilimab to pemetrexed-platinum significantly prolonged overall survival (OS, HR 0.60, 95 % CI 0.45–0.79, $P = 0.0003$) and progression-free survival (PFS, HR 0.49, 95 % CI 0.38–0.63, $P < 0.0001$), irrespective of PD-L1 expression levels [10,17,18]. Sintilimab plus pemetrexed-platinum was also well tolerated. To assess whether or not these survival benefits were accompanied by improved HRQoL, patient-reported outcomes (PRO) were evaluated as prespecified exploratory endpoints in the ORIENT-11 study. Here, we presented the results from the PRO.

2. Material and methods

2.1. Patients and study design

Design details of the ORIENT-11 trial (NCT03607539) have been previously provided [10]. Patients with stage IIIB to IV non-squamous NSCLC, Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0–1, no sensitive EGFR mutations or ALK rearrangements, no previous systemic treatment, and who were ineligible for radical surgery or radiotherapy were included. Patients were randomized 2:1 to receive intravenous sintilimab 200 mg or placebo in combination with four cycles of pemetrexed (500 mg/m^2) and either cisplatin (75 mg/m^2) or carboplatin (area under the concentration–time curve, 5 mg/mL/min) every 3 weeks. This was followed by intravenous sintilimab 200 mg or placebo plus pemetrexed (500 mg/m^2) every 3 weeks as maintenance therapy for up to 24 months

The study was conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice and the Declaration of Helsinki. Ethical approval was sought and granted at each participating center. Written informed consent was collected from all patients before any study-specific procedures.

2.2. Endpoints and assessments

The primary endpoint (PFS), second endpoints, and safety were previously reported [10]. PRO analysis was performed as a prespecified exploratory endpoint. PROs were measured using two instruments: the European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire Core 30 items (EORTC QLQ-C30) and the Lung Cancer Symptom Scale (LCSS) questionnaire. Questionnaires were administered at baseline, week 6, week 12, then every 9 weeks until week 48, and every 12 weeks after that, at the treatment discontinuation visit and the 30-day safety assessment visit.

The QLQ-C30 measures a global health status (GHS)/QoL scale, five functional scales (physical, role, cognitive, emotional, and social), and nine symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) [19]. QLQ-C30 were scored according to the EORTC scoring manual, ranging from 0 to 100 [20]. A higher score for the QLQ-C30 GHS/QoL scale and functional scales represented better QoL and function. Furthermore, a higher score represented a heavier symptom burden on the QLQ-C30 symptom scale. Moreover, the minimally clinically important difference (MCID) was defined as a score change between baseline and a given time point of $\geq$ 10 points [21].

The LCSS measures six symptom scales (loss of appetite, fatigue, cough, dyspnea, pain, and hemoptysis) and three global scales (symptom distress, interference with activity level, and HRQoL) [22–24]. The average symptom burden index (ASBI) was calculated as the mean of scores for six symptom scales. The 3-item global index (3-IGI) was the sum score of the three global scales. LCSS scales were scored by 100 mm visual analog scale (VAS), with 0 representing the best health state and minimal symptom burden and 100 representing the worst health state and maximum symptom burden [22–24]. ASBI scores range from 0 to 100, and 3-IGI scores range from 0 to 300. The minimally clinically important difference (MCID) was defined as a score change between baseline and a given time point of $\geq$ 10 points for all LCSS scales (except for LCSS 3-IGI) and of $\geq$ 30 points for LCSS 3-IGI [25].

The prespecified exploratory endpoints included evaluation of mean changes from baseline to week 12 (platinum-containing treatment) and week 21 (maintenance treatment), time to true deterioration (TTD), and overall improvement or stability rate for QLQ-C30 and LCSS scales. TTD is defined as the time intervals from baseline to the first deterioration ($\geq$10 points change) with confirmation by a second adjacent deterioration or death [21,26]. An improved score was defined as $\geq$ 10 points improvement in score at any time during the study, confirmed at the next visit; stable as a < 10-point score change at any time during the study, confirmed at the next visit; and deterioration as worsening $\geq$ 10 points in score at any time during the study in patients not otherwise meeting criteria for improved or stable score [26]. The overall improvement or stability rate was the sum of the proportion of patients who improved or stabilized [26].

2.3. Statistical analysis

PRO analysis was carried out in all randomly assigned patients who received at least one dose of study treatment and had a baseline and at least one postbaseline PRO assessment. The completion rate was defined as the proportion of patients who completed at least one PRO questionnaire in the full population. The compliance rate was the percentage of patients who completed at least one PRO questionnaire at each visit among those expected to complete the questionnaires (i.e., those who

were alive and still in study).

PRO scores in two groups were compared using the Mann–Whitney test. Least squares (LS) mean changes from baseline to week 12, week 21, and other time points were assessed with mixed-effect model repeated measures analysis, with age, ECOG-PS, sex, smoking status, tumor stage, and baseline PRO score as covariates. TTD was calculated using the Kaplan-Meier method and compared with the Cox proportional hazards model between groups. A two-sided *P*-value of less than 0.05 was considered to be of significance. Statistical analyses were done with R Language (version 4.3.1).

3. Results

3.1. Patients

Between 23 August 2018 and 30 June 2019, 397 subjects were randomly assigned to sintilimab plus chemotherapy group (n = 266) or placebo plus chemotherapy group (n = 131; Fig. 1). As of the data cutoff on 15 September 2021, the median follow-up duration was 30.8 months. As previously described, the baseline clinical characteristics of the two arms were well-balanced [10].

Two-hundred fifty-two (94.7 %) patients in the sintilimab-combination group and 123 (93.9 %) patients in the placebo-combination group had a baseline and at least one post-baseline PRO assessment (Fig. 1). PRO questionnaire compliance rates were high and similar between arms at baseline, week 12, and week 21 (Supplementary Table 1). The decline in completion rates over study time correlated with an increase in the number of patients who discontinued the study due to disease progression, study withdrawal, adverse events, physician decision, or death. QLQ-C30 and LCSS completion rates at baseline were 99.6 % in the sintilimab-combination group and 100 % in the placebo-combination group. Completion rates were 86.5 % and 83.2 % in two arms at week 12 and were 76.7 % and 64.1 % at week 21 for both QLQ-C30 and LCSS (Supplementary Table 1).

3.2. EORTC-QLQ-C30

Baseline mean scores were similar between the two groups for all individual domains on the QLQ-C30, except for dyspnea and insomnia (Supplementary Table 2). We also included baseline PRO scores as covariates in the mixed-effect model repeated measures analysis for correction.

Baseline GHS/QoL scores of the sintilimab-combination and placebo-combination groups were 65.7 and 63.5, respectively (Supplementary Table 2). The mean GHS/QoL scores were maintained in both groups from baseline to week 12, with a between-group LS mean difference of 0.26 points (95 % CI: −4.95,5.46, $P = 0.922$, Fig. 2A). There was a modest change for GHS/QoL from baseline to week 21 in both groups, with a between-group LS mean difference of −1.34 points (95 % CI: −7.03,4.34, $P = 0.643$, Fig. 2C). Compared with the placebo-combination group, the overall improvement or stability rates for GHS/QoL were higher (60.7 % vs. 47.9 %), and the overall deterioration rate was lower in sintilimab-combination group (37.3 % vs. 51.2 %, Fig. 3B). One-hundred twenty-two of 252 individuals (48.4 %) in the sintilimab-combination group and 42 of 123 (34.1 %) in the placebo-combination group had improved GHS/QoL scores; 31 of 252 (12.3 %), 17 of 123 (13.8 %), respectively, had stable scores; and 94 of 252 (37.3 %), 63 of 123 (51.2 %), respectively, had deteriorated scores (Fig. 3B).

LS mean changes were more favorable in the sintilimab-combination arm for most functional and symptom domains than in the placebo-combination arm from baseline to week 12 and week 21 (Fig. 2A-D). In contrast to the sintilimab-combination group, the decline of physical, emotional, role, cognitive, and social function scores was obvious in the

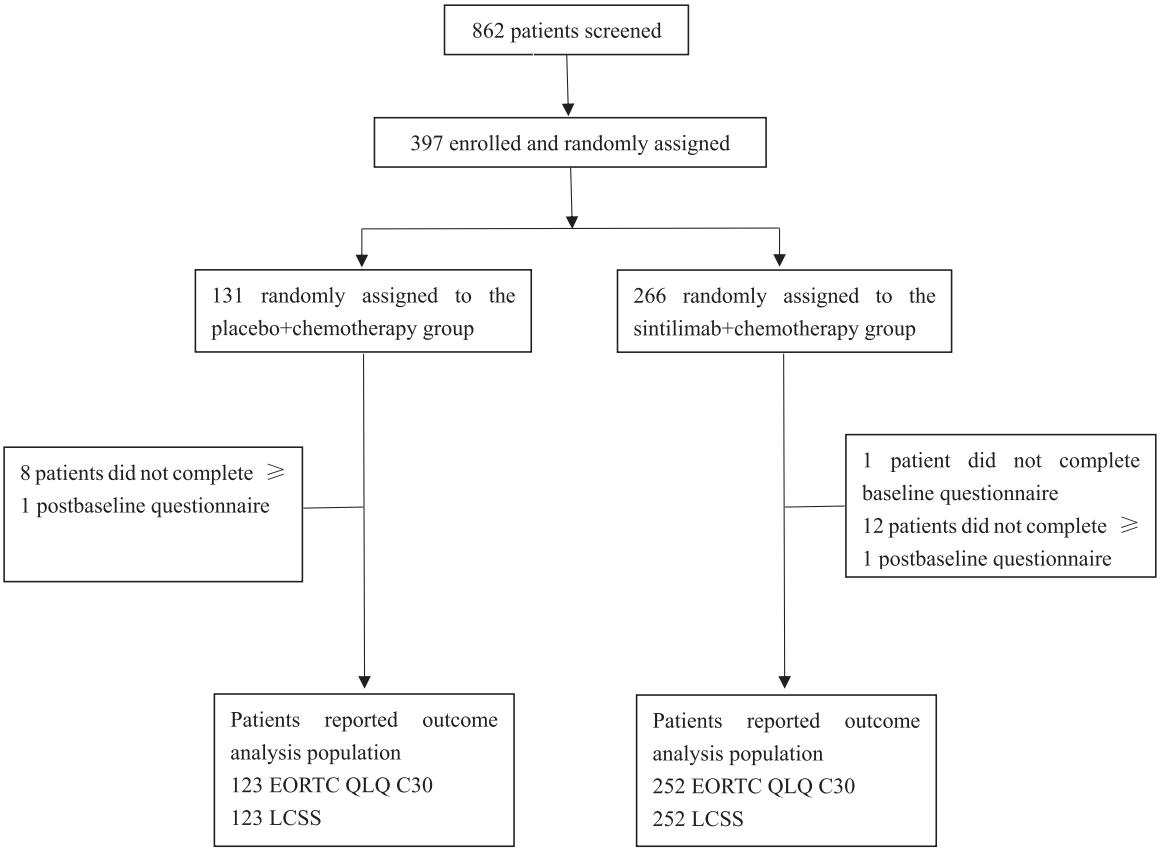

Fig. 1. Trail profile.

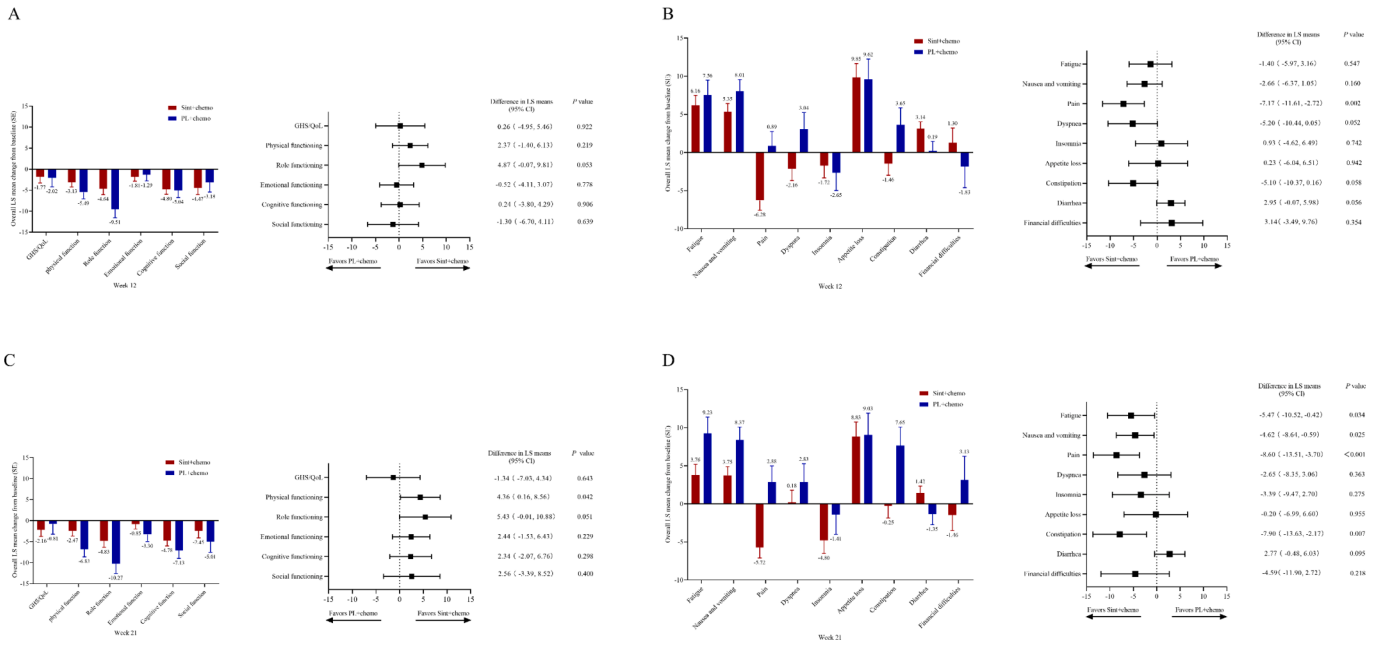

Fig. 2. Mean changes from baseline and differences between groups in QLQ-C30 scales at week 12 and week 21. Mean changes from baseline and differences between groups in GHS/QoL and functional scales scores at week 12 (A) and week 21 (C), and symptom scale scores at week 12 (B) and week 21 (D). QLQ-C30, Quality of Life of Cancer Patients Questionnaire Core 30; GHS/QoL, global health status/quality of life; Sint: sintilimab; PL, placebo; chemo, chemotherapy; SE, standard error; LS, least squares; CI: confidence interval.

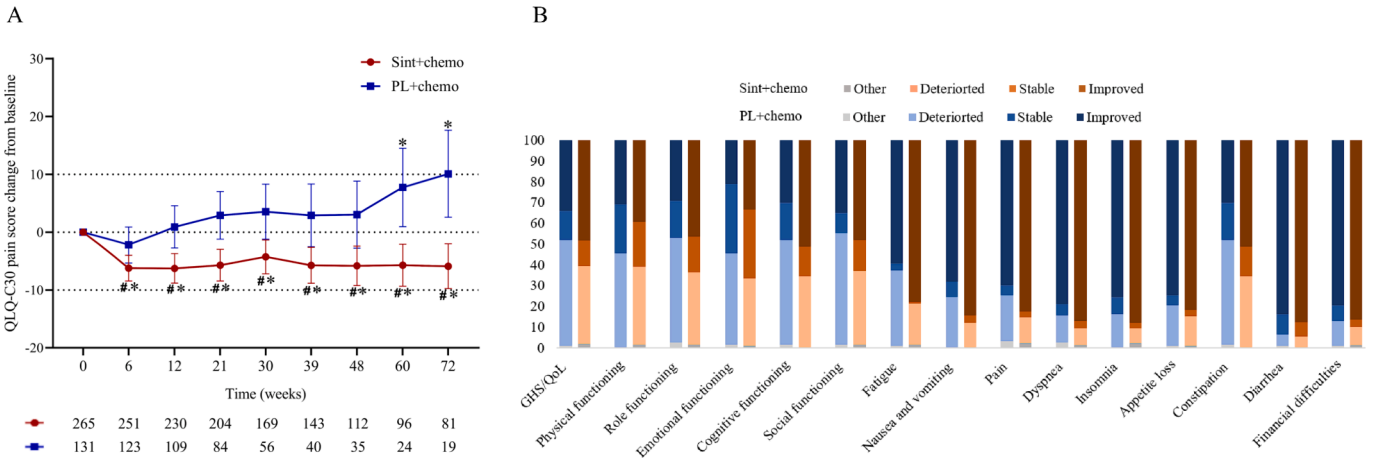

Fig. 3. Mean changes from baseline and differences between groups in pain scores (A) during treatment, the overall improvement, stability and deterioration rate in GHS/QoL, functional and symptom scales (B). *Significant change from baseline ($P < 0.05$); #significant difference in changes between groups ($P < 0.05$). QLQ-C30, Quality of Life of Cancer Patients Questionnaire Core 30; GHS/QoL, global health status/quality of life; Sint: sintilimab; PL, placebo; chemo, chemotherapy.

placebo-combination group at week 21, with a significant difference between groups in physical function (Fig. 2C). The LS mean score of role function was significantly worsened in the placebo-combination group at week 21, exceeding the MCID (Fig. 2C). From baseline to week 12 and week 21, each symptom scale's LS mean score change worsened in the placebo-combination group versus the sintilimab-combination group (Fig. 2B, 2D). Constipation, nausea and vomiting, and fatigue scores changed statistically significantly between arms at week 21 (Fig. 2D). Notably, the pain score was worsened in the placebo-combination group at week 12 and week 21 and gradually further exacerbated with the extension of treatment time. In contrast, this was improved in the sintilimab-combination group at week 12 and week 21, and this improvement persisted over time with later treatment (Fig. 2B, 2D, 3A). The overall improvement or stability rates were 154 (61.1 %) in the sintilimab-combination group vs. 67 (54.5 %) in the placebo-combination group for physical function, 215 (85.3 %) vs. 92 (74.8 %) for pain, 198 (78.6 %) vs. 77 (62.6 %) for fatigue, 222 (88.1 %) vs. 93 (75.6 %) for nausea and vomiting, and 165 (65.5 %) vs. 59 (50.0 %) for constipation (Fig. 3B). We performed an exploration analysis to evaluate score changes from baseline to week 12/21 in all scales among patients with $< 1\%$ or ≥ 1 % PD-L1 expression, the mean differences between groups were consistent with the overall treatment effect for each scale (Supplementary Fig. 1).

Patients treated with sintilimab plus chemotherapy experienced numerically longer median TTD of GHS/QoL at 8.85 months compared with 7.07 months with placebo plus chemotherapy (HR, 95 % CI: 0.700, 0.543–0.902, $P = 0.006$, Fig. 4A). Median TTD for physical function was 9.42 months in the sintilimab-combination group and 7.77 months in the placebo-combination group (HR, 95 % CI: 0.698, 0.539–0.904, $P = 0.006$, Fig. 4B). For pain, patients with sintilimab plus chemotherapy

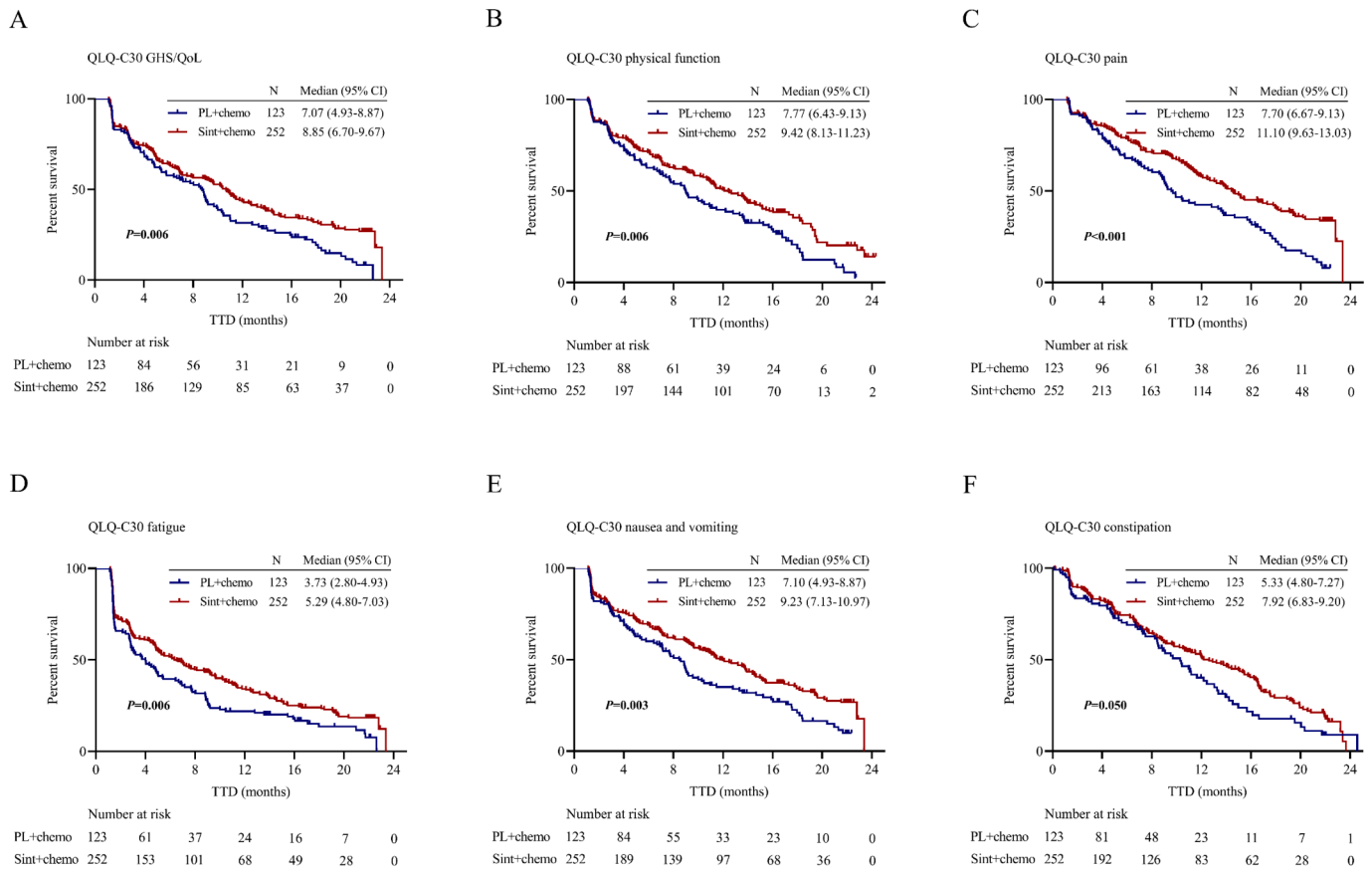

Fig. 4. Kaplan-Meier curves of TTD. (A) GHS/QoL, (B) physical function, (C) pain, (D) fatigue, (E) nausea and vomiting, and (F) constipation. QLQ-C30, Quality of Life of Cancer Patients Questionnaire Core 30; GHS/QoL, global health status/quality of life; TTD, time to true deterioration; Sint: sintilimab; PL, placebo; chemo, chemotherapy; CI, confidence interval. Bolded *P*-value indicates statistical significance ($P < 0.05$).

significantly prolonged TTD than those with placebo plus chemotherapy (median, 11.10 vs. 7.70 months; HR, 95 % CI, 0.583, 0.445–0.763; $P < 0.001$, Fig. 4C). Similar results were observed for fatigue (median, 5.29 vs. 3.73 months; HR, 95 % CI, 0.715, 0.563–0.909; $P = 0.006$, Fig. 4D), nausea and vomiting (median, 9.23 vs. 7.10 months; HR, 95 % CI, 0.676, 0.522–0.876; $P = 0.003$, Fig. 4E), and constipation (median, 7.92 vs. 5.33 months; HR, 95 % CI, 0.754, 0.568–1.002; $P = 0.050$, Fig. 4F). Sintilimab plus chemotherapy also significantly delayed the TTD compared with placebo plus chemotherapy for other functional domains (role, emotional, cognitive, and social) and symptoms of dyspnea, insomnia, appetite loss, and diarrhea (Supplementary Fig. 2).

3.3. LCSS

QoL outcomes, as measured by the LCSS, were consistent with the results of the EORTC QLQ-C30 analysis. At baseline, LS mean scores for all scales were similar between groups (Supplementary Table 2).

LS mean ASBI scores were stable from baseline to week 12 or week 21 in both treatment arms, with a between-group difference of −0.24 points at week 12 and −2.61 points at week 21 (Fig. 5A). The LS mean 3-IGI scores decline in the sintilimab-combination group was statistically significant from baseline to week 12 (difference value: −9.53 points, $P = 0.015$) and week 21 (difference value: −9.79 points, $P = 0.023$). The decline degree of LS mean 3-IGI scores were greater in the sintilimab-combination group than in the placebo-combination group at week 12 or week 21. However, it did not reach statistical significance (Fig. 5A). The overall improvement or stability rates on ASBI were 80.5 % in the sintilimab-combination group and 85.3 % in the placebo-combination group, respectively; the deterioration rates were 19.5 % and 13.9 %, respectively. The overall improvement or stability rates on 3-IGI were 78.0 % and 82.9 % in the sintilimab-combination and placebo-combination groups, respectively; the deterioration rates were 17.9 % and 13.1 %, respectively (Supplementary Fig. 3).

Mean score changes in individual global and symptom scale seemed better for the sintilimab-combination arm than the placebo-combination arm from baseline to week 12 and week 21 (Fig. 5). In the sintilimab combination group, a clinical improvement that exceeded MCID was seen in cough. The difference in symptom distress scores was statistically significant between the two groups at week 12 or week 21 (Fig. 5). The trends for the change from baseline to week 12/21, as measured by the LCSS, were in line with the overall treatment effect regardless of PD-L1 expression (< 1% or ≥ 1 %) for each scale (Supplementary Fig. 4).

TTD was significantly delayed with sintilimab-combination therapy versus placebo-combination therapy on 3-IGI and ASBI (Fig. 6). The median TTD in 3-IGI was 9.55 months in sintilimab-combination and 7.67 months in the placebo-combination group (HR, 95 % CI: 0.723, 0.554–0.944, $P = 0.017$). Additionally, the median TTD in ASBI was 10.40 months in the sintilimab combination group and 7.10 months in the placebo combination group (HR, 95 % CI: 0.627, 0.480–0.819, $P < 0.001$). Hazard ratios favored the sintilimab-combination group over the placebo-combination group for TTD for all LCSS measures (Supplementary Fig. 5).

4. Discussion

Here, we report that sintilimab plus pemetrexed-platinum stabilized or improved HRQoL and symptoms in locally advanced and metastasis NSCLC patients and delayed TTD in multiple scales compared with placebo plus chemotherapy in the ORIENT-11 trial. The clinical benefit measured by PRO scales further supports applying sintilimab plus

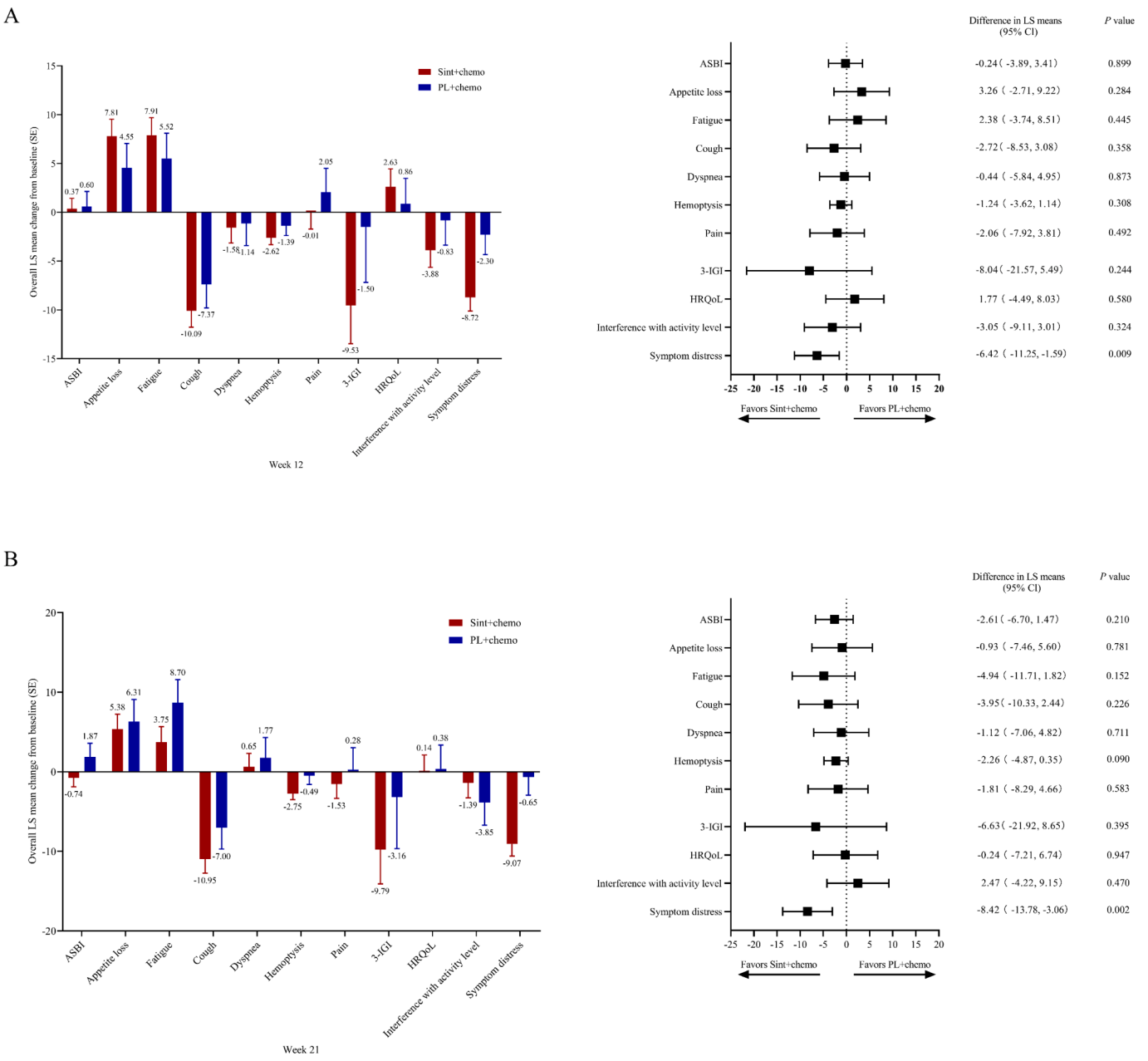

Fig. 5. Mean changes from baseline and differences between groups in LCSS scales at week 12 and week 21. Mean changes from baseline and differences between groups in symptom and global scale scores at week 12 (A) and week 21 (B). ASBI, average symptom burden index; 3-IGI, 3-item global index; HRQoL, health-related quality of life; Sint: sintilimab; PL, placebo; chemo, chemotherapy; SE: standard error, LS, least squares; CI, confidence interval.

pemetrexed-platinum as a standard of care for advanced NSCLC.

Although QLQ-C30 GHS/QoL decreased slightly from baseline in both groups at week 12 or week 21, the mean GHS/QoL scores of two arms were still higher than the reference values in advanced lung cancer patients [27]. Additionally, no difference between groups was observed in the GHS/QoL scale, indicating that GHS/QoL was maintained in both groups at week 12 or week 21. Importantly, TTD in the sintilimab-combination group was significantly longer than in the placebo-combination group for GHS/QoL, and the overall improvement or stability rate was higher in the sintilimab-combination group than in the placebo-combination group. The QLQ-C30 GHS/QoL analysis results supported HRQoL benefits in patients treated with sintilimab plus chemotherapy.

HRQoL results favoring the sintilimab-combination group were also supported by QLQ-C30 function and symptom scales. Physical function was significantly improved in the sintilimab-combination group than in the placebo-combination group at week 21. TTD was prolonged considerably in physical function in the sintilimab-combination group versus the placebo-combination group; similar results were observed in social, emotional, role, and cognitive function. Consistency in functional improvement and survival benefits has been reported [28–30], which is consistent with the findings in our study. Symptom burden in patients with cancer is one of the biggest concerns, with pain, nausea and vomiting, fatigue, and constipation as frequently reported outcomes affecting HRQoL in lung cancer[31–34]. We observed statistically significant symptoms improvement of pain, nausea and vomiting, fatigue, and constipation in QLQ-C30 at week 21 for sintilimab plus chemotherapy versus the placebo plus chemotherapy. Notably, we observed that the QLQ-C30 pain scores of patients in the placebo-combination group gradually deteriorated with the increase in treatment. In

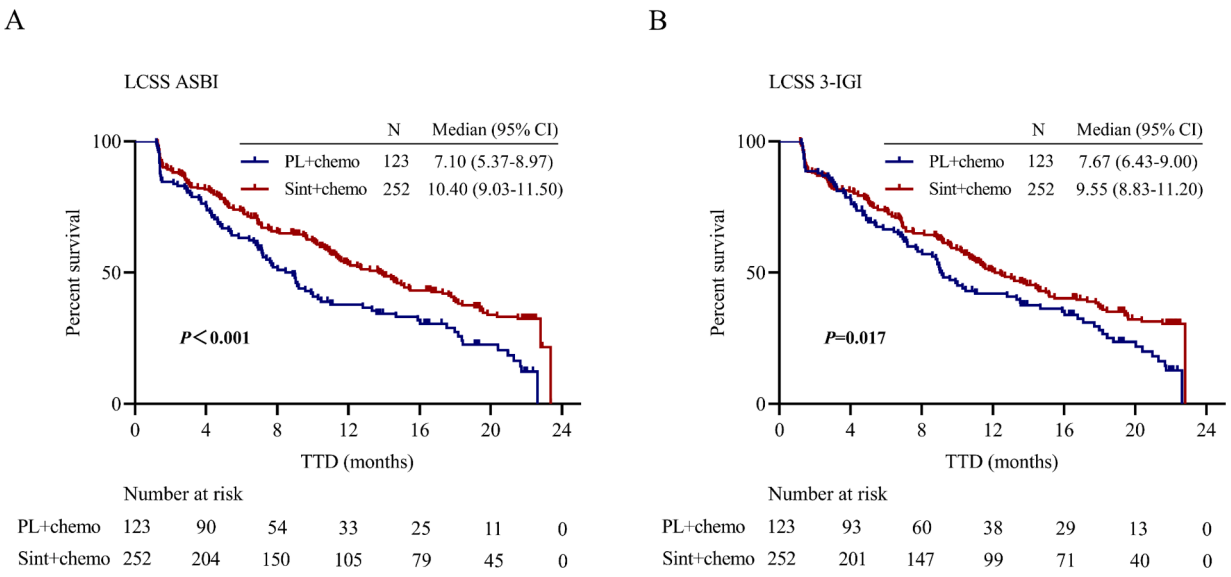

Fig. 6. Kaplan-Meier curves of TTD. (A) ASBI. (B) 3-IGI. LCSS, Lung Cancer Symptom Scale; ASBI, average symptom burden index; 3-IGI, 3-item global index; TTD, time to true deterioration; Sint: sintilimab; PL, placebo; chemo, chemotherapy; CI, confidence interval. Bolded *P*-value indicates statistical significance ($P < 0.05$).

contrast, the pain scores of patients in the sintilimab-combination group improved significantly 6 weeks later, and the improvement was sustained in subsequent courses of treatment. The improvement or stabilization rates were high, and the median TTD was improved for all QLQ-C30 and LCSS symptom scales, including pain, nausea and vomiting, fatigue, and constipation, in patients receiving sintilimab plus chemotherapy versus placebo plus chemotherapy. These findings suggested that sintilimab may be a more applicable choice to patients with cancer pain at baseline.

These PRO results provided additional important context for safety data assessment from the ORIENT-11 trial and informed patients' experience [10]. The incidence of ≥ Grade 3 adverse events was comparable between the sintilimab combination group (61.7 %) and placebo combination group (58.8 %) in the primary analysis. Results from the current PRO analysis indicate this minor difference did not appear to have a meaningful effect on HRQoL. Overall, PRO analysis in this study further supported the manageable safety of sintilimab plus chemotherapy. HRQOL and symptoms were improved or maintained to a greater degree with sintilimab plus chemotherapy than with chemotherapy.

Findings from the current analysis observed in the ORIENT-11 trial align with previous PRO studies of immunotherapy, with or without chemotherapy, versus chemotherapy in advanced NSCLC. The addition of pembrolizumab in pemetrexed-platinum maintained or improved HRQoL and most symptoms compared with pemetrexed-platinum in stage IV non-squamous NSCLC regardless of PD-L1 expression in KEYNOTE-189 clinical trial [32]. In the KEYNOTE-407 trial with metastatic squamous NSCLC patients, pembrolizumab plus paclitaxel-carboplatin maintained improved HRQoL versus paclitaxel-carboplatin, symptoms of fatigue, pain, dyspnea, and insomnia improvements were favored in the pembrolizumab combination group, irrespective of PD-L1 expression [35]. First-line nivolumab plus ipilimumab with chemotherapy reduces the risk of definitive deterioration in HRQoL and disease-related symptoms versus chemotherapy alone in metastatic NSCLC patients in the CheckMate 9LA trial [36]. The POSEIDON study showed that tremelimumab plus durvalumab and chemotherapy delayed deterioration in GHS/QoL, functional, and symptom scales versus chemotherapy alone [37]. Similar conclusions were also reported in several studies where patients received PD-1/PD-L1 inhibitors alone versus chemotherapy alone [33,34,38–41]. In summary, adding sintilimab to standard chemotherapy does not impair HRQoL. As such, it can maintain or improve HRQoL and various disease-related symptoms, supporting its clinical application in advanced NSCLC.

Limitations remain in the present study. Firstly, the PRO questionnaire collection was discontinued at disease progression, and the 30-day visit followed treatment discontinuation, limiting the HRQoL analysis to the period during treatment. The longer-term effect of sintilimab plus chemotherapy on HRQoL in advanced NSCLC patients remains uncertain. Secondly, the reduction in the number of patients considered evaluable by PRO over time due to disease progression or the presence of adverse events in the placebo-combination group might affect the QoL outcomes. Thirdly, although the EORTC-QLQ-C30 and LCSS instruments were not explicitly developed for studies of immunotherapy, the former was widely used in studies of a variety of cancers [42–45], and the latter was specially used for NSCLC [34,41]. Notably, both have been well-validated in previous studies. Despite these limitations, PRO analysis provides basic data that is difficult to obtain outside of clinical trials, which plays an important role in deepening investigators' understanding of the safety of treatment regimens.

5. Conclusion

In conclusion, along with the previous efficacy and safety results, these data support the addition of sintilimab to standard chemotherapy in locally advanced and metastatic non-squamous NSCLC maintained or improved the HRQoL and symptoms. The improved overall survival, progression-free survival, comparable incidence of adverse events, and improved HRQoL outcomes with sintilimab plus chemotherapy versus chemotherapy further support that sintilimab plus chemotherapy should be considered as a first-line treatment option for advanced NSCLC patients.

Ethics approval.

The study was conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice and the Declaration of Helsinki. Ethical approval was sought and granted at each participating center.

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CRediT authorship contribution statement

Tingting Liu: Conceptualization, Data curation, Formal analysis,

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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