Phase 2 trial of neoadjuvant toripalimab with chemotherapy for resectable stage III non-small-cell lung cancer
Ze-Rui Zhao\textsuperscript{a,b,1}, Chao-Pin Yang\textsuperscript{c}, Si Chen\textsuperscript{a,b,1}, Hui Yu\textsuperscript{a,b,1}, Yong-Bin Lin\textsuperscript{a,b,1}, Yao-Bin Lin\textsuperscript{a,b}, Han Qi\textsuperscript{d}, Jie-Tian Jin\textsuperscript{e}, Shan-Shan Lian\textsuperscript{f}, Yi-Zhi Wang\textsuperscript{a,b}, Jin-Qi You\textsuperscript{f}, Wen-Yu Zha\textsuperscript{a,b}, and Hao Long\textsuperscript{a,b}

\textsuperscript{a}State Key Laboratory of Oncology in Southern China, Collaborative Innovation Center for Cancer Medicine, and Department of Thoracic Surgery, Sun Yat-Sen University Cancer Center, Guangzhou, China; \textsuperscript{b}Lung Cancer Research Center, Sun Yat-Sen University, Guangzhou, China; \textsuperscript{c}Department of Biotherapy, Sun Yat-Sen University Cancer Center, Guangzhou, China; \textsuperscript{d}Department of Minimally Invasive Interventional Therapy, Sun Yat-Sen University Cancer Center, Guangzhou, China; \textsuperscript{e}Department of Pathology, Sun Yat-Sen University Cancer Center, Guangzhou, China; \textsuperscript{f}Department of Radiology, Sun Yat-Sen University Cancer Center, Guangzhou, China

ABSTRACT
Multimodality treatment provides modest survival benefits for patients with locally advanced (stage III) non-small-cell lung cancer (NSCLC). Nevertheless, preoperative immunotherapy has continuously been shown to be promising in treating resectable NSCLC. This phase 2 trial enrolled patients with AJCC-defined stage IIIA or T3-4N2 IIIB NSCLC deemed surgically resectable. Patients received three cycles of neoadjuvant treatment with intravenous PD-1 inhibitor toripalimab (240 mg), carboplatin (area under the curve 5), and pemetrexed (500 mg/m\textsuperscript{2} for adenocarcinoma) or nab-paclitaxel (260 mg/m\textsuperscript{2} for other subtypes) on day 1 of each 21-day cycle. Surgical resection was performed 4–5 weeks afterward. The primary endpoint was major pathological response (MPR), defined as less than 10% residual tumor remaining at the time of surgery. Thirty-three patients were enrolled, of whom 13 (39.4%) had T3-4N2 stage IIIB disease. Thirty (90.9%) patients underwent resection and all (96.7%) achieved R0 resection. Twenty patients (60.6%) in the intention-to-treat population achieved an MPR, including 15 patients (45.5%) who achieved a pathological complete response (pCR). The MPR and pCR rates in the per-protocol population were 66.7% and 50.0%, respectively. The surgical complications included three cases of arrhythmias, one case of a prolonged air leak, and one case of chylothorax. The most common grade 3 treatment-related adverse event (TRAE) was anemia (2, [6.1%]). Severe TRAEs included one (3.0%) case of grade 3 peripheral neuropathy that resulted in surgical cancellation. Toripalimab plus platinum-based doublet chemotherapy yields a high MPR rate, manageable toxicity, and feasible resection in stage III NSCLC. Trial ClinicalTrials.gov (NCT04304248)

INTRODUCTION
Approximately 1/3 of non-small-cell lung cancer (NSCLC) patients are diagnosed with stage III disease.\textsuperscript{1} Stage III NSCLC are a very heterogeneous group, with tumor diameters ranging from less than 1 cm to 7 cm, the presence of local tumor invasion, ipsilateral mediastinal lymph nodes (N2) metastasis, etc.\textsuperscript{2} NSCLC tumors with positive N2 lymph node metastasis may indicate systemic disease, hence a sequential modality treatment is critical.\textsuperscript{3,4}

Previous trials of induction chemotherapy or chemoradiation following surgical resection have achieved limited tumor regression and disease downstaging in stage III NSCLC, with a pathological complete response (pCR) rate of 5 to 14% and a 5-year overall survival (OS) rate of approximately 25%.\textsuperscript{5,6}

Compared with chemotherapy, neoadjuvant immunotherapy has an advantage in resectable NSCLC due to an intact host immunity status, and a tumor remaining in situ increasing potential release or exposure to cancer neoantigens for activating tumor-specific T cells to eradicate tumor cells and micrometastases.\textsuperscript{7} Accumulating evidence supports the use of anti-PD-1/PD-L1 treatment in patients with NSCLCs. Toripalimab, a novel humanized IgG4 monoclonal antibody against PD-1, has shown manageable safety and antitumor activity in patients with advanced NSCLC.\textsuperscript{8} However, the role of toripalimab in NSCLC in the neoadjuvant setting has not been established.

Two recent studies indicated that neoadjuvant immunotherapy with nivolumab or atezolizumab plus chemotherapy is feasible prior to radical surgery for stage IB-III NSCLC in a Caucasian population.\textsuperscript{9,10} The ongoing phase III CheckMate-816 trial reported on the American Association of Cancer Research annual meeting 2021 showed greater depth of pathological response following neoadjuvant nivolumab plus chemotherapy versus chemotherapy alone.\textsuperscript{11} Given the comprehensive factors such as oncogene mutation and hepatitis B virus infection, ethnic differences between Asian and Caucasian populations remain unclear when applying
immunotherapy.12 To date, only one study has reported the utility of neoadjuvant PD-1 monotherapy (sintilimab) in Asian patients with resectable NSCLCs, of which stage III cases accounted for less than 45% and no invasive mediastinal evaluation was performed to confirm the N status.13

This study was conducted to investigate the application value and safety of the neoadjuvant toripalimab plus platinum-based doublet chemotherapy in stage III Asian NSCLC patients.

METHODS

Design and participants

This phase 2 trial of toripalimab, nab-paclitaxel or pemetrexed, and carboplatin in stage III NSCLC was performed in a tertiary referral center in South China. Eligible patients were aged 18 years or older with American Joint Committee on Cancer (AJCC)-defined (8th-edition) stage IIIA or T3-4N2 IIIB NSCLC that was deemed surgically resectable by a multidisciplinary team.14 All patients had brain magnetic resonance imaging as standard stage requirement to rule out brain metastasis. A preoperative evaluation of the mediastinal lymph nodes at baseline was performed via mediastinoscopy or endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) for clinical N2 cases.

All participants had an Eastern Cooperative Oncology Group performance status of 0 or 1, with measurable disease according to the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1). The exclusion criteria included the presence of a known EGFTR exon 19/21 mutation or EML4-ALK translocation; known or suspected autoimmune disease; other conditions that required systemic corticosteroid treatment or immunosuppressive medicines within 14 days of enrollment (see Study protocol in the Supplementary appendix).

This study was completed in accordance with the Declaration of Helsinki. Written informed consent was provided by all participants. The study protocol was approved by the Research Ethics Committee of the Sun Yat-Sen University Cancer Center (2019-FXY-084) and is registered with ClinicalTrials.gov (NCT04304248).

Treatment procedures

Patients received neoadjuvant treatment with intravenous toripalimab (240 mg) on day 1, carboplatin (area under the curve 5) on day 1, and pemetrexed (500 mg/m² for adenocarcinoma) or nab-paclitaxel (260 mg/m² for other subtypes) on day 1 of each 21-day cycle for three cycles. Patients who did not progress after treatment by radiographic evaluation underwent surgery, which included resection of the primary tumor and ipsilateral lymph nodes 4–5 weeks following the first day of the third cycle of treatment. Thoracotomy or video-assisted thoracoscopic surgery (VATS) was chosen according to the surgeon’s preference. Adjuvant toripalimab monotherapy commencing 4–8 weeks after surgery and continuing until month 12 was the recommended therapeutic option but other adjuvant modalities may be determined by the multidisciplinary team.

Clinical analyses

A radiographic evaluation (18F-FDG PET plus contrast-enhanced CT [PET-CT] preferred) was performed three weeks after the completion of neoadjuvant treatment to assess patient response according to the RECIST. The diagnosis of whether there was viable tumor remaining was recorded by PET-CT interpretation. Chest tomography was performed every 3 months during the first two years and every 6 months afterward following surgery.

Comorbidities were assessed by the Charlson Comorbidity Index. Surgical complications, morbidity, and mortality were monitored for three months after surgery. Treatment-related adverse events (TRAEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. If an adverse event occurred, treatment could be interrupted or delayed at the discretion of the investigator.

Pathological assessment was performed according to the methods described by Cottrell et al.15 In brief, all tumor bed samples less than 6 cm were submitted entirely. For tumor bed samples that were 6 cm or more, a minimum of one section/cm of the greatest tumor bed dimension was assessed. A major pathological response (MPR) was defined as the presence of 10% or less viable residual tumor in the resected specimen. For patients who achieved pCR (no viable tumor on all slides), the entire tumor bed was examined.

Exploratory analyses, including the PD-L1 expression assessment, next-generation sequencing (NGS), and immuno-histochemistry are described in the Appendix Methods.

Outcomes

The primary endpoint was the proportion of patients who achieved an MPR after resection. The secondary endpoints included the pCR rate, resection rate, disease-free survival (DFS) rate (calculated from the completion of neoadjuvant treatment until disease recurrence or death), and safety, which included events related to neoadjuvant treatment and surgery. DFS and OS were assessed in the modified intention-to-treat (ITT) population, which included all patients who received neoadjuvant treatment; and in the per-protocol population, which included all patients who underwent tumor resection. TRAEs were analyzed in all patients who received at least one dose of neoadjuvant treatment.

Statistical analysis

Simon’s optimal two-stage design was used to assess MPR as the primary endpoint.16 We assumed that adding toripalimab to chemotherapy would increase the MPR rate from 20% to 45%. Eighteen patients were enrolled in the first stage under the following conditions: if ≤4 patients achieved an MPR, the study would be considered negative and terminated. Otherwise, the study would proceed by enrolling 12 additional patients. Thirty evaluable patients were ultimately enrolled, with a type 1 error rate of 0.05. The protocol provided a power of 80% to detect an MPR rate of 45% under alternative hypotheses.
The exact two-sided 95% confidence intervals (CIs) were calculated with the Clopper-Pearson method. The Kaplan-Meier method was used to estimate DFS, OS. The reverse Kaplan-Meier method was used to calculate the median follow-up time and corresponding interquartile range (IQR).

Post hoc comparisons were performed by dividing patients into groups by histology, stage, PD-L1 expression, and oncogene alteration. Categorical variables were analyzed by Pearson’s χ² test. The degree of concordance between PET and pathological response was interpreted as follows: slight, 0.00–0.20; fair, 0.21–0.40; moderate, 0.41–0.60; substantial, 0.61–0.80; and almost perfect, ≥0.81. Statistical analyses were performed with SPSS (ver. 20.0; SPSS Inc, Chicago, Ill), and a P-value less than 0.05 indicated a statistically significant difference.

RESULTS

Patient characteristics

Sixty-two patients were screened for eligibility between August 2019 and July 2020, and 33 patients were eventually enrolled (Table 1, Supplementary Fig. S1). Reasons for exclusion included small cell lung cancer (n = 3), benign disease (n = 7), positive EGFR/ALK (n = 10), restaging to stage II due to negative findings via invasive mediastinal assessments (n = 5), and refusal to participate (n = 4).

All of the participants received three cycles of neoadjuvant treatment and were included in the modified ITT population. Eighteen (54.5%) had squamous cell carcinoma (SQCC), 13 (39.4%) had adenocarcinoma, and 2 (6.1%) had lymphoid epithelial-like carcinoma (LELC). For patients with LELC, endoscopic examination of the nasopharynx was conducted to rule out metastatic LELC from the nasopharynx. At presentation, 20 (60.6%) patients had stage IIIA disease, and 13 (39.4%) had stage IIIB disease. A baseline mediastinal evaluation was performed in 22 (66.7%) patients: 10 underwent mediastinoscopy, and 12 underwent EBUS-TBNA. One patient in each modality group was eventually found to be N2 negative. The other 5 patients were defined as N2 positive by PET-CT.

Table 1. Patient characteristics.

| Characteristics         | Patients (n = 33) |
|-------------------------|------------------|
| Age, y                  | 61 (56–66)       |
| Sex                     |                  |
| Female                  | 6 (18.2%)        |
| Male                    | 27 (81.8%)       |
| Histology               |                  |
| Adenocarcinoma          | 13 (39.4%)       |
| Squamous cell cancer    | 18 (54.5%)       |
| Lymphoepithelioma-like carcinoma | 2 (6.1%) |
| Charlson Comorbidity Index | 5 (4–6)    |
| Stage at diagnosis      |                  |
| IIIA                    | 20 (60.6%)       |
| IIIB                    | 13 (39.4%)       |
| Tumor diameter, mm      | 49 (36–61)       |
| Clinical nodal status   |                  |
| N0                      | 1 (3.0%)         |
| N1                      | 7 (21.2%)        |
| N2                      | 25 (75.8%)       |
| Single zone             | 6 (18.2%)        |
| Multizone               | 19 (57.6%)       |

Data are shown as the n (%) or median (IQR, interquartile range)

Surgery and outcomes

Thirty patients (91.9%) received pulmonary resection and were included in the per-protocol population. There were no treatment-related surgical delays, and the median interval between day 1 of the last neoadjuvant treatment and surgery was 36.5 days (IQR 30.0–42.5). Most patients underwent lobectomy (22/30, 73.3%). One of the 6 patients who underwent VATS was converted to thoracotomy due to incarcerated lymph nodes on the pulmonary artery. The 30-day mortality was 0.

Multiple ipsilateral pulmonary metastases were found in one patient intraoperatively, and R2 resection was performed. Therefore, R0 resection was achieved in 29 of 30 patients (96.7%). Severe hilum fibrosis was observed in 9/30 (30.0%) patients during the operation. One patient developed chylothorax and required repeat surgery for thoracic duct ligation two days after lung resection. Surgical complications are reported in Table 2.

At the time of data cutoff (August 6, 2021), all 30 patients who received tumor resection were alive, with a median follow-up of 10.13 months (IQR 9.00–16.43). Two patients in the per-protocol population had disease progression: one patient had MPR following treatment developed contralateral lung metastases and was confirmed by transthoracic centesis; the other patient that did not achieve MPR developed contralateral mediastinal lymph node metastasis and was confirmed by EBUS-TBNA. The median OS and DFS were not reached in the per-protocol population (Supplementary Fig. S2).

Of the three patients who did not undergo surgery, one developed disease progression of the primary tumor during neoadjuvant treatment and died 5 months after receiving immunotherapy due to cancer. Two patients refused

Table 2. Surgical details.

|Patients (n = 30)† |
|-------------------|
|R0 resection        | 29 (96.7%)        |
|Interval between the neoadjuvant treatment and surgery (d) | 36.5 (30–42.5) |
|Surgical approach  |                  |
|Video-assisted thoracoscopic surgery | 6 (20.0%)‡ |
|Thoracotomy         | 24 (80.0%)        |
|Resection type      |                  |
|Wedge resection     | 1 (3.3%)          |
|Lobectomy           | 22 (73.3%)        |
|Pneumonecomy        | 6 (20.0%)         |
|Nodal downstaging in patients with cN2 at baseline (n = 24) |                  |
|N2 to N0            | 15 (62.5%)        |
|N2 to N1            | 1 (4.2%)          |
|N2 to N2            | 8 (33.3%)         |
|Surgical outcome    |                  |
|No. of lymph nodes harvested | 18 (14.8–23.8) |
|Severe hilar fibrosis | 9 (30.0%)        |
|Estimated blood loss (ml) | 100 (100–200) |
|Intraoperative blood transfusion | 5 (16.7%)   |
|Length of postoperative hospital stay (d) | 5 (4–6)        |
|Prolonged air leak   | 1 (3.3%)          |
|Postoperative arrhythmia | 3 (10.0%)   |
|Chylothorax          | 1 (3.3%)          |

Data are shown as the n/N (%) or median (IQR, interquartile range). †Two patients refused surgery, and another patient progressed after neoadjuvant therapy and did not undergo resection. ‡One conversion due to incarcerated interlobar lymph nodes.
surgery after neoadjuvant treatment; of these patients, one achieved a complete response radiographically, and the other had 75% partial regression radiographically but developed Guillain- Barré syndrome with grade 3 peripheral neuralgia following the third cycle of neoadjuvant treatment. The median OS and DFS were not reached in the ITT population.

**Radiographic findings and pathological response**

Of all 33 patients, 29 (87.9%) met the RECIST for an overall response radiographically; 3 (9.1%) achieved a complete response, 26 (78.8%) achieved a partial response, 3 (9.1%) had stable disease, and one (3.0%) had progressive disease during neoadjuvant treatment (Figure 1). The correlation between radiographic findings and pathological response was not significant \( (P = .06, \text{Figure 2a}). \)

Among the 30 patients who underwent surgery (per-protocol population), 20 (66.7%; 95% CI 47.2–82.7) achieved an MPR, of whom 15 (50.0%; 31.3–68.7) achieved a pCR. The MPR and pCR rates in the ITT population were 60.6% (95% CI 42.1–77.1) and 45.5% (95% CI 28.1–63.6), respectively. The pathological response did not differ between the stage IIIA and IIIB subgroups (MPR: 13/20 [65.0%] vs. 7/13 [53.8%], \( P = .72 \); pCR: 10/20 [50.0%] vs. 5/13 [38.5%], \( P = .72 \)). No difference between adenocarcinoma and SQCC was found in terms of pathological response (Supplementary Table S1). The two patients with LELC had complete remission of the primary tumor. However, one patient had parabronchial lymph node metastasis after treatment, which was defined as MPR.

In the per-protocol population, downstaging was achieved in 24 (80.0%) patients, with 62.5% of cN2 patients (15/24) downstaged to ypN0 postoperatively. The total rate of complete lymph node clearance (ypN0) was 70.0% (21/30). Adjuvant immunotherapy was administered in 27 (90.0%) patients following the operation; two patients received adjuvant osimertinib, and the other patient received gefitinib after surgery.

Additionally, the PET results showed a moderate ability to predict the extent of pathological response of tumors and lymph nodes after neoadjuvant immunotherapy (concordance rate: 56.7% [95% CI 41.1–77.5%] and 53.3% [95% CI 38.2–74.5%] for the primary tumor and lymph nodes, respectively; Supplementary Table S2). However, the decline in the maximum standardized uptake value (SUVmax) was more extensive in the MPR/pCR subgroup of 18 patients who underwent paired PET scans (Figure 2b).

**TRAEs**

The TRAEs related to neoadjuvant therapy are summarized in Table 3. The most common TRAEs of any grade were alopecia and anemia, which occurred in 15 (45.5%) of 33 patients, followed by nausea (10, 30.3%), increased aminotransferase levels (9, 27.3%), hypothyroidism (6, 18.2%), thrombocytopenia (5, 15.2%), and fatigue (5, 15.2%). No grade 4 or 5 events were observed, and the most common grade 3 TRAE was anemia (2, 6.1%). Treatment discontinuation or dose reduction was not caused by TRAEs. There were no treatment-related deaths.

![Figure 1](image.png)

**Figure 1.** Radiographic findings and pathologic response following neoadjuvant toripalimab plus platinum-based doublet chemotherapy in the intention-to-treat population. TPS, tumor proportion score; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LELC, lymphoid epithelial-like carcinoma.
Exploratory analysis

In the analysis regarding exploratory endpoints, among patients with positive PD-L1 expression, the percentage of patients who achieved an MPR was similar to that of those with negative PD-L1 expression (Supplementary Table S3). A subset of 21 (63.6%) patients underwent NGS. Interestingly, four patients who had negative results from molecular testing for baseline core biopsy (amplification-refractory mutation system for EGFR mutation screening and immunohistochemistry for EML4-ALK rearrangement testing) had a positive result from NGS using a postoperative specimen (two with an EGFR exon 19 del, one with EGFR L858R, and one with focal [5%] ALK positivity). The percentages of viable tumor cells in these patients were 80%, 50%, 75%, and 45%, respectively (Supplementary Table S4). More CD8+ lymphocytes, CD19 + B-cells (surrogate for the presence of tertiary lymphoid structures) and Granzyme B were found in tumor bed after receiving neoadjuvant immunotherapy (Figure 2 c & d; Supplementary Fig. S3).

DISCUSSION

To the best of our knowledge, this is the third study worldwide and the first study in the Asian population to investigate the feasibility and tolerability of neoadjuvant PD-1 inhibitor with chemotherapy specifically in patients with surgically resectable stage III NSCLC. The neoadjuvant regimen of toripalimab plus
Table 3. Treatment-related adverse events during neoadjuvant treatment in the modified intention-to-treat population.

| Patients (n = 33) | Grades 1–2 | Grade 3 |
|-----------------|------------|---------|
| Alopecia        | 15 (45.5%) | 0       |
| Anemia          | 15 (45.5%) | 2 (6.1%)|
| Anorexia        | 4 (12.1%)  | 0       |
| Arthralgia or myalgia† | 4 (12.1%) | 1 (3.0%)|
| Diarrhea        | 0          | 1 (3.0%)|
| Fatigue         | 5 (15.2%)  | 0       |
| Hypothyroidism† | 6 (18.2%)  | 0       |
| Increased aminotransferase level† | 9 (27.3%) | 1 (3.0%)|
| Nausea          | 10 (30.3%) | 0       |
| Neutropenia     | 2 (6.1%)   | 0       |
| Peripheral sensory neuropathy† | 4 (12.1%) | 1 (3.0%)|
| Pneumonia†      | 1 (3.0%)   | 0       |
| Pruritus        | 1 (3.0%)   | 0       |
| Rash            | 6 (18.2%)  | 0       |
| Thrombocytopenia| 5 (15.2%)  | 0       |
| Vomiting        | 1 (3.0%)   | 0       |

Data are shown as the n (%). No grade 4 or 5 treatment-related adverse events were observed. †Deemed possible immune-related adverse events.

Chemotherapy was well tolerated and was associated with acceptable TRAEs. The promising high pathological response rate in the per-protocol population supports the necessity of future investigation of induction chemoimmunotherapy for locally advanced NSCLC.

Although pseudoprogression, defined as tumor progression from baseline that is not confirmed as progression on a subsequent assessment radiographically, has been reported after neoadjuvant PD-1 monotherapy,18 neither the current study nor the two other trials that investigated the utility of neoadjuvant atezolizumab or nivolumab with chemotherapy found pseudoenlargement of tumors following combined chemoimmunotherapy.9,10 It is plausible that adding chemotherapy to immunotherapy improved the objective response rate; hence, pseudoprogression was less commonly seen than that with immune checkpoint inhibitor monotherapy. Although majority of tumors showed various extent of regression radiographically, the correlation between radiographic findings and pathological response was not significant in this study, which was different from Shu and colleagues’ finding of a significant association between MPR and the RECIST response categories.10 Nonetheless, MPR has been considered a surrogate endpoint for predicting long-term survival in many studies of neoadjuvant treatment.19 In concordance with a previous report, this study demonstrated that a greater than 30% reduction in the SUVmax was an indicator of MPR.13,20 Additionally, Corsini et al. noted that patients who achieved an MPR and complete nodal clearance benefited most from neoadjuvant chemotherapy.21 In this study, the complete N2 downstaging rate was 62.5% (Supplementary Table S5), which is comparable to that with neoadjuvant immunotherapy (58 to 83%) and is higher than that in a historical study of neoadjuvant chemotherapy in which nearly 30% of mediastinal lymph nodes became free of metastasis.22 The MPR and pCR rates of the per-protocol population in the current study and the NADIM trial were 66.7% vs. 83% and 50% vs. 63%, respectively. More than half of the patients (57.6%) in this study had multiple N2 metastases, which was comparable to that in the NADIM trial (54%) that investigated the feasibility of neoadjuvant nivolumab plus chemotherapy in stage IIIA NSCLC in a Caucasian population.21 It is worth noting that the staging in the NADIM trial was confirmed using the 7th edition of the AJCC staging system. According to the 8th edition of the staging system, 13 patients (28%) in the NADIM trial were stage IIIIB, which was lower than the 39.4% in our trial. This may, to some extent, explain why the MPR and pCR rates in this study were lower than those in the NADIM trial. In another trial that investigated the combination of neoadjuvant atezolizumab with carboplatin and nab-paclitaxel for 30 cases of stage IB-IIIA NSCLC in a Caucasian population, of which 77% (n = 20) were stage III, the MPR and pCR rates were 57% and 33%.10 The recent published SAKK16/14 trial explored the additional benefit of two doses of durvalumab following three cycles of docetaxel plus cisplatin as neoadjuvant treatment in stage IIIA(N2) NSCLC, the MPR and pCR rates were 62% and 18%.23 The best combination strategy of immunotherapy and chemotherapy, whether simultaneously or sequentially, warrants future investigation.

Interestingly, two patients had LELC in the current study, and both achieved complete remission of the primary tumor. This special type of tumor, which is associated with Epstein-Barr virus infection and is preferentially found in nonsmoking Asians, may be a good candidate for immunotherapy given its high PD-L1 expression (defined as a positive tumor proportion score greater than 5%) (75.8%; compared with 52% in SQCC and 17% in adenocarcinoma).24–26

In this study, the combination of toripalimab with platinum-based doublet chemotherapy was safe and well tolerated, with grade 3 or above TRAEs found in 18.2% of patients, a rate that is slightly lower than other neoadjuvant immunotherapy agents including atezolizumab (>50%) and nivolumab (34%).9,10 Only one case was converted to thoracotomy during the VATS procedure; thus, the conversion rate was lower than that in a previous report (nearly 50% during minimally invasive surgery).27

The use of neoadjuvant immunotherapy in driver gene-positive NSCLCs remains controversial.28 None of the three patients with EGFR exon 19/21 mutations in the current study achieved an MPR. In comparison, among the four EGFR-sensitive patients who received neoadjuvant atezolizumab plus chemotherapy in a separate study, two patients achieved a pCR.10 Interestingly, two of the patients with an EGFR mutation in this study had PIK3CA and TP53 comutations, and it remains unclear whether a high comutational status in Asian patients with an EGFR mutation would affect the therapeutic impacts of immunotherapy.29 Post hoc analysis in the NADIM trial demonstrated that specific gene mutations, such as those in STK11, KEAP1, RB1, and EGFR, may not be associated with MPR and were associated with short progression-free survival.9 Our study, however, demonstrated that such mutations might indicate a low MPR rate (4/11, 36.4% vs. 16/22, 72.7%, P = .04; Supplementary Fig. S4).

The limitations of our study include but are not limited to the following: there was no randomized control arm for comparison; one-third of patients did not undergo invasive mediastinal
staging; and there was a limited follow-up period for demonstrating the fundamental benefit of neoadjuvant chemoimmuno-therapy. Nonetheless, the results from the current study may still be convincing, as the pathological response was promising, and most patients successfully underwent surgery.

In conclusion, our findings provide evidence that neoadjuvant toripalimab with platinum-based doublet chemotherapy produces high MPR/pCR rates and merits further investigation for patients with resectable stage III NSCLC.

Acknowledgments
The authors would like to thank Ms. Xi Dai for her kind assistance in this trial.

Declarations
Ethics approval and consent to participate: The study was approved by the Clinical Research Ethic Committee of Sun Yat-Sen University Cancer Center (SYSUCC 2019-FXY-084) and is registered with ClinicalTrials.gov (NCT04304248). All patients signed an informed consent for the participating this trial.

Data availability statement:
De-identified individual data might be available following publication by reasonable request to the corresponding author accompanied by research proposal.

Disclosure statement:
No potential conflict of interest was reported by the author(s).

Funding
This work was supported by the National Natural Science Foundation of China Youth Science Fund Project [82002407].

ORCID
Hao Long http://orcid.org/0000-0001-5623-9799

Role of the Funder/Sponsor:
The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References
1. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, Watanabe H, Wu Y-L, Zielinski M, Ball D, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015;10 (12):1675–1684. doi:10.1097/JTO.0000000000000678.
2. Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC, Balekian AA, Diekemper R, Detterbeck FC, Arenberg DA. Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: american College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5):e314S–40S. doi:10.1378/chest.12-2360.
3. Zhao ZR, Ng CSH. Tri-modality treatment in N2 stage IIIa non-small cell lung cancer: proper sequence remains unknown. J Thorac Dis. 2018;10(9):S1096–8. doi:10.21037/jtd.2018.03.69.
4. Putora PM, Leskow P, McDonald F, Batchelor T, Evison M. International guidelines on stage III N2 non-small cell lung cancer: surgery or radiotherapy? ERJ Open Res. 2020;6(1):00159–2019. doi:10.1183/23212541.00159-2019.
5. Van Meerbeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, Tjan-Heijnen VC, Biesma B, Debruyne C, van Zandwijk N, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer. J Natl Cancer Inst. 2007;99(6):442–450. doi:10.1093/jnci/djk093.
6. Albain KS, Swann RS, Rusch VW, Turrisi AT, Shepherd FA, Smith C, Chen Y, Livingston RB, Feins RH, Gandara DR, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379–386. doi:10.1016/S1470-2045(20)30453-8.
7. McGranahan N, Furness AJ, Roshenthal R, Ramskov S, Lyngaa R, Saini SK, Jamal-Hanjani M, Wilson GA, Birkbak NJ, Hiley CT, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science. 2016;351 (6280):1463–1469. doi:10.1126/science.aaf1490.
8. Wang Z, Ying J, Xu J, Yuan P, Duan J, Bai H, Guo C, Li L, Yang Z, Wan R, et al. Safety, Antitumor Activity, and Pharmacokinetics of Toripalimab, a Programmed Cell Death 1 Inhibitor, in Patients With Advanced Non-Small Cell Lung Cancer: A Phase 1 Trial. JAMA Netw Open. 2020;3:e2013770.
9. Provencio M, Nadal E, Insa A, Garcia-Campelo M, Casal-Rubio J, Domíne M, Majem M, Rodriguez-Abreu D, Martinez-Marti A, Carpejo J, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020;21 (11):1413–1422. doi:10.1016/S1470-2045(20)30453-8.
10. Shu CA, Gainor JF, Awad MM, Chiuwan C, Grigg CM, Pabani A, Garofano BF, Stoopler MB, Cheng SK, White A, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020;21(6):786–795. doi:10.1016/S1470-2045(20)30140-6.
11. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, Felip E, Broderick S, Brahmer J, Swanson SJ, et al. Nivolumab + platinum-doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (IB–IIIA) non-small cell lung cancer in the phase 3 CheckMate 816 trial [EB/OL]. Cancer Res. 2021;81(13 Supplement):CT003. doi:10.1158/1538-7445.AM2021-CT003.
12. Peng L, Wu YL. Immunotherapy in the Asiatic population: any differences from Caucasian population? J Thorac Dis. 2018;10 (S13):S1482–93. doi:10.21037/jtd.2018.05.106.
13. Gao S, Li N, Gao S, Xue Q, Ying J, Wang S, Tao X, Zhao J, Mao Y, Wang B, et al. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. J Thorac Oncol. 2020;15(5):816–826. doi:10.1016/j.jtho.2020.01.017.
14. Detterbeck FC, Bofia DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017;151(1):193–203. doi:10.1016/j.chest.2016.10.010.
15. Cottrell TR, Thompson ED, Forde PM, Stein JE, Duffield AS, Anagnostou Y, Bekhtman N, Anders RA, Cuda JD, Illei PB, et al. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). Ann Oncol. 2018;29(8):1853–1860. doi:10.1093/annonc/mdy218.
16. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1–10. doi:10.1016/0197-2456(89)90015-9.
17. Kundel HL, Polansky M. Measurement of observer agreement. Radiology. 2003;228(2):303–308. doi:10.1148/radiol.228211860.
18. Forde PM, Chaha JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, Zaharak M, Yang SC, Jones DR, Broderick S, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med. 2018;378(21):1976–1986. doi:10.1056/NEJMoa1716078.

19. Hellmann MD, Chaha JE, William WN Jr., Rusch V, Pisters KMW, Kalhor N, Pater A, Travis WD, Swisher SG, Kris MG, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers; proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol. 2014;15(1):e42–50. doi:10.1016/S1470-2045(13)70334-6.

20. Tao X, Li N, Wu N, He J, Ying J, Gao S, Wang S, Wang J, Wang Z, Ling Y, et al. The efficiency of (18) F-FDG PET-CT for predicting the major pathologic response to the neoadjuvant PD-1 blockade in resectable non-small cell lung cancer. Eur J Nucl Med Mol Imaging. 2020;47(5):1209–1219. doi:10.1007/s00259-020-04711-3.

21. Corsini EM, Weissferdt A, Pater A, Zhou N, Antonoff MB, Hofstetter WL, Mehran RJ, Rajaram R, Rice DC, Roth JA, et al. Pathological nodal disease defines survival outcomes in patients with lung cancer with tumour major pathological response following neoadjuvant chemotherapy. Eur J Cardiothorac Surg. 2021;59(1):100–108. doi:10.1093/ejcts/exaa290.

22. Betticher DC, Hsu Schmitz S-F, Totsch M, Hansen E, Joss C, von Briel C, Schmid RA, Pless M, Habicht J, Roth AD, et al. Mediastinal Lymph Node Clearance After Docetaxel-Cisplatin Neoadjuvant Chemotherapy Is Prognostic of Survival in Patients With Stage IIIA pN2 Non–Small-Cell Lung Cancer: a Multicenter Phase II Trial. J Clin Oncol. 2003;21(9):1752–1759. doi:10.1200/JCO.2003.11.040.

23. Rothschild SI, Zippelius A, Eboulet EI, Savic Prince S, Betticher D, Bettini A, Früh M, Joerg M, Lardinois D, Gelpke H, et al. SAKK 16/14: durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non-small-cell lung cancer - a multicenter single-arm phase II trial. J Clin Oncol. 2021;39(26):2872–2880. doi:10.1200/JCO.21.00276.

24. Ho JC, Wong MP, Lam WK. Lymphoepithelioma-like carcinoma of the lung. Respirology. 2006;11(5):539–545. doi:10.1111/j.1440-1843.2006.00910.x.

25. Chang YL, Yang CY, Lin MW, Wu CT, Yang PC. PD-L1 is highly expressed in lung lymphoepithelioma-like carcinoma: a potential rationale for immunotherapy. Lung Cancer. 2015;88(3):254–259. doi:10.1016/j.lungcan.2015.03.017.

26. Janzic U, Kern I, Janzic A, CAVKA L, Cufer T. PD-L1 Expression in Squamous-cell Carcinoma and Adenocarcinoma of the Lung. Radiol Oncol. 2017;51(3):357–362. doi:10.1515/raon-2017-0037.

27. Bott MJ, Yang SC, Park BJ, Adusumilli PS, Rusch VW, Isbell JM, Downey RJ, Brahmer JR, Battafarano R, Bush E, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg. 2019;158(1):269–276. doi:10.1016/j.jtcvs.2018.11.124.

28. Stiles BM, Sepsesi BG, Broderick SR, Bott MJ. Perioperative considerations for neoadjuvant immunotherapy in non-small cell lung cancer. J Thorac Cardiovasc Surg. 2020;160(5):1376–1382. doi:10.1016/j.jtcvs.2020.05.119.

29. Zhao ZR, Lin YB, Ng CSH, Zhang R, Wu X, Ou Q, Chen W, Zhou W-J, Lin Y-B, Su X-D, et al. Mutation Profile of Resected EGFR-Mutated Lung Adenocarcinoma by Next-Generation Sequencing. Oncologist. 2019;24(10):1368–1374. doi:10.1634/theoncologist.2018-0567.