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ORIGINAL RESEARCH

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Phase 2 trial of neoadjuvant toripalimab with chemotherapy for resectable stage III non-small-cell lung cancer

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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^2 for adenocarcinoma) or nab-paclitaxel (260 mg/m^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 except one (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)

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INTRODUCTION

Approximately 1/3 of non-small-cell lung cancer (NSCLC) patients are diagnosed with stage III disease.[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.[2] NSCLC tumors with positive N2 lymph node metastasis may indicate systemic disease, hence a sequential modality therapy is critical.[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%.[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.[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.[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.[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.[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

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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 (8^{th}-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 *EGFR* 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/m^2 for adenocarcinoma) or nab-paclitaxel (260 mg/m^2 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 (^{18}F-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 immunohistochemistry 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 χ^2 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.[17] 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.

	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 immunochemotherapy 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%)
Bilobectomy	1 (3.3%)
Pneumonectomy	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, 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.

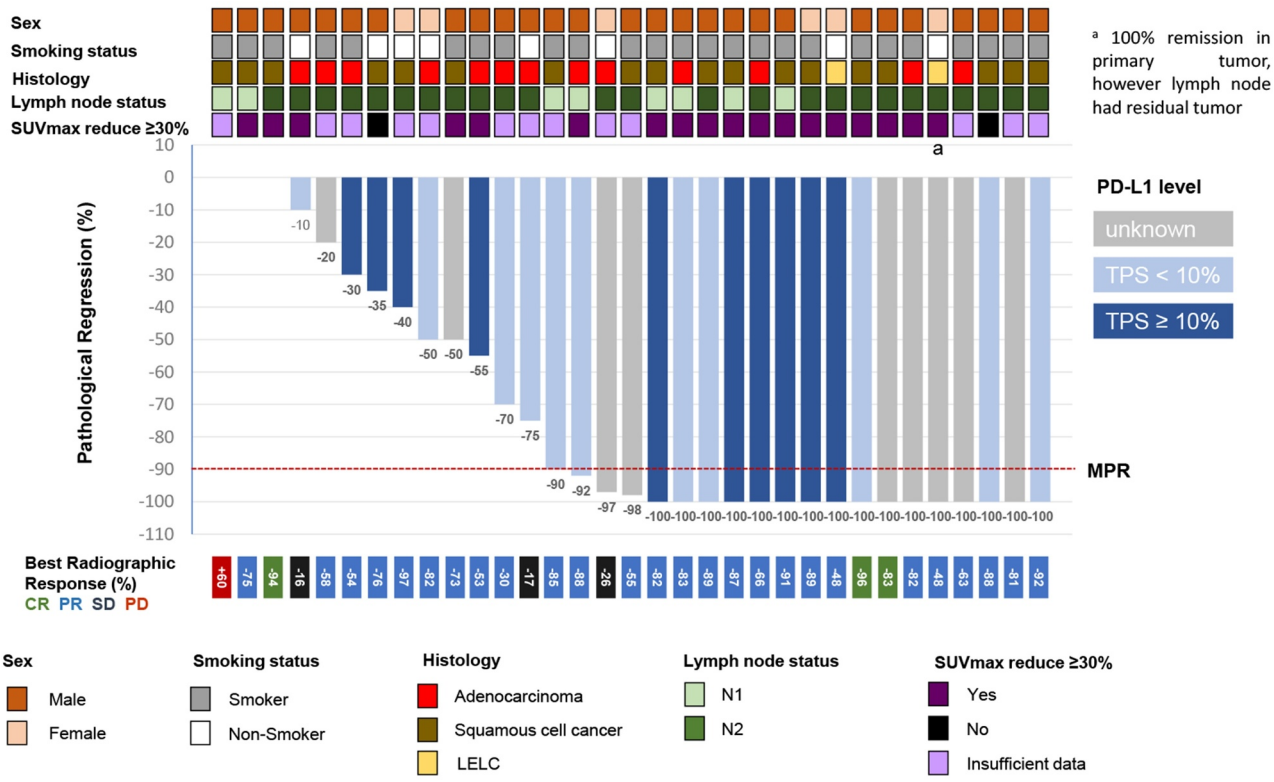

Figure 1. Radiographic findings and pathologic response following neoadjuvant toripalimab plus platinum-based doublet chemotherapy in the intention-to-treat population. TPS, tumor proportion score; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LELC, lymphoid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

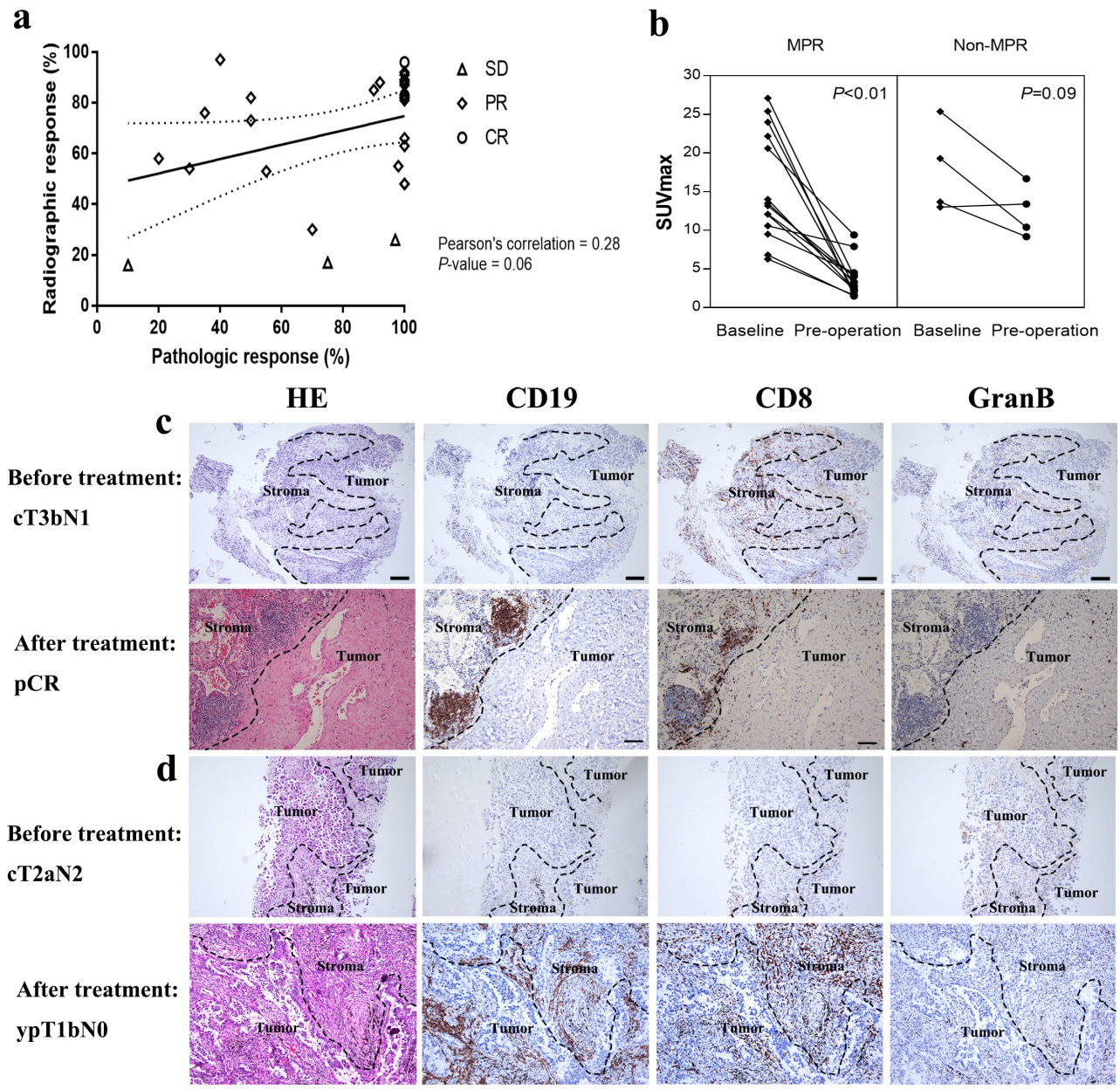

Figure 2. A) Correlation between radiographic findings and pathologic response (each point indicates a single patient) CR, complete response; PR, partial response; SD, stable disease; b) maximum standardized uptake value (SUVmax) at baseline and before the operation (each line indicates the change in the SUVmax in a single patient); and c & d) the representative immunohistochemistry images of paired baseline biopsies (top) and post-treatment (bottom) sections stained with H&E, and antibodies targeting CD19, CD8 and Granzyme B respectively for two patients who achieved pathological complete response (pCR, c) and major pathological response (MPR, d), black scale bars = 100 μm.

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 immunochemotherapy (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 immunochemotherapy (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.[9] 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 IIIB, 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 immunochemotherapy 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 chemoimmunotherapy. 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.

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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).

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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.

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