Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Efficacy of subsequent docetaxel +/− ramucirumab and S-1 after nivolumab for patients with advanced non-small cell lung cancer

Nobumasa Tamura, Hidehito Horinouchi, Katsutoshi Sekine, Yuji Matsumoto, Shuji Murakami, Yasushi Goto, Shintaro Kanda, Yutaka Fujiwara, Noboru Yamamoto & Yuichiro Ohe

Department of Thoracic Oncology, National Cancer Center Hospital, Chuo-ku, Japan

Keywords
Chemocentric chemoimmunotherapy; docetaxel; immune checkpoint inhibitor; NSCLC; S-1.

Correspondence
Hidehito Horinouchi, Department of Thoracic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
Tel: +81 3 3542 2511
Fax: +81 3 3542 3815
Email: hhorinou@ncc.go.jp

Received: 18 February 2019;
Accepted: 10 March 2019.

doi: 10.1111/1759-7714.13055

Thoracic Cancer **10** (2019) 1141–1148

Abstract

Background: Cytotoxic chemotherapy for advanced non-small cell lung cancer (NSCLC) as second-line or subsequent treatment generally results in a poor treatment outcome. Several reports have indicated that subsequent cytotoxic chemotherapy in patients who have received immune checkpoint inhibitors (ICIs) might have relatively better efficacy.

Methods: The clinical data of advanced NSCLC patients treated with nivolumab during clinical practice at the National Cancer Center Hospital between 17 December 2015 and 31 August 2017 were consecutively reviewed, and the treatment outcomes of docetaxel-based chemotherapy (docetaxel +/− ramucirumab) or S-1 after nivolumab were analyzed. The results were then compared with those of advanced NSCLC patients treated with docetaxel or S-1 but not ICIs during clinical practice between 17 December 2014 and 16 December 2015.

Results: Thirty patients were administered docetaxel-based chemotherapy and 21 patients were administered S-1 in any line after nivolumab. Twenty-four patients were administered docetaxel-based chemotherapy and 15 patients were administered S-1 immediately after nivolumab. Sixty-six patients were administered docetaxel and 23 patients were administered S-1 without ICIs. The objective response rate, disease control rate, and median progression-free survival duration were 28.6%, 53.6%, and 5.26 months for patients receiving docetaxel-based chemotherapy or S-1 immediately after nivolumab treatment; 24.3%, 51.4%, and 3.88 months for patients receiving docetaxel-based chemotherapy or S-1 in any line after nivolumab; and 16.4%, 56.7%, and 2.74 months, for patients receiving docetaxel or S-1 without ICIs, respectively.

Conclusion: Subsequent cytotoxic chemotherapy, especially immediately after nivolumab, has better treatment efficacy than that of regimens without ICI pretreatment.

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide.[1] Patients with NSCLC often have distant metastases at the time of diagnosis. Systemic chemotherapy is the standard treatment for patients with advanced NSCLC and includes cytotoxic chemotherapy, molecular targeted therapy (such as EGFR and ALK tyrosine kinase inhibitors [TKIs]), and immune checkpoint inhibitors (ICIs, such as PD-1 and PD-L1 inhibitors).

Among the ICIs, pembrolizumab is used as first-line therapy in patients with advanced NSCLC with a PD-L1 tumor proportion score (TPS) of ≥ 50%.[2] Nivolumab (regardless of PD-L1 TPS) and pembrolizumab (PD-L1 TPS ≥ 1%) are used as second-line or subsequent therapy

following cytotoxic chemotherapy.[3–5] Single-agent chemotherapy (such as docetaxel with or without ramucirumab, or S-1) is administered in clinical practice after progression in patients who have received ICIs and platinum-doublet chemotherapy.

The administration of single-agent chemotherapy as second-line or subsequent treatment for patients with advanced NSCLC generally results in a poor treatment outcome. In a recent phase 3 study, the objective response rate (ORR), median progression-free survival (PFS), and median overall survival (OS) in patients administered docetaxel plus ramucirumab were 23–28.9%, 4.5–-5.22 months, and 10.5–15.15 months, respectively;[6,7] in patients administered docetaxel were 9.9–18.5%, 2.89–-4.21 months, and 9.1–14.65 months, respectively;[6–8] and in patients administered S-1 were 8.3%, 2.86 months, and 12.75 months, respectively.[8]

Recently, it has been suggested that the efficacy of chemotherapy involves not only direct cytotoxic effects, but also activation of tumor-targeting immune responses.[9] In a phase 2 study, a combination of pembrolizumab, carboplatin, and pemetrexed was suggested as an effective first-line treatment for patients with advanced non-squamous NSCLC.[10]

Moreover, an increased number of activated T cells induced by exposure to ICIs may enhance subsequent chemotherapy administered after ICI treatment. Several reports have indicated that subsequent cytotoxic chemotherapy among patients who have received ICIs might have relatively better efficacy.[11–14] However, two of these studies did not report control data. Other studies have compared results with a small number of control data of non-platinum cytotoxic chemotherapies without ICIs administered during the same term, but selection bias may have existed because the data were collected in a non-consecutive manner.

The purpose of the present study was to investigate the efficacy of subsequent cytotoxic chemotherapy after nivolumab compared to the same regimen without pretreatment with ICIs in patients with advanced non-small cell lung cancer.

Methods

Data collection

The clinical data of advanced NSCLC patients treated with nivolumab during clinical practice at the National Cancer Center Hospital between 17 December 2015 and 31 August 2017 were consecutively reviewed (nivolumab was approved in Japan on 17 December 2015), and the treatment outcomes of docetaxel-based chemotherapy (docetaxel +/− ramucirumab) or S-1 after nivolumab administration were analyzed (nivolumab-treated group). We then compared these results with those of advanced NSCLC patients treated with docetaxel or S-1 during clinical practice between 17 December 2014 and 16 December 2015 (i.e. in the last year prior to nivolumab approval) who had not previously received ICIs (ICI-untreated group). None of the patients received docetaxel plus ramucirumab without ICIs because ramucirumab was approved in Japan on 20 June 2016.

Information on gender, histology, driver oncogenes, tumor node metastasis (TNM) staging (Union for International Cancer Control 7th edition TNM classification for lung cancer), age, Eastern Cooperative Oncology Group performance status (ECOG PS), treatment line, and chemotherapy regimen were collected.

All NSCLC histologies, except for carcinoid or sarcomatoid carcinoma, double cancer, NSCLC containing a small cell component, and NSCLC that had transformed to small cell cancer, were eligible for inclusion. Patients who had received molecular targeted therapy, chemoradiotherapy, or the re-administration of previously administered agents as subsequent treatments were excluded from analysis.

The ORR, disease control rate (DCR), PFS, and follow-up duration of patients administered cytotoxic chemotherapies were assessed as of 31 December 2017.

The institutional review board of the National Cancer Center Hospital approved this study.

Statistical analysis

ORRs and DCRs were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients who could not be assessed using RECIST version 1.1 were excluded from ORR and DCR analyses. PFS was measured from the date of initial treatment until death before progression, the date of disease progression, or the date of clinical progression. The follow-up period was measured from the date of initial treatment until the data cutoff date of 31 December 2017, or until patients were lost to follow-up. All patients were included in PFS and follow-up period analyses.

The PFS and the follow-up period were estimated using the Kaplan–Meier method. Odds ratios (ORs) were assessed with the use of a nominal logistic regression model, and hazard ratios (HRs) were assessed with the use of a Cox proportional hazards model. All statistical analyses were performed using JMP version 13.1.0.

Results

Patients

Nivolumab-treated group

A total of 230 patients with NSCLC were treated with nivolumab during clinical practice at the National Cancer

Center Hospital between 17 December 2015 and 31 August 2017. Eight patients were excluded because of a particular histology (1 carcinoid tumor, 4 sarcomatoid carcinomas, 1 double cancer, 1 NSCLC containing a small cell component, and 1 NSCLC that had transformed to small cell cancer). In total, 163 patients discontinued nivolumab treatment because of disease progression.

Fifty-four patients were administered cytotoxic chemotherapy (any line of treatment) after receiving nivolumab. Thirty patients were administered docetaxel-based chemotherapy and 21 patients were administered S-1. Twenty-two patients who received docetaxel-based chemotherapy and 15 patients who received S-1 were evaluable using RECIST.

Fifty patients were administered subsequent cytotoxic chemotherapy immediately following nivolumab. Twenty-four patients were administered docetaxel-based chemotherapy and 15 patients were administered S-1. Eighteen patients who received docetaxel-based chemotherapy and 10 patients who received S-1 were evaluable using RECIST (Fig 1a).

Immune checkpoint inhibitor-untreated group

Overall, 81 patients with NSCLC were treated with docetaxel during clinical practice between 17 December 2014 and 16 December 2015. Three patients were excluded because of a particular histology (2 sarcomatoid carcinomas and 1 double cancer). Five patients who had previously been treated with ICIs and seven patients who had received docetaxel as a trial therapy were also excluded. In total, 66 patients who received docetaxel without ICIs were analyzed. Fifty patients administered docetaxel-based chemotherapy were evaluable using RECIST (Fig 1b).

Twenty-nine patients with NSCLC were treated with S-1 during clinical practice between 17 December 2014 and 16 December 2015. One patient with double cancer was excluded. Four patients who had been previously treated with ICIs and one patient who had received S-1 as a re-challenge therapy were also excluded. In total, 23 patients who received S-1 without ICIs were analyzed. Seventeen patients who received S-1 were evaluable using RECIST (Fig 1c).

Patient characteristics at the time of cytotoxic chemotherapy

In general, the patient characteristics were similar among the groups (docetaxel-based chemotherapy immediately after nivolumab, S-1 immediately after nivolumab, any line of docetaxel-based chemotherapy after nivolumab, any line of S-1 after nivolumab, docetaxel without ICIs, and S-1 without ICIs), although more women than men received S-1 immediately after nivolumab (Table 1).

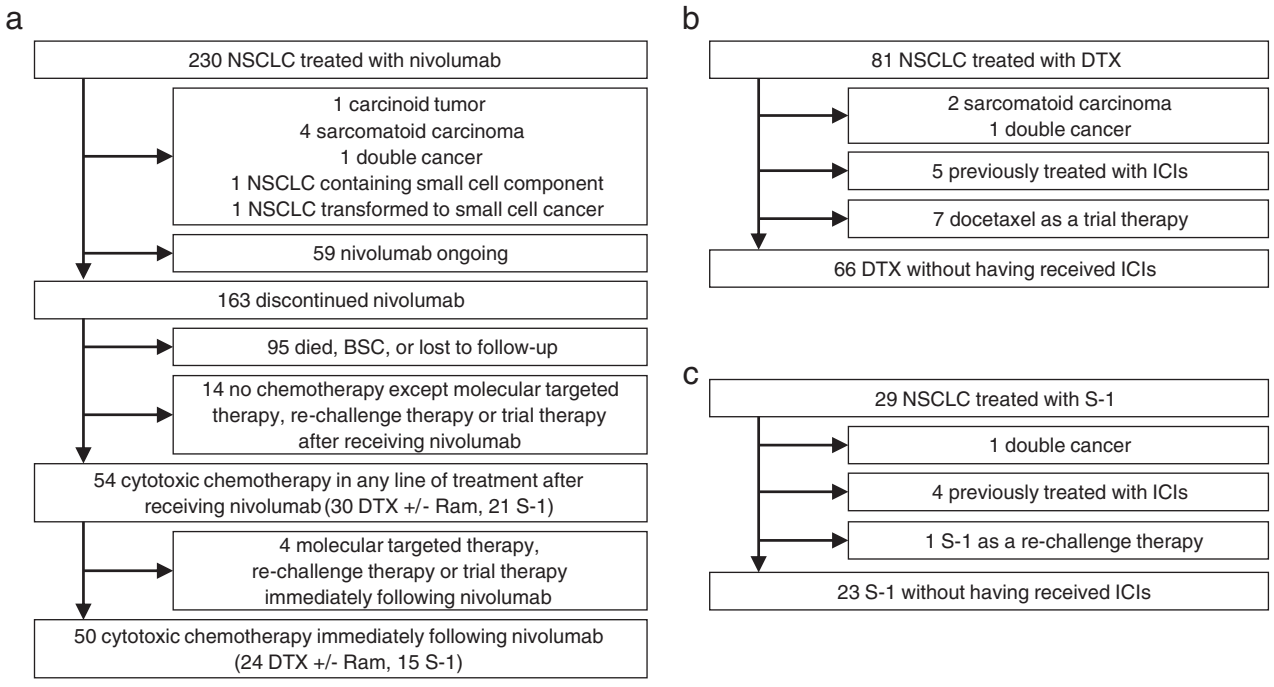

Figure 1 Flow diagram: patients administered (**a**) cytotoxic chemotherapy after nivolumab, (**b**) docetaxel without immune checkpoint inhibitors (ICIs), and (**c**) S-1 without ICIs. BSC, best-supportive care; DTX, docetaxel; NSCLC, non-small cell lung cancer; Ram, ramucirumab.

Table 1 Patient characteristics at the time of cytotoxic chemotherapy

Characteristic	DTX-based CT immediately after Nivo	S-1 immediately after Nivo	DTX-based CT in any line after Nivo	S-1 in any line after Nivo	DTX without ICIs	S-1 without ICIs
N	24	15	30	21	66	23
Gender						
Male	13 (54.2%)	5 (33.3%)	16 (53.3%)	11 (52.4%)	52 (78.8%)	15 (65.2%)
Female	11 (45.8%)	10 (66.7%)	14 (46.7%)	10 (47.6%)	14 (21.2%)	8 (34.8%)
Age, median (range)	64 (39–76)	60 (42–77)	63 (39–76)	60 (42–77)	63 (35–82)	62 (35–73)
ECOG PS						
0/1	22 (91.7%)	13 (86.7%)	25 (83.3%)	19 (90.5%)	61 (92.4%)	20 (87.0%)
2	2 (8.3%)	2 (13.3%)		2 (9.5%)	5 (7.6%)	1 (4.3%)
NA	0	0	5 (16.7%)	0	0	2 (8.7%)
			0			
Histology						
Ad	17 (70.8%)	12 (80.0%)	23 (76.7%)	17 (81.0%)	51 (77.3%)	14 (60.9%)
Sq	6 (25.0%)	3 (20.0%)	6 (20.0%)	4 (19.0%)	13 (19.7%)	9 (39.1%)
LCNEC	0	0	0	0	2 (3.0%)	0
NSCLC, NOS	1 (4.2%)	0	1 (3.3%)	0	0	0
Driver oncogenes						
EGFR mutation	5 (20.8%)	2 (13.3%)	8 (26.7%)	4 (19.0%)	13 (19.7%)	2 (8.7%)
ALK rearrangement	0	0	1 (3.3%)	0	4 (6.1%)	0
TNM staging (at diagnosis)						
IA/IB	3 (12.5%)	0	4 (13.3%)	2 (9.5%)	3 (4.5%)	2 (8.7%)
IIA/IIB	0	3 (20.0%)	1 (3.3%)	4 (19.0%)	10 (15.2%)	3 (13.0%)
IIIA/B	4 (16.7%)	5 (33.3%)	6 (20.0%)	5 (23.8%)	15 (22.7%)	3 (13.0%)
IVA/B	17 (70.8%)	7 (46.7%)	19 (63.3%)	10 (47.6%)	38 (57.6%)	15 (65.2%)
Treatment line						
1	0	0	0	0	6 (9.1%)	0
2	0	1 (6.7%)	0	1 (4.8%)	36 (54.5%)	7 (30.4%)
3	18 (75.0%)	9 (60.0%)	18 (60.0%)	9 (42.9%)	14 (21.2%)	9 (39.1%)
4	3 (12.5%)	3 (20.0%)	5 (16.7%)	5 (23.8%)	7 (10.6%)	6 (26.1%)
5	1 (4.2%)	1 (6.7%)	1 (3.3%)	2 (9.5%)	2 (3.0%)	0
6	2 (8.3%)	0	3 (10.0%)	0	0	0
7	0	0	2 (6.6%)	1 (4.8%)	1 (1.5%)	1 (4.3%)
8	0	1 (6.7%)	0	2 (9.5%)	0	0
9	0	0	1 (3.3%)	0	0	0
10	0	0	0	0	0	0
11	0	0	0	1 (4.8%)	0	0
Regimen						
DTX-based						
DTX	6 (25.0%)	—	10 (33.3%)	—	66 (100%)	—
DTX + Ram	18 (75.0%)	—	20 (66.7%)	—	—	—
S-1	—	15 (100%)	—	21 (100%)	—	23 (100%)
Interval from the last infusion of Nivo, median months (range)	0.9 (0.5–12.7)	1.3 (0.5–3.0)	1.2 (0.5–15.5)	1.4 (0.5–9.1)	—	—

Ad, adenocarcinoma; CBDCA, carboplatin; CT, chemotherapy; DTX, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; ETP, etoposide; GEM, gemcitabine; ICIs, immune checkpoint inhibitors; LCNEC, large-cell neuroendocrine carcinoma; NA, not analyzed; Nivo, nivolumab; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PEM, pemetrexed; Ram, ramucirumab; Sq, squamous-cell carcinoma; TNM, tumor node metastasis.

Efficacy

Objective response and disease control rates

While the ORR to docetaxel without ICIs was 16.0% (8/50), the ORRs to docetaxel-based chemotherapy immediately after nivolumab and in any line after nivolumab were 27.8% (5/18, OR 2.02, 95% confidence interval [CI] 0.56–7.25; $P = 0.28$) and 27.3% (6/22, OR 1.97, 95% CI 0.59–6.57; $P = 0.27$), respectively. The ORR to S-1 without ICIs was 17.6% (3/17), and the ORRs to S-1

immediately after nivolumab and in any line after nivolumab were 30.0% (3/10, OR 2.00, 95% CI 0.32–12.59; $P = 0.46$) and 20.0% (3/15, OR 1.17, 95% CI 0.20–6.89; $P = 0.86$), respectively. The ORR to docetaxel or S-1 without ICIs was 16.4% (11/67), and the ORRs to docetaxel-based chemotherapy or S-1 immediately after nivolumab and in any line after nivolumab were 28.6% (8/28, OR 2.04, 95% CI 0.72–5.78; $P = 0.18$) and 24.3% (9/37, OR 1.64, 95% CI 0.61–4.41; $P = 0.33$), respectively.

In addition, we analyzed the DCRs. The DCR to docetaxel without ICIs was 56.0% (28/50), and the DCRs to docetaxel-based chemotherapy immediately after nivolumab and in any line after nivolumab were 55.6% (10/18, OR 0.98, 95% CI 0.33–2.91; $P = 0.97$) and 54.5% (12/22, OR 0.94, 95% CI 0.34–2.58; $P = 0.91$), respectively. The DCR to S-1 without ICIs was 58.8% (10/17), and the DCRs to S-1 immediately after nivolumab and in any line after nivolumab were 50.0% (5/10, OR 0.70, 95% CI 0.15–3.37; $P = 0.66$) and 46.7% (7/15, OR 0.61, 95% CI 0.15–2.49; $P = 0.49$), respectively. The DCR to docetaxel or S-1 without ICIs was 56.7% (38/67), and the DCRs to docetaxel-based chemotherapy or S-1 immediately after nivolumab and in any line after nivolumab were 53.6% (15/28, OR 0.88, 95% CI 0.36–2.14; $P = 0.78$) and 51.4% (19/37, OR 0.81; 95% CI 0.36–1.80; $P = 0.60$), respectively (Table 2).

We observed a tendency toward an objective response to chemotherapy after nivolumab; however, the difference was not significant because of the small sample size. No significant difference in the DCR between chemotherapy after nivolumab and without ICIs was observed.

Progression-free survival

While the median PFS for docetaxel without ICIs was 2.87 months, the median PFS rates for docetaxel-based chemotherapy immediately after nivolumab and in any line after nivolumab were 5.98 months (HR 0.69, 95% CI 0.35–1.26; $P = 0.23$) and 4.67 months (HR 0.76, 95% CI 0.41–1.32; $P = 0.34$), respectively. The median PFS to S-1 without ICIs was 2.63 months, and the median PFS rates to S-1 immediately after nivolumab and in any line after nivolumab were 3.88 months (HR 1.00, 95% CI 0.40–2.38; $P = 1.00$) and 3.06 months (HR 0.81, 95% CI 0.36–1.81; $P = 0.60$), respectively. The median PFS to docetaxel or S-1 without ICIs was 2.74 months, and the median PFS rates to docetaxel-based chemotherapy or S-1 immediately after nivolumab and in any line after nivolumab were 5.26 months (HR 0.79, 95% CI 0.47–1.29; $P = 0.36$) and 3.88 months (HR 0.92, 95% CI 0.58–1.43; $P = 0.72$), respectively (Table 2, Fig 2).

We observed a positive tendency in PFS of chemotherapy after nivolumab; however, the difference was not significant because of the small sample size.

Subgroup analyses

We analyzed subgroups of chemotherapies by treatment lines and subgroups of docetaxel monotherapy after nivolumab. Subgroup analyses of chemotherapies by treatment line demonstrated similar trends, but subgroup analyses of docetaxel monotherapy showed no difference after nivolumab. The details are shown in Table 3.

Follow-up period

The percentages of patients evaluated after three and six-month follow-up periods and the median follow-up period after docetaxel or S-1 without ICIs were 97.7%, 97.7%, and not evaluable, respectively, while those after docetaxel-

Table 2 Responses and progression-free survival of patients administered cytotoxic chemotherapy

Response	DTX-based CT immediately after Nivo	S-1 immediately after Nivo	DTX-based CT or S-1 immediately after Nivo	DTX-based CT in any line after Nivo	S-1 in any line after Nivo	DTX-based CT or S-1 in any line after Nivo	DTX without ICIs	S-1 without ICIs	DTX or S-1 without ICIs
N	24	15	39	30	21	51	66	23	89
Evaluable by RECIST	18	10	28	22	15	37	50	17	67
CR	0	0	0	0	0	0	0	0	0
PR	5	3	8	6	3	9	8	3	11
SD	5	2	7	6	4	10	20	7	27
PD	8	5	13	10	8	18	22	7	29
NE	6	5	11	8	6	14	16	6	22
ORR (%)	27.8	30.0	28.6	27.3	20.0	24.3	16.0	17.6	16.4
DCR (%)	55.6	50.0	53.6	54.5	46.7	51.4	56.0	58.8	56.7
Median PFS (months)	5.98	3.88	5.26	4.67	3.06	3.88	2.87	2.63	2.74

CR, complete response; CT, chemotherapy; DCR, disease control rate; DTX, docetaxel; ICIs, immune checkpoint inhibitors; NE, not evaluable; Nivo, nivolumab; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD stable disease.

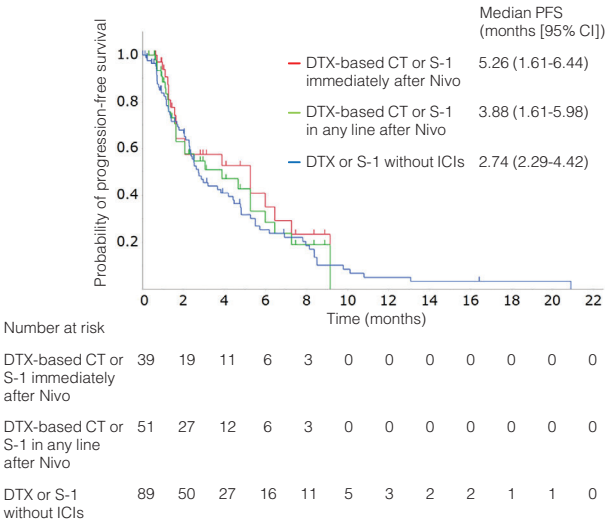

Figure 2 Kaplan–Meier curve of progression-free survival (PFS). CI, confidence interval; CT, chemotherapy; DTX, docetaxel; ICIs, immune checkpoint inhibitors; Nivo, nivolumab.

based chemotherapy or S-1 in any line after nivolumab were 98.0%, 80.9%, and 8.35 months, respectively.

Discussion

We assessed the efficacy of subsequent cytotoxic chemotherapy among patients with advanced NSCLC. The ORR, DCR, and median PFS of patients administered docetaxel-based chemotherapy or S-1 after nivolumab, especially immediately after nivolumab, tended to be better than those of patients administered docetaxel or S-1 without ICIs.

A previous preclinical study demonstrated that nivolumab enhances T cell proliferation and cytokine production in vitro,[15] while another study reported that the addition of nonspecifically activated $CD4^+$ T cells as a chemosensitizer greatly enhanced the cytotoxic effect of chemotherapy in both in vitro and in vivo human tumor models.[16]

Several retrospective clinical studies have also reported that subsequent cytotoxic chemotherapy after ICI treatment may have better efficacy (Table 4).[11–14] The reported ORRs, DCRs, and median PFS periods were 26.9–53.4%, 48.5–77.6%, and 2.5–4.7 months, respectively. However, these studies might have contained some biases. Grigg[11] and Schvartsman *et al.*[13] did not analyze the patients who were not treated with ICIs, while Leger[12] compared patients treated with and without ICIs during the same term. Park *et al.* compared the efficacy of chemotherapy immediately before and after ICIs in the same patients.[14] However, selection bias may have existed because these data were collected in a non-consecutive manner. To overcome this bias, we consecutively reviewed patients treated with nivolumab during clinical practice and compared the results with those of patients who had not received ICIs before the approval of nivolumab.

Subsequent docetaxel-based chemotherapy or S-1 immediately after nivolumab demonstrated slightly better treatment efficacy, compared to that observed in patients not pretreated with ICIs. The ORR and median PFS of patients

Table 3 Subgroup analyses of responses and progression-free survival of patients administered cytotoxic chemotherapy

Response	DTX immediately after Nivo	DTX in any line after Nivo	DTX-based CT in third-line immediately after Nivo	S-1 in second or third-line immediately after Nivo	DTX-based CT or S-1 in second or third-line immediately after Nivo	DTX in first or second-line without ICIs	S-1 in second-line without ICIs	DTX or S-1 in first or second-line without ICIs
N	6	10	18	10	28	42	7	49
Evaluable by RECIST	3	5	14	8	22	32	6	38
CR	0	0	0	0	0	0	0	0
PR	0	0	4	2	6	4	1	5
SD	1	1	5	1	6	17	2	19
PD	2	4	5	5	10	11	3	14
NE	3	5	4	2	6	10	1	11
ORR (%)	0	0	28.6	25.0	27.3	12.5	16.7	13.2
DCR (%)	33.3	20.0	64.3	37.5	54.5	65.6	50.0	63.2
Median PFS (months)	1.61	1.61	6.44	3.88	5.26	3.66	1.32	3.20

CR, complete response; CT, chemotherapy; DCR, disease control rate; DTX, docetaxel; ICIs, immune checkpoint inhibitors; NE, not evaluable; Nivo, nivolumab; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Table 4 Recent studies of cytotoxic chemotherapy after ICIs

Study	N	ORR (%)	DCR (%)	Median PFS (months)
Grigg[11]				
CT following ICIs	39	30.8	53.8	2.5
No prior CT	6	50.0	83.3	NA
≧1 prior CT	33	27.3	48.5	NA
Leger[12]				
CT following ICIs	67	26.9	77.6	NA
CT without ICIs	15	6.7	60.0	NA
Schvartsman *et al*.[13]				
Single agent CT following ICIs	28	39.3	71.4	4.7
Park *et al*.[14]				
Last CT before ICIs	63	34.9	NA	4.7
Non-platinum	20	25.0	NA	3.5
CT immediately after ICIs	73	53.4	NA	4.5
Non-platinum	49	46.9	NA	3.8
Present study				
DTX-based CT or S-1 immediately after Nivo	39	28.6	53.6	5.26
DTX-based CT or S-1 in any line after Nivo	51	24.3	51.4	3.88
DTX or S-1 without ICIs	89	16.4	56.7	2.74

CT, cytotoxic chemotherapy; DTX, docetaxel; ICIs, immune checkpoint inhibitors; NA, not analyzed; Nivo, nivolumab; PFS, progression-free survival.

administered docetaxel-based chemotherapy after nivolumab were better than those administered docetaxel without ICIs. Additionally, the ORR and the median PFS of the patients who received S-1 immediately after nivolumab were better than those who received S-1 without ICIs. However docetaxel monotherapy after nivolumab showed no difference; we consider some confounding factors, such as small sample size and the selection of patients unable to receive ramucirumab in combination with docetaxel, responsible for this result. Although the addition of ramucirumab to docetaxel might have led to better efficacy, the similar result of S-1 treatment after nivolumab cannot be explained in this manner because S-1 was used as single-agent chemotherapy.

The treatment efficacy of cytotoxic chemotherapy after nivolumab might increase when it is administered immediately after nivolumab. The number of activated T cells induced by exposure to nivolumab might decrease with time, or the response to nivolumab might continue for a while after progression. It may be desirable to use ICIs early during the treatment of advanced NSCLC and to administer subsequent treatments as soon as possible once the ICIs have been discontinued.

The present study had some limitations. First, we could not analyze the PD-L1 TPS because nivolumab can be administered regardless of the PD-L1 TPS. Whether the expression of PD-L1 is correlated with the efficacy of a chemosensitizer remains uncertain. Second, this study included patients administered chemotherapy at various treatment lines. Third, a few of the patients were administered docetaxel monotherapy without ramucirumab after nivolumab because combination therapy with docetaxel and ramucirumab has only recently become standard therapy.

In conclusion, subsequent cytotoxic chemotherapy, especially immediately after nivolumab treatment, demonstrated better treatment efficacy than that of regimens without ICI pretreatment.

Disclosure

HH has received research grants from Bristol-Myers Squibb, ONO, Kyowa Kirin, Taiho, Chugai, Novartis, MSD, Merck Serono, Astellas, and Genomic Health, and received honoraria from Lilly, Bristol-Myers Squibb, ONO, Kyowa Kirin, Taiho, Chugai, and Novartis.

KS has received honoraria from MSD, ONO, AstraZeneca, and Daiichi-Sankyo.

YM has received research grants from Hitachi, Hitachi High-Technologies and Boston Scientific, and served on speakers' bureaus from Olympus, Cook Medical, and AstraZeneca.

SM has received research grants from Takeda and honoraria from AstraZeneca, Chugai, Boehringer Ingelheim, Taiho, and ONO.

YG has received research grants from Abbvie, Lilly, Taiho, Bristol Myers Squibb, and ONO; served on speakers' bureaus from AstraZeneca, Lilly, Chugai, Taiho, Boehringer Ingelheim, ONO, Bristol-Myers Squibb, Pfizer, MSD, Shionogi, and Novartis; and had consulting or advisory roles for Lilly, Chugai, Taiho, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, and Glaxo Smith Kline.

SK has received research grants from AstraZeneca, ONO, and AbbVie and honoraria from AstraZeneca, ONO, Bristol-Myers Squibb, and Chugai.

YF has received research grants from Abbvie, AstraZeneca, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Incyte, Merck Serono, MSD, and Novartis; served on speakers' bureaus from AstraZeneca, Bristol-Myers Squibb, MSD, Novartis, ONO, Sysmex, and Taiho; and had consulting or advisory roles for Astra Zeneca, BMS, MSD, Novartis, and ONO.

NY has received research grants from Quintiles, Astellas, Chugai, Eisai, Taiho, Bristol-Myers Squibb, Pfizer, Novartis, Daiichi-Sankyo, Bayer, Boehringer Ingelheim, Kyowa Kirin, Takeda, ONO, Janssen, Lilly, MSD, and

Merck Serono; served on speakers' bureaus from Eisai, Takeda, Otsuka, Boehringer Ingelheim, and Cimic; and had consulting or advisory roles for Bristol-Myers Squibb, Pfizer, AstraZeneca, Lilly, ONO, and Chugai.

YO has received grants from Lilly, ONO, Bristol-Myers Squibb, Taiho, AstraZeneca, Chugai, Pfizer, MSD, Kyorin, Takeda, Kissei, Dainippon-Sumitomo, and Ignyta; and received honoraria from Lilly, ONO, Bristol-Myers Squibb, Taiho, AstraZeneca, Chugai, Pfizer, MSD, Celltrion, Amgen, Kyorin, Takeda, Boehringer Ingelheim, and Novartis.

NT reports no conflict of interest.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87–108.

2 Reck M, Rodriguez-Abreu D, Robinson AG *et al.* Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; **375**: 1823–33.

3 Borghaei H, Paz-Ares L, Horn L *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; **373**: 1627–39.

4 Brahmer J, Reckamp KL, Baas P *et al.* Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; **373**: 123–35.

5 Herbst RS, Baas P, Kim DW *et al.* Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. *Lancet* 2016; **387**: 1540–50.

6 Garon EB, Ciuleanu TE, Arrieta O *et al.* Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014; **384**: 665–73.

7 Yoh K, Hosomi Y, Kasahara K *et al.* A randomized, double-blind, phase II study of ramucirumab plus docetaxel vs placebo plus docetaxel in Japanese patients with stage IV non-small cell lung cancer after disease progression on platinum-based therapy. *Lung Cancer* 2016; **99**: 186–93.

8 Nokihara H, Lu S, Mok TSK *et al.* Randomized controlled trial of S-1 versus docetaxel in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy (East Asia S-1 trial in lung cancer). *Ann Oncol* 2017; **28**: 2698–706.

9 Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. *Cancer Cell* 2015; **28**: 690–714.

10 Langer CJ, Gadgeel SM, Borghaei H *et al.* Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* 2016; **17**: 1497–508.

11 Grigg C. Clinical outcomes of patients of non-small cell lung cancer (NSCLC) receiveng chemotherapy after immune checkpoint blockage. *J Clin Oncol* 2017; **35**: 9082.

12 Leger P. Salvage chemotherapy following exposure to immune checkpoints inhibitors in patients with NSCLC. *J Clin Oncol* 2017; **35**: 9084.

13 Schvartsman G, Peng SA, Bis G *et al.* Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer. *Lung Cancer* 2017; **112**: 90–5.

14 Park SE, Lee SH, Ahn JS, Ahn MJ, Park K, Sun JM. Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer. *J Thorac Oncol* 2018; **13**: 106–11.

15 Wang C, Thudium KB, Han M *et al.* In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. *Cancer Immunol Res* 2014; **2**: 846–56.

16 Radfar S, Wang Y, Khong HT. Activated CD4+ T cells dramatically enhance chemotherapeutic tumor responses in vitro and in vivo. *J Immunol* 2009; **183**: 6800–7.

