Original Article

Open-label, multi-center, phase II study of adjuvant pemetrexed plus cisplatin for completely resected stage IB to IIIA adenocarcinoma of the lung: APICAL trial

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Background: We aimed to evaluate the efficacy of postoperative adjuvant pemetrexed plus cisplatin (Pem-Cis) in pathologic stage IB–IIIA lung adenocarcinoma (LUAD) patients.

Methods: A prospective, phase II study was performed in seven institutions in South Korea. Patients with completely resected stage IB–IIIA LUAD received pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2). Adjuvant treatments were administered every 3 weeks for 4 cycles. The primary endpoint was to prove the Pem-Cis's superiority in terms of 2-year disease-free survival rate (DFSR) compared with historical control without adjuvant chemotherapy (50%).

Results: Between August 2015 and February 2018, 105 patients were enrolled in this study. Approximately 31.4% (n=33), 43.8% (n=46), and 24.8% (n=26) of patients had pathologic stage IB, II, and IIIA, respectively. Most of the patients underwent lobectomy (n=98, 93.3%). Moreover, 41.1% and 12.1% of the patients had epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase rearrangement. Four cycles of Pem-Cis were administered in 99 patients (94.3%). At a median follow-up of 57.7 months, the 2-year DFSR was 78.1%. Multivariable analysis showed that pathologic stage IIIA and EGFR mutation were significant risk factors for DFS. Grade 3 adverse events occurred in 10 patients (9.5%), and leukopenia (n=3, 2.9%) was the most common adverse event.

Conclusions: Adjuvant Pem-Cis is superior to historical control without adjuvant treatment in terms of 2-year DFSR; the proportion of patients with stage IB and driver mutations were higher than that of patients in previous trials. Pem-Cis showed favorable tolerability as adjuvant chemotherapy (clinicaltrial.gov; Identifier: NCT02498860).

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide. In South Korea, the crude mortality rates per 100,000 population in 2018 were 51.5 in men and 18.1 in women; lung cancer had the highest cancer death rate both in men and women (1-3). Since approximately 40% of patients with non-small cell lung cancer (NSCLC) were diagnosed with stage IV disease (4), the role of lung cancer screening and surgery has been increasingly important in improving the survival rate. According to previous studies of lung cancer registry in South Korea, patients with NSCLC underwent surgery as an initial treatment (37.6%) with (33.8%) or without adjuvant therapy (66.2%) (4,5).

Even for early-stage NSCLC resected with curative intent, nearly half of patients experienced relapse within 5 years after surgery. In a study of Japanese registry, the 5-year postoperative survival rates were reported to be 64.1% for stage IIA, 56.1% for stage IIB, and 47.9% for stage IIIA (6). Postoperative adjuvant chemotherapy using platinum doublet in patients with NSCLC showed a modest survival benefit with a hazard ratio of 0.89 [95% confidence interval (CI): 0.82–0.96] for death in a meta-analysis of 4,584 patients [the Lung Adjuvant Cisplatin Evaluation (LACE) trial] from phase III trials comparing cisplatin-based doublet chemotherapy and no chemotherapy (7). As the vinorelbine-platinum combination only showed a significant survival benefit in the subgroup analysis of the LACE trial, vinorelbine plus cisplatin was used as the standard adjuvant chemotherapy.

As the pemetrexed-platinum combination had been used as a standard regimen for metastatic non-squamous cell NSCLC (8), the Japanese group conducted a randomized phase III trial (JIPANG, a multi-center, open-label phase III trial) to evaluate the efficacy of adjuvant pemetrexed plus cisplatin (Pem-Cis) and that of vinorelbine plus cisplatin (Vin-Cis) in patients with stage II–IIIA non-squamous NSCLC (9). Although the superiority of Pem-Cis was not proven, Pem-Cis showed a better toxicity profile compared with Vin-Cis.

In South Korea, the pemetrexed-platinum combination regimen as postoperative adjuvant chemotherapy had not been reimbursed by the Korean Health Insurance Review and Assessment at the time of trial initiation in 2015 (which was later reimbursed in May 2021). To confirm the efficacy of Pem-Cis, a single-arm Pem-Cis adjuvant chemotherapy trial was conducted in patients with completely resected lung adenocarcinoma (LUAD). The primary endpoint was to confirm the superiority of a 2-year disease-free survival rate (DFSR) compared to historical control without adjuvant treatment (50%). We present the following article in accordance with the TREND reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-183/rc).

Methods

Study participants and procedures

An open-label, multi-center, prospective phase II study was conducted to evaluate the efficacy of postoperative adjuvant Pem-Cis. Between August 2015 and February 2018, patients from seven tertiary medical centers in South Korea were recruited. Those with completely resected pathologic stage IB–IIIA LUAD (Union for International Cancer Control TNM classification, seventh edition) were enrolled in this study. *Figure 1* shows the flowchart of the patient enrollment process. The eligible patients were aged >20 years, had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2, had no history of receiving chemotherapy, and had adequate marrow, hepatic, and renal function. The other inclusion and exclusion criteria are described in Appendix 1.

The enrolled patients received intravenous infusions of pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) on day 1. Adjuvant treatments were initiated within 4 to 8 weeks after surgery and were administered every 3 weeks for 4 cycles. A daily dose of oral folic acid (1 mg per day) was administered a week before the initiation of pemetrexed treatment and maintained until at least 3 weeks after the final dose. In addition, an intramuscular injection of vitamin B12 (1 mg) was administered within 7 days after the first dose of pemetrexed and until 3 weeks after the last dose of pemetrexed was provided. Monitoring of toxicity, including

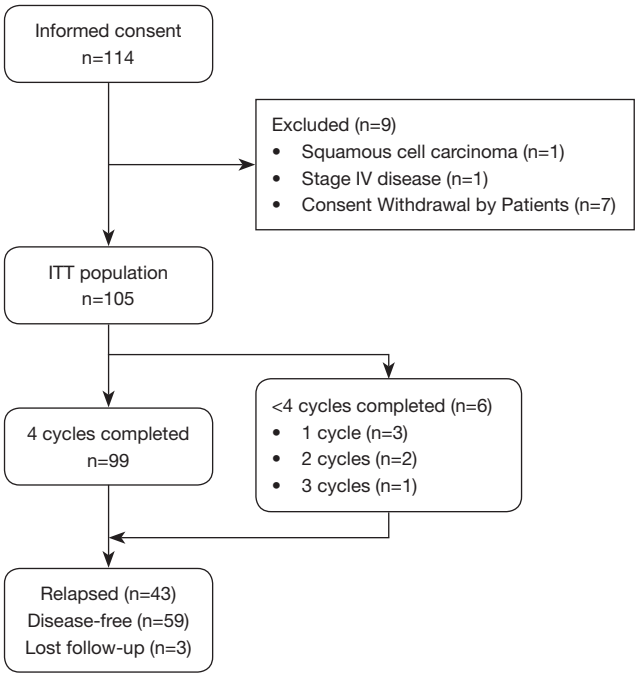

Figure 1 Patients enrollment. ITT, intention-to-treat.

physical examination and laboratory tests, were performed at every visit for administration and on days 8 to 15 at each cycle. In patients without recurrence, postoperative radiotherapy was not permitted. Follow-up assessment with chest computed tomography and bone scan was continued every 3 months for the first year and then every 4 months for the second year.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice guidelines. This study was approved by the ethics review board of Chonnam National University Hwasun Hospital (IRB No. CNUHH-2015-007) and also approved by each participating institution. All patients were required to provide written and informed consent before participating in the study. The trial was registered at clinicaltrial.gov (Identifier: NCT02498860).

Outcomes and statistical analysis

The primary endpoint was to confirm whether adjuvant Pem-Cis in patients with completely resected LUAD is superior to historical control without adjuvant treatment (50%) in terms of a 2-year DFSR. The 2-year DFSR of the control group was calculated based on the median disease-free survival (DFS) reported in the ANITA trial, using a sample size calculation software, nQuery (2015, Statsols, Statistical Solutions Ltd., Cork, Ireland). The median DFS in the control and intervention groups were 20.7 months (95% CI: 16.1–28.6) and 36.3 months (95% CI: 28.0–52.1), respectively (10). Assuming that the DFS showed an exponential tendency, the 2-year DFSR was estimated to be 44.8% in the control group and 63.2% in the intervention group. In the present trial, we hypothesized that the 2-year DFSR of the historical control would be 50% because the survival rate of Asians is generally higher than that of Caucasians, and the 2-year DFSR of adjuvant Pem-Cis is at least 63%. Taken together with the expected follow-up time of 2 years, a significant level of 5% (two-sided), a power of 80%, and a drop-out rate of 10%, the required number of patients for enrollment was calculated as 105.

The secondary endpoints were overall survival (OS), toxicity profiles, ECOG PS score, and 4-cycle completion rate. According to the study protocol, DFS was measured from the first date of drug administration to the first date of objective recurrence or death from any cause and was censored at the date of last patient contact before the data lock point. OS was measured from the first date of drug administration to the date of death from any cause and was censored on the date of the last patient contact before the cut-off date. The adverse events were graded based on the severity, using the Common Terminology Criteria for Adverse Events (version 4.3). Efficacy analysis was performed for the intention-to-treat (ITT) population. For toxicity profiles, only patients who received at least one dose of Pem-Cis were included.

All data were expressed as mean ± standard deviation or as numbers and percentages. Intergroup comparisons were performed using *t*-test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables. Survival times were estimated using the Kaplan-Meier method. Statistical analysis was performed using IBM® SPSS® statistics version 25 (IBM Corp., Armonk, NY, USA) and R statistics (11), and a P value of <0.05 was considered significant.

Results

Patients' characteristics

As shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram of *Figure 1*, 114 patients were recruited between August 2015 and February 2018. Nine patients were excluded due to squamous cell

Table 1 Characteristics of 105 participants enrolled in this trial

Characteristic	No. of patients (%)
Age, years, median [range]	63.0 [38–78]
Sex: male/female	51 (48.6)/54 (51.4)
Smoking: never/current/ex-smoker	56 (53.3)/14 (33.3)/35 (13.3)
ECOG PS[†]: 0/1/2	60 (57.7)/44 (42.3)/0 (0.0)
Pathologic stage (TNM 7th)	
IB/IIA/IIB/IIIA	33 (31.4)/34 (32.4)/12 (11.4)/26 (24.8)
pT1/pT2/pT3/pT4	22 (21.0)/69 (65.7)/13 (12.4)/1 (1.0)
pN0/pN1/pN2	49 (46.7)/32 (30.5)/24 (22.6)
Histology, adenocarcinoma	105 (100.0)
Differentiation	
Well/moderate/poor/undifferentiated	7 (6.7)/47 (44.8)/41 (39.0)/10 (9.5)
Surgery	
Sublobar resection[‡]	3 (2.9)
Lobectomy	98 (93.3)
Bilobectomy/pneumonectomy	3 (2.9)/1 (1.0)
TTF-1 IHC (n=73): positive/negative	65(89.0)/8(11.0)
EGFR (n=90): mutant/wild	37 (41.1)/53 (58.9)
ALK (n=91): mutant/wild	11 (12.1)/80 (87.9)
ROS1 (n=28): mutant/wild	0 (0.0)/28 (100.0)
Cycles of chemotherapy	
1/2/3/4	3 (2.9)/2 (1.9)/1 (1.0)/99 (94.3)

[†], PS status data was missed in one patient; [‡], segmentectomy (n=2) or wedge resection (n=1). ECOG PS, Eastern Cooperative Oncology Group performance status; TTF-1, thyroid transcription factor-1; IHC, immunohistochemistry; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TNM, Tumor-Node-Metastasis.

carcinoma (n=1), stage IV disease (n=1), and consent withdrawal (n=7). A total of 105 patients from seven institutions were enrolled in the study and designated as the ITT population.

The baseline characteristics of the 105 patients are shown in *Table 1*. The median age was 63 years (range, 38–78), and 54 (51.4%) patients were women. Thirty-three (31.4%) patients had pathologic stage IB, 34 (32.4%) had stage IIA, 12 (11.4%) had stage IIB, and 26 (24.8%) had stage IIIA determined based on the TNM staging 7th edition. When the 8th Edition of the TNM staging system was applied, six patients with stage IIIA were upstaged to stage IIIB. Most of the patients underwent lobectomy (n=98, 93.3%), three underwent sublobar resection (segmentectomy or wedge resection), and four underwent bilobectomy or pneumonectomy. The most frequent type of gene alteration was epidermal growth factor receptor (EGFR) mutation (37/90, 41.1%), followed by anaplastic lymphoma kinase (ALK) rearrangement (11/91, 12.1%). Four cycles of Pem-Cis were administered in 99 patients (94.3%), and dose reduction was performed in 38 patients (36.2%).

Survival outcomes

The survival outcomes of patients treated with Pem-Cis are shown in *Figure 2*. At a median follow-up of 57.7 months (95% CI: 55.3–58.7), the median DFS was not reached, while the 2-year DFSR was 78.1% (95% CI: 70.6–86.4,

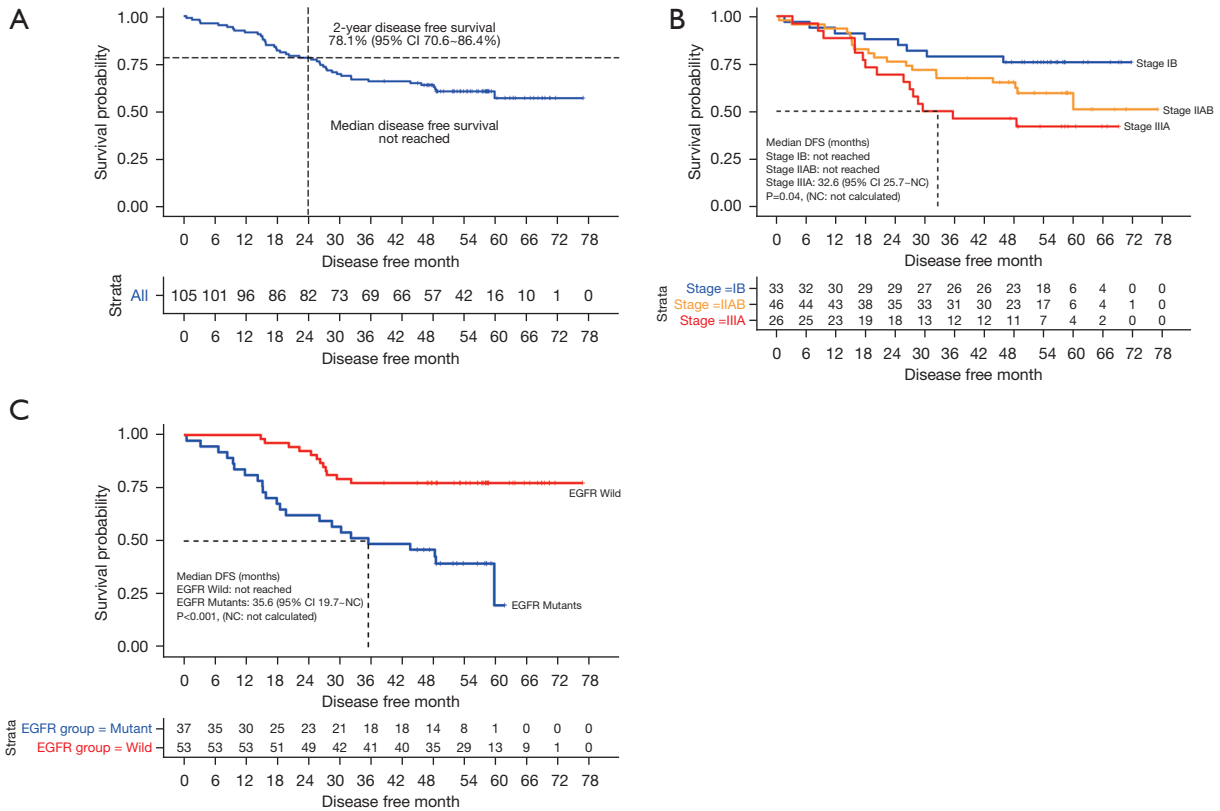

Figure 2 Kaplan-Meier curves for DFS of the overall population (n=105) (A), and DFS according to pathologic stages (B) and EGFR mutation (C). DFS, disease-free survival; EGFR, epidermal growth factor receptor; NC, not calculated.

Figure 2A). In patients with pathologic stage IIA to IIIA, the median DFS was 60.0 months (95% CI: 35.6–not calculated, Figure S1A), while the 2-year DFSR was 73.6% (95% CI: 64.1–84.5%, Figure S1B). The OS was not yet mature (17 events, 16.2%).

At the time of data cut-off (January 5, 2022), 43 patients (41.0%) experienced relapse (*Figure 1*). The characteristics of relapsed patients and subsequent treatment are described in *Table 2*. Seventeen patients (16.2%) experienced local relapse, while 23 patients (21.9%) showed distant metastasis. Distant metastasis commonly occurred in contralateral lung (9.5%, n=10), followed by the brain (7.6%, n=8) and bones (6.7%, n=7). With regard to the subsequent treatment after relapse (n=43), tyrosine kinase inhibitors (TKIs) for EGFR mutation or ALK rearrangement (51.2%, n=22) were frequently used, followed by cytotoxic chemotherapy (23.3%, n=10) and radiation therapy, including concurrent chemoradiation therapy (CCRT) (9.3%, n=4).

The Kaplan-Meier curves for DFS were clearly separated according to the pathologic stage from IB to IIIA (P=0.04; *Figure 2B*). The median DFS of stage IB and IIA–IIB disease was not yet reached, while that of stage IIIA disease was 32.6 months (95% CI: 25.7–not calculated). Although we did not investigate TTF-1 immunohistochemistry (IHC) prospectively, TTF-1 IHC was performed in 73 patients (69.5%), and a majority of patients showed positivity (n=65, 89.0%) (*Table 1*). There was no significant difference in DFS between TTF-1 IHC positive and negative patients (P=0.386). Patients with EGFR mutation showed a significantly higher recurrence rate (62.2% *vs.* 24.5%, P=0.001; *Table 2*) and shorter median DFS (35.6 months *vs.* not reached, P<0.001; *Figure 2C*) than patients with wild-type EGFR. In the multivariable analysis for DFS, pathologic stage IIIA disease and EGFR mutation were significant risk factors for DFS (*Table 3*).

Toxicity and safety

The adverse events of 101 patients are summarized in Tables S1,S2. Fatigue, cough, and gastrointestinal

Table 2 Characteristics of relapsed patients and treatment in the overall and EGFR mutation-tested population

Characteristic, n (%)	Total (n=105)	EGFR mutation test (n=90)	EGFR wild-type (n=53)	EGFR mutant (n=37)	P
Progression status					
Disease-free	59 (56.2)	51	37 (69.8)	14 (37.8)	0.001
Relapsed	43 (41.0)	36	13 (24.5)	23 (62.2)	
Lost follow-up	3 (2.9)	3	3 (5.7)	0 (0.0)	
Relapse pattern					
Local	17 (16.2)	14	4 (7.5)	10 (27.0)	0.452
Distant metastasis	23 (21.9)	22	9 (17.0)	13 (35.1)	
Contralateral lung	10 (9.5)	9	3 (33.3)	6 (46.2)	–
Pleura	5 (4.8)	5	2 (22.2)	3 (23.1)	–
Brain	8 (7.6)	8	4 (44.4)	4 (30.8)	–
Bones	7 (6.7)	7	1 (11.1)	6 (46.2)	–
Adrenal gland	1 (1.0)	1	0 (0.0)	1 (7.7)	–
Unknown	3 (2.9)	0	0 (0.0)	0 (0.0)	–
Subsequent treatment after relapse[†]					
Operation	2 (1.9)	2	0 (0.0)	2 (8.7)	–
Radiation therapy	4 (3.8)	3	0 (0.0)	3 (13.0)	–
Radical RT/CCRT	1 (1.0)/3 (2.9)	1/2	0 (0.0)	1 (4.3)/2 (8.7)	
Cytotoxic chemotherapy	10 (9.5)	9	8 (61.5)	1 (4.3)	–
Platinum doublet/monotherapy	9 (8.6)/1 (1.0)	8/1	7 (53.8)/1 (7.7)	1 (4.3)/0 (0.0)	
Tyrosine kinase inhibitor	22 (21.0)	20	3 (23.1)	17 (73.9)	–
EGFR/ALK	20 (19.0)/2 (1.9)	17/3	0 (0.0)/3 (23.1)	17 (73.9)/0 (0.0)	
Immune checkpoint inhibitor	1 (1.0)	1	1 (7.7)	0 (0.0)	–

[†], only the first treatment after relapse was described. RT, radiation therapy; CCRT, concurrent chemoradiation therapy; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Table 3 Univariable and multivariable analyses of disease-free survival

Variables, n (%)	Total (n=105)	Univariable		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P
Age			0.799		–
<65 years	60 (57.1)	1		–	
≥65 years	45 (42.9)	1.081 (0.592–1.975)		–	
Sex			0.643		–
Female	54 (51.4)	1		–	
Male	51 (48.6)	0.867 (0.475–1.584)		–	

Table 3 (*continued*)

Table 3 (*continued*)

Variables, n (%)	Total (n=105)	Univariable		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P
Smoking			0.767		–
Never	56 (53.3)	1		–	
Ever	49 (46.7)	1.095 (0.601–1.994)		–	
ECOG PS (n=104)			0.378		–
0	60 (57.7)	1		–	
1	44 (42.3)	1.309 (0.719–2.385)		–	
Pathologic stage (TNM 7th)					
IB	33 (31.4)	1	0.028	1	0.008
IIA–IIB	46 (43.8)	1.978 (0.865–4.522)	0.106	2.125 (0.776–5.815)	0.142
IIIA	26 (24.8)	3.172 (1.355–7.428)	0.008	4.741 (1.672–13.440)	0.006
Pathologic T stage			0.151		–
pT1–2	91 (86.7)	1		–	
pT3–4	14 (13.3)	1.757 (0.815–3.789)		–	
Pathologic N stage			0.071		–
pN0–1	81 (77.1)	1		–	
pN2	24 (22.9)	1.800 (0.950–3.409)		–	
Differentiation			0.215		–
Well or moderate	54 (51.4)	1		–	
Poor or Undifferentiated	51 (48.6)	0.681 (0.371–1.250)		–	
Surgery			0.917		–
Lobectomy	98 (93.3)	1		–	
Others†	7 (6.7)	0.939 (0.290–3.039)		–	
EGFR mutation (n=90)			<0.001		<0.001
Negative	53 (58.9)	1		1	
Positive	37 (41.1)	3.548 (1.789–7.039)		4.178 (2.055–8.492)	
ALK rearrangement (n=91)			0.457		–
Negative	80 (87.9)	1		–	
Positive	11 (12.1)	0.674 (0.239–1.904)		–	
Cycles of chemotherapy			0.508		–
Complete (4 cycles)	99 (94.3)	1		–	
Incomplete (<4 cycles)	6 (5.7)	1.486 (0.460–4.808)		–	

†, segmentectomy (n=2), wedge resection (n=1), bilobectomy (n=3) or pneumonectomy (n=1). HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TNM, Tumor-Node-Metastasis.

Table 4 Serious adverse events (N=21)

Adverse events	No. of patients (%)
Pneumonia	3 (2.9)
Pulmonary thromboembolism	3 (2.9)
Nausea	3 (2.9)
Vomiting	2 (1.9)
Liver enzyme increased	2 (1.9)
Abdominal pain	1 (1.0)
Colitis	1 (1.0)
Fever	1 (1.0)
Hyponatremia	1 (1.0)
Leukocytosis	1 (1.0)
White blood cell decreased	1 (1.0)
Other infections[†]	1 (1.0)
Pleural effusion	1 (1.0)

[†], acute phase reactant elevation.

symptoms, including anorexia, nausea, and vomiting, were common treatment-related adverse events of Pem-Cis. None of the patients developed grade 4 adverse events. A total of 21 serious adverse events were reported, including pneumonia and pulmonary thromboembolism, in each of the three patients (2.9%) (*Table 4*). Grade 3 adverse events occurred in 10 patients (9.5%) with leukopenia as the most common adverse event (n=3, 2.9%). No treatment-related death was reported.

Monitoring of toxicity, including ECOG PS score, physical examination, and laboratory tests, was performed at every visit for administration and on days 8–15 at each cycle. The proportions of patients with ECOG PS score 1 or 2 increased on days 8–15 at cycles 1–3, while the proportion of patients whose ECOG PS score was obtained on cycle 4 and end-of-treatment (EOT) visit remained unchanged (*Figure 3*).

Discussion

This open-label, multi-center, prospective phase II trial showed the favorable efficacy of Pem-Cis as postoperative adjuvant chemotherapy for LUAD compared with historical control without adjuvant treatment. The 2-year DFSR as the primary endpoint was 78.1% (95% CI: 70.6–86.4), while the median DFS was not reached. Although we cannot compare DFS directly with prior trials, the 2-year DFSR was numerically longer than historical control (50%) and chemotherapy group of ANITA trial (63.2%). Compared with previous trials on Pem-Cis as adjuvant therapy (*Table 5*), the median follow-up duration of the present trial is the longest, which is close to 5 years (57.7 months), and the survival rate is outstanding (9,10,12-15). Although the proportion of patients with stage IB disease was relatively high, the median DFS of the present trial was superior even if it was evaluated only in patients with stage IIA–IIIA disease (60.0 months). The relatively low percentage of stage IIIA patients in this trial might have contributed to a longer DFS compared with the ANITA trial. The proportion of pathologic stage IIIA patients (24.8%) in the present trial was numerically lower compared with that in the control arm of ANITA trial (36.7%). However, these two studies applied different editions of TNM classification: the 7th edition in the present trial and the 1986 version in the ANITA trial. The T descriptors have changed with version updates, while the N descriptors have remained consistent. The proportions of pathologic N stage (N0, N1, N2) between two trials were similar: 46.7%, 30.5%, 22.6% in the present trial, and 43.4%, 31.4%, 24.5% in the control arm of ANITA trial.

The present trial had no control arm comparable to adjuvant Pem-Cis. To date, two representative randomized trials comparing the efficacy of adjuvant Pem-Cis and Vin-Cis have been reported (9,13). The TREAT trial was conducted in Caucasian patients with stage IB–IIIA (TNM 6th) NSCLC (13), while the JIPANG trial was performed in Asian patients with stage II–IIIA (TNM 7th) non-squamous NSCLC (9). These two trials reported that Pem-Cis had better feasibility with less toxicity compared with Vin-Cis; however, they failed to prove the superiority of Pem-Cis in terms of survival rates (9,14). Although the outcomes between the two previous studies and the present trial should be carefully compared, the DFS rates and DFS of Pem-Cis in the present trial were better compared with that of Vin-Cis in the two previous studies (*Table 5*). The high proportion of women, high rates of completion of four treatment cycles, low frequency of severe adverse events, and advances in surgical techniques and perioperative management might improve the survival of patients in the present trial. Therefore, Pem-Cis could be a favorable adjuvant chemotherapy for non-squamous NSCLC.

The high completion rate of this trial might be associated with the well-known tolerability of the Pem-Cis regimen and advances in supportive care during chemotherapy.

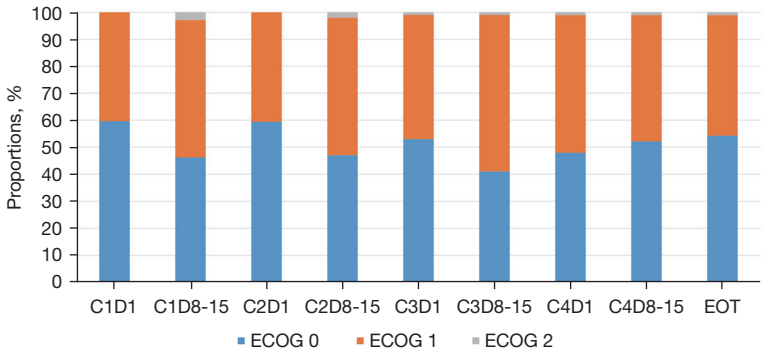

Figure 3 Variability of performance status during adjuvant pemetrexed plus cisplatin treatment. ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment.

Figure 3 depicts the serial changes in ECOG PS score; in this figure, the patients showed generally favorable PS during chemotherapy. A temporary decrease in PS score was observed during the first three cycles of Pem-Cis, while no changes were observed in the fourth cycle and at the EOT visit. Cisplatin is a typical antineoplastic agent with high emetic risk; several guidelines recommend the use of a 3- or 4-antiemetic drug combination, such as an NK_1 receptor antagonist, a serotonin ($5\text{-}HT_3$) receptor antagonist, dexamethasone, and/or olanzapine in cisplatin-containing regimens (16-18). The optimal management of chemotherapy-induced nausea and vomiting using guideline-driven antiemetics has been associated with improved quality of life, longer duration of anticancer treatment, and decreased utilization of emergency care (19). In South Korea, a 3-drug combination with NK_1 receptor antagonist, $5\text{-}HT_3$ receptor antagonist, and dexamethasone has been reimbursed, and this regimen was used in all participating institutions.

Previous adjuvant trials demonstrated the superiority in safety profiles of Pem-Cis over Vin-Cis, especially in terms of hematologic toxicity such as neutropenia. In TREAT and JIPANG trials, the incidence of > grade 3 neutropenia was significantly lower in Pem-Cis compared with that in Vin-Cis, 9% versus 69% in TREAT trial (13) and 22.7% versus 81.2% in JIPANG trial, respectively (9). In the present trial, grade 3 leukopenia was reported in only three patients (2.9%). Although the possibility that it has been underreported could not be ruled out, only one case of leukopenia was reported, and grade 3 adverse events occurred only in 10 patients (9.5%). Therefore, Pem-Cis could be an alternative to Vin-Cis due to its safety and efficacy.

The efficacy of the first-line Pem-Cis treatment in patients with advanced non-squamous NSCLC was superior compared with that of other platinum doublet regimens, especially in East Asian patients (20). In addition, the use of a pemetrexed-containing regimen improved the progression-free survival (PFS) as a first-line treatment or a sequential option following TKI failure in advanced NSCLC patients with targetable driver mutations, such as EGFR, ALK, or ROS1 (21,22). However, in the present trial, patients who harbored EGFR mutations showed a worse DFS compared with those with wild-type EGFR. In the JIPANG trial, the subgroup analysis of patients who harbored EGFR mutations showed that recurrence-free survival tended to be worse in patients treated with Pem-Cis compared with those treated with Vin-Cis (9). However, in patients without EGFR mutations, recurrence-free survival tended to be better in patients treated with Pem-Cis compared with those treated with Vin-Cis. Hence, EGFR mutation status could influence the action of pemetrexed, which is a multi-target antifolate agent, and affect the efficacy of chemotherapy. This hypothesis was based on the result of a previous study, which indicated that EGFR-mutant cells were less sensitive to fluorouracil compared with EGFR wild-type cells in an *in vitro* experiment; moreover, the adjuvant chemotherapy with uracil-tegafur (an antimetabolite), which combines fluorouracil prodrug and uracil, did not prolong the survival of patients with resected EGFR-mutant LUAD (23).

Besides the molecular mechanism mentioned above, EGFR mutations have been associated with a higher risk of systemic recurrence and a worse PFS after definitive treatment in patients with stage I to III NSCLC (24,25). In a Korean retrospective study, patients with EGFR mutation

Table 5 Comparisons of previous trials on adjuvant pemetrexed-platinum combination therapy

Characteristics, n (%)	ANITA (10) - control	Zhang, *et al.* (12)	TREAT (13,14)	JIPANG (9)	Tachihara, *et al.* (15)	APICAL - Present trial
Nationality	Europe (14 countries)	China	Germany and Belgium	Japan	Japan	South Korea
Ethnicity	Caucasian	Asian	Caucasian	Asian	Asian	Asian
No. of patients	433	82	67	389	21	105
Age, mean or median	59	58	58	64	66	63
Sex: female/male	13%/87%	32%/68%	28%/72%	42%/58%	43%/57%	51%/49%
Stage	IB–IIIA (TNM 1986)	II–IIIA (TNM 7th)	IB–IIIA(T3N1) (TNM 6th)	II–IIIA (TNM 7th)	II–IIIA (TNM 7th)	IB–IIIA (TNM 7th)
Histology	NSCLC	Non-squamous NSCLC	NSCLC	Non-squamous NSCLC	Non-squamous NSCLC	Adenocarcinoma
EGFR mutation	NA	NA	NA	24.9%	19.0%	41.1% (37/90)
Regimen	Observation	Pemetrexed-Carboplatin	Pemetrexed-Cisplatin	Pemetrexed-Cisplatin	Pemetrexed-Cisplatin	Pemetrexed-Cisplatin
Planned cycle	NA	4	4	4	4	4
Completion rate	NA	85.4%	77.6%	87.9%	81.0%	94.3%
Median follow-up, months (range)	77 (43–116)	33 (9–53)	34.1 (1.2–58.3)	45.2 (34.7–57.1)	20.7 (7.6–55.9)	57.7 (95% CI: 55.3–58.7)
Median DFS, months (95% CI)	20.7 (16.1–28.6)	Stage II, 38.0 (28.1–47.9); IIIA, 21.0 (13.7–28.3)	NR	38.9 (28.7–55.3)	25.8 (19.6–NR)	Stage IB–IIIA, NR; IIA–IIIA, 60.0 (95% CI: 35.6–NR)
2-year DFSR, % (95% CI)	44.8% (estimation)	Stage II, 70.5%; IIIA, 45.9%	59% (3 years)	58.3% (53.2–63.0%) (2 years); 51.1% (45.8–56.0%) (3 years)	57.3% (32.2–76.1%)	Stage IB–IIIA, 78.1% (95% CI: 70.6–86.4%); IIA–IIIA, 73.6% (64.1–84.5%)
Median OS, months (95% CI)	43.7 (35.7–52.3)	Stage II, NR; IIIA, 36 (25.9–46.1)	NR	NR; 3-year OS rate, 87.2%	NA	NR
Grade 3 or 4 neutropenia	<1%	13.4%	9%	19.4%	0%	2.9% (leukopenia)

NSCLC, non-small cell lung cancer; NA, not applicable; DFS, disease-free survival; CI, confidence interval; NR, not reached; DFSR, disease-free survival rate; OS, overall survival; EGFR, epidermal growth factor receptor; TNM, Tumor-Node-Metastasis.

showed shorter PFS compared with those without EGFR mutation, and the brain was the most common site of distant metastasis in patients with stage III non-squamous NSCLC who underwent CCRT (24). In another retrospective study, the metastatic recurrence rate was significantly higher in NSCLC patients with EGFR mutation than those with wild-type EGFR, especially in stage I patients who underwent definitive surgery (25). In the present trial, compared with wild-type EGFR, EGFR mutation was significantly associated with a higher recurrence rate and shorter median DFS. In the ADAURA study, osimertinib, a third-generation EGFR-TKI, as adjuvant therapy, was associated with a significantly longer DFS in stage IB to IIIA EGFR-mutated NSCLC compared with placebo, regardless of prior adjuvant cytotoxic chemotherapy (26). Thus, EGFR-TKI, especially osimertinib, can be an effective adjuvant regimen for this patient group, while the OS results of the ADAURA trial were immature; the impact of osimertinib with or without adjuvant chemotherapy on the cure rate still needs to be evaluated further. In a real-

world study of Chinese patients with resected stage I to III LUAD, adjuvant chemotherapy did not improve the DFS and OS of patients with EGFR mutation (27). In the present trial, the median OS of patients with an EGFR mutation was not statistically different. The majority of patients who harbored EGFR mutation and developed recurrence after adjuvant Pem-Cis treatment received EGFR-TKI therapy (73.9%, 17/23), while the remaining 6 patients were treated with radiation, surgery or chemotherapy for local relapses (*Table 2*).

In the last few years, immune checkpoint inhibitor (ICI) therapy with or without chemotherapy is a well-established adjuvant or neoadjuvant treatment for NSCLC. The IMpower 010 study demonstrated significantly improved the DFS of stage II–IIIA NSCLC patients treated with adjuvant atezolizumab following surgery and adjuvant chemotherapy, particularly those with tumor PD-L1 of ≥1% (28). Moving forward, neoadjuvant immunotherapy has been in the spotlight owing to the fact that ICI therapy prior to surgery resulted in an increase in diverse T-cell responses compared with adjuvant therapy; moreover, a systemic antitumor response from previously activated T-cells still occurred even after the surgical resection of tumors (29). In the CheckMate 816 study, neoadjuvant platinum-doublet chemotherapy plus nivolumab produced significant improvements in pathologic complete response compared with chemotherapy alone (30). Therefore, ICI therapy combined with cytotoxic chemotherapy as adjuvant and neoadjuvant treatments could have a synergistic influence on the survival benefit of early-stage high-risk NSCLC patients; at the same time, a more personalized approach with reliable biomarkers should be developed for optimal treatment.

This trial has several limitations. First, OS was not yet mature, and no control arm was used to compare the effect of Pem-Cis in patients who relapsed. Hence, a longer follow-up should be performed, and other parameters for predicting the survival should be considered in order to assess whether the DFS benefit can safely be presumed as an OS benefit. Second, a biomarker study to select the appropriate patients who would have benefitted from adjuvant Pem-Cis therapy was not performed. However, the significantly poor survival of EGFR mutants suggests the need to further study the role of adjuvant chemotherapy and/or target treatments in patients with driver mutations. Lastly, we had no plan to proceed to a phase III trial. When we planned this trial, adjuvant Pem-Cis was not reimbursed by national health insurance in South Korea. Thus, the purpose of this trial was to support Pem-Cis as one of the adjuvant chemotherapy regimen.

In conclusion, this study proved the superiority of adjuvant Pem-Cis in terms of 2-year DFSR compared with historical control without adjuvant treatment; meanwhile, the proportion of patients with stage IB disease and driver mutations were relatively higher compared with that of patients included in previous trials (*Table 5*) (9,10,12-15). The Pem-Cis regimen also showed favorable efficacy in stage IIA to IIIA LUAD; moreover, patients with EGFR mutation might consider EGFR-TKI therapy as an adjuvant or subsequent treatment. In addition, Pem-Cis showed favorable tolerability as an adjuvant chemotherapy.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki

(as revised in 2013) and Good Clinical Practice guidelines. This study was approved by the ethics review board of Chonnam National University Hwasun Hospital (IRB No. CNUHH-2015-007) and also approved by each participating institution. All patients were required to provide written and informed consent before participating in the study. The trial was registered at clinicaltrial.gov (Identifier: NCT02498860).

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Supplementary

Appendix 1 Inclusion and exclusion criteria

Inclusion criteria

For inclusion in this study, subjects were required to fulfil the following criteria:

(I) Age >20 years
(II) Histologically confirmed adenocarcinoma by WHO classification
(III) Pathologic stage IB-IIIA
(IV) Completely resected primary tumor after surgery (R0 resection) before participating this study. R0 resection is defined as follows:
  i. N1-2: R0 resection with lobectomy and mediastinal lymph node dissection (MLND)
  ii. N0: R0 resection with lobectomy with or without MLND
(V) Less than 10% of body weight loss 3 months ago
(VI) Normal function of the main organs:
  i. WBC: >3,000/mm^3 (Neutrophil count: >1,500/mm^3)
  ii. Hemoglobin: >9.0 g/dL
  iii. Platelet count: >100,000/mm^3
  iv. Both AST and ALT: <2.5× UNL
  v. Total bilirubin: ≤1.5× ULN
  vi. Serum creatinine: ≤1.5 mg/dL
  vii. Creatinine clearance: >30 mL/min (actual measurement or the value obtained using the Cockcroft-Gault formula)
(VII) Absence of hematological toxicity or hormonal therapy
(VIII) Provision of informed consent prior to any study-specific procedures
(IX) Performance status (ECOG) of 0 or 1.
(X) Willingness and ability to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations, including follow-up
(XI) Females must be taking medically approved contraceptive measures (condom, infertility surgery, oral contraceptives, etc.) during the treatment, and must have a negative urine stick or blood pregnancy test result 21 days prior to the start of dosing, if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening: (i) post-menopausal, defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments, (ii) women under 50 years of age were considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution; (iii) documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation.

Exclusion criteria

Subjects did not enter the study if any of the following exclusion criteria were fulfilled:

(I) Presence of active double cancer (synchronous double cancer and metachronous double cancer within a 5-year disease-free interval are defined as active double cancer)
(II) Previously treated with preoperative chemotherapy
(III) The need for postoperative radiation therapy
(IV) Distant metastasis except regional lymph node metastasis
(V) Less than 2 weeks after serious infections requiring antibiotics administration
(VI) Positive for HIV infection
(VII) Serious cardiopulmonary dysfunction by investigator assessment

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(VIII) Women who will not be compliant with a medically approved contraceptive regimen during the treatment period or lactating women.

(IX) History of autoimmune disorder or current treatment with immunotherapy

(X) Symptomatic neuropathy > CTC grade 1

(XI) Any evidence of severe disease or medical condition, which in the investigator's opinion make it undesirable for the patient to participate in the trial or would jeopardize compliance with the protocol, including uncontrolled hypertension, coronary artery disease, diabetes, metabolic syndrome or other serious systemic illness.

(XII) Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements

(XIII) Any evidence of active bleeding diatheses, regardless of cancer

(XIV) Participation in other clinical trials after registration in this trial, or having participated in other clinical trials within 3 months before registration in this trial

(XV) Others judged by the investigator to be unsuitable for the study

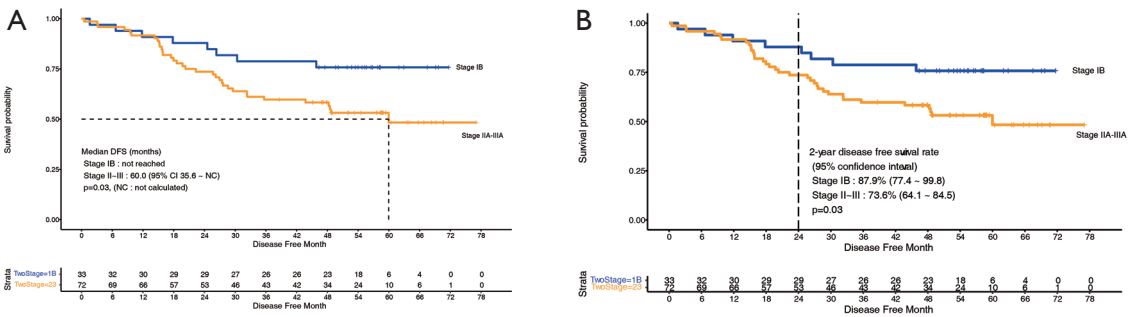

Figure S1 Kaplan-Meier curves for DFS. Stage IB versus IIA–IIIA disease (A), and 2-year DFSR in stage IB versus IIA–IIIA disease (B). DFS, disease-free survival; DFSR, disease-free survival rate.

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Table S1 Adverse events that occurred in the safety population (n=105)

Adverse events	No. of patients (%)			
	All Grades	Grade 1	Grade 2	Grade 3
Any adverse events	101 (96.2)	101 (96.2)	48 (45.7)	10 (9.5)
Hematologic adverse events				
White blood cell decreased	16 (15.2)	6 (5.7)	7 (6.7	3 (2.9)
Anemia	5 (4.8)	3 (2.9)	2 (1.9)	0 (0.0)
Platelet count decreased	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Leukocytosis	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Non-hematologic adverse events				
Nausea	63 (60.0)	41 (39.0)	22 (21.0)	1 (1.0)
Anorexia	47 (44.8)	45 (42.9)	3 (2.9)	0 (0.0)
Cough	41 (39.0)	41 (39.0)	1 (1.0)	0 (0.0)
Fatigue	41 (39.0)	39 (37.1)	3 (2.9)	0 (0.0)
Constipation	28 (26.7)	26 (24.8)	3 (2.9)	0 (0.0)
Vomiting	28 (26.7)	20 (19.0)	8 (7.6)	1 (1.0)
Abdominal pain	20 (19.0)	19 (18.1)	1 (1.0)	0 (0.0)
Diarrhea	18 (17.1)	18 (17.1)	1 (1.0)	0 (0.0)
Insomnia	18 (17.1)	17 (16.2)	1 (1.0)	0 (0.0)
Dyspnea	16 (15.2)	13 (12.4)	4 (3.8)	0 (0.0)
Productive cough	16 (15.2)	14 (13.3)	2 (1.9)	0 (0.0)
Dizziness	12 (11.4)	12 (11.4)	0 (0.0)	0 (0.0)
Upper respiratory infection	12 (11.4)	12 (11.4)	0 (0.0)	0 (0.0)
Myalgia	10 (9.5)	8 (7.6)	2 (1.9)	0 (0.0)
Dyspepsia	9 (8.6)	8 (7.6)	1 (1.0)	0 (0.0)
Liver enzyme increased	9 (8.6)	6 (5.7)	2 (1.9)	1 (1.0)
Pruritus	9 (8.6)	8 (7.6)	1 (1.0)	0 (0.0)
Hiccups	8 (7.6)	8 (7.6)	0 (0.0)	0 (0.0)
Mucositis oral	8 (7.6)	8 (7.6)	0 (0.0)	0 (0.0)
Paresthesia	8 (7.6)	8 (7.6)	0 (0.0)	0 (0.0)
Allergic rhinitis	7 (6.7)	7 (6.7)	0 (0.0)	0 (0.0)
Headache	7 (6.7)	6 (5.7)	1 (1.0)	0 (0.0)
Back pain	6 (5.7)	4 (3.8)	2 (1.9)	0 (0.0)
Rash maculo-papular	6 (5.7)	6 (5.7)	0 (0.0)	0 (0.0)
Sore throat	6 (5.7)	5 (4.8)	1 (1.0)	0 (0.0)
Edema limbs	5 (4.8)	5 (4.8)	0 (0.0)	0 (0.0)
Fever	5 (4.8)	3 (2.9)	2 (1.9)	0 (0.0)
Hyperglycemia	5 (4.8)	3 (2.9)	1 (1.0)	1 (1.0)
Lung infection	5 (4.8)	2 (1.9)	3 (2.9)	0 (0.0)
Pain in extremity	5 (4.8)	3 (2.9)	2 (1.9)	0 (0.0)
Skin infection	5 (4.8)	5 (4.8)	0 (0.0)	0 (0.0)
Alopecia	4 (3.8)	4 (3.8)	0 (0.0)	0 (0.0)
Gastroesophageal reflux disease	4 (3.8)	3 (2.9)	1 (1.0)	0 (0.0)
Peripheral sensory neuropathy	4 (3.8)	4 (3.8)	0 (0.0)	0 (0.0)
Urticaria	4 (3.8)	3 (2.9)	1 (1.0)	0 (0.0)
Acute kidney injury	3 (2.9)	2 (1.9)	1 (1.0)	0 (0.0)
Arthralgia	3 (2.9)	2 (1.9)	1 (1.0)	0 (0.0)
Bloating	3 (2.9)	3 (2.9)	0 (0.0)	0 (0.0)
Chest pain - cardiac	3 (2.9)	3 (2.9)	0 (0.0)	0 (0.0)
Cystitis	3 (2.9)	3 (2.9)	0 (0.0)	0 (0.0)
Gastritis	3 (2.9)	2 (1.9)	1 (1.0)	0 (0.0)
Thromboembolic event	3 (2.9)	0 (0.0)	0 (0.0)	3 (2.9)
Hoarseness	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Hyperhidrosis	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Hypokalemia	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Hypomagnesemia	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Neoplasms	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Pharyngitis	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Pleuritic pain	2 (1.9)	1 (1.0)	1 (1.0)	0 (0.0)
Tremor	2 (1.9)	2 (1.9)	0 (0.0)	0 (0.0)
Acute coronary syndrome	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Anxiety	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Blurred vision	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Colitis	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Dry mouth	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Edema face	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Esophageal infection	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Eyelid function disorder	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Facial nerve disorder	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Facial pain	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Hearing impaired	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Hematuria	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Hemorrhoids	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Hypertension	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Hypocalcemia	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Hyponatremia	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Hypothyroidism	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Irregular menstruation	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Malaise	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Mucosal infection	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Neuralgia	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Otitis media	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Pancreatitis	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Pleural effusion	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Pneumothorax	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Proteinuria	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Sinus tachycardia	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Skin hyperpigmentation	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Upper gastrointestinal hemorrhage	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Urinary frequency	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Urinary incontinence	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Urinary tract pain	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Vaginal infection	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Bronchial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Table S2 Adverse events that occurred in the safety population (all events)

Adverse events	No. of events (%)			
	All Grades	Grade 1	Grade 2	Grade 3
Any adverse events	603	500	92	11
Hematologic adverse events				
Anemia	5 (0.8)	3 (0.6)	2 (2.2)	0 (0.0)
Leukocytosis	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Platelet count decreased	2 (0.3)	2 (0.4)	0 (0)	0 (0.0)
White blood cell decreased	16 (2.7)	6 (1.2)	7 (7.6)	3 (27.3)
Non-hematologic adverse events				
Abdominal pain	20 (3.3)	19 (3.8)	1 (1.1)	0 (0.0)
Acute coronary syndrome	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Acute kidney injury	3 (0.5)	2 (0.4)	1 (1.1)	0 (0.0)
Allergic rhinitis	7 (1.2)	7 (1.4)	0 (0)	0 (0.0)
Alopecia	4 (0.7)	4 (0.8)	0 (0)	0 (0.0)
Anorexia	47 (7.8)	45 (9)	3 (3.3)	0 (0.0)
Anxiety	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Arthralgia	3 (0.5)	2 (0.4)	1 (1.1)	0 (0.0)
Back pain	6 (1.0)	4 (0.8)	2 (2.2)	0 (0.0)
Bloating	3 (0.5)	3 (0.6)	0 (0)	0 (0.0)
Blurred vision	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Chest pain - cardiac	3 (0.5)	3 (0.6)	0 (0)	0 (0.0)
Colitis	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Constipation	28 (4.6)	26 (5.2)	3 (3.3)	0 (0.0)
Cough	41 (6.8)	41 (8.2)	1 (1.1)	0 (0.0)
Cystitis	3 (0.5)	3 (0.6)	0 (0)	0 (0.0)
Diarrhea	18 (3.0)	18 (3.6)	1 (1.1)	0 (0.0)
Dizziness	12 (2.0)	12 (2.4)	0 (0)	0 (0.0)
Dry mouth	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Dyspepsia	9 (1.5)	8 (1.6)	1 (1.1)	0 (0.0)
Dyspnea	16 (2.7)	13 (2.6)	4 (4.3)	0 (0.0)
Edema face	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Edema limbs	5 (0.8)	5 (1)	0 (0)	0 (0.0)
Esophageal infection	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Eyelid function disorder	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Facial nerve disorder	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Facial pain	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Fatigue	41 (6.8)	39 (7.8)	3 (3.3)	0 (0.0)
Fever	5 (0.8)	3 (0.6)	2 (2.2)	0 (0.0)
Gastritis	3 (0.5)	2 (0.4)	1 (1.1)	0 (0.0)
Gastroesophageal reflux disease	4 (0.7)	3 (0.6)	1 (1.1)	0 (0.0)
Headache	7 (1.2)	6 (1.2)	1 (1.1)	0 (0.0)
Hearing impaired	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Hematuria	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Hemorrhoids	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Hiccups	8 (1.3)	8 (1.6)	0 (0)	0 (0.0)
Hoarseness	2 (0.3)	2 (0.4)	0 (0)	0 (0.0)
Hyperglycemia	5 (0.8)	3 (0.6)	1 (1.1)	1 (9.1)
Hyperhidrosis	2 (0.3)	2 (0.4)	0 (0)	0 (0.0)
Hypertension	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Hypocalcemia	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Hypokalemia	2 (0.3)	2 (0.4)	0 (0)	0 (0.0)
Hypomagnesemia	2 (0.3)	2 (0.4)	0 (0)	0 (0.0)
Hyponatremia	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Hypothyroidism	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Insomnia	18 (3.0)	17 (3.4)	1 (1.1)	0 (0.0)
Irregular menstruation	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Liver enzyme increased	9 (1.5)	6 (1.2)	2 (2.2)	1 (9.1)
Lung infection	5 (0.8)	2 (0.4)	3 (3.3)	0 (0.0)
Malaise	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Mucosal infection	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Mucositis oral	8 (1.3)	8 (1.6)	0 (0)	0 (0.0)
Myalgia	10 (1.7)	8 (1.6)	2 (2.2)	0 (0.0)
Nausea	63 (10.4)	41 (8.2)	22 (23.9)	1 (9.1)
Neoplasms	2 (0.3)	2 (0.4)	0 (0)	0 (0.0)
Neuralgia	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Non-cardiac chest pain	2 (0.3)	2 (0.4)	0 (0)	0 (0.0)
Otitis media	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Pain in extremity	5 (0.8)	3 (0.6)	2 (2.2)	0 (0.0)
Pancreatitis	1 (0.2)	0 (0)	0 (0)	1 (9.1)
Paresthesia	8 (1.3)	8 (1.6)	0 (0)	0 (0.0)
Peripheral sensory neuropathy	4 (0.7)	4 (0.8)	0 (0)	0 (0.0)
Pharyngitis	2 (0.3)	2 (0.4)	0 (0)	0 (0.0)
Pleural effusion	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Pleuritic pain	2 (0.3)	1 (0.2)	1 (1.1)	0 (0.0)
Pneumothorax	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Productive cough	16 (2.7)	14 (2.8)	2 (2.2)	0 (0.0)
Proteinuria	1 (0.2)	0 (0)	1 (1.1)	0 (0.0)
Pruritus	9 (1.5)	8 (1.6)	1 (1.1)	0 (0.0)
Rash maculo-papular	6 (1.0)	6 (1.2)	0 (0)	0 (0.0)
Sinus tachycardia	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Skin hyperpigmentation	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Skin infection	5 (0.8)	5 (1)	0 (0)	0 (0.0)
Sore throat	6 (1.0)	5 (1)	1 (1.1)	0 (0.0)
Thromboembolic event	3 (0.5)	0 (0)	0 (0)	3 (27.3)
Tremor	2 (0.3)	2 (0.4)	0 (0)	0 (0.0)
Upper gastrointestinal hemorrhage	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Upper respiratory infection	12 (2.0)	12 (2.4)	0 (0)	0 (0.0)
Urinary frequency	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Urinary incontinence	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Urinary tract pain	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Urticaria	4 (0.7)	3 (0.6)	1 (1.1)	0 (0.0)
Vaginal infection	1 (0.2)	1 (0.2)	0 (0)	0 (0.0)
Vomiting	28 (4.6)	20 (4)	8 (8.7)	1 (9.1)

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