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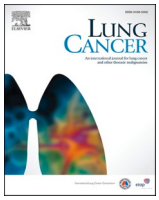

Durvalumab in combination with chemoradiotherapy for patients with unresectable stage III non-small-cell lung cancer: Results from the phase 1 CLOVER study

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ABSTRACT

Introduction: For patients with unresectable, stage III non-small-cell lung cancer (NSCLC), current standard of care is concurrent chemoradiotherapy (cCRT) followed by consolidation durvalumab. However, earlier initiation of durvalumab simultaneously with cCRT may increase antitumor activity relative to initiation after cCRT. The phase 1 CLOVER study (NCT03509012) evaluated durvalumab combined with cCRT in patients with advanced solid tumors; we report findings from the NSCLC cohort.

Methods: CLOVER comprised a dose-limiting toxicity (DLT) assessment part, followed by an expansion part. In the NSCLC cohort, patients with previously untreated, unresectable, stage III NSCLC were enrolled in three treatment arms: durvalumab every 4 weeks (Q4W) + cisplatin + etoposide + radiotherapy (Arm 1); durvalumab

Abbreviations: AE, adverse event; AJCC, American Joint Committee on Cancer; APC, antigen-presenting cell; AUC, area under the concentration–time curve; Carbo, carboplatin; cCRT, concurrent chemoradiotherapy; CI, confidence interval; Cis, cisplatin; CR, complete response; D, durvalumab; DCO, data cutoff; DLT, dose-limiting toxicity; DoR, duration of response; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; etop, etoposide; HNSCC, head and neck squamous cell carcinoma; imAE, immune-mediated AEs; IV, intravenous infusion; NE, not estimable; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; pac, paclitaxel; PD-L1, programmed cell death ligand-1; peme, pemetrexed; PFS, progression-free survival; PR, partial response; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; SAE, serious adverse event; SCLC, small-cell lung cancer; Q3W, every 3 weeks; Q4W, every 4 weeks; WHO, World Health Organization.

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Q4W + carboplatin + paclitaxel + radiotherapy (Arm 2); or durvalumab Q4W + carboplatin or cisplatin + pemetrexed + radiotherapy (non-squamous histology only; Arm 3). Patients received durvalumab until disease progression or unacceptable toxicity. The primary endpoint was safety and tolerability.
Results: Sixty-four patients were enrolled: 21, 22, and 21 in Arms 1, 2, and 3, respectively. One patient in Arm 1 had DLT (grade 3 aspartate aminotransferase increase and grade 4 alanine aminotransferase increase); no DLTs were observed in Arms 2 or 3. Grade 3/4 adverse events occurred in 76.6 % of patients overall; the most common were neutropenia (51.6 %), leukopenia (20.3 %), and anemia (17.2 %). In a post-hoc analysis, 7.8 % of patients had grade 3 pneumonitis/radiation pneumonitis (grouped term) events. Overall, the objective response rate was 60.9 % (95 % confidence interval [CI], 47.9–72.9); median duration of response was 15.8 months (95 % CI, 9.0–not estimable [NE]). Median progression-free survival was 13.4 months (95 % CI, 8.8–20.1) and median overall survival was not reached (95 % CI, 21.9–NE).
Conclusion: Durvalumab in combination with cCRT was well tolerated, with a manageable safety profile and showed encouraging antitumor activity in patients with unresectable, stage III NSCLC.

1. Introduction

Approximately 80–85% of all lung cancer cases are non-small-cell lung cancer (NSCLC), with around 20–35% of patients presenting with stage III disease [1–4]. In the placebo-controlled, phase 3 PACIFIC trial (NCT02125461) of patients with unresectable, stage III NSCLC whose disease had not progressed following concurrent chemoradiotherapy (cCRT), consolidation therapy with the programmed cell death ligand-1 (PD-L1) inhibitor durvalumab significantly improved overall survival (OS) and progression-free survival (PFS), with a manageable safety profile [5,6]. Durvalumab received global approvals based on these findings [7–9], and the 'PACIFIC regimen' has subsequently become the standard of care in this disease setting [10,11]. Five-year data from PACIFIC also demonstrated sustained OS benefit and durable PFS with durvalumab, with estimated 5-year OS and PFS rates of 42.9% and 33.1%, respectively [12]. Unfortunately, a significant proportion of patients with unresectable stage III NSCLC may not be eligible to receive consolidation durvalumab due to early progression during or shortly after cCRT [13].

A substantial body of evidence suggests both radiotherapy and chemotherapy can favorably modulate the immune system, thereby enhancing tumoral sensitivity to PD-L1 inhibition [14–16]. Radiation and chemotherapy have been shown to induce immunogenic cell death, leading to upregulation of various pro-inflammatory signals and cytokines, including antigen-presenting cells (APCs) [17–19]. APCs activate cytotoxic T-cell function, enhancing the ability of the immune system to recognize and respond to tumors [20,21]. Ionizing radiation is also known to cause upregulation of various pro-inflammatory signals and cytokines, which play a vital role in immune regulatory pathways, leading to improved antitumor immunity [21,22]. Radiotherapy also upregulates tumoral PD-L1 expression, potentially enhancing tumors' sensitivity to PD-L1 inhibition [23,24].

Earlier initiation of durvalumab simultaneously with cCRT may result in increased antitumor activity relative to initiation after cCRT, with the potential to reduce early disease progression during or immediately following cCRT. Combining simultaneous durvalumab with cCRT may be a valid strategy not only in patients with unresectable stage III NSCLC but also in other patient populations for whom cCRT is a standard treatment option, such as those with locally advanced head and neck squamous cell carcinoma (HNSCC) not amenable to surgical resection or with limited-stage small cell lung cancer (SCLC). In all three populations, disease recurrence after cCRT is common and new approaches are needed to improve long-term outcomes. The phase 1 CLOVER study (NCT03509012) was therefore designed to evaluate the safety, tolerability, and preliminary efficacy of durvalumab combined with cCRT in patients with unresectable, stage III NSCLC or locally advanced HNSCC, and durvalumab combined with cCRT, with or without tremelimumab, in patients with limited-stage SCLC. Here we present results from the NSCLC cohort of the CLOVER study.

2. Methods

2.1. Patients

Patients enrolled in the NSCLC cohort were aged ≥18 years, suitable candidates for curative-intent cCRT and had previously untreated histologically/cytologically documented unresectable, stage III NSCLC; a World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; at least one lesion, not previously irradiated, that qualified as a target lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at baseline; no prior exposure to immune-mediated therapy; adequate organ and marrow function; and life expectancy of ≥12 weeks at treatment assignment. Patients with mixed SCLC and NSCLC histology, simultaneous primary malignancies or bilateral tumors, current or prior use of immunosuppressive medication within 14 days prior to the first dose of study drug, history of allogeneic organ transplantation, or active or prior documented autoinflammatory disorders were excluded. Further exclusion criteria included uncontrolled intercurrent illness, history of another primary malignancy, leptomeningeal carcinomatosis or active prior immunodeficiency, brain metastases or spinal cord compression, and history of active prior immunodeficiency.

2.2. Study design and treatment

The CLOVER trial consisted of a dose-limiting toxicity (DLT) assessment part, followed by an expansion part. In the NSCLC cohort, the initial DLT part was composed of three treatment arms, with a target enrollment of six patients per arm. Recruitment into the subsequent expansion part for each arm was dependent on a review of data from the DLT part by the Safety Review Committee, with up to 30 additional patients enrolled per arm (Supplementary Fig. 1). In Arm 1, patients received durvalumab 1500 mg via intravenous infusion (IV) every 4 weeks (Q4W) + cisplatin 50 mg/m^2 IV on Days 1, 8, 29, and 36 + etoposide 50 mg/m^2 IV on Days 1–5 and 29–33 + radiotherapy. In Arm 2, patients received durvalumab 1500 mg IV Q4W + carboplatin area under the concentration–time curve (AUC) 2 mg/mL per minute IV + paclitaxel 45–50 mg/m^2 IV once weekly for up to six doses + radiotherapy. Depending on local practice, investigators had the option to administer two consolidation doses of carboplatin AUC 6 mg/mL per minute IV and paclitaxel 200 mg/m^2 IV on Days 43 and 64. In Arm 3, which enrolled patients with non-squamous histology only, patients received durvalumab 1500 mg IV Q4W + investigator's choice of carboplatin AUC 5 mg/mL per minute IV every 3 weeks (Q3W) or cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W for 3 cycles + radiotherapy. In all three arms, planned radiotherapy consisted of a prescription dose of 60 Gy in 30 daily fractions (2 Gy/fraction, 5 fractions per week) over 6 weeks. Investigators were permitted to enroll patients into whichever arm they felt was most appropriate. The choice of chemotherapy allowed as part of the administered cCRT offered flexibility for individual clinician choice and facilitated tailoring of

chemotherapy to each patient, providing an opportunity to describe outcomes with different chemotherapy regimens in the context of a PACIFIC-type regimen. All patients received durvalumab treatment until RECIST v1.1-defined progression or clinical progression, unacceptable toxicity (including any adverse event [AE] that met the definition of a DLT), withdrawal of consent, or another protocol-defined discontinuation criterion was met. After durvalumab discontinuation, patients were followed for survival until the data cutoff (DCO; December 31, 2020).

2.3. Outcomes and assessments

The primary endpoint was the safety and tolerability of durvalumab in combination with cCRT in terms of DLTs and AEs. A DLT was defined as a severe AE that had a reasonable possibility of being related to durvalumab (alone or in combination with cCRT) that occurred in the period from the first dose of therapy until 28 days after completion of radiotherapy. Full details of AEs that were considered to be DLTs are included in the Supplementary Appendix. Patients were monitored for safety for the duration of the study and AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Secondary endpoints were objective response rate (ORR), best objective response, duration of response (DoR), disease control rate (DCR), progression-free survival (PFS) rate at 12, 18, and 24 months (all based on investigator assessments per RECIST v1.1), and OS.

Tumors were assessed by investigators according to RECIST v1.1 using computed tomography (preferred) or magnetic resonance imaging scans at baseline then at 16 weeks after the first dose of durvalumab, and every 8 weeks thereafter through to Week 48, then every 12 weeks until DCO, clinical progression, disease progression per RECIST v1.1, or for the duration of study treatment in patients treated through RECIST v1.1-confirmed disease progression. Survival status was assessed for all patients at Weeks 4, 8, and 12 after the last dose of durvalumab, and every 12 weeks thereafter until DCO.

2.4. Statistical analyses

Safety results were assessed in the safety analysis set, which comprised all patients who received at least one dose of durvalumab. The incidence, time course, and management of the grouped term ‘pneumonitis or radiation pneumonitis’ events were summarized in a post-hoc analysis, in order to estimate the true incidence of these events among unique patients. The grouped term ‘pneumonitis or radiation pneumonitis’ includes the following preferred terms: acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, hypersensitivity pneumonitis, idiopathic interstitial pneumonia, idiopathic pneumonia syndrome, immune-mediated pneumonitis, interstitial lung disease, lung opacity, organizing pneumonia, pleuroparenchymal fibroelastosis, pneumonitis, pulmonary fibrosis, and radiation pneumonitis. Pneumonia terms with an infectious etiology were not included as part of this analysis and, as such, are reported separately in the results tables.

Efficacy was assessed in the full analysis set, which comprised all treated patients who had a baseline tumor assessment and (investigator-assessed) measurable disease at baseline. DoR, PFS, and OS were estimated using the Kaplan–Meier method. All variables were summarized using descriptive statistics and SAS version 9.4.

3. Results

3.1. Study population and treatment

The NSCLC cohort completed enrollment in all three treatment arms in the DLT part and all three treatment arms proceeded to the expansion part. Between May 09, 2018 and March 13, 2020, a total of 64 patients were enrolled from 13 centers in South Korea, Spain, Taiwan, and the USA: 21 in Arm 1 (six in the DLT assessment part and 15 in the expansion part), 22 in Arm 2 (seven in the DLT assessment part and 15 in the expansion part), and 21 in Arm 3 (six in the DLT assessment part and 15 in the expansion part). Demographics and baseline characteristics are listed in Table 1. Overall, median age (range) was 63.0 (32–82) years and most patients were male (70.3%), Asian (78.1%), current or former smokers (73.4%), and had stage IIIB or IIIC disease (76.6%). All enrolled patients received at least one dose of durvalumab and were included in the safety analysis set. In Arms 1, 2, and 3, respectively, 12 (57.1%), 11 (50.0%), and seven (33.3%) patients were continuing durvalumab treatment at the DCO (Supplementary Table 1); the median number (range) of doses received was 15.0 (1–30), 14.0 (1–33), and 10.0 (2–28), respectively. Eighteen (85.7%) patients in Arm 1 completed chemotherapy treatment with cisplatin and etoposide; 13 (59.1%) patients in Arm 2 completed chemotherapy treatment with carboplatin and paclitaxel; and all 21 patients in Arm 3 completed chemotherapy, with 20 patients receiving carboplatin and pemetrexed and one patient receiving cisplatin and pemetrexed (Supplementary Table 1). All patients in Arms 1 and 3 received radiotherapy; 21 (95.5%) patients in Arm 2 received radiotherapy. One patient in Arm 2 received no radiotherapy because their radiotherapy plan failed to meet study requirements; this patient subsequently discontinued all other study treatment after receiving one dose each of carboplatin, paclitaxel, and durvalumab. In Arms 1 and 3, all patients received a total radiation dose ≥57 Gy; in Arm 2, 19 patients received ≥57 Gy and two patients received <57 Gy.

Table 1
Demographics and baseline characteristics (full analysis set).

	Arm 1 D + cis + etop + RT (n = 21)	Arm 2 D + carbo + pac + RT (n = 22)	Arm 3 D + carbo/cis + peme + RT (n = 21)	Total (N = 64)
Median age (range), years	60.0 (43–76)	64.5 (36–82)	63.0 (32–75)	63.0 (32–82)
Age group, n (%)				
<65 years	14 (66.7)	11 (50.0)	13 (61.9)	38 (59.4)
≥65 to <75 years	6 (28.6)	7 (31.8)	7 (33.3)	20 (31.3)
≥75 years	1 (4.8)	4 (18.2)	1 (4.8)	6 (9.4)
Sex, n (%)				
Male	15 (71.4)	17 (77.3)	13 (61.9)	45 (70.3)
Female	6 (28.6)	5 (22.7)	8 (38.1)	19 (29.7)
Race, n (%)				
Asian	13 (61.9)	18 (81.8)	19 (90.5)	50 (78.1)
Black or African American	0	0	1 (4.8)	1 (1.6)
White	8 (38.1)	4 (18.2)	1 (4.8)	13 (20.3)
Smoking history, n (%)				
Current smoker	5 (23.8)	3 (13.6)	2 (9.5)	10 (15.6)
Former smoker	12 (57.1)	15 (68.2)	10 (47.6)	37 (57.8)
Never smoker	4 (19.0)	4 (18.2)	9 (42.9)	17 (26.6)
PD-L1 status*, n (%)				
Positive	10 (47.6)	12 (54.5)	16 (76.2)	38 (59.4)
Negative	6 (28.6)	7 (31.8)	4 (19.0)	17 (26.6)
Missing	5 (23.8)	3 (13.6)	1 (4.8)	9 (14.1)
WHO/ECOG performance status, n (%)				
0	9 (42.9)	1 (4.5)	11 (52.4)	21 (32.8)
1	12 (57.1)	21 (95.5)	10 (47.6)	43 (67.2)
AJCC disease stage, n (%)				
IIIA	5 (23.8)	5 (22.7)	5 (23.8)	15 (23.4)
IIIB	11 (52.4)	16 (72.7)	14 (66.7)	41 (64.1)
IIIC	5 (23.8)	1 (4.5)	2 (9.5)	8 (12.5)
Histology, n (%)				
Squamous cell	13 (61.9)	10 (45.5)	0	23 (35.9)
Undifferentiated	1 (4.8)	1 (4.5)	0	2 (3.1)
Adenocarcinoma	7 (33.3)	11 (50.0)	21 (100.0)	39 (60.9)

Abbreviations: AJCC, American Joint Committee on Cancer; Carbo, carboplatin; Cis, cisplatin; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; etop, etoposide; pac, paclitaxel; PD-L1, programmed cell death ligand-1; peme, pemetrexed; RT, radiotherapy; WHO, World Health Organization.
*Positive PD-L1 status defined as tumor cell PD-L1 expression ≥ 1 %.

3.2. Safety

DLTs were observed in one patient in Arm 1 (grade 3 aspartate aminotransferase increase and grade 4 alanine aminotransferase increase); no DLTs were observed in Arms 2 or 3. All patients in the NSCLC cohort had at least one AE of any cause, and these were grade 3/4 in 49 (76.6%) patients (Table 2). Across all arms, the most common grade 3/4 AEs were neutropenia (n = 33; 51.6%), leukopenia (n = 13; 20.3%), and anemia (n = 11; 17.2%) (Table 3). Serious AEs occurred in 38 (59.4%) patients; the most common were pneumonia (n = 6; 9.4%), sepsis and pneumonitis (each n = 4; 6.3%), and febrile neutropenia (n = 3; 4.7%) (Supplementary Table 2). AEs resulting in discontinuation of any treatment (durvalumab, chemotherapy, or radiotherapy) occurred in 14 (21.9%) patients: seven (33.3%) in Arm 1; four (18.2%) in Arm 2; and three (14.3%) in Arm 3 (Supplementary Table 3). AEs with an outcome of death were reported in eight (12.5%) patients in the NSCLC cohort: three patients in Arm 1 (cardio-respiratory arrest [n = 2] and pneumocystis jirovecii pneumonia [n = 1]); three patients in Arm 2 (acute coronary syndrome, acute respiratory failure, and sepsis [each n = 1]); and two patients in Arm 3 (cardiac arrest and pneumonia [each n = 1]). All four patients with a fatal cardiac AE had a medical history that included cardiac risk factors (such as history of smoking, hypertension, myocardial infarction, and hypercholesterolemia). The fatal sepsis AE in Arm 2 was considered by the investigator to be possibly related to carboplatin and the fatal cardiac arrest AE in Arm 3 was considered by the investigator to be possibly related to durvalumab.

Immune-mediated AEs (imAEs) occurred in 20 (31.3%) patients across the three treatment arms: three (14.3%) in Arm 1; 10 (45.5%) in Arm 2; and seven (33.3%) in Arm 3 (Supplementary Table 4). Two (9.5%) patients experienced imAEs that led to treatment discontinuation (hepatic events and pneumonitis in Arms 1 and 3, respectively). There were no fatal imAEs.

Post-hoc analyses showed any grade, grade ≥2 (i.e., symptomatic), and grade 3 pneumonitis/radiation pneumonitis (grouped term) events occurred in 25 (39.1%), 16 (25.0%), and five (7.8%) patients, respectively; there were no grade 4 or 5 pneumonitis/radiation pneumonitis events. For a breakdown of pneumonitis/radiation pneumonitis rates by treatment arm, see Supplementary Table 5. Median time to first onset of pneumonitis/radiation pneumonitis following first dose of durvalumab was 113 days (range, 29–503). Sixteen (25.0%) patients received systemic corticosteroids to manage pneumonitis/radiation pneumonitis (Supplementary Table 6). Pneumonitis/radiation pneumonitis led to interruptions in durvalumab treatment in eight (12.5%) patients and interruptions in chemotherapy and radiotherapy each in one (1.6%) patient. In addition, one (1.6%) patient permanently discontinued durvalumab and one (1.6%) patient permanently discontinued radiotherapy due to pneumonitis/radiation pneumonitis (Supplementary Table 7).

Table 2
Safety summary (safety analysis set).

Adverse event, n (%)	Arm 1 D + cis + etop + RT (n = 21)	Arm 2 D + carbo + pac + RT (n = 22)	Arm 3 D + carbo/cis + peme + RT (n = 21)	Total (N = 64)
Any-cause AEs	21 (100.0)	22 (100.0)	21 (100.0)	64 (100.0)
Grade 3/4 AEs	18 (85.7)	19 (86.4)	12 (57.1)	49 (76.6)
AE with outcome of death*	3 (14.3)	3 (13.6)	2 (9.5)	8 (12.5)
SAE	16 (76.2)	13 (59.1)	9 (42.9)	38 (59.4)
AE leading to dose delay/interruption	14 (66.7)	16 (72.7)	9 (42.9)	39 (60.9)
AEs leading to treatment discontinuation[a]	7 (33.3)	4 (18.2)	3 (14.3)	14 (21.9)
Immune-mediated AEs[b]	3 (14.3)	10 (45.5)	7 (33.3)	20 (31.3)
Grade 3/4 immune-mediated AEs	2 (9.5)	1 (4.5)	1 (4.8)	4 (6.3)

Includes AEs that started before the first treatment and worsened with the first dose, or with an onset date on or after the date of the first dose and up to and including 90 days following the date of the last dose of study medication or until the start of the first subsequent therapy (whichever came first).
Abbreviations: AE, adverse event; carbo, carboplatin; cis, cisplatin; D, durvalumab; etop, etoposide; pac, paclitaxel; peme, pemetrexed; RT, radiotherapy; SAE, serious adverse event.
*AEs leading to death were cardio-respiratory arrest (n = 2) and pneumocystis jirovecii pneumonia (n = 1) in Arm 1; acute coronary syndrome, acute respiratory failure, and sepsis (each n = 1) in Arm 2; and cardiac arrest and pneumonia (each n = 1) in Arm 3.
[a] Any AE resulting in permanent discontinuation of durvalumab, chemotherapy, or radiotherapy.
[b] Defined as an event that was associated with drug exposure and consistent with an immune-mediated mechanism of action, where there was no clear alternate etiology, and that required the use of systemic steroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy. There were no fatal immune-mediated AEs.

3.3. Efficacy

All 64 patients were included in the full analysis set. The confirmed ORR in the NSCLC cohort overall was 60.9% (95% CI, 47.9–72.9), including three (4.7%) complete responses (CRs) and 36 (56.3%) partial responses (PRs) (Table 4). Among patients with a confirmed response, median DoR was 15.8 months (95% CI, 9.0–not estimable [NE]); an estimated 56.7% of patients remained in response at 12 months and 42.6% of patients remained in response at 18 months. The confirmed ORR was 66.7% (95% CI, 43.0–85.4) in Arm 1, 54.5% (95% CI, 32.2–75.6) in Arm 2, and 61.9% (95% CI, 38.4–81.9) in Arm 3; median DoR in Arm 3 was 10.5 months (95% CI, 4.1–16.7) and was not reached (NR) in Arms 1 and 2. The DCR in the NSCLC cohort overall was 94.7% (54/57 patients; 95% CI, 85.4–98.9) at 18 weeks and 77.2% (44/57 patients; 95% CI, 64.2–87.3) at 48 weeks.

At the time of the DCO, progression events had occurred in 35 patients across all arms and median duration (range) of PFS follow-up in censored patients was 16.4 months (0.0–27.7): 13.6 months (0.0–24.7) in Arm 1, 17.8 months (10.9–27.7) in Arm 2, and 16.6 months (7.8–24.9) in Arm 3. Median PFS was 13.4 months (95% CI, 8.8–20.1) for the NSCLC cohort overall (Fig. 1A). Median PFS was 14.4 months (95% CI, 7.3–NE), 12.8 months (95% CI, 4.9–NE), and 10.8 months (95% CI, 7.5–19.4) in Arms 1, 2, and 3, respectively (Fig. 1B). The PFS rate at 12, 18, and 24 months in the NSCLC cohort overall was 53.6% (95% CI, 40.2–65.2), 42.6% (95% CI, 29.3–55.3) and 34.1% (95% CI, 19.8–48.9), respectively. The PFS rate at 12 months was 67.3% (95% CI, 41.1–83.8), 54.5% (95% CI, 32.1–72.4), and 40.8% (95% CI, 19.9–60.8) in Arms 1, 2, and 3, respectively.

Overall, 17 (26.6%) patients had died at DCO and median duration (range) of OS follow-up in censored patients was 16.9 months (2.1–31.3): 14.2 months (2.1–27.4) in Arm 1, 18.4 months (8.4–29.8) in Arm 2, and 17.6 months (9.1–31.3) in Arm 3. Median OS was NR (95% CI, 21.9–NE); median OS was also NR in any of the individual treatment arms (Fig. 2). The OS rate at 12 months was 82.4% (95% CI, 70.4–89.8) overall, and 79.5% (95% CI, 54.0–91.8), 81.8% (58.5–92.8), and 85.7% (62.0–95.2) in Arms 1, 2, and 3, respectively.

4. Discussion

A substantial proportion of patients with unresectable stage III NSCLC have progressive disease during or shortly after standard of care cCRT [13] and have limited treatment options. Preclinical and early phase clinical evidence suggests that anti-PD-(L)1 therapy administered simultaneously with cCRT may be synergistic [20,21,23–27], offering

Table 3
Any-cause adverse events occurring in ≥10 % of patients overall (safety analysis set).

Adverse event,* n (%)	Arm 1 D + cis + etop + RT (n = 21)		Arm 2 D + carbo + pac + RT (n = 22)		Arm 3 D + carbo/cis + peme + RT (n = 21)		Total (N = 64)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	21 (100)	18 (85.7)	22 (100)	19 (86.4)	21 (100)	12 (57.1)	64 (100)	49 (76.6)
Neutropenia	15 (71.4)	13 (61.9)	13 (59.1)	12 (54.5)	11 (52.4)	8 (38.1)	39 (60.9)	33 (51.6)
Esophagitis	7 (33.3)	0	13 (59.1)	3 (13.6)	7 (33.3)	0	27 (42.2)	3 (4.7)
Nausea	10 (47.6)	0	7 (31.8)	0	10 (47.6)	0	27 (42.2)	0
Constipation	11 (52.4)	0	8 (36.4)	0	6 (28.6)	0	25 (39.1)	0
Pneumonitis/radiation pneumonitis[a]	7 (33.3)	2 (9.5)	9 (40.9)	2 (9.1)	9 (42.9)	1 (4.8)	25 (39.1)	5 (7.8)
Decreased appetite	6 (28.6)	1 (4.8)	10 (45.5)	0	8 (38.1)	0	24 (37.5)	1 (1.6)
Anemia	11 (52.4)	7 (33.3)	5 (22.7)	2 (9.1)	4 (19.0)	2 (9.5)	20 (31.3)	11 (17.2)
Alanine aminotransferase increased	5 (23.8)	1 (4.8)	6 (27.3)	2 (9.1)	5 (23.8)	0	16 (25.0)	3 (4.7)
Fatigue	7 (33.3)	0	4 (18.2)	0	5 (23.8)	0	16 (25.0)	0
Rash	4 (19.0)	0	7 (31.8)	0	5 (23.8)	0	16 (25.0)	0
Diarrhea	4 (19.0)	1 (4.8)	6 (27.3)	1 (4.5)	5 (23.8)	0	15 (23.4)	2 (3.1)
Leukopenia	6 (28.6)	6 (28.6)	4 (18.2)	4 (18.2)	5 (23.8)	3 (14.3)	15 (23.4)	13 (20.3)
Pyrexia	8 (38.1)	0	5 (22.7)	0	2 (9.5)	0	15 (23.4)	0
Insomnia	2 (9.5)	0	8 (36.4)	0	4 (19.0)	0	14 (21.9)	0
Stomatitis	4 (19.0)	0	2 (9.1)	0	8 (38.1)	0	14 (21.9)	0
Thrombocytopenia	5 (23.8)	2 (9.5)	3 (13.6)	0	6 (28.6)	2 (9.5)	14 (21.9)	4 (6.3)
Dyspnea	5 (23.8)	0	4 (18.2)	0	4 (19.0)	0	13 (20.3)	0
Cough	5 (23.8)	0	4 (18.2)	0	3 (14.3)	0	12 (18.8)	0
Arthralgia	3 (14.3)	0	5 (22.7)	0	3 (14.3)	0	11 (17.2)	0
Aspartate aminotransferase increased	5 (23.8)	1 (4.8)	3 (13.6)	1 (4.5)	3 (14.3)	0	11 (17.2)	2 (3.1)
Pneumonia	3 (14.3)	3 (14.3)	4 (18.2)	2 (9.1)	4 (19.0)	1 (4.8)	11 (17.2)	6 (9.4)
Productive cough	6 (28.6)	0	3 (13.6)	0	2 (9.5)	0	11 (17.2)	0
Dysphagia	3 (14.3)	0	3 (13.6)	1 (4.5)	4 (19.0)	00	10 (15.6)	1 (1.6)
Hypothyroidism	3 (14.3)	0	2 (9.1)	0	5 (23.8)	0	10 (15.6)	0
Radiation skin injury	3 (14.3)	0	4 (18.2)	0	3 (14.3)	0	10 (15.6)	0
Vomiting	3 (14.3)	0	1 (4.5)	0	5 (23.8)	1 (4.8)	9 (14.1)	1 (1.6)
Asthenia	6 (28.6)	2 (9.5)	2 (9.1)	1 (4.5)	0	0	8 (12.5)	3 (4.7)
Musculoskeletal chest pain	4 (19.0)	0	2 (9.1)	0	2 (9.5)	0	8 (12.5)	0
Myalgia	5 (23.8)	0	3 (13.6)	0	0	0	8 (12.5)	0
Upper abdominal pain	4 (19.0)	0	4 (18.2)	0	0	0	8 (12.5)	0
Back pain	2 (9.5)	0	2 (9.1)	1 (4.5)	3 (14.3)	0	7 (10.9)	1 (1.6)
Dizziness	2 (9.5)	0	3 (13.6)	0	2 (9.5)	0	7 (10.9)	0
Herpes zoster	2 (9.5)	0	3 (13.6)	0	2 (9.5)	0	7 (10.9)	0
Hiccups	5 (23.8)	0	0	0	2 (9.5)	0	7 (10.9)	0
Pruritus	2 (9.5)	0	2 (9.1)	0	3 (14.3)	0	7 (10.9)	0

Includes AEs that started before the first treatment and worsened with the first dose, or with an onset date on or after the date of the first dose and up to and including 90 days following the date of the last dose of study medication or until the start of the first subsequent therapy (whichever came first).
Abbreviations: AE, adverse event; carbo, carboplatin; cis, cisplatin; D, durvalumab; etop, etoposide; pac, paclitaxel; peme, pemetrexed; RT, radiotherapy.
*AEs are listed in order of frequency across all arms.
[a] Pneumonitis or radiation pneumonitis (grouped term) includes the following reported preferred terms: pneumonitis, pulmonary fibrosis, and radiation pneumonitis; pneumonia events are reported separately.

the potential to increase eligibility for consolidation therapy in this setting. The phase 1 CLOVER study assessed safety/tolerability and preliminary clinical efficacy of durvalumab in combination with cCRT in 64 patients with unresectable, stage III NSCLC. Demographics and baseline characteristics were generally as expected for this patient population, although a higher proportion of patients in Arm 2 had a WHO/ECOG PS of 1, compared with Arms 1 and 3. Despite the small patient numbers, exposure to treatment was adequate to evaluate safety and tolerability across all treatment arms. Most patients were able to complete the planned courses of cCRT, suggesting the addition of durvalumab did not impact safety, tolerability, or treatment adherence. Although this study was conducted during the COVID-19 pandemic, there were no major protocol deviations related to the pandemic or that meaningfully impacted the overall results.

The safety profile of durvalumab in combination with cCRT was consistent with the known safety profiles for durvalumab and cCRT in this setting, and the expected medical history and comorbidities of this patient population [6,28,29]. There were no unexpected safety findings nor new safety signals, and only one patient (in Arm 2) experienced DLTs: grade 3 alanine aminotransferase increase and grade 4 aspartate aminotransferase increase, events which were already known to be associated with durvalumab therapy. As such, treatment with durvalumab did not appear to compromise the administration of cCRT. Of the eight deaths across the NSCLC cohort, four were cardiac in nature and consistent with the expected safety profile in a patient population containing elderly patients with co-existing smoking-related cancer and underlying cardiovascular disease; the remaining fatal events were also consistent with the expected safety profile, given the immunocompromised state precipitated by treatment with chemotherapy.

cCRT and anti-PD-(L)1 therapy have been associated with pneumonitis and radiation pneumonitis in patients with locally-advanced lung cancer [30,31], with rates reported to be around 30% in an international *meta*-analysis [32]. In the durvalumab arm of the phase 3 PACIFIC trial, in which durvalumab was administered after cCRT, pneumonitis/radiation pneumonitis was reported in 161/475 (33.9%) patients, while grade 3/4 pneumonitis/radiation pneumonitis was reported in 16 (3.4%) patients (grade 5 pneumonitis/radiation pneumonitis occurred in five [1.1%] patients) [6]. As combining immunotherapy with cCRT is thought to exacerbate the incidence of imAEs [33], simultaneous administration of durvalumab and cCRT could result in higher rates of pneumonitis. Among patients in the NSCLC cohort of the CLOVER trial, any-grade and grade 3 pneumonitis/radiation pneumonitis occurred in 25/64 (39.1%) and five (7.8%) patients, respectively. Most events were manageable and rarely led to treatment discontinuation; there were no

Table 4
Summary of confirmed tumor response (full analysis set).

	Arm 1 D + cis + etop + RT (n = 21)	Arm 2 D + carbo + pac + RT (n = 22)	Arm 3 D + carbo/cis + peme + RT (n = 21)	Total (N = 64)
Objective response rate, n (%)	14 (66.7)	12 (54.5)	13 (61.9)	39 (60.9)
95 % CI	43.0–85.4	32.2–75.6	38.4–81.9	47.9–72.9
Best objective response, n (%)				
Complete response	0	0	3 (14.3)	3 (4.7)
Partial response	14 (66.7)	12 (54.5)	10 (47.6)	36 (56.3)
Stable disease ≥16 weeks	4 (19.0)	4 (18.2)	6 (28.6)	14 (21.9)
Progressive disease*	2 (9.5)	6 (27.3)	1 (4.8)	9 (14.1)
Not evaluable	1 (4.8)	0	1 (4.8)	2 (3.1)
Median duration of response, months	NR	NR	10.5	15.8
95 % CI	7.9–NE	4.2–NE	4.1–16.7	9.0–NE
Remaining in response, %				
12 months	59.2	67.5	44.9	56.7
18 months	59.2	67.5	15.0	42.6
Disease control rate at 18 weeks,[a] n/N (%)	18/18 (100.0)	16/18 (88.9)	20/21 (95.2)	54/57 (94.7)
95 % CI	81.5–100.0	65.3–98.6	76.2–99.9	85.4–98.9
Disease control rate at 48 weeks,[a] n/N (%)	16/19 (84.2)	13/18 (72.2)	15/20 (75.0)	44/57 (77.2)
95 % CI	60.4–96.6	46.5–90.3	50.9–91.3	64.2–87.3

Responses were investigator-assessed per RECIST v1.1.
Abbreviations: carbo, carboplatin; CI, confidence interval; cis, cisplatin; D, durvalumab; etop, etoposide; NE, not estimable; NR, not reached; pac, paclitaxel; peme, pemetrexed; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy.
*Overall, four (6.3%) patients had disease progression per RECIST v1.1 and five (7.8%) died.
[a] Defined as the percentage of patients with best objective response of complete or partial response in that period, or who have demonstrated stable disease for a minimum interval of 17 weeks or 47 weeks (as applicable). Assessed in patients with at least one post-baseline RECIST v1.1 assessment.

grade 4 or 5 events. These findings are broadly consistent with other trials involving PD-(L)1 inhibition and cCRT for the treatment of lung cancer, including those evaluating the PD-1 inhibitors pembrolizumab [26,34] and nivolumab [27], and the PD-L1 inhibitor atezolizumab [35]. However, the small dataset in CLOVER makes comparisons with other trials challenging. In addition, it is worth noting that in PACIFIC, patients were randomized after completion of cCRT provided they were not actively experiencing any significant toxicity from cCRT, while in CLOVER patients were randomized prior to receiving cCRT. As a consequence, CLOVER may have detected more pneumonitis due to the timing of enrollment, as patients with pneumonitis following cCRT may not have been eligible for treatment in PACIFIC. This could similarly have affected the rates of other types of AEs associated with chemotherapy and radiotherapy, such as hematologic toxicities and infections.

In terms of efficacy, the ORR in patients with NSCLC was 60.9%, which is in line with other studies involving anti-PD-(L)1 therapy in combination with cCRT [26,36,37]. Median PFS was 13.4 months, while median OS was NR; however, the small number of patients enrolled in the CLOVER NSCLC cohort and lack of a control arm for comparison limits further interpretation of the data. The phase 3 placebo-controlled PACIFIC-2 trial (NCT03519971) in patients with unresectable, stage III NSCLC stipulated similar eligibility criteria to those for the CLOVER NSCLC cohort, and used the same experimental treatment regimen [25]. In PACIFIC-2, durvalumab in combination with cCRT did not achieve statistical significance for the primary endpoint of PFS versus cCRT alone [38], indicating that further research is required to identify treatment options for patients who progress during or shortly after CRT or have inadequate recovery from CRT-related toxicity (i.e. patients ineligible for the PACIFIC regimen, which remains the standard of care).

In summary, findings from this phase 1 study demonstrated that durvalumab in combination with cCRT was well tolerated, with a manageable safety profile, and showed encouraging antitumor activity in patients with unresectable, stage III NSCLC.

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CRediT authorship contribution statement

Dong-Wan Kim: Writing – review & editing, Visualization, Project administration, Investigation, Formal analysis, Data curation. **Byoung Chul Cho:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Krishna Pachipala:** Writing – review & editing, Project administration, Investigation. **Sang-We Kim:** Writing – review & editing, Project administration, Investigation. **Chih-Liang Wang:** Writing – review & editing, Project administration, Investigation. **Gee-Chen Chang:** Writing – review & editing, Project administration, Investigation. **Myung-Ju Ahn:** Writing – review & editing, Visualization, Project administration, Investigation, Formal analysis, Data curation. **Rosa Alvarez:** Writing – review & editing, Project administration, Investigation. **Chao-Hua Chiu:** Writing – review & editing, Visualization, Project administration, Investigation, Formal analysis, Data curation. **José Trigo:** Writing – review & editing, Visualization, Project administration, Investigation, Formal analysis, Data curation. **Anna Estival:** Writing – review & editing, Project administration, Investigation. **Sana D. Karam:** Writing – review & editing, Project administration, Investigation. **Cathy O'Brien:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Hema Gowda:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Haiyi Jiang:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Julie E. Bauman:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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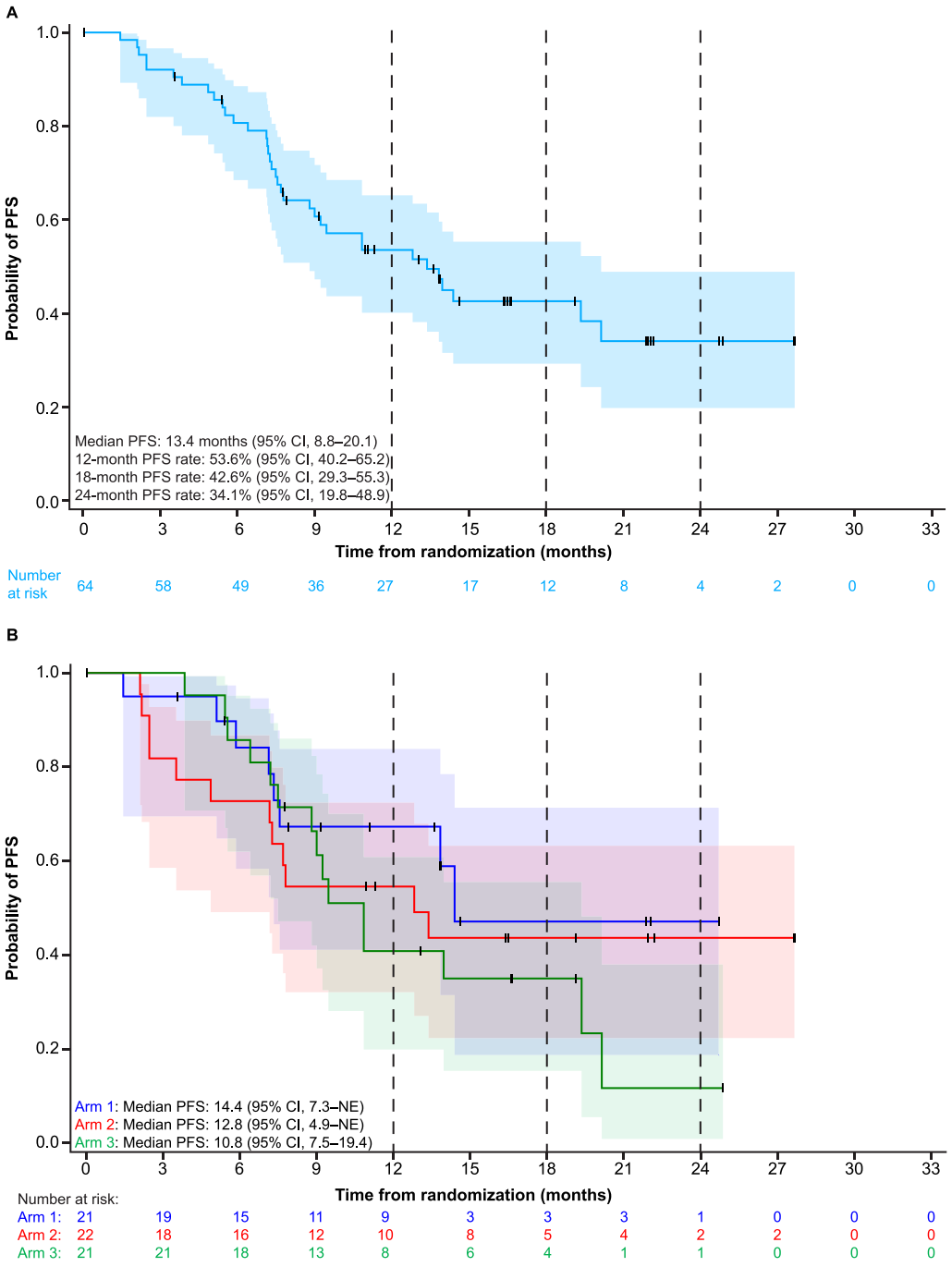

Fig. 1. Kaplan–Meier plots of progression-free survival in (A) the NSCLC cohort overall and (B) Arm 1 (durvalumab + cisplatin + etoposide + radiotherapy), Arm 2 (durvalumab + carboplatin + paclitaxel + radiotherapy) and Arm 3 (durvalumab + carboplatin/cisplatin + pemetrexed + radiotherapy) (full analysis set). Shaded areas indicate 95% CI. *Abbreviations: CI, confidence interval; NE, not estimable; NSCLC, non-small-cell lung cancer; PFS, progression-free survival.*

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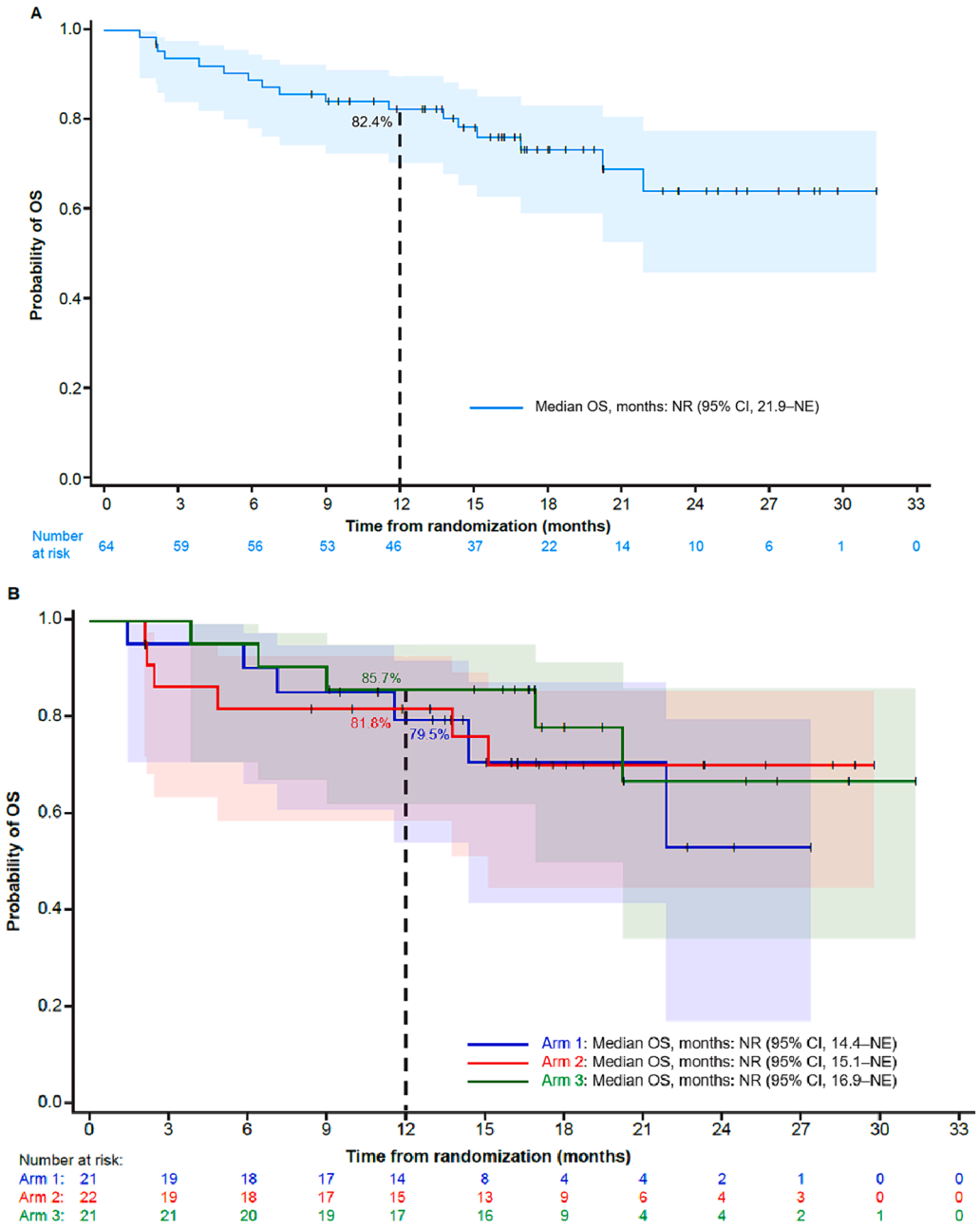

Fig. 2. Kaplan–Meier plots of overall survival in (A) the NSCLC cohort overall and (B) Arm 1 (durvalumab + cisplatin + etoposide + radiotherapy), Arm 2 (durvalumab + carboplatin + paclitaxel + radiotherapy) and Arm 3 (durvalumab + carboplatin/cisplatin + pemetrexed + radiotherapy) (full analysis set). Shaded areas indicate 95% CI. *Abbreviations: CI, confidence interval; NE, not estimable; NR, not reached; NSCLC, non-small-cell lung cancer; OS, overall survival.*

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Ethics approval and consent to participate

All patients provided written informed consent prior to participation in the study. The study was carried out in accordance with the principles set out in the Declaration of Helsinki and was consistent with the International Conference on Harmonisation guidelines on Good Clinical Practice, and any applicable local laws and requirements. The protocol and all subsequent amendments were approved by the relevant Ethics Committees/Independent Review Boards.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2024.107530.

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