

Phase III PACIFIC-5 Trial Evaluating Consolidation Durvalumab in Unresectable Stage III NSCLC with No Progression Following Concurrent or Sequential Chemoradiotherapy

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Abstract

For patients with unresectable stage III non-small-cell lung cancer (NSCLC), durvalumab given as consolidation treatment after concurrent chemoradiotherapy (cCRT) without disease progression has become the worldwide standard approach. Nevertheless, many individuals in real-world settings are treated with sequential chemoradiotherapy (sCRT) instead. The PACIFIC-5 study was therefore initiated to examine the clinical effectiveness and tolerability of consolidation durvalumab in this population following either cCRT or sCRT without progression. This global phase III trial used a randomised, double-blind, placebo-controlled design. It included adults (≥ 18 years) diagnosed with unresectable stage III NSCLC who had stable disease after completing cCRT or sCRT, regardless of PD-L1 levels or sensitising EGFR/ALK mutations. Participants were allocated in a 2:1 ratio to durvalumab (1500 mg IV every 4 weeks) or matching placebo, stratified by PD-L1 tumour expression and type of prior chemoradiotherapy. Therapy continued until progression, severe toxicity, or patient withdrawal. The main outcome was progression-free survival (PFS) determined by blinded independent central review within the modified intention-to-treat (mITT) group. Additional outcomes covered overall survival (OS) in the mITT population along with safety evaluations. Safety was analysed in all patients who received ≥ 1 dose of the study medication. In total, 407 individuals were randomised (272 to durvalumab and 135 to placebo), with 405 ultimately receiving treatment (271 and 134, respectively). The mITT analysis set included 381 patients (252 on durvalumab, 129 on placebo). Treatment with durvalumab led to a meaningful extension of PFS relative to placebo in the mITT group (median 14.0 months [95% CI: 10.9–18.0] compared with 6.5 months [95% CI: 5.4–13.8]; HR: 0.75 [95% CI: 0.58–0.99]; $P = 0.038$). An encouraging but non-significant trend was observed for OS (median 38.3 months [95% CI: 28.9–42.8] vs 32.5 months [95% CI: 20.6–40.4]; HR: 0.87 [95% CI: 0.66–1.17]; $P = 0.346$ at interim analysis). Grade 3/4 adverse events from any cause arose in 26.9% (73/271) of the durvalumab arm and 23.9% (32/134) of the placebo arm. Fatal treatment-related adverse events occurred in 1.5% (4/271) and 0% (0/134) of patients, respectively. The PACIFIC-5 trial achieved its primary goal by demonstrating improved PFS with durvalumab consolidation after either chemoradiotherapy regimen. Continued monitoring for overall survival differences is underway.

Keywords: Non-small-cell lung cancer, Immunotherapy, Chemoradiotherapy, Clinical trial, Phase III, Durvalumab

Introduction

Lung cancer continues to be one of the primary drivers of cancer incidence and mortality across the globe,

accounting for an estimated 2.5 million fresh diagnoses—equivalent to 12.4% of all new cancer cases—in 2022 [1]. The majority of lung cancers ($> 80\%$) are classified as non-small-cell lung cancer (NSCLC), and approximately one in three patients present with unresectable stage III disease at diagnosis [2–4]. Current international guidelines endorse definitive concurrent chemoradiotherapy (cCRT), which delivers platinum-based chemotherapy together with radiation, as the cornerstone curative-intent therapy for eligible patients with unresectable stage III NSCLC [5–7]. Those whose

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tumours remain stable after cCRT are then advised to receive up to one year of consolidation durvalumab, an anti-PD-L1 monoclonal antibody [5-8].

The foundational evidence supporting this consolidation strategy originated from the PACIFIC phase III study (NCT02125461), which demonstrated that durvalumab markedly improved PFS (HR: 0.52; 95% CI: 0.42–0.65; $P < 0.001$) and OS (HR: 0.68; 95% CI: 0.53–0.87; $P = 0.0025$) versus placebo in patients without progression following platinum-based cCRT [9-11]. The safety profile was acceptable, with only a small 4.4% rise in maximum grade 3/4 adverse events of any cause compared with placebo and no adverse influence on patient-reported outcomes [9, 10, 12]. Subsequent long-term data reinforced these advantages, revealing 5-year PFS rates of 33.1% (durvalumab) versus 19.0% (placebo) and 5-year OS rates of 42.9% versus 33.4%, respectively [11].

Despite clear evidence that cCRT (defined here as ≥ 2 cycles of chemotherapy overlapping with radiation) yields superior survival outcomes compared with sequential chemoradiotherapy (sCRT), the latter remains commonly employed in routine care—especially among older adults or those with multiple health issues—owing to concerns about treatment tolerance [13-15]. A pooled analysis of head-to-head randomised studies indicated that cCRT raises the incidence of severe (grade 3–4) oesophageal toxicity from 4% to 18%, with a relative risk of 4.9 (95% CI: 3.1–7.8; $P < 0.001$) [13]. Because the original PACIFIC trial did not enrol sCRT recipients, high-quality prospective data on durvalumab consolidation in this group have been lacking [15]. Additionally, earlier research underrepresented certain geographic regions such as China, Russia, and broader areas of Asia [9, 10, 16].

To address these gaps, PACIFIC-5 (NCT03706690) was launched as an international, randomised, double-blind, placebo-controlled multicentre phase III investigation evaluating consolidation durvalumab in a more inclusive cohort of patients with unresectable stage III NSCLC who had completed either cCRT or sCRT without subsequent progression.

Materials and Methods

Patients

Entry criteria required participants to be adults (≥ 18 years) with an ECOG/WHO performance status of 0–1 and histologically or cytologically verified unresectable

stage III NSCLC (staged according to the 8th edition of the IASLC manual) [17] who had not experienced disease progression after definitive platinum-based cCRT or sCRT completed within 1–28 days before starting study treatment. While PET/CT, brain MRI, and endobronchial ultrasound were recommended at initial diagnosis, they were not obligatory if unavailable locally. Tumour PD-L1 expression was centrally assessed using the VENTANA SP263 assay before randomisation, and EGFR/ALK status was documented either locally or centrally. Complete eligibility details appear in the trial protocol.

cCRT was defined as ≥ 2 cycles of platinum-doublet chemotherapy given concurrently with radiotherapy, with the final chemotherapy administration occurring no later than the end of radiation. Induction chemotherapy (up to 2 cycles) before cCRT was allowed, but consolidation chemotherapy after radiation was prohibited. sCRT required ≥ 2 cycles of platinum-based chemotherapy before radiation, with radiotherapy commencing no more than 6 weeks after the last chemotherapy dose. Permitted chemotherapy partners included etoposide, vinblastine, vinorelbine, paclitaxel, docetaxel, or pemetrexed combined with cisplatin or carboplatin (gemcitabine was excluded). Total radiation dose was mandated at 60 Gy $\pm$ 10% (range 54–66 Gy). Recommended organ dose limits included: mean lung dose < 20 Gy and/or V20 $< 35\%$; mean oesophageal dose < 34 Gy; and cardiac constraints of V45 $< 35\%$ or V30 $< 50\%$.

A protocol amendment (version 5) was introduced during active recruitment to exclude patients with confirmed sensitising EGFR mutations or ALK rearrangements from primary secondary analyses. This adjustment reflected the growing availability of targeted agents for these driver alterations and preliminary PACIFIC findings suggesting uncertain benefit of durvalumab in the EGFR-mutated subgroup [18-20].

Trial design and treatment

Eligible patients showing no signs of disease progression after finishing definitive platinum-based chemoradiotherapy—either concurrent (cCRT) or sequential (sCRT)—were assigned randomly in a double-blind fashion at a 2:1 ratio to receive durvalumab at a dose of 1500 mg or a matching placebo. Both were delivered intravenously once every four weeks and continued until objective disease progression, intolerable

side effects, or voluntary withdrawal of consent. No crossover to the other treatment arm was permitted.

Stratification factors for randomisation included tumour cell PD-L1 expression level ($< 1\%$ vs $\geq 1\%$) and the type of prior chemoradiotherapy received (cCRT vs sCRT). An interactive voice response system handled the randomisation process, drawing from a centrally generated, computer-based list for each stratum, incorporating blocked randomisation to reduce imbalance. The same lists were applied across all participating centres.

AstraZeneca sponsored the trial and was involved in its overall design. Every participant gave written informed consent before enrolment. An independent external data monitoring committee oversaw both efficacy and safety. All protocol versions and amendments were reviewed and approved by appropriate ethics committees and institutional review boards. The study was conducted in full compliance with the Declaration of Helsinki, ICH Good Clinical Practice standards, and applicable local laws and regulations. Study investigators handled data collection. All listed authors contributed to the drafting and revision of the manuscript and gave final approval for publication. They also confirm the integrity and accuracy of the data presented and the study's fidelity to the protocol. Initial manuscript development received medical writing support funded by the sponsor.

Endpoints and assessments

Progression-free survival (PFS), assessed centrally by blinded independent reviewers using RECIST version 1.1 criteria, served as the primary endpoint in the modified intention-to-treat (mITT) population. This population specifically omitted patients with identified EGFR or ALK genetic alterations. PFS was calculated as the interval from randomisation until the earliest date of confirmed radiological progression or death from any cause.

Overall survival (OS) in the same mITT population was the key secondary endpoint, measured from randomisation to death from any cause. Other secondary measures encompassed PFS and OS evaluated in the entire intention-to-treat (ITT) population, the OS rate at 24 months post-randomisation, objective response rate (ORR) per BICR, duration of response (DoR) per BICR, PFS rates at 12 and 18 months by BICR, time to second progression (PFS2) based on investigator assessment, and time to death or distant metastasis (TTDM) determined by central review.

Imaging evaluations (CT or MRI scans) took place at baseline, followed by scans every 8 weeks during the first 48 weeks after randomisation, and then every 12 weeks until progression was radiologically confirmed (including at least one follow-up scan for verification), study termination, patient death, discontinuation, or sponsor decision. Safety monitoring covered the entire study period and applied to every patient who received at least one dose of study drug (safety analysis set). Adverse events were documented from the screening visit through 90 days after the final dose, classified using MedDRA version 26.1, and graded per NCI CTCAE version 5.0. Given the difficulty in clearly separating radiation-induced lung injury from immune-related pneumonitis due to overlapping features, these events were combined and analysed together as "pneumonitis or radiation pneumonitis" [21, 22].

Statistical analysis

The trial planned to enrol around 400 patients in the ITT population at a 2:1 ratio, anticipating approximately 375 patients would qualify for the mITT population after excluding those with EGFR or ALK aberrations enrolled before the protocol update. The primary analysis for PFS in the mITT group was triggered by the first occurrence of approximately 262 events, as determined by central review (about 70% maturity), or when follow-up from the last randomised patient reached approximately 28 months. This setup achieved at least 90% power to detect a hazard ratio of 0.65 at a two-sided 5% significance level. The threshold HR for statistical significance was set at 0.773.

Kaplan-Meier estimates were used to determine median values and landmark rates for both PFS and OS. Confidence intervals around the medians were calculated using the Brookmeyer-Crowley method with a log-log transformation. Hazard ratios along with their confidence intervals were generated from stratified Cox proportional hazards models that accounted for PD-L1 status ($< 1\%$ vs $\geq 1\%$) and previous treatment type (cCRT or sCRT), with treatment group as the sole covariate; ties were managed using the Efron method, and profile likelihood provided the CIs. Two-sided p-values were derived from stratified log-rank tests using the same adjustment factors. Subgroup evaluations used unstratified Cox models and log-rank tests. Analyses for PFS2 and TTDM followed the same general methods as those for PFS and OS. Safety outcomes were reported only through descriptive summaries.

The statistical plan included no interim analyses of PFS and a maximum of 2 for OS. Control of type I error across survival endpoints utilised the Lan-DeMets alpha-spending function approximating O'Brien-Fleming boundaries [23]. A fixed hierarchical testing sequence was applied to preserve the overall two-sided 5% type I error rate: testing started with PFS in the mITT population. Upon success, alpha was reallocated to OS in the mITT. If that endpoint also reached significance (at interim or final), alpha moved next to PFS in the ITT population and, finally, to OS in the ITT.

Results and Discussion

Patients

Recruitment took place from 27 November 2018 to 17 January 2022. During this period, 773 patients were screened across 71 study sites, and 407 were ultimately randomised to durvalumab ($n = 272$) or placebo ($n = 135$). Sites were distributed as follows: mainland China (33), Russia (10), Taiwan (7), Turkey (6), Poland (4), India (3), Philippines (3), Republic of Korea (3), Hong Kong (1), and Mexico (1) (**Figure 1**).

The ITT population included every randomised patient. The mITT population comprised 381 individuals without documented EGFR or ALK aberrations (durvalumab, $n = 252$; placebo, $n = 129$). Finally, 405 patients who received at least 1 dose formed the safety analysis set (durvalumab, $n = 271$; placebo, $n = 134$).

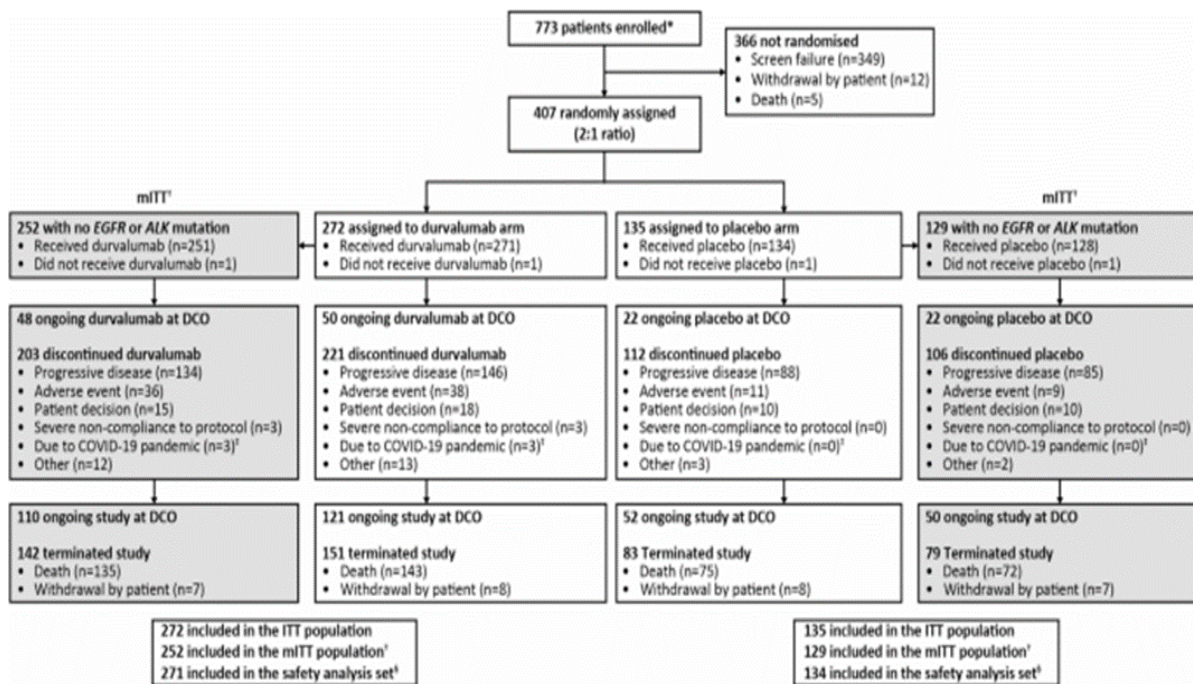


Figure 1. CONSORT diagram. *Informed consent was obtained.

†The mITT population was formed by removing from the ITT population those patients who had documented EGFR mutations (durvalumab arm: $n = 12$; placebo arm: $n = 4$), ALK rearrangements (durvalumab arm: $n = 7$; placebo arm: $n = 2$), or unknown EGFR status (durvalumab arm: $n = 1$; placebo arm: $n = 0$) or ALK status ($n = 0$ in both arms). ‡This category took precedence over others and was assigned when the reason for stopping treatment specifically mentioned COVID. §The safety analysis set consisted of all randomised patients who received at least one dose of the assigned study treatment. Abbreviations: ALK = anaplastic

lymphoma kinase; COVID-19 = coronavirus disease of 2019; DCO = data cut-off; EGFR = epidermal growth factor receptor; ITT = intention-to-treat; mITT = modified intention-to-treat.

Baseline demographics and disease characteristics

Patient characteristics at study entry were generally well balanced between the ITT and mITT populations (**Table 1**). Within the mITT population, the median age was 63.0 years in each treatment group. In the durvalumab arm compared with the placebo arm of the mITT, the majority of participants were male (92.1% versus 88.4%), of

Asian ethnicity (71.4% versus 72.9%), had squamous cell histology (69.8% versus 65.1%), showed PD-L1 tumour cell expression of $\geq 1\%$ (59.9% versus 60.5%), and had a history of smoking (84.9% versus 88.4%). A WHO/ECOG performance status of 1 was more frequent in the durvalumab group (68.3% versus 55.0%), as was stage IIIC disease (23.4% versus 14.7%).

Details regarding previous radiotherapy and chemotherapy were comparable across the two arms (**Table 1**). In the mITT population, 66.7% of patients in the durvalumab group and 69.8% in the placebo group had undergone concurrent chemoradiotherapy. Additionally, most patients in both arms achieved a best response of partial response to the prior chemoradiotherapy (64.7% versus 65.1%).

Table 1. Patient characteristics in the mITT and ITT.

	mITT (n = 381)		ITT (n = 407)	
	Durvalumab (n = 252)	Placebo (n = 129)	Durvalumab (n = 272)	Placebo (n = 135)
Median age (range), years	63.0 (39–80)	63.0 (33–79)	62.5 (35–80)	63.0 (33–79)
Age category, n (%)				
< 50 years	17 (6.7)	5 (3.9)	21 (7.7)	6 (4.4)
≥ 50 to < 65 years	129 (51.2)	73 (56.6)	139 (51.1)	77 (57.0)
≥ 65 to < 75 years	91 (36.1)	45 (34.9)	96 (35.3)	46 (34.1)
≥ 75 years	15 (6.0)	6 (4.7)	16 (5.9)	6 (4.4)
Sex, n (%)				
Male	232 (92.1)	114 (88.4)	247 (90.8)	117 (86.7)
Female	20 (7.9)	15 (11.6)	25 (9.2)	18 (13.3)
Race, n (%)				
Asian	180 (71.4)	94 (72.9)	197 (72.4)	97 (71.9)
White	72 (28.6)	35 (27.1)	75 (27.6)	38 (28.1)
Smoking status, n (%)				
Current or former	214 (84.9)	114 (88.4)	227 (83.5)	116 (85.9)
Never	38 (15.1)	15 (11.6)	45 (16.5)	19 (14.1)
Median (range) time from last dose of radiation to randomisation, days	23.0 (3–42)	24.0 (7–32)	23.0 (3–42)	24.0 (7–33)
Time from last dose of radiation to randomisation group, n (%)				
< 14 days	26 (10.3)	14 (10.9)	28 (10.3)	16 (11.9)
≥ 14 days	226 (89.7)	115 (89.1)	244 (89.7)	119 (88.1)
Prior CRT, n (%)				
Concurrent	168 (66.7)	90 (69.8)	182 (66.9)	92 (68.1)
Sequential	84 (33.3)	39 (30.2)	90 (33.1)	43 (31.9)
Best response to prior CRT, n (%)				
Complete response	0	1 (0.8)	0	1 (0.7)
Partial response	163 (64.7)	84 (65.1)	176 (64.7)	85 (63.0)
Stable disease	89 (35.3)	44 (34.1)	96 (35.3)	49 (36.3)
Platinum-based chemotherapy				
Cisplatin	122 (48.4)	64 (49.6)	132 (48.5)	66 (48.9)
Carboplatin	124 (49.2)	62 (48.1)	133 (48.9)	65 (48.1)
Cisplatin and carboplatin	6 (2.4)	3 (2.3)	7 (2.6)	4 (3.0)
Definitive radiotherapy*	252 (100)	129 (100)	272 (100)	135 (100)
Total radiation dose [†]				
n	256	132	276	138
Mean (SD), Gy	60.2 (6.11)	59.7 (7.61)	60.2 (5.95)	59.7 (7.45)
Median (range), Gy	60.0 (10–66)	60.0 (5–66)	60.0 (10–66)	60.0 (5–66)
Total radiation dose, n (%) [†]				
< 54 Gy	3 (1.2)	3 (2.3)	3 (1.1)	3 (2.2)

≥ 54 to ≤ 66 Gy	250 (99.2)	129 (100)	270 (99.3)	135 (100)
> 66 Gy to ≤ 74 Gy	0	0	0	0
> 74 Gy	0	0	0	0
PD-L1 status, n (%)				
TC < 1%	101 (40.1)	51 (39.5)	107 (39.3)	53 (39.3)
TC ≥ 1%	151 (59.9)	78 (60.5)	165 (60.7)	82 (60.7)
ECOG/WHO PS, n (%)				
0 – normal activity	80 (31.7)	58 (45.0)	88 (32.4)	62 (45.9)
1 – restricted activity	172 (68.3)	71 (55.0)	184 (67.6)	73 (54.1)
AJCC staging at study entry, n (%)				
IIIA	77 (30.6)	45 (34.9)	86 (31.6)	48 (35.6)
IIIB	116 (46.0)	64 (49.6)	124 (45.6)	67 (49.6)
IIIC	59 (23.4)	19 (14.7)	62 (22.8)	19 (14.1)
IV	0	1 (0.8)	0	1 (0.7)
Histology at study entry, n (%)				
Squamous	176 (69.8)	84 (65.1)	182 (66.9)	85 (63.0)
Non-squamous	76 (30.2)	45 (34.9)	90 (33.1)	50 (37.0)
EGFR mutation				
Negative	252 (100)	129 (100)	259 (95.2)	131 (97.0)
Positive	0	0	12 (4.4)	4 (3.0)
Unknown	0	0	1 (0.4)	0
ALK rearrangement				
Negative	252 (100)	129 (100)	265 (97.4)	133 (98.5)
Positive	0	0	7 (2.6)	2 (1.5)
Unknown	0	0	0	0
EGFR mutation or ALK rearrangement				
Negative	252 (100)	129 (100)	252 (92.6)	129 (95.6)
Positive	0	0	19 (7.0)	6 (4.4)
Unknown	0	0	1 (0.4)	0

1. AJCC = American Joint Committee on Cancer; ALK = anaplastic lymphoma kinase; COVID-19 = coronavirus disease of 2019; CRT = chemoradiotherapy; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; Gy = gray; ITT = intention-to-treat; mITT = modified intention-to-treat; PD-L1 = programmed cell death ligand-1; PS = performance status; SD = standard deviation; TC = tumour cell expression; WHO = World Health Organisation.

2. *Represents the count of distinct patients who underwent prior definitive radiotherapy.

3. †The summary can reflect more than one course of radiotherapy per patient.

Treatment exposure

Nearly all patients in the mITT population initiated study treatment: 99.6% in the durvalumab group and 99.2% in the placebo group (**Figure 1**). In total, 80.9% of durvalumab-treated patients and 82.8% of placebo-treated patients in the mITT population eventually discontinued the study drug. The leading reason for discontinuation was disease progression, which occurred in 53.4% of the durvalumab arm compared with 66.4% in the placebo arm. Adverse events led to treatment discontinuation in 14.3% of patients receiving durvalumab and 7.0% of those receiving placebo.

Patients in the durvalumab arm received a median of 12.0 cycles, while those in the placebo arm received a median of 7.0 doses. The median duration of actual treatment exposure was 48.4 months with durvalumab compared to

28.3 months with placebo. Roughly half (49.1%) of durvalumab recipients completed at least one full year of therapy (equivalent to 13 cycles), and nearly one-third (29.9%) continued treatment for two years (26 cycles).

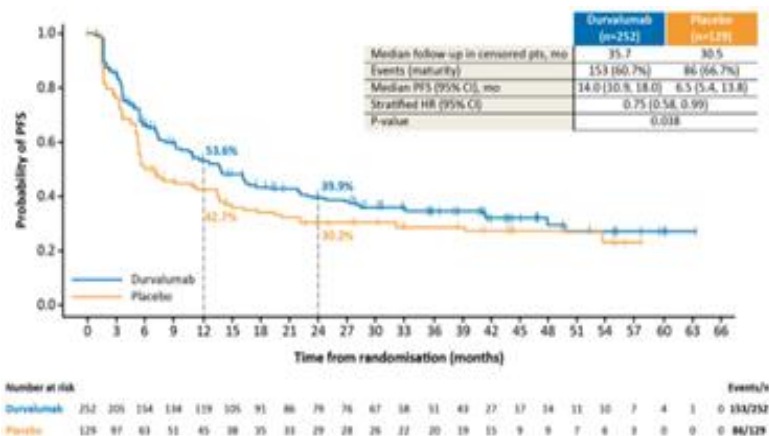
Following the end of study treatment, 165 of 381 patients in the mITT population received subsequent anticancer therapies. This included 95/252 (37.7%) patients from the durvalumab group and 70/129 (54.3%) from the placebo group. The most frequently used subsequent therapies were chemotherapy (31.3% [n = 79] in the durvalumab arm versus 38.8% [n = 50] in the placebo arm) and immunotherapy (9.5% [n = 24] versus 17.8% [n = 23], respectively).

Efficacy

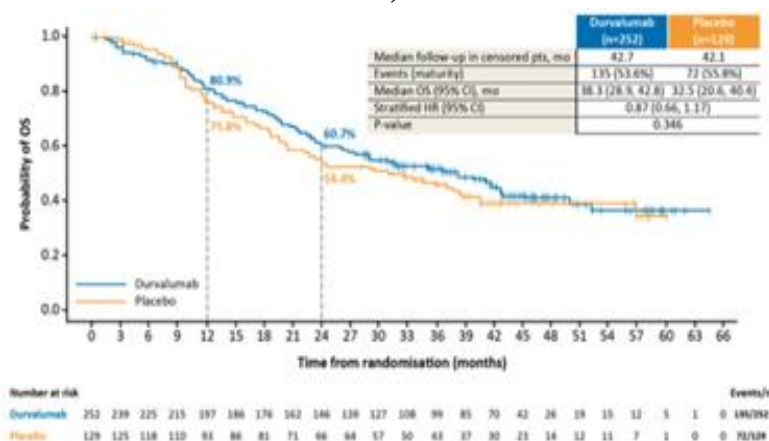
Durvalumab produced a statistically significant benefit over placebo for the primary endpoint of PFS in the mITT population (**Figure 2a**). At the time of analysis, the median follow-up duration for patients still censored for PFS was 35.7 months in the durvalumab arm and 30.5 months in the placebo arm. Median PFS was 14.0 months (95% CI: 10.9–18.0) with durvalumab versus 6.5 months (95% CI: 5.4–13.8) with placebo, corresponding to a

stratified hazard ratio of 0.75 (95% CI: 0.58–0.99; $P = 0.038$).

Consistent findings were noted in the broader ITT population, although formal statistical testing was not performed due to the pre-specified hierarchical testing rules. In the mITT population, the PFS rates at 12, 18, and 24 months were 53.6%, 43.4%, and 39.9% in the durvalumab group compared with 42.7%, 34.1%, and 30.2% in the placebo group.



a)



b)

Figure 2. (a) Progression-free survival by blinded independent central review and (b) overall survival in the modified intention-to-treat population.

Median values and landmark survival rates for both PFS and OS were estimated with the Kaplan-Meier method. Confidence intervals around the medians were obtained using the Brookmeyer-Crowley procedure with log-log transformation. Hazard ratios and their corresponding confidence intervals were generated from a stratified Cox proportional hazards model that adjusted for PD-L1 expression level and type of prior therapy, incorporating

treatment group as the sole covariate. Ties were handled using the Efron method, and confidence intervals were computed using the profile likelihood method. Two-sided p-values were calculated with the stratified log-rank test, accounting for PD-L1 status and previous treatment type. An HR below 1 indicates a benefit in favour of durvalumab over placebo. Abbreviations: BICR = blinded independent central review; CI =

confidence interval; HR = hazard ratio; mITT = modified intention-to-treat; mo = months; OS = overall survival; PD-L1 = programmed death ligand-1; PFS = progression-free survival; pts = patients.

Subgroup analyses

Hazard ratios for PFS generally favoured durvalumab over placebo across the majority of predefined subgroups within the mITT population, although most 95% confidence intervals crossed 1, with only limited exceptions. Comparable advantages were seen regardless of whether patients had previously received concurrent chemoradiotherapy (HR: 0.76; 95% CI: 0.55–1.06) or

sequential chemoradiotherapy (HR: 0.75; 95% CI: 0.49–1.18) (**Figure 3**).

Notable exceptions where benefit was not observed included patients with PD-L1 tumour cell expression below 1% (HR: 0.97; 95% CI: 0.63–1.53), those with non-squamous histology (HR: 1.07; 95% CI: 0.66–1.80), and individuals treated with cisplatin-based regimens (HR: 0.98; 95% CI: 0.66–1.47). However, within each subgroup, the median PFS in the placebo arm was unusually high (13.6 months for PD-L1 TC < 1%, 19.9 months for non-squamous histology, and 13.8 months for cisplatin) compared with the overall mITT placebo median of 6.5 months.

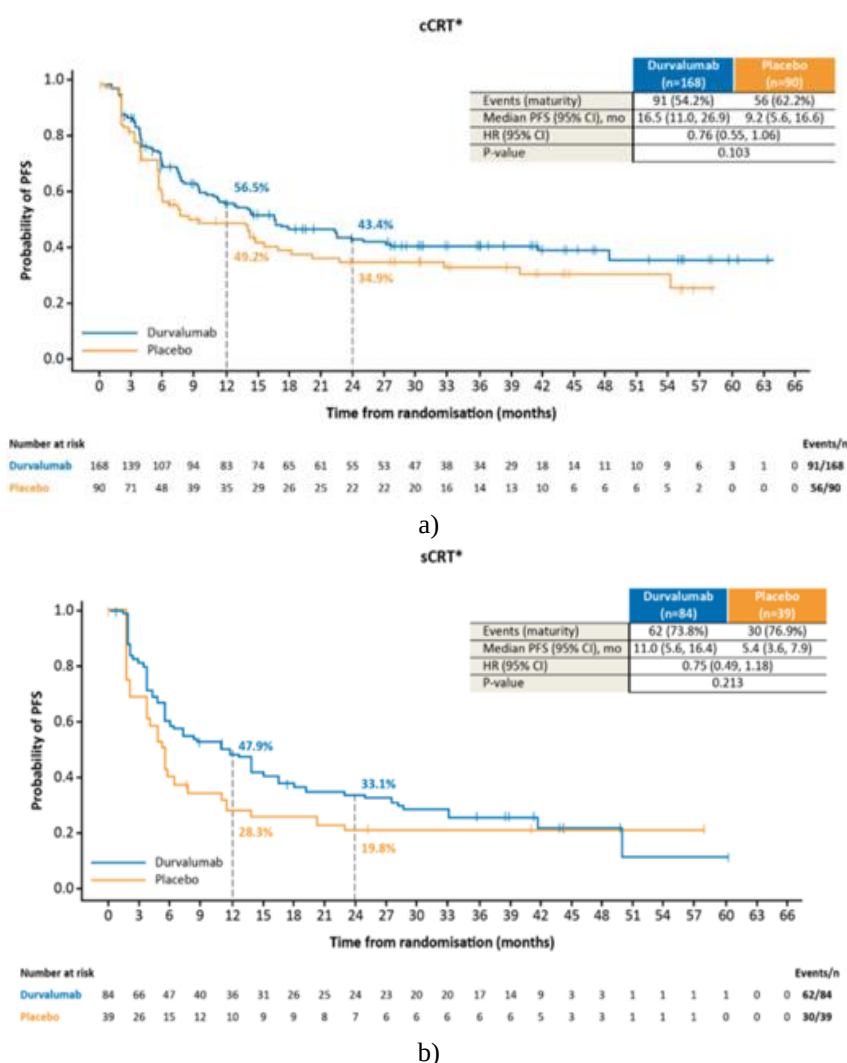


Figure 3. PFS according to prior treatment with (a) concurrent chemoradiotherapy and (b) sequential chemoradiotherapy among patients in the modified intention-to-treat set.

Medians and landmark progression-free survival rates were estimated using the Kaplan-Meier method.

Confidence intervals for median PFS values were calculated using the Brookmeyer-Crowley method with

a log-log transformation. Hazard ratios and their confidence intervals were obtained from unstratified Cox proportional hazards models with treatment assignment as the sole variable; ties were resolved using the Efron method, and profile likelihood was used to estimate the CIs. Two-sided p-values were derived from unstratified log-rank testing. Hazard ratios below 1 indicate a benefit for durvalumab relative to placebo. *Data as captured on the electronic case report form. Abbreviations: cCRT = concurrent chemoradiotherapy; CI = confidence interval; eCRF = electronic case report form; HR = hazard ratio; mITT = modified intention-to-treat; mo = months; sCRT = sequential chemoradiotherapy.

Overall survival results

During this first planned interim look, overall survival results in the mITT population pointed to a potential advantage for the durvalumab group over placebo (**Figure 2b**). For patients whose data remained censored for the OS endpoint, the median follow-up time reached 42.7 months in those assigned to durvalumab and 42.1 months in the placebo group. The median overall survival time was 38.3 months (95% CI: 28.9–42.8) for durvalumab-treated patients, compared with 32.5 months (95% CI: 20.6–40.4) for placebo-treated patients, yielding a stratified hazard ratio of 0.87 (95% CI: 0.66–

1.17; $P = 0.346$). A parallel pattern appeared when evaluating the full ITT population, although the protocol's hierarchical testing rules prevented formal statistical testing at this stage. OS rates at 12 and 24 months within the mITT were 80.9% and 60.7% with durvalumab, versus 75.8% and 54.4% with placebo.

Other efficacy measures

Objective response rates reached 27.6% in the durvalumab arm of the mITT population and 20.7% in the placebo arm (odds ratio 1.51, 95% CI: 0.891–2.607; $P = 0.128$) (**Table 2**). The median duration of response was not reached in the durvalumab group (95% CI: 16.6–not estimable), while it was 37.6 months (95% CI: 5.4–not estimable) for placebo recipients.

In the mITT analysis, median time to death or distant metastasis was 42.6 months (95% CI: 33.2–not estimable) among durvalumab patients and was not reached (95% CI: 20.3–not estimable) in the placebo arm (stratified HR: 1.06; 95% CI: 0.73–1.58; $P = 0.769$). Time to second progression as evaluated by local investigators using RECIST v1.1 criteria in the mITT population also leaned in favour of durvalumab, with medians of 26.4 months (95% CI: 22.1–36.0) versus 19.5 months (95% CI: 14.7–28.9) for placebo (stratified HR: 0.86; 95% CI: 0.65–1.14; $P = 0.275$).

Table 2. Tumour response in the mITT.

	mITT (n = 381)	
	Durvalumab (n = 252)	Placebo (n = 129)
Measurable disease at baseline, n (%)	221	121
Objective response, n (%) ^{*†}	61 (27.6)	25 (20.7)
OR (95% CI)	1.51 (0.891, 2.607)	
P-value	0.128	
Best objective response, n (%) [†]		
Complete response*	2 (0.9)	2 (1.7)
Partial response*	59 (26.7)	23 (19.0)
Stable disease ≥ 8 weeks	125 (56.6)	67 (55.4)
Progression	30 (13.6)	26 (21.5)
RECIST progression	24 (10.9)	25 (20.7)
Death	6 (2.7)	1 (0.8)
Not evaluable	5 (2.3)	3 (2.5)
Stable disease < 8 weeks	1 (0.5)	0
Incomplete post baseline assessments	4 (1.8)	3 (2.5)
Median DoR (95% CI), months ^{*‡}	NR (16.6–NE)	37.6 (5.4–NE)

1. BICR = blinded independent central review; CI= confidence interval; DoR= duration of response; mITT= modified intention-to-treat; NE= not estimable; NR= not reached; OR= odds ratio; RECIST= Response Evaluation Criteria in Solid Tumors.

2. Tumor responses were assessed centrally in a blinded fashion using RECIST guidelines. Any patient who passed away without available RECIST evaluations up to 17 weeks following randomization was placed in the progression group. Patients who died without RECIST data beyond 17 weeks after randomization were placed in the not evaluable group.

3. *No confirmation of response was necessary for inclusion of patients.

4. †All percentages were derived from the subgroup of patients presenting with measurable disease at study entry.

5. ‡DoR corresponds to the period starting from the first recorded response and ending at the initial documentation of progression or death (if progression had not yet been observed). This was analyzed via the Kaplan-Meier method. The 95% CI around the median DoR was computed using the Brookmeyer-Crowley technique with log-log transformation.

Safety

Adverse events that emerged during treatment, regardless of causality, developed in 94.8% of participants on durvalumab compared with 83.6% on placebo (**Table 3**). The highest severity reached grade 3 or 4 in 26.9% and 23.9% of patients in the respective arms. The predominant any-grade treatment-emergent AEs included pneumonitis/radiation pneumonitis (observed in 39.5% of the durvalumab cohort and 40.3% of the placebo cohort), hypothyroidism (18.8% versus 7.5%),

pneumonia (18.8% versus 11.2%), and anemia (15.1% versus 14.9%). Leading grade 3/4 AEs encompassed pneumonia (5.9% with durvalumab and 5.2% with placebo), pneumonitis or radiation pneumonitis (3.7% and 2.2%), and anemia (2.2% and 1.5%). Investigators most often attributed the following AEs to the study drug: pneumonitis/radiation pneumonitis (18.5% in the durvalumab arm versus 11.9% in the placebo arm), hypothyroidism (15.5% and 7.5%), and hyperthyroidism (10.7% and 5.2%).

Table 3. Summary of adverse events in the safety analysis set.

	Safety analysis set (n = 405)	
	Durvalumab (n = 271)	Placebo (n = 134)
Any AE	257 (94.8)	112 (83.6)
Causally related to study treatment*	172 (63.5)	53 (39.6)
Any AE of maximum Grade 3 or 4	73 (26.9)	32 (23.9)
Causally related to study treatment*	23 (8.5)	5 (3.7)
Any AE with outcome = death	25 (9.2) [†]	2 (1.5) [‡]
Causally related to study treatment*	4 (1.5) [§]	0
Any SAE	104 (38.4)	45 (33.6)
Causally related to study treatment*	34 (12.5)	12 (9.0)
Any AE leading to discontinuation of study treatment	39 (14.4)	11 (8.2)
Any imAE [¶]	75 (27.7)	20 (14.9)
Any imAE of maximum Grade 3 or 4 [¶]	11 (4.1)	0
Any AE of pneumonitis** or radiation pneumonitis	107 (39.5)	54 (40.3)
Maximum Grade 3 or 4	10 (3.7)	3 (2.2)

AE: adverse event; imAE: immune-mediated adverse event; SAE: serious adverse event.

When patients experienced multiple events of the same type, they were counted only once for that type. Individuals with events across multiple categories were included only once per applicable category.

*Determined by investigator assessment. Any cases lacking causality data were treated as treatment-related.

†Deaths due to AEs in durvalumab recipients encompassed acute coronary syndrome (n = 1), acute myocardial infarction (n = 2), cardiac arrest (n = 2), cardiac failure (n = 1), cerebral haemorrhage (n = 1), cerebral infarction (n = 1), cerebrovascular disorder (n = 1), COVID-19 pneumonia (n = 2), death (n = 3), haemoptysis (n = 1), interstitial lung disease (n = 1), laryngeal neoplasm (n = 1), pneumocystis jirovecii pneumonia (n = 1), pneumonia (n = 2), bacterial pneumonia (n = 1), pneumonitis (n = 3), pulmonary embolism (n = 1), respiratory failure (n = 1), and homicide victim (n = 1). Multiple occurrences of the

same preferred term were counted only once. Each preferred term was counted individually.

‡Deaths from AEs in the placebo group were limited to bacterial pneumonia (n = 1) and pneumonitis (n = 1).

§In the durvalumab arm, investigator-assessed possibly treatment-related fatal AEs involved pneumonia (n = 1), pneumonitis (n = 3), and interstitial lung disease (n = 1). One individual had overlapping pneumonia and pneumonitis events that both contributed to a fatal outcome considered possibly linked to therapy.

¶ImAEs represent adverse events of special interest tied to drug administration, exhibiting an immune-based mechanism, and without an obvious other explanation.

**The term pneumonitis groups together interstitial lung disease, immune-mediated lung disease, and pneumonitis itself. **

Any-cause fatal AEs arose in 25 (9.2%) durvalumab-treated patients versus 2 (1.5%) placebo-treated patients

(Table 3). Investigator-determined treatment-related fatal events affected 4 (1.5%) patients given durvalumab—specifically one with combined pneumonia and pneumonitis, two with pneumonitis alone, and one with interstitial lung disease—while none occurred on placebo. Adverse events led to treatment discontinuation in 14.4% of the durvalumab cohort and 8.2% of the placebo cohort, driven chiefly by pneumonitis or radiation pneumonitis (6.6% and 3.7%, respectively).

Any-grade immune-mediated AEs, irrespective of attribution, occurred in 27.7% of durvalumab patients and 14.9% of placebo patients, with a peak severity of grade 3 or 4 in 4.1% and 0% of cases, respectively. Incidence of pneumonitis or radiation pneumonitis remained nearly identical across arms (39.5% durvalumab, 40.3% placebo), with the bulk being mild to moderate (grade 1 or 2).

PACIFIC-5 fulfilled its primary goal by showing a clear, meaningful extension of progression-free survival using durvalumab over placebo in people with unresectable stage III NSCLC who remained progression-free after either concurrent or sequential chemoradiation. The first interim look also hinted at an overall survival benefit favoring durvalumab. Most other secondary measures favored benefit with active treatment, except for time to distant metastasis or death, where no separation was observed—probably because squamous-cell cases, known for a higher local-regional relapse risk, accounted for a large share of the study [24, 25]. Overall tolerability of durvalumab matched expectations from prior experience, with no unexpected risks emerging even when therapy continued until disease advancement [9, 10]. Grade 5 events were higher numerically with durvalumab (9.2%, $n = 25$) than placebo (1.5%, $n = 2$), yet drug-related deaths stayed uncommon at 1.5% ($n = 4$) versus zero. These figures align closely with the phase III PACIFIC trial despite longer exposure here (grade 5 treatment-related events: 1.5% durvalumab vs 1.3% placebo) [9].

PFS gains from durvalumab held up across the majority of planned subgroup analyses in the modified intention-to-treat set (including the prior chemoradiation approach), except for non-squamous histology, tumor PD-L1 below 1% on tumor cells, and prior cisplatin chemotherapy recipients. In those subsets, placebo performance exceeded the overall mITT placebo result, whereas durvalumab outcomes tracked similarly to those of the full mITT durvalumab group. Median PFS values

illustrate this: placebo reached 19.9, 13.6, and 13.8 months in the non-squamous, PD-L1 < 1%, and cisplatin subgroups (compared with 6.5 months overall mITT), while durvalumab medians were 15.0, 12.7, and 14.1 months (compared with 14.0 months overall). Differences likely stemmed from an uneven distribution of favorable prognostic factors (better performance status, stage IIIA, non-squamous features) that tilted toward placebo at baseline. Subgroup results require careful review because hazard ratio confidence intervals included 1.0 everywhere, numbers were modest, and the trial was not designed for subgroup significance testing. Roughly 90% of enrolled patients were male in both groups, possibly linked to EGFR mutation exclusion (more frequent in women) or China's enrollment dominance where male lung cancer rates are roughly double those in females [26, 27].

PACIFIC-5 backs consolidation durvalumab use after concurrent or sequential chemoradiation, mirroring the phase III GEMSTONE-301 findings (NCT03728556) where sugemalimab outperformed placebo post-chemoradiation in Chinese patients (median PFS: 9.0 [8.1–14.1] vs 5.8 [4.2–6.6] months; HR: 0.64 [0.48–0.85]) and the phase II PACIFIC-6 experience (NCT03693300) showing good tolerability and activity for durvalumab after sequential chemoradiation (median PFS: 10.9 [7.3–15.6] months) [16, 28]. GEMSTONE-301 omitted mandatory EGFR/ALK testing; given the Asian-heavy population with frequent driver mutations, this may account for some efficacy differences compared with other studies. Even allowing for cross-trial limitations, practice differences, and population traits, PACIFIC-5's durvalumab median PFS of 14.0 months compared well to GEMSTONE-301's 10.5 months and approached PACIFIC's 16.9 months [11, 29]. Placebo controls performed comparably too (PACIFIC-5: 6.5 months; GEMSTONE-301: 6.2 months; PACIFIC: 5.6 months) [9, 11, 28]. The substantial use of sequential chemoradiation in PACIFIC-5 implies enrollment of frailer patients than in trials relying mostly on concurrent approaches, as sequential regimens are chosen for tolerability reasons [13-15]. Still, safety remained manageable and consistent with prior durvalumab data, including comparable rates of severe AEs and pneumonitis [9, 10]. Results across PACIFIC-5, PACIFIC, and real-world sources collectively affirm the consolidation of durvalumab after either chemoradiation strategy [9, 10, 16, 30-34].

While consolidation durvalumab is established after concurrent chemoradiation and promising after sequential therapy, more options are needed to raise outcomes further [35]. Possibilities include earlier immunotherapy introduction alongside chemoradiation, though recent studies found little advantage [36, 37], or pairing PD-L1 blockade with novel agents like anti-TIGIT (domvanalimab), anti-CD73 (oleclumab), or anti-NKG2A (monalizumab) to create additive effects. Positive signals emerged from the phase II COAST study (NCT03822351) testing durvalumab plus oleclumab or monalizumab, with phase III readouts expected soon from PACIFIC-8 (NCT05211895, durvalumab + domvanalimab) and PACIFIC-9 (NCT05221840, durvalumab + oleclumab or monalizumab) [38-40]. Induction immunotherapy—solo or combined with chemotherapy or anti-angiogenics—before chemoradiation or surgery also continues to generate interest, supported by early-phase and retrospective evidence of activity [41-48].

Conclusion

Overall, PACIFIC-5 met its PFS primary endpoint with durvalumab versus placebo in a broader, unresectable stage III NSCLC population than in the original PACIFIC trial, without new safety concerns, even with ongoing treatment until progression. This evidence strengthens the case for consolidation immunotherapy following either concurrent or sequential chemoradiotherapy.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-63.
2. Casal-Mourino A, Ruano-Ravina A, Lorenzo-Gonzalez M, Rodriguez-Martinez A, Giraldo-Osorio A, Varela-Lema L, et al. Epidemiology of stage III lung cancer: frequency, diagnostic characteristics, and survival. *Transl Lung Cancer Res*. 2021;10(1):506-18.
3. Provencio M, Carcereny E, Rodriguez-Abreu D, Lopez-Castro R, Guirado M, Camps C, et al. Lung cancer in Spain: information from the Thoracic Tumors Registry (TTR study). *Transl Lung Cancer Res*. 2019;8(4):461-75.
4. Walters S, Maringe C, Coleman MP, Peake MD, Butler J, Young N, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. *Thorax*. 2013;68(6):551-64.
5. Daly ME, Singh N, Ismaila N, Antonoff MB, Arenberg DA, Bradley J, et al. Management of stage III non-small-cell lung cancer: ASCO guideline. *J Clin Oncol*. 2022;40(12):1356-84.
6. Remon J, Soria JC, Peters S. Early and locally advanced non-small-cell lung cancer: an update of the ESMO clinical practice guidelines focusing on diagnosis, staging, systemic and local therapy. *Ann Oncol*. 2021;32(12):1637-42.
7. Park K, Vansteenkiste J, Lee KH, Pentheroudakis G, Zhou C, Prabhash K, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with locally-advanced unresectable non-small-cell lung cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS. *Ann Oncol*. 2020;31(2):191-201.
8. Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res*. 2015;3(9):1052-62.
9. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919-29.
10. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-50.
11. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *J Clin Oncol*. 2022;40(12):1301-11.

12. Hui R, Ozguroglu M, Villegas A, Daniel D, Vicente D, Murakami S, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. *Lancet Oncol.* 2019;20(12):1670-80.
13. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol.* 2010;28(13):2181-90.
14. De Ruysscher D, Botterweck A, Dirx M, Pijls-Johannesma M, Wanders R, Hochstenbag M, et al. Eligibility for concurrent chemotherapy and radiotherapy of locally advanced lung cancer patients: a prospective, population-based study. *Ann Oncol.* 2009;20(1):98-102.
15. Mielgo-Rubio X, Rojo F, Mezquita-Perez L, Casas F, Wals A, Juan M, et al. Deep diving in the PACIFIC: practical issues in stage III non-small cell lung cancer to avoid shipwreck. *World J Clin Oncol.* 2020;11(11):898-917.
16. Garassino MC, Mazieres J, Reck M, Chouaid C, Bischoff H, Reinmuth N, et al. Durvalumab after sequential chemoradiotherapy in stage III, unresectable NSCLC: the phase 2 PACIFIC-6 trial. *J Thorac Oncol.* 2022;17(12):1415-27.
17. Rami-Porta R. International Association for the Study of Lung Cancer. IASLC Staging Manual in Thoracic Oncology. 2016.
18. Yuan M, Huang LL, Chen JH, Wu J, Xu Q. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. *Signal Transduct Target Ther.* 2019;4:61.
19. Tan AC, Tan DSW. Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. *J Clin Oncol.* 2022;40(6):611-25.
20. Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. *J Thorac Oncol.* 2021;16(5):860-7.
21. Chen X, Sheikh K, Nakajima E, Lin CT, Lee J, Hu C, et al. Radiation versus immune checkpoint inhibitor associated pneumonitis: distinct radiologic morphologies. *Oncologist.* 2021;26(10):e1822-32.
22. Vansteenkiste JF, Naidoo J, Faivre-Finn C, Ozguroglu M, Villegas A, Daniel D, et al. Symptomatic pneumonitis with durvalumab after concurrent chemoradiotherapy in unresectable stage III NSCLC. *JTO Clin Res Rep.* 2024;5(3):100638.
23. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika.* 1983;70(3):659-63.
24. Nygard L, Vogelius IR, Fischer BM, Kjaer A, Langer SW, Aznar MC, et al. A competing risk model of first failure site after definitive chemoradiation therapy for locally advanced non-small cell lung cancer. *J Thorac Oncol.* 2018;13(4):559-67.
25. Kishi N, Matsuo Y, Shintani T, Ogura M, Mitsuyoshi T, Araki N, et al. Recurrence patterns and progression-free survival after chemoradiotherapy with or without consolidation durvalumab for stage III non-small cell lung cancer. *J Radiat Res.* 2023;64(1):142-53.
26. Gao S, Li N, Wang S, Zhang F, Wei W, Li N, et al. Lung cancer in People's Republic of China. *J Thorac Oncol.* 2020;15(10):1567-76.
27. Zhang S, Sun K, Zheng R, Zeng H, Wang S, Chen R, et al. Cancer incidence and mortality in China, 2015. *J Natl Cancer Cent.* 2021;1(1):2-11.
28. Zhou Q, Chen M, Jiang O, Pan Y, Hu D, Lin Q, et al. Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol.* 2022;23(2):209-19.
29. Wu YL, Zhou Q, Chen M, Pan Y, Jian O, Hu D, et al. Sugemalimab vs placebo after cCRT or sCRT in Pts with unresectable stage III NSCLC: final PFS analysis of a phase 3 study. *J Thorac Oncol.* 2022;17(9):S7-8.
30. Girard N, Bar J, Garrido P, Garassino MC, McDonald F, Mornex F, et al. Treatment characteristics and real-world progression-free survival in patients with unresectable stage III NSCLC who received durvalumab after chemoradiotherapy: findings from the PACIFIC-R study. *J Thorac Oncol.* 2023;18(2):181-93.
31. Mooradian MJ, Cai L, Wang A, Qiao Y, Chander P, Whitaker RM. Durvalumab after chemoradiotherapy in patients with unresectable stage III non-small cell lung cancer. *JAMA Netw Open.* 2024;7(4):e247542.
32. Pringle N, Fletcher JA, Morton C, Mullally WJ, Arneil M, O'Byrne K, et al. EP08.02-03 real world

- experience of survival outcomes in consolidative durvalumab in unresectable stage III non-small cell lung cancer (NSCLC). *J Thorac Oncol.* 2023;18(Suppl 11):S569.
33. Wheatley-Price P, Navani V, Pabani A, Routy B, Snow S, Denault MH, et al. MA16.06 Real-world survival with CRT + durvalumab for unresectable, stage III NSCLC in Canada: the RELEVANCE study. *J Thorac Oncol.* 2023;18(11):S159.
 34. Hu HP, Walker C, Swaminath A. Real-world outcomes of chemoradiation and consolidative durvalumab in unresectable stage III non-small-cell lung cancer — a systematic review. *Int J Radiat Oncol Biol Phys.* 2021;111(Suppl 3):e438.
 35. Liu SM, Zheng MM, Pan Y, Liu SY, Li Y, Wu YL. Emerging evidence and treatment paradigm of non-small cell lung cancer. *J Hematol Oncol.* 2023;16(1):40.
 36. Bradley JD, Sugawara S, Lee KHH, Ostoros G, Demirkazik A, Zemanova M, et al. LBA1 durvalumab in combination with chemoradiotherapy for patients with unresectable stage III NSCLC: final results from PACIFIC-2. *ESMO Open.* 2024;9:102986.
 37. Peters S, Tan DSW, Gerber DE, Urbanic J, Ramalingam SS, Yu J, et al. 650 Checkmate 73L: phase III study comparing nivolumab (N) + concurrent chemoradiotherapy (CCRT) followed by N + ipilimumab (I) v CCRT followed by durvalumab (D) for previously untreated, locally advanced stage (stg) III NSCLC. *IOTech.* 2024;24:100808.
 38. Ozguroglu M, Levy B, Horinouchi H, Yu J, Grainger E, Phuong P, et al. 971TiP phase III trial of durvalumab combined with domvanalimab following concurrent chemoradiotherapy (cCRT) in patients with unresectable stage III NSCLC (PACIFIC-8). *Ann Oncol.* 2022;33:S991.
 39. Barlesi F, Cho BC, Goldberg SB, Yoh K, Zimmer Gelatti AC, Mann H, et al. PACIFIC-9: phase III trial of durvalumab + oleclumab or monalizumab in unresectable stage III non-small-cell lung cancer. *Future Oncol.* 2024;20(29):2137-47.
 40. Aggarwal C, Martinez-Marti A, Majem M, Barlesi F, Carcereny E, Chu QS, et al. Updated results from COAST, a phase 2 study of durvalumab (D) ± oleclumab (O) or monalizumab (M) in patients (pts) with stage III unresectable non-small cell lung cancer (uNSCLC). *J Clin Oncol.* 2024;42(16_suppl):8046.
 41. Dickhoff C, Heineman DJ, Bahce I, Senan S. Unresectable stage III NSCLC can be reevaluated for resectability after initial treatment. *J Thorac Oncol.* 2023;18(9):1124-8.
 42. Reck M, Nadal E, Girard N, Filippi AR, Martin LW, Gay CM, et al. MDT-BRIDGE: neoadjuvant durvalumab plus chemotherapy followed by either surgery and adjuvant durvalumab or chemoradiotherapy and consolidation durvalumab in resectable or borderline-resectable stage IIB-IIIB NSCLC. *Clin Lung Cancer.* 2024;25(6):587-93. e3.
 43. Zhou Q, Pan Y, Yang X, Zhao Y, Han G, Pang Q, et al. Neoadjuvant SHR-1701 with or without chemotherapy in unresectable stage III non-small-cell lung cancer: A proof-of-concept, phase 2 trial. *Cancer Cell.* 2024;42(7):1258-67. e2.
 44. Zheng J, Li Y, Jin C, Ruan K, Sun K, Chen H, et al. Efficacy and surgical safety of sequential surgical resection after pembrolizumab plus chemotherapy for initial unresectable stage IIIB non-small cell lung cancer. *Lung Cancer.* 2023;184:107326.
 45. Furrer K, Weder W, Eboulet EI, Betticher D, Pless M, Stupp R, et al. Extended resection for potentially operable patients with stage III non-small cell lung cancer after induction treatment. *J Thorac Cardiovasc Surg.* 2022;164(6):1587-602. e5.
 46. Guan S, Zhang S, Ren K, Li X, Li X, Zhao L. Induction chemoimmunotherapy may improve outcomes of chemoradiotherapy in patients with unresectable stage III NSCLC. *Front Immunol.* 2023;14:1289207.
 47. Yi C, Bian D, Wang J, Hu S, Sun L, Yan Y, et al. Anti-PD1 based precision induction therapy in unresectable stage III non-small cell lung cancer: a phase II umbrella clinical trial. *Nat Commun.* 2025;16(1):1932.
 48. Smeenk MM, van Diessen JNA, Boellaard TN, Hartemink KJ, de Vries JF, van der Noort V, et al. Tremelimumab plus durvalumab prior to chemoradiotherapy in unresectable, locally advanced non-small cell lung cancer: the induction trial. *Clin Cancer Res.* 2025;31(6):1037-46.