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Nivolumab plus chemoradiotherapy followed by nivolumab with or without ipilimumab for untreated locally advanced stage III NSCLC: a randomized phase 3 trial

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Over 50% of persons with unresectable stage III non-small cell lung cancer (NSCLC) treated with standard-of-care concurrent chemoradiotherapy (CCRT) and durvalumab consolidation progress or die within 18 months. Here adults with untreated, unresectable stage III NSCLC were randomized to nivolumab plus CCRT followed by consolidation with nivolumab plus ipilimumab (arm A) or nivolumab alone (arm B) or CCRT followed by consolidation with durvalumab (arm C). The primary endpoint was progression-free survival (PFS) in arm A versus arm C and secondary endpoints included overall survival (OS), PFS in arm B versus arm C, response rates and safety. At a median follow-up of 30.5 months, there was no statistically significant difference in the primary endpoint of PFS in the nivolumab plus ipilimumab arm versus durvalumab arm (hazard ratio (HR): 0.95, 96% confidence interval (CI): 0.77–1.19; $P = 0.65$). Descriptive OS analysis showed no improvement (HR: 1.12, 95% CI: 0.87–1.43). Nivolumab alone did not improve PFS or OS versus durvalumab (PFS, HR: 0.84, 95% CI: 0.69–1.04; OS, HR: 0.97, 95% CI: 0.76–1.24). Nivolumab plus ipilimumab and nivolumab alone plus CCRT resulted in increased pneumonitis. These results emphasize the need for novel efficacious treatments for these individuals. (ClinicalTrials.gov: NCT04026412)

Locally advanced stage III non-small cell lung cancer (NSCLC) represents approximately 30% of NSCLC cases[1]. Concurrent chemoradiotherapy (CCRT) followed by durvalumab consolidation is the standard of care (SOC) for these persons on the basis of results from the phase 3 PACIFIC study, which showed significantly improved progression-free survival (PFS) with durvalumab versus placebo consolidation (hazard ratio (HR): 0.52, 95% confidence interval (CI): 0.42–0.65; $P < 0.001$)[2]. Despite this benefit, more than 50% of participants experienced disease progression or death within 18 months (18-month PFS rate of 44%)[2] and the 5-year overall survival (OS) rate was 43% (ref. 3). Thus, there remains an unmet need for an efficacious and safe treatment regimen that improves long-term outcomes and cure rates for persons with locally advanced, unresectable, stage III NSCLC.

Combined radiotherapy and immunotherapy (IO) approaches have been investigated in the treatment of NSCLC to exploit their complementary and potentially synergistic mechanisms. Radiotherapy

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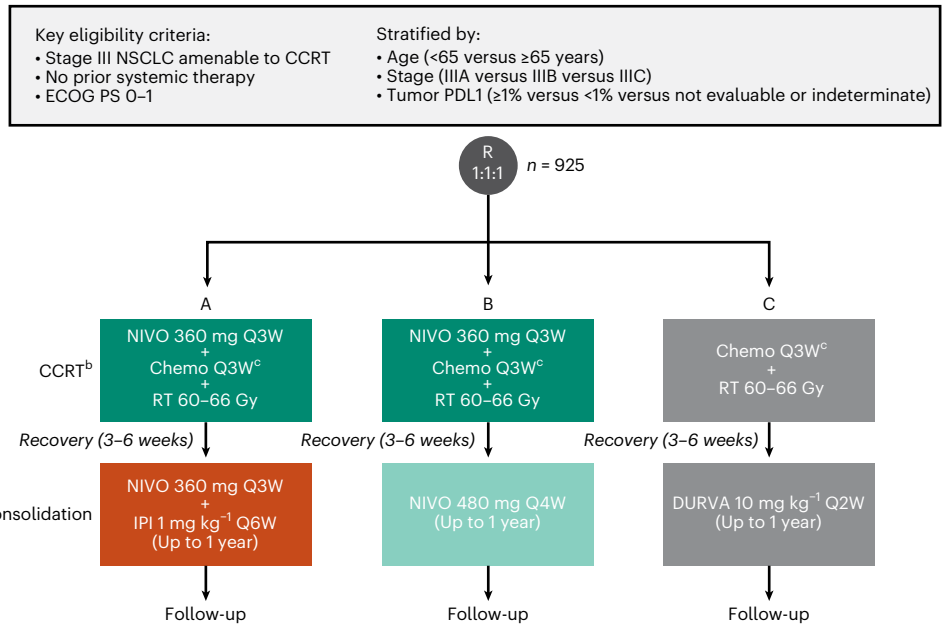

Fig. 1 | CheckMate 73L[a] study design. The data cutoff date was March 22, 2024. The database lock date was April 26, 2024. The median follow-up duration (range) was 30.5 months (16.0–52.5 months). Arm A, nivolumab plus ipilimumab treatment; arm B, nivolumab treatment; arm C, durvalumab treatment. [a]NCT04026412. [b]Up to three cycles with 21 days per cycle. If radiotherapy planning is complete before the initiation of systemic anticancer therapy at cycle 1 of the CCRT period (arms A, B or C), cycle 1 may have been skipped and treatment initiated with concurrent radiotherapy and systemic anticancer therapy (started at cycle 2). [c]Participants with squamous tumor histology received etoposide plus cisplatin or paclitaxel plus carboplatin. Participants with nonsquamous tumor histology received etoposide plus cisplatin, paclitaxel plus carboplatin or pemetrexed plus cisplatin. Chemo, chemotherapy; DURVA, durvalumab; IPI, ipilimumab; NIVO, nivolumab; Q#W, every # weeks; RT, radiotherapy.

primes a broad T cell response[4], while immune checkpoint inhibitors prevent exhaustion and suppression, converting a local immunogenic event into a systemic, durable antitumor response[5–7]. In preclinical NSCLC models, radiotherapy plus anti-programmed death ligand 1 (PDL1) therapy has achieved superior tumor control and off-target responses compared to either alone[6–8]. Consolidative therapy with anti-cytotoxic T lymphocyte antigen 4 (CTLA4) therapy may further enhance this synergy by promoting T cell activation, reducing regulatory T cells (T_{regs}) and supporting durable immune control[9].

On the basis of this rationale, it has been hypothesized that the addition of IO earlier in combination with CCRT may improve outcomes. Several phase 2 studies in participants with stage III NSCLC assessing a concurrent approach demonstrated promising clinical benefits[10–12]. In the single-arm NICOLAS study, nivolumab (an anti-programmed death protein 1 (PD1) antibody), in combination with CCRT and used as consolidation, resulted in a 1-year PFS rate of 54% (ref. 10). Similarly, pembrolizumab (an anti-PD1 antibody) plus CCRT (KEYNOTE-799) also demonstrated promising antitumor activity (1-year PFS of 67%)[11]. Lastly, in the DETERRED study, chemoradiation with concurrent and/or consolidation atezolizumab (an anti-PDL1 antibody) resulted in a 1-year PFS of 50% and 57%, respectively[13]. All three studies demonstrated manageable safety profiles[10,11,13]; collectively, these results suggested an opportunity for the use of IO plus CCRT in stage III NSCLC.

The combination of nivolumab plus ipilimumab, with or without chemotherapy, has demonstrated long-term, durable survival benefits over chemotherapy alone as a first-line treatment in metastatic NSCLC, regardless of tumor PDL1 expression, in the CheckMate 9LA (ref. 14) and CheckMate 227 (ref. 15) studies. These data led to the hypothesis that this dual IO combination as consolidation after CCRT may further enhance antitumor activity in persons with untreated, unresectable stage III NSCLC.

We conducted the phase 3 CheckMate 73L (NCT04026412) study to compare concomitant nivolumab plus CCRT followed by nivolumab plus ipilimumab (nivolumab plus ipilimumab arm) or nivolumab alone (nivolumab arm) versus CCRT followed by durvalumab (durvalumab arm) in participants with untreated, locally advanced, unresectable stage III NSCLC. Here, we report the final efficacy and safety results.

Results

Participant and tumor characteristics

Between November 2019 and November 2022, a total of 1,787 previously untreated individuals with unresectable stage III NSCLC from 159 sites in 26 countries were screened, of whom 925 were randomized to the nivolumab plus ipilimumab arm ($n = 287$), nivolumab arm ($n = 320$) or durvalumab arm ($n = 318$) (Fig. 1). Baseline participant and clinical characteristics were similar across the three arms (Table 1). Across all arms, most participants (~78%) had stage IIIA or IIIB disease and up to 58% had tumors with squamous histology. More than 60% of the participants had tumor PDL1 ≥ 1% and one third had tumor PDL1 ≥ 50%.

Treatment summary

Data cutoff and database lock dates were March 22, 2024 and April 26, 2024, respectively (median follow-up duration: 30.5 months; range: 16.0–52.5 months). At the data cutoff, nearly all randomized participants received CCRT (nivolumab plus ipilimumab, 98.3%; nivolumab alone, 99.4%; durvalumab, 99.7%). Approximately 80% received at least one cycle of consolidation therapy (78%, 83% and 82%, respectively) and fewer than half of the participants completed both CCRT and consolidation treatment (36%, 43% and 45%, respectively) (Fig. 2). The most common reasons for discontinuation during the consolidation phase were disease progression (19%, 23% and 24%, respectively) and study drug toxicity (20%, 14% and 8%, respectively), with pneumonitis being the most common treatment-related adverse event (TRAE) leading to discontinuation in the nivolumab plus ipilimumab (6%) and nivolumab alone (5%) arms.

During the CCRT phase, exposure to chemotherapy (median, three cycles) and radiotherapy (median cumulative dose, 60 Gy) was similar across all arms. Nivolumab exposure was also comparable between the nivolumab plus ipilimumab arm and nivolumab arm (median, three

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Table 1 | Participant baseline characteristics

	Nivolumab plus ipilimumab (*n*=287)	Nivolumab (*n*=320)	Durvalumab (*n*=318)
Median age, years (range)	64 (33–85)	64 (37–92)	64 (32–84)
Male, *n* (%)	220 (77)	244 (76)	239 (75)
Geographic region[a], *n* (%)			
North America	9 (3)	18 (6)	17 (5)
Europe	132 (46)	124 (39)	129 (41)
Asia	93 (32)	119 (37)	105 (33)
Rest of the world	53 (18)	59 (18)	67 (21)
ECOG PS[b], *n* (%)			
0	132 (46)	149 (47)	139 (44)
1	154 (54)	171 (53)	179 (56)
Disease stage III[c], *n* (%)			
IIIA	95 (33)	106 (33)	110 (35)
IIIB	128 (45)	143 (45)	141 (44)
IIIC	62 (22)	71 (22)	67 (21)
Histology, *n* (%)			
Squamous	155 (54)	184 (58)	165 (52)
Nonsquamous	132 (46)	136 (42)	153 (48)
Smoking status, *n* (%)			
Current/former	258 (90)	297 (93)	287 (90)
Never	24 (8)	21 (7)	30 (9)
Unknown	5 (2)	2 (1)	1 (<1)
Tumor PDL1 expression, *n* (%)			
Not evaluable	22 (8)	24 (8)	30 (9)
<1%[d]	90 (31)	99 (31)	93 (29)
≥1%[d]	175 (61)	197 (62)	195 (61)
1–49%	92 (32)	89 (28)	98 (31)
≥50%	83 (29)	108 (34)	97 (30)
T stage, *n* (%)			
T1	30 (10)	31 (10)	30 (9)
T2	28 (10)	47 (15)	45 (14)
T3	41 (14)	56 (18)	51 (16)
T4	185 (64)	186 (58)	186 (58)
Other/not reported	3 (1)	0	6 (2)
N stage, *n* (%)			
N0	31 (11)	30 (9)	42 (13)
N1	28 (10)	24 (8)	27 (8)
N2	139 (48)	159 (50)	147 (46)
N3	87 (30)	106 (33)	95 (30)
Other/not reported	2 (1)	1 (<1)	7 (2)

[a]A total of 30 participants from Russia were required to discontinue. [b]One participant was considered ECOG PS 3 in the nivolumab plus ipilimumab arm. [c]Two participants had stage IV cancer (one stage IVA and one stage IVB). [d]Denominator: tumor PDL1-quantifiable population. N, nodes; T, tumor.

doses) (Supplementary Table 1). In the consolidation phase, the median duration of therapy was approximately 10 months and was generally comparable across the treatment arms.

PFS and OS endpoints

There was no statistically significant difference observed in the primary endpoint of PFS by blinded independent central review (BICR) between the nivolumab plus ipilimumab and durvalumab arms. The median PFS was 16.7 months in the nivolumab plus ipilimumab arm and 15.6 months in the durvalumab arm, with an HR of 0.95 (96% CI, 0.77–1.19; $P = 0.65$) (Fig. 3a).

Post hoc PFS analysis by key subgroups showed no improvement with nivolumab plus ipilimumab versus durvalumab across all subgroups assessed (Fig. 3b). However, there was a numerical improvement in PFS with nivolumab plus ipilimumab versus durvalumab in an exploratory analysis of participants with tumor PDL1 expression ≥50% (median PFS of 25.5 months versus 19.4 months) (Fig. 3b and Extended Data Fig. 1).

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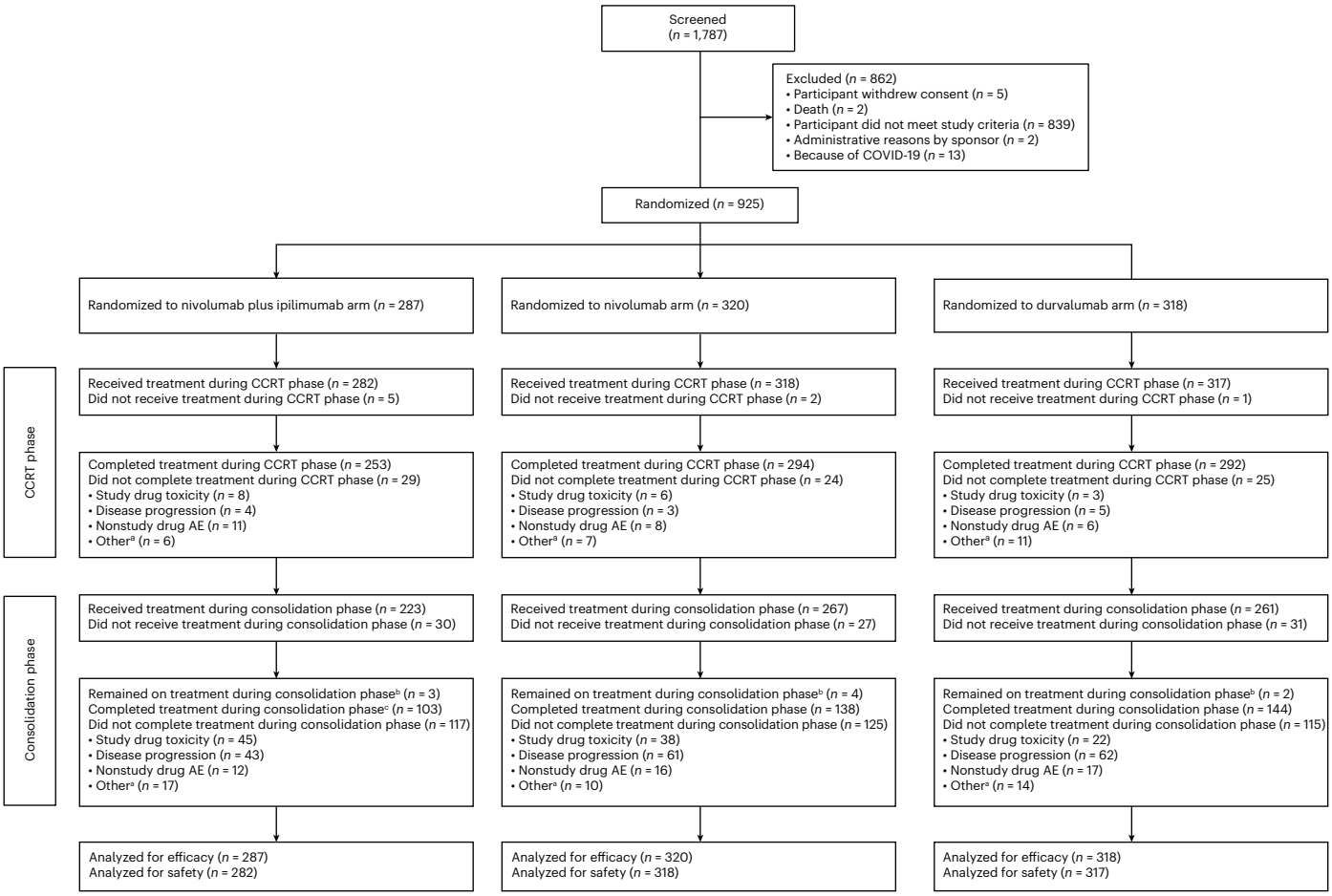

Fig. 2 | Consort diagram. [a]Other includes participants requesting to discontinue study drug, no longer meeting criteria, withdrawing consent, dying or being lost to follow-up. [b]All nine participants were off treatment. [c]Participants completed treatment with both nivolumab and ipilimumab.

OS, a key secondary endpoint subject to hierarchical statistical testing, was not formally tested per protocol, as the primary endpoint of PFS did not reach statistical significance. According to the descriptive analysis, median OS was 34.6 months in the nivolumab plus ipilimumab arm and 40.2 months in the durvalumab arm (HR: 1.12, 95% CI: 0.87–1.43) (Fig. 4).

As with the findings between the nivolumab plus ipilimumab and durvalumab arms, no differences in PFS or OS (PFS, HR: 0.84, 95% CI: 0.69–1.04; OS, HR: 0.97, 95% CI: 0.76–1.24) were observed between the nivolumab alone arm compared to the durvalumab arm (Fig. 5).

Overall, 25% of participants in the nivolumab plus ipilimumab arm, 25% in the nivolumab arm and 32% in the durvalumab arm (Supplementary Table 2) received any subsequent anticancer therapy. Subsequent systemic therapy was received by 24% of participants in each of the nivolumab-containing arms and 31% of participants in the durvalumab arm.

Response and disease progression

Objective response rates (ORRs) by BICR were 68% for nivolumab plus ipilimumab, 72% for nivolumab and 64% for durvalumab. The median duration of response (DOR) was 25.1 months, 31.1 months and 25.2 months for the nivolumab plus ipilimumab, nivolumab and durvalumab arms, respectively (Supplementary Table 3). The waterfall plots of the best reduction in target lesion from baseline to the end of the CCRT phase illustrated a similar trend across the three treatment arms, with most participants having at least a 30% reduction (Extended Data Fig. 2).

Disease progression (per investigator) occurred in 111 participants (39%) in the nivolumab plus ipilimumab arm, 127 (40%) in the nivolumab arm and 146 (46%) in the durvalumab arm. To better understand the patterns of progression, an exploratory analysis was conducted to assess the occurrence of distant versus only locoregional metastases by treatment arm. Of the participants who progressed, 59%, 56% and 51% in the nivolumab plus ipilimumab, nivolumab and durvalumab arms, respectively, had locoregional metastases, and 41%, 44% and 49%, respectively, had distant metastases. The most common sites of distant metastases across all treatment arms ($n = 174$) were the brain (45%), liver (17%), bone (17%) and adrenal gland (11%).

Participant-reported outcomes

Characterizing changes in cancer-related symptoms and quality of life between treatment arms was a prespecified exploratory endpoint. The mean (s.d.) NSCLC symptom assessment questionnaire (NSCLC-SAQ) total scores were similar across all three arms, with 5.93 (3.69) in the nivolumab plus ipilimumab arm, 5.79 (3.73) in the nivolumab only arm and 6.00 (3.68) in the durvalumab arm. Because the study's primary endpoint was not statistically significant ($P = 0.6460$), no formal or further testing of symptom deterioration based on NSCLC-SAQ was performed per the statistical design.

Safety

Among all treated participants, any-grade AEs were reported in 99% of those in the nivolumab plus ipilimumab arm, 99% in the nivolumab arm and 98% in the durvalumab arm (Table 2). Any-grade TRAEs occurred in 95% of participants in the nivolumab plus ipilimumab arm, 96% in the nivolumab arm and 96% in the durvalumab arm; the most common were anemia, decreased white blood cell count, nausea, esophagitis,

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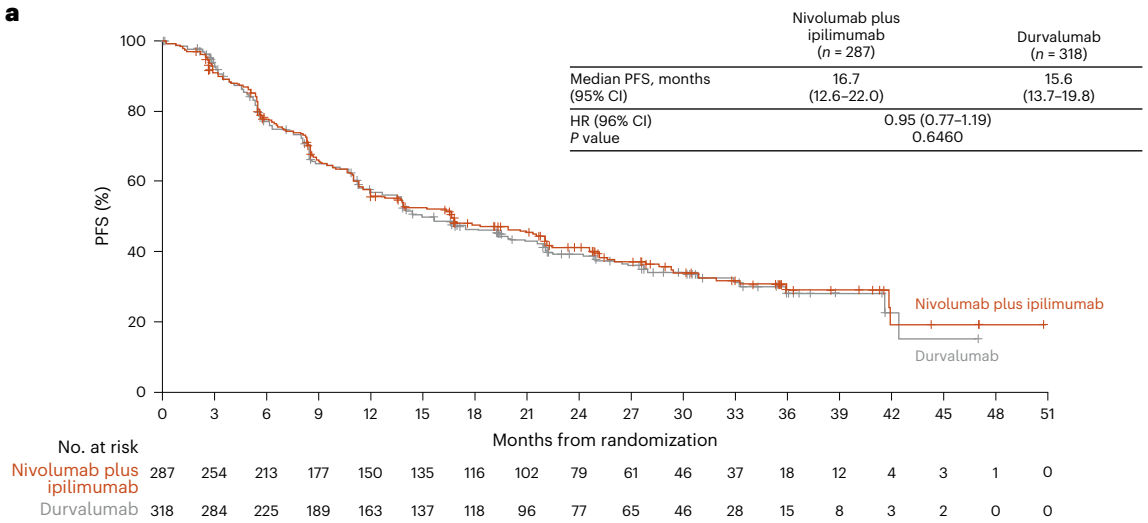

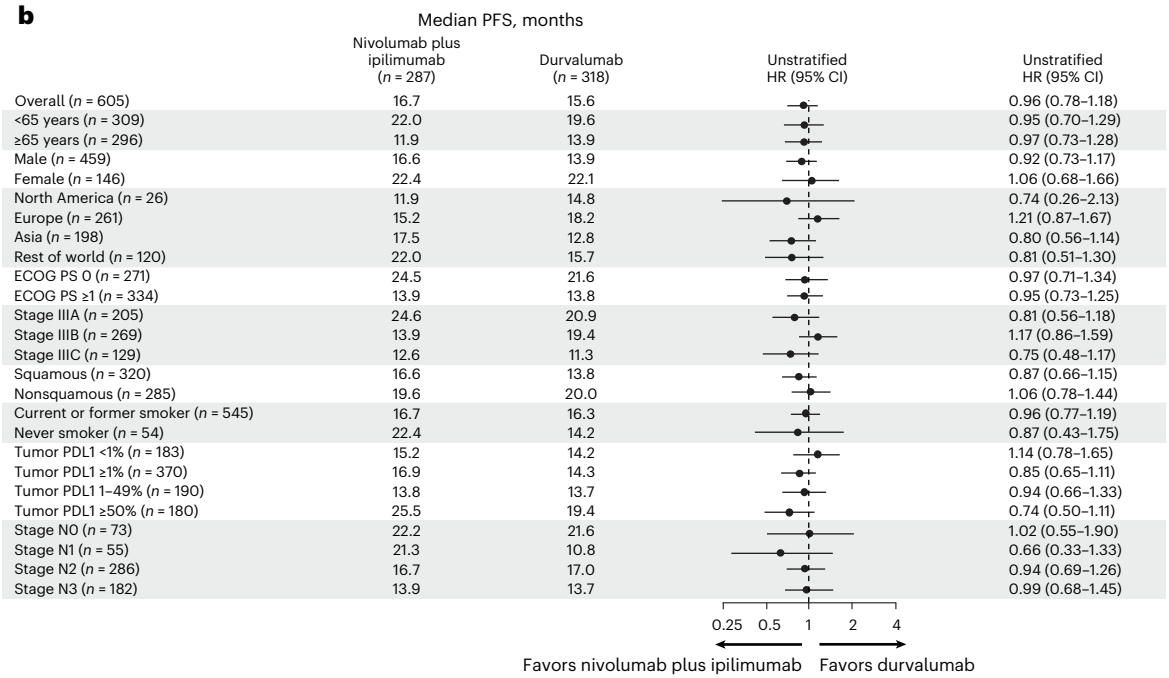

Fig. 3 | PFS in participants from the nivolumab plus ipilimumab versus durvalumab arms. a,**b**, PFS by BICR in the intent-to-treat population (**a**) and participant subgroups (**b**). Symbols (tick marks) indicate censored data. A stratified two-sided log-rank test was used to compare PFS between the nivolumab plus ipilimumab arm and durvalumab arm. A Cox proportional hazards model with treatment as the single covariate was used to estimate the HR and corresponding CI.

pneumonitis, decreased neutrophil count and fatigue. TRAEs of grades 3–4 occurred in 57% of the participants in the nivolumab plus ipilimumab arm, 54% in the nivolumab arm and 49% in the durvalumab arm (Extended Data Fig. 3), leading to discontinuation in 14%, 9% and 8% of participants, respectively (Table 2). Radiotherapy-related AEs of grades 3–4 were reported in 30% of participants in the nivolumab plus ipilimumab arm, 26% of those in the nivolumab arm and 25% of those in the durvalumab arm. The incidence of TRAEs of grades 3–4 by treatment phase were 50%, 47% and 44%, respectively, in the CCRT phase and 20%, 15% and 15%, respectively, in the consolidation phase (Supplementary Table 4).

Grade 1 and 2 treatment-related pneumonitis was reported in 4% and 14%, respectively, of participants in the nivolumab plus ipilimumab arm, 5% and 17% in the nivolumab arm and 5% and 9% in the durvalumab arm; rates for grade 3–4 treatment-related pneumonitis were 4%, 3% and <1%, respectively (Fig. 6 and Supplementary Table 5). There were no treatment-related grade 5 pneumonitis events in any arm, which includes events reported between the first dose and 30 days after the last dose of consolidation treatment or at the first dose of retreatment. Across all arms, most pneumonitis events occurred during the consolidation phase and approximately 90% of participants developed pneumonitis within 6 months of their last dose of radiotherapy, with 63% of these participants developing pneumonitis within the first 3 months of radiotherapy (Supplementary Table 6).

The most common immune-mediated AEs—AEs consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (for example, infection or tumor progression) were ruled out—were pneumonitis, rash and diarrhea (Extended Data Fig. 4). Immune-mediated pneumonitis (including pneumonitis, immune-related lung disease and interstitial lung disease) was reported in 23% of the participants in the nivolumab plus ipilimumab arm, 23% of those in the nivolumab arm and 10% of those in the durvalumab arm.

Treatment-related deaths occurred in ten participants (4%) in the nivolumab plus ipilimumab arm, 11 participants (4%) in the nivolumab

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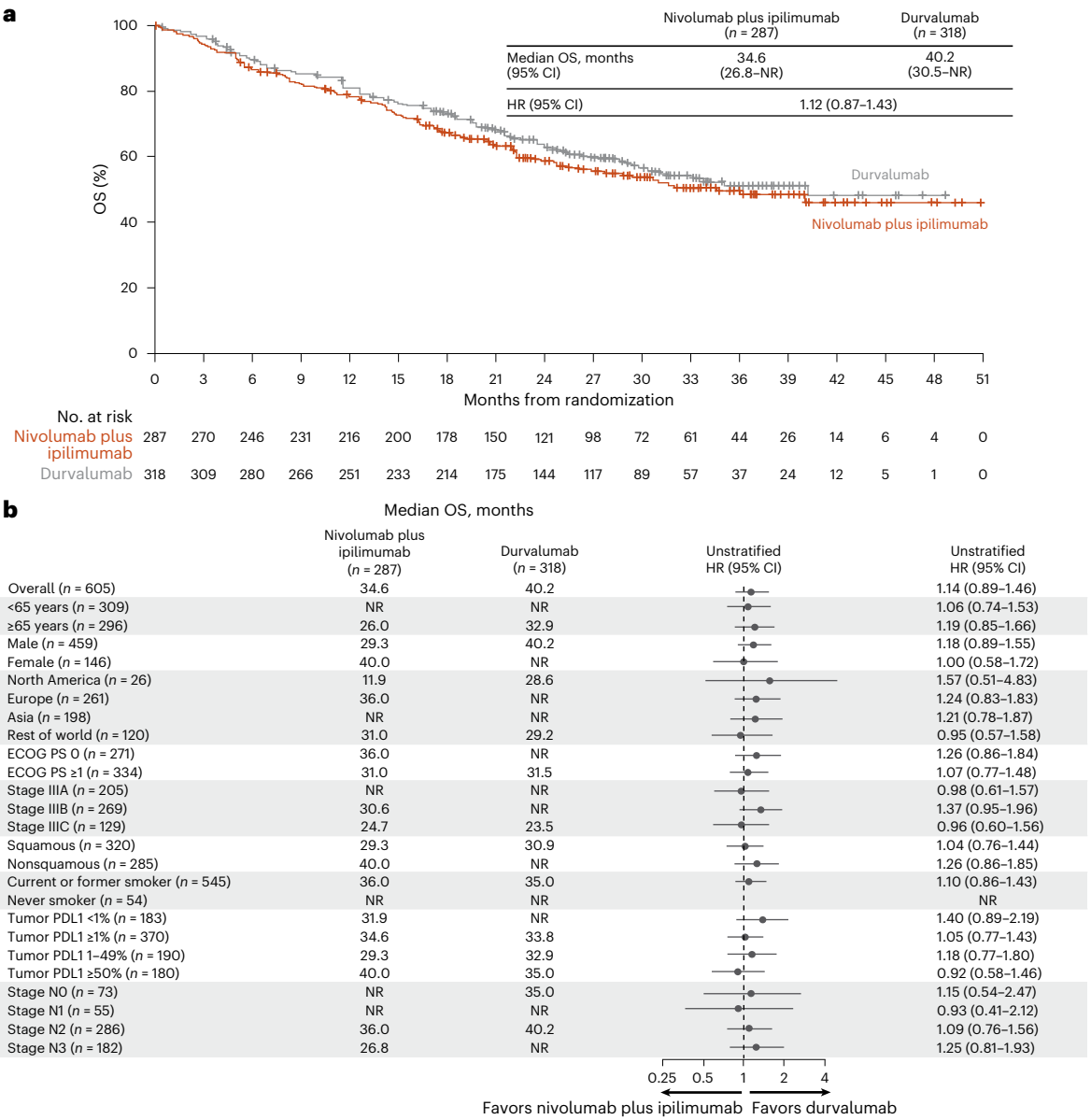

Fig. 4 | OS in participants from the nivolumab plus ipilimumab versus durvalumab arms. a,**b**, OS in the intent-to-treat population (**a**) and participant subgroups (**b**). Subsequent radiotherapy, surgery or systemic therapy received: nivolumab plus ipilimumab arm, 2%, 1% and 24%, respectively; durvalumab arm, 4%, <1% and 31%, respectively. Participants may have received ≥1 type of subsequent therapy (cancer-related therapy initiated after or on first dosing date or randomization date if the participant was never treated). Symbols (tick marks) indicate censored data. NR, not reached.

arm, and one participant (<1%) in the durvalumab arm (Supplementary Table 7). Of these, seven (2%), five (2%) and one (<1%) deaths occurred during the CCRT phase, while three (1%), six (2%) and zero deaths occurred during the consolidation phase. In total, 15 of the 22 treatment-related deaths (68%) were because of pneumonitis (two deaths were because of immune pneumonitis), all of which occurred between 31 and 100 days after the last dose of consolidation treatment. Other causes of death included sepsis ($n = 2$), cardiac arrest ($n = 1$), infection ($n = 2$), tumor invasion of blood vessels ($n = 1$) and cytokine release syndrome ($n = 1$).

Discussion

In CheckMate 73L, the addition of nivolumab concurrent to CRT followed by nivolumab plus ipilimumab consolidation did not improve PFS over SOC CCRT followed by durvalumab for participants with unresectable, stage III NSCLC. A descriptive analysis of OS also showed no improvement in the nivolumab plus ipilimumab arm. Additionally, there was no improvement in PFS or OS with nivolumab plus CCRT followed by nivolumab alone versus CCRT followed by durvalumab. While a formal comparison between the nivolumab plus ipilimumab and nivolumab alone arms could provide useful insights that may inform future use of these regimens, the study was not powered to compare outcomes between these two arms. No unexpected safety signal was observed in either the nivolumab plus ipilimumab or nivolumab arms. As observed previously, concomitant IO and CCRT were associated with increased pneumonitis rates[10,12,16,17].

Similar to the overall participant population, no improvement in survival was observed in the nivolumab plus ipilimumab arm across key subgroups with the exception of a numerical trend toward improved PFS observed in the exploratory tumor PDL1 ≥ 50% subgroup analysis. These results are consistent with findings from studies of IO-based regimens in metastatic NSCLC, where persons with high PDL1 expression derived maximal benefit with nivolumab-based regimens[14,15,18]. A similar study evaluating IO plus CCRT regimens in untreated, unresectable

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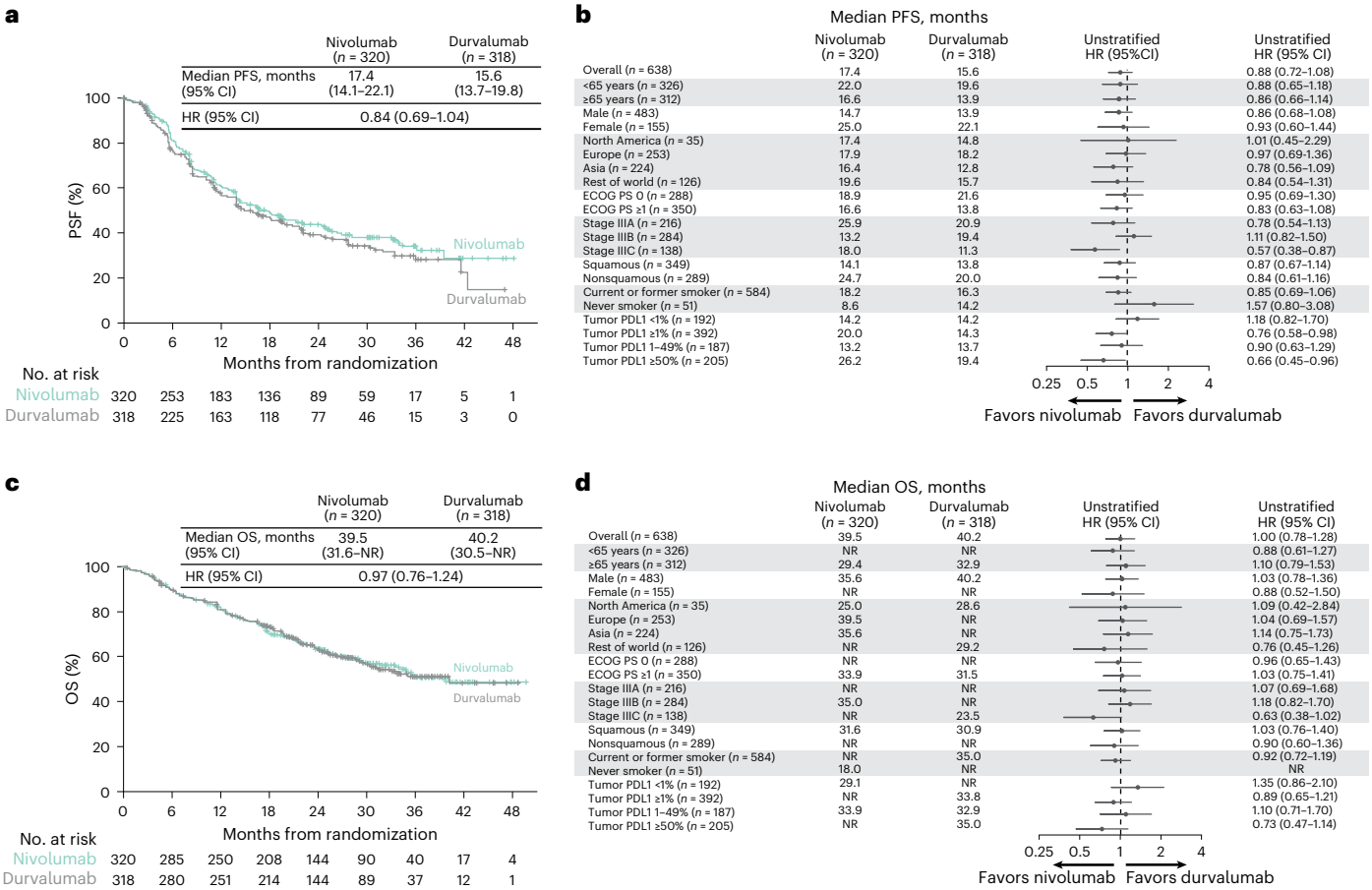

	Nivolumab (*n* = 320)	Durvalumab (*n* = 318)	Unstratified HR (95%CI)
Overall (*n* = 638)	17.4	15.6	0.88 (0.72–1.08)
<65 years (*n* = 326)	22.0	19.6	0.88 (0.65–1.18)
≥65 years (*n* = 312)	16.6	13.9	0.86 (0.66–1.14)
Male (*n* = 483)	14.7	13.9	0.86 (0.68–1.08)
Female (*n* = 155)	25.0	22.1	0.93 (0.60–1.44)
North America (*n* = 35)	17.4	14.8	1.01 (0.45–2.29)
Europe (*n* = 253)	17.9	18.2	0.97 (0.69-1.36)
Asia (*n* = 224)	16.4	12.8	0.78 (0.56–1.09)
Rest of world (*n* = 126)	19.6	15.7	0.84 (0.54–1.31)
ECOG PS 0 (*n* = 288)	18.9	21.6	0.95 (0.69–1.30)
ECOG PS ≥1 (*n* = 350)	16.6	13.8	0.83 (0.63–1.08)
Stage IIIA (*n* = 216)	25.9	20.9	0.78 (0.54–1.13)
Stage IIIB (*n* = 284)	13.2	19.4	1.11 (0.82–1.50)
Stage IIIC (*n* = 138)	18.0	11.3	0.57 (0.38–0.87)
Squamous (*n* = 349)	14.1	13.8	0.87 (0.67–1.14)
Nonsquamous (*n* = 289)	24.7	20.0	0.84 (0.61–1.16)
Current or former smoker (*n* = 584)	18.2	16.3	0.85 (0.69–1.06)
Never smoker (*n* = 51)	8.6	14.2	1.57 (0.80–3.08)
Tumor PDL1 <1% (*n* = 192)	14.2	14.2	1.18 (0.82–1.70)
Tumor PDL1 ≥1% (*n* = 392)	20.0	14.3	0.76 (0.58–0.98)
Tumor PDL1 1–49% (*n* = 187)	13.2	13.7	0.90 (0.63–1.29)
Tumor PDL1 ≥50% (*n* = 205)	26.2	19.4	0.66 (0.45–0.96)

	Nivolumab (*n* = 320)	Durvalumab (*n* = 318)	Unstratified HR (95% CI)
Overall (*n* = 638)	39.5	40.2	1.00 (0.78–1.28)
<65 years (*n* = 326)	NR	NR	0.88 (0.61–1.27)
≥65 years (*n* = 312)	29.4	32.9	1.10 (0.79–1.53)
Male (*n* = 483)	35.6	40.2	1.03 (0.78–1.36)
Female (*n* = 155)	NR	NR	0.88 (0.52–1.50)
North America (*n* = 35)	25.0	28.6	1.09 (0.42–2.84)
Europe (*n* = 253)	39.5	NR	1.04 (0.69–1.57)
Asia (*n* = 224)	35.6	NR	1.14 (0.75–1.73)
Rest of world (*n* = 126)	NR	29.2	0.76 (0.45–1.26)
ECOG PS 0 (*n* = 288)	NR	NR	0.96 (0.65–1.43)
ECOG PS ≥1 (*n* = 350)	33.9	31.5	1.03 (0.75–1.41)
Stage IIIA (*n* = 216)	NR	NR	1.07 (0.69–1.68)
Stage IIIB (*n* = 284)	35.0	NR	1.18 (0.82–1.70)
Stage IIIC (*n* = 138)	NR	23.5	0.63 (0.38–1.02)
Squamous (*n* = 349)	31.6	30.9	1.03 (0.76–1.40)
Nonsquamous (*n* = 289)	NR	NR	0.90 (0.60–1.36)
Current or former smoker (*n* = 584)	NR	35.0	0.92 (0.72–1.19)
Never smoker (*n* = 51)	18.0	NR	NR
Tumor PDL1 <1% (*n* = 192)	29.1	NR	1.35 (0.86–2.10)
Tumor PDL1 ≥1% (*n* = 392)	NR	33.8	0.89 (0.65–1.21)
Tumor PDL1 1–49% (*n* = 187)	33.9	32.9	1.10 (0.71–1.70)
Tumor PDL1 ≥50% (*n* = 205)	NR	35.0	0.73 (0.47–1.14)

Fig. 5 | PFS and OS in participants from the nivolumab versus durvalumab arms. **a**, PFS by BICR in the intent-to-treat population. **b**, PFS by BICR in the participant subgroups. **c**, OS in the intent-to-treat population. **d**, OS in the participant subgroups. Subsequent radiotherapy, surgery or systemic therapy received: nivolumab arm: 4%, <1% and 24%, respectively; durvalumab arm, 4%, <1% and 31%, respectively. Participants may have received ≥1 type of subsequent therapy (cancer-related therapy initiated on or after first dosing date (or randomization date if the participant was never treated). Symbols (tick marks) indicate censored data.

NSCLC (KEYNOTE-867) did not assess differences in survival by PDL1 expression to our knowledge[19]; further research is needed to definitively assess this treatment effect.

The phase 3 PACIFIC study demonstrated survival benefit with CCRT followed by durvalumab consolidation over CCRT alone[2], establishing CCRT followed by durvalumab as the SOC for persons with untreated, unresectable, stage III NSCLC. Notably, the median PFS results across all arms of CheckMate 73L were comparable to the durvalumab arm from PACIFIC (16.8 months)[2]; however, in CheckMate 73L, there appeared to be a trend toward improved PFS with durvalumab in the tumor PDL1 < 1% subgroup compared to the higher PDL1 subgroups. Nevertheless, cross-trial comparisons should be made with caution because of potential differences in study designs and participant populations. Of note, in the PACIFIC study, enrolled participants who had successfully completed CCRT and maintained adequate performance status were randomized to receive consolidation durvalumab, whereas participants in CheckMate 73L who were treatment-naive were randomized to receive CCRT on study.

Although phase 2 studies have demonstrated the promising efficacy of concurrent IO and CRT in stage III NSCLC[10,12,16], similar to CheckMate 73L, the phase 3 PACIFIC-2 trial did not demonstrate clinical benefit. In that trial, durvalumab and CCRT followed by durvalumab consolidation provided no significant PFS improvement over CCRT alone[17]. In KEYNOTE-867, in participants with stage I or II NSCLC, pembrolizumab plus stereotactic body radiation therapy (SBRT) did not improve event-free survival over SBRT alone[19]. Furthermore, another phase 2, single-arm study in participants with stage III NSCLC evaluating concurrent radiotherapy plus durvalumab without chemotherapy followed by durvalumab consolidation was closed because of early disease progression and high-grade toxicity[20].

The reason for a lack of meaningful benefit when adding IO to CCRT remains unclear. One potential explanation is that IO may be more effective after CCRT in the presence of minimal residual disease compared to concurrent administration when notable disease burden may still be present[6]. Additionally, radiotherapy may negatively impact local and systemic adaptive immune responses and inhibit IO efficacy. Nevertheless, preclinical data have demonstrated improved antitumor activity with radiotherapy administered simultaneously with anti-PD1 or anti-PDL1 monoclonal antibodies, which was attributed to radiotherapy-mediated PDL1 upregulation in tumor cells[21,22], and have also shown that radiotherapy draws immunosuppressive cells, including T_{regs}, to the tumor microenvironment[22]. Irradiating tumor-draining lymph nodes has been shown to impair trafficking of $CD8^+$ T cells into the tumor microenvironment[23]. Taken together, the optimal timing of IO with CCRT and the optimal duration of radiotherapy have not yet been established. Of note, participants enrolled in studies using concurrent strategies are treatment-naive, with variability in the feasibility and efficacy of CRT. Consequently, demonstrations of improvement in clinical outcomes in this population may require a better understanding of the optimal radiation dose, fractionation and timing, which all remain key elements and the topics of ongoing research[24].

Pneumonitis remains a key clinical concern with CCRT, even more so when combined with IO[25]. Higher rates of treatment-related pneumonitis of any grade and of grades 3–4 were observed in the nivolumab

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Table 2 | Safety summary

Participants[a], *n* (%)	Nivolumab plus ipilimumab (*n*=282)	Nivolumab (*n*=318)	Durvalumab (*n*=317)
AEs			
Any grade	279 (99)	315 (99)	312 (98)
Grade 3–4	191 (68)	210 (66)	183 (58)
AEs leading to discontinuation			
Any grade	71 (25)	62 (20)	58 (18)
Grade 3–4	44 (16)	37 (12)	37 (12)
SAEs			
Any grade	155 (55)	156 (49)	136 (43)
Grade 3–4	103 (36)	112 (35)	90 (28)
TRAEs			
Any grade	269 (95)	307 (96)	305 (96)
Grade 3–4	161 (57)	172 (54)	154 (49)
Radiotherapy-related AEs			
Any grade	226 (80)	257 (81)	248 (78)
Grade 3–4	85 (30)	81 (26)	80 (25)
TRAEs leading to discontinuation			
Any grade	61 (22)	50 (16)	40 (13)
Grade 3–4	40 (14)	30 (9)	24 (8)
Treatment-related SAEs			
Any grade	94 (33)	86 (27)	72 (23)
Grade 3–4	63 (22)	63 (20)	53 (17)

[a]AEs per Common Terminology Criteria for AEs version 4.0 and Medical Dictionary for Regulatory Activities version 26.1. Data include events reported between the first dose and 30 days after the last dose of consolidation treatment or at the first dose of retreatment, whichever occurred first. SAE, serious AE.

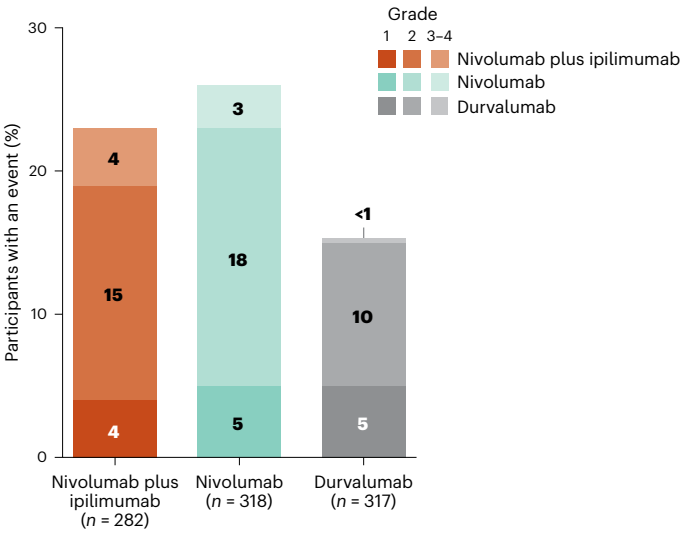

Fig. 6 | Any-cause pneumonitis by treatment arm. Data include events reported between the first dose and 30 days after the last dose of study therapy, excluding retreatment. No grade 5 pneumonitis was reported.

plus ipilimumab and nivolumab arms versus the durvalumab arm in CheckMate 73L; a total of 15 treatment-related deaths were because of pneumonitis across the treatment arms. Compared to the durvalumab arm, a greater number of pneumonitis-related deaths occurred in the nivolumab plus ipilimumab and the nivolumab alone arms ($n = 6$, $n = 8$ and $n = 1$, respectively). Similar findings were observed in other studies that have added IO to CCRT in NSCLC[10,13,16,17].

In the CheckMate 73L study, beyond pneumonitis, TRAEs and immune-mediated AEs were generally comparable across all treatment arms and were less common during the consolidation period versus the CCRT period, including in the nivolumab plus ipilimumab arm. Furthermore, no unexpected safety signals were observed with nivolumab or ipilimumab; the overall safety profile in CheckMate 73L is aligned with those in studies of participants with nonmetastatic or metastatic NSCLC treated with nivolumab or nivolumab plus ipilimumab[14,18,26,27].

The treatment paradigm for stage IIIA NSCLC continues to evolve, particularly for persons with N2 disease who were once considered unresectable. Increasingly, these individuals are being offered chemo-IO aimed at mediastinal downstaging to facilitate surgical resection[28]. In the phase 3 CheckMate 77T study (NCT04025879), which evaluated neoadjuvant nivolumab plus chemotherapy in participants with stage III NSCLC, an exploratory analysis by nodal status showed that, compared to placebo, participants who received nivolumab had improved event-free survival and pathologic complete response rates, as well as higher rates of definitive surgery and postoperative nodal downstaging[29]. In the interim analysis of the phase 2, single-arm, MDT-Bridge study (NCT05925530), 82% of baseline borderline-resectable NSCLC tumors were deemed resectable at reassessment following two cycles of neoadjuvant durvalumab plus chemotherapy[30]. For persons with stage IIIA NSCLC who remain unresectable, retrospective propensity score-matched analyses have suggested an OS advantage for surgery over CCRT; however, this benefit diminished after adjusting for baseline differences[31]. Moreover, as the use of IO has increased in both CCRT and induction regimens, higher rates of pneumonitis have been reported in the CheckMate 73L and other studies[10,13,16,17]. These findings underscore the importance of careful recipient selection, considering tumor burden, nodal status, pulmonary reserve, comorbidities and molecular and immunologic features, when determining the optimal use of CCRT.

The CheckMate 73L study uniquely evaluates both the timing (consolidative ± concomitant) and type (PD1/PDL1 ± CTLA4) of IO in combination with CCRT in a large population. This meticulous and robust study design allowed for a conclusive assessment of multiple hypotheses, the results of which may help guide clinical treatment strategies for both induction and maintenance for persons with unresectable stage III NSCLC and future analyses.

In this final analysis of CheckMate 73L, we found no significant improvement in survival outcomes with nivolumab plus CCRT followed by consolidation with nivolumab plus ipilimumab versus CCRT followed by consolidation durvalumab in participants with unresectable, stage III NSCLC. There were no unexpected safety signals with nivolumab or ipilimumab; however, there was increased rates of pneumonitis with IO plus CCRT versus CCRT alone. These results emphasize the need to investigate novel efficacious treatment options for this population.

Methods

Ethical oversight

CheckMate 73L was designed by the sponsor (Bristol Myers Squibb) and study steering committee. Data were collected by investigators (the list of investigators is provided in the Supplementary Information) and analyzed in collaboration with the sponsor, with an independent data monitoring committee providing oversight. The study was performed in accordance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines, with independent ethics committees or institutional review boards at each study site approving the protocol (additional information provided in the Supplementary Information). Participants provided written informed consent to participate. This manuscript was developed using medical writing support, with direction from the authors and funded by the sponsor. The authors confirmed the accuracy and completeness of

data reported herein and approved the submission of this manuscript for publication. CONSORT guidelines were followed in the development of this manuscript[32].

Participants

Adults with newly diagnosed, treatment-naive, locally advanced, unresectable, stage III histologically confirmed NSCLC (per the American Joint Committee on Cancer Staging Manual, eighth edition) amenable to definitive CCRT and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 were eligible to enroll. Participants were not eligible if they received prior radiotherapy, had tumors that were positive for any *EGFR* mutation, *ALK* translocation and/or *ROS1* rearrangement or had inadequate pulmonary function (defined as forced expiratory volume in 1 s ≤ 50% of predicted normal volume and/or carbon monoxide lung diffusing capacity ≤ 40% of predicted normal value). The full study protocol and statistical analysis plan are provided in the Supplementary Information.

Study design and treatments

CheckMate 73L (ClinicalTrials.gov number: NCT04026412) is a multicenter, randomized open-label, parallel, phase 3 study in which participants were screened between November 2019 and November 2022 and randomized (through an interactive response technology system) 1:1:1 to receive nivolumab 360 mg every 3 weeks (Q3W) plus CCRT followed by up to 1 year of consolidation with nivolumab 360 mg Q3W plus ipilimumab 1 mg kg^{-1} every 6 weeks (nivolumab plus ipilimumab arm), nivolumab 360 mg Q3W plus CCRT followed by up to 1 year of consolidation with nivolumab 480 mg every 4 weeks alone (nivolumab arm) or CCRT followed by up to 1 year of consolidation with durvalumab 10 mg kg^{-1} every 2 weeks (durvalumab arm) (Fig. 1). During the CCRT phase, all participants received histology-based, platinum-doublet chemotherapy (that is, participants with squamous tumor histology received etoposide plus cisplatin or paclitaxel plus carboplatin; participants with nonsquamous tumor histology received etoposide plus cisplatin, paclitaxel plus carboplatin or pemetrexed plus cisplatin) and thoracic radiotherapy in the form of intensity-modulated radiation therapy, volumetric-modulated arc therapy or three-dimensional radiotherapy. Irradiation commenced on day 1 of cycle 2 of systemic anticancer therapy (chemotherapy ± nivolumab; skipping cycle 1 was optional) and was delivered 5 days per week in a once daily fraction, 2 Gy per fraction, to a target dose of 60–66 Gy in 30–33 fractions (radiotherapy dose constraints are available in the radiotherapy guidelines in the Supplementary Information).

Randomization was stratified according to age (<65 years versus ≥65 years), disease stage (IIIA versus IIIB versus IIIC) and tumor PDL1 expression (≥1% versus <1% versus not evaluable or indeterminate), as determined with the use of the PDL1 IHC 28-8 pharmDx assay (Dako). It should be noted that randomization to the nivolumab plus ipilimumab arm was temporarily suspended because of an Interactive Response Technology registration platform error. During that suspension period, 43 participants could be randomized to only the nivolumab alone or durvalumab arms.

Treatment was discontinued as follows: if participants experienced investigator-assessed disease progression, death, unacceptable toxicity or symptomatic deterioration, the investigator's decision to discontinue treatment, withdrawal of consent on further treatment or lost to follow-up.

Endpoints and assessments

The primary endpoint was PFS by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) per BICR for the nivolumab plus ipilimumab arm versus the durvalumab arm. PFS was defined as the time between the date of randomization and the first date of documented progression (RECIST v1.1 per BICR) or death because of any cause, whichever occurred first, regardless of receipt of subsequent anticancer therapy before the documented progression per BICR.

Key secondary endpoints included OS for the nivolumab plus ipilimumab arm versus the durvalumab arm, PFS by RECIST v1.1 per BICR and per investigator assessment and OS for the nivolumab arm versus the durvalumab arm, tumor response assessment for both nivolumab arms versus the durvalumab arm (included ORR, DOR and time to response by RECIST v1.1 per BICR and per investigator assessment) and safety.

A key exploratory endpoint was the proportion of participants without meaningful symptom deterioration following 48 weeks after initiation of consolidation therapy using the NSCLC-SAQ, a seven-item participant-reported outcome measure.

Additional exploratory analyses included patterns of progression, onset of pneumonitis after last dose of radiotherapy (<3 months, 3–6 months or >6 months) and a comparison of PFS in participants with a PDL1 expression ≥50% in the nivolumab plus ipilimumab and durvalumab arms.

Data collection and analysis were not performed blind to the conditions of the experiments.

Statistical analysis

The sample size was determined on the basis of the primary endpoint of PFS between the nivolumab plus ipilimumab and durvalumab arms. A total of 346 PFS events (that is, progression events or deaths) in the nivolumab plus ipilimumab and durvalumab arms would provide approximately 82% power to detect an HR of 1 during the first 3 months and an HR of 0.69 thereafter, with a 0.05 two-sided α. On the basis of the enrollment projection and the accrual duration, a total of 888 participants were planned for randomization across the three treatment groups in a 1:1:1 ratio. The stopping boundary for the final PFS analyses reported here was based on the actual number of PFS events at the time of the analysis using the Lan–DeMets α spending function with O'Brien–Fleming boundaries. Formal testing of OS for the nivolumab plus ipilimumab and durvalumab arms and the nivolumab and durvalumab arms was planned but was not performed because PFS for the nivolumab plus ipilimumab and durvalumab arms was not significant. No formal testing was planned for PFS between the nivolumab arm versus durvalumab arm or for PFS or OS for the nivolumab plus ipilimumab arm versus the nivolumab arm.

Efficacy was evaluated in all randomized participants, with stratified analyses performed for main and supportive analyses of the efficacy outcomes and unstratified analyses performed for supplementary and subgroup analyses of the efficacy outcomes. A stratified two-sided log-rank test was used to compare PFS between the nivolumab plus ipilimumab arm and durvalumab arm. A Cox proportional hazards model with treatment as the single covariate was used to estimate the HR and corresponding CI ($100 \times (1 - \alpha)$% CI (adjusted for interim)). Because the other outcomes were not formally compared, standard 95% CIs are reported.

Safety was evaluated in participants who received at least one dose of a study treatment. Attribution of pneumonitis to radiation, IO or both was at the discretion of the investigator.

Classification of deaths were differentiated by time of occurrence related to treatment dosing. Grade 5 deaths were defined as those events reported between the first dose and 30 days after the last dose of consolidation treatment or at the first dose of retreatment. Treatment-related deaths were defined as those occurring between 31 and 100 days after the last dose of consolidation treatment.

The NSCLC-SAQ was administered at baseline, before dosing on day 1 of each cycle during the CCRT and consolidation phases and at each clinic visit during the recovery period. The minimal important difference was used to assess any meaningful deterioration in the NSCLC-SAQ total score by 48 weeks after the initiation of consolidation treatment.

All analyses were performed using Statistical Analysis System software (SAS Institute; version 9.04.01M7P08062020).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Researchers with a clearly defined scientific objective may submit requests for deidentified and anonymized datasets to Bristol Myers Squibb through the Vivli platform (https://vivli.org/resources/requestdata/). Criteria for data requests are available online (https://vivli.org/ourmember/bristol-myers-squibb/) and additional information on Bristol Myers Squibb's policy on data sharing may be found on their website (https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html). Data considered for sharing may include nonidentifiable participant-level and study-level clinical trial data and full clinical study reports. The remaining data are available within the article or its Supplementary Information. The study protocol and statistical analysis plan are available in the Supplementary Information. Source data are provided with this paper.

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Author contributions

S.P., R.N., G.P., L.Y. and D.D.R. contributed to the conceptualization or design. S.P., D.S.W.T., D.E.G., J.U., S.R., J.Y., L.X., A.R., T.-E.C., J.d.M., H.R.K., C.R., K.S., H.H., A.H., D.C., D.B., M.K., A.C. and D.D.R. contributed to data acquisition. R.N., G.P. and L.Y. contributed to data analysis. All authors contributed to data interpretation.

Competing interests

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Additional information

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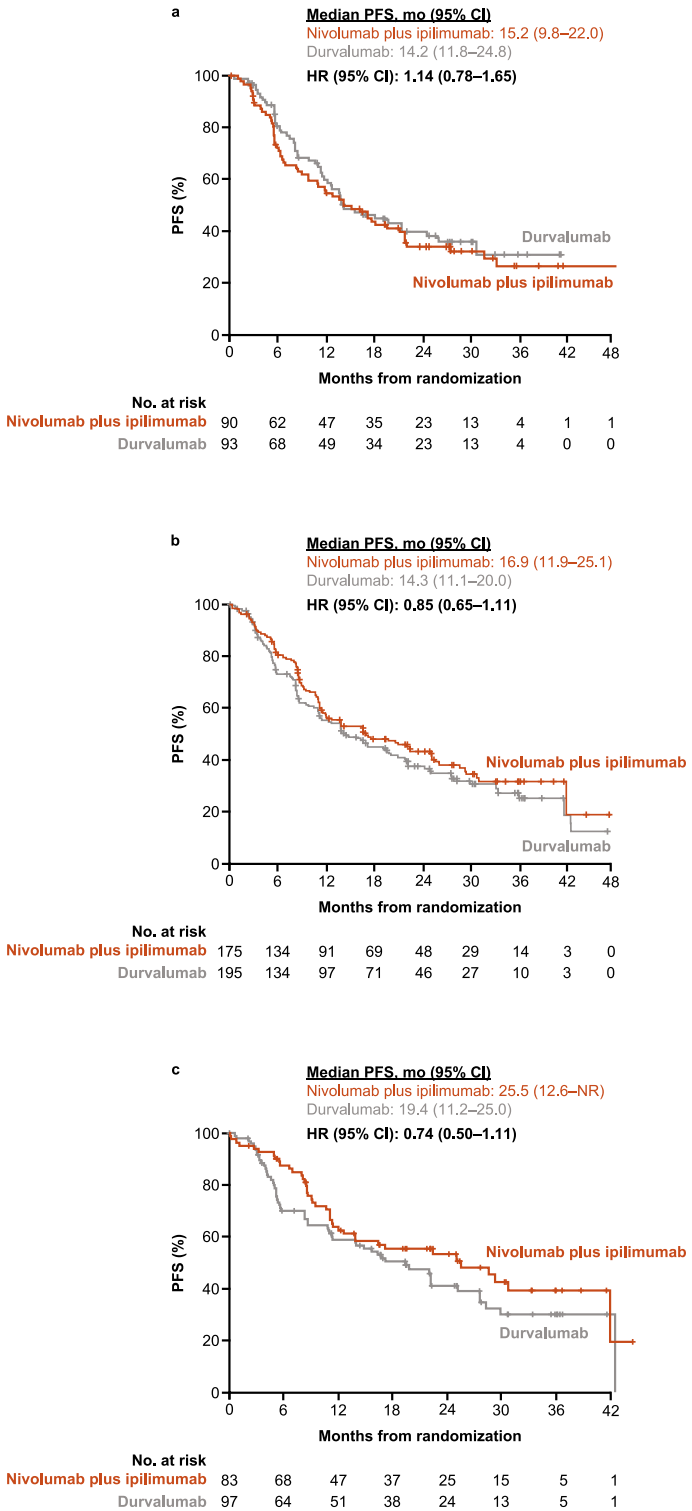

Extended Data Fig. 1 | PFS in patients from the nivolumab plus ipilimumab versus durvalumab arms by tumor PD-L1 expression. PFS in patients with tumor PD-L1 expression (**a**) <1%, (**b**) ≥1%, and (**c**) ≥50%. Symbols (tick marks) indicate censored data. NR, not reached; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

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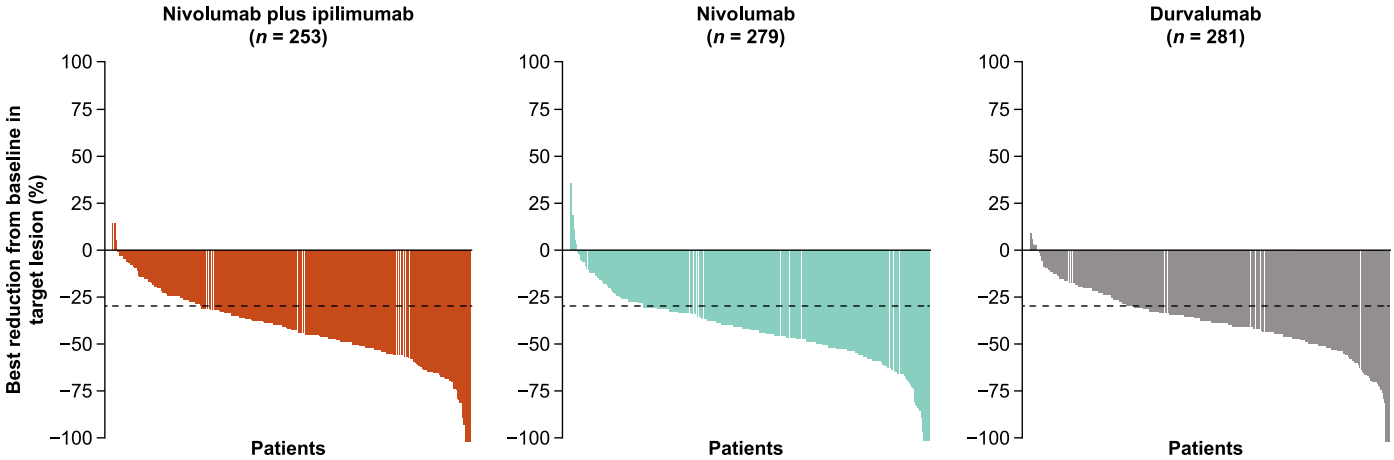

Extended Data Fig. 2 | Best reduction from baseline in target lesion (at end of CCRT phase) in patients from the nivolumab plus ipilimumab, nivolumab, and durvalumab arms. Patients with a target lesion at baseline and ≥1 evaluable post-baseline tumor assessment prior to consolidation or who did not enter consolidation were included. Best reduction was maximum reduction in the sum of the diameters of target lesions (negative values mean true reduction; positive values mean increase only observed over time). Horizontal reference line indicates the 30% reduction consistent with RECIST v1.1 response. CCRT, concurrent chemoradiotherapy; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version1.1.

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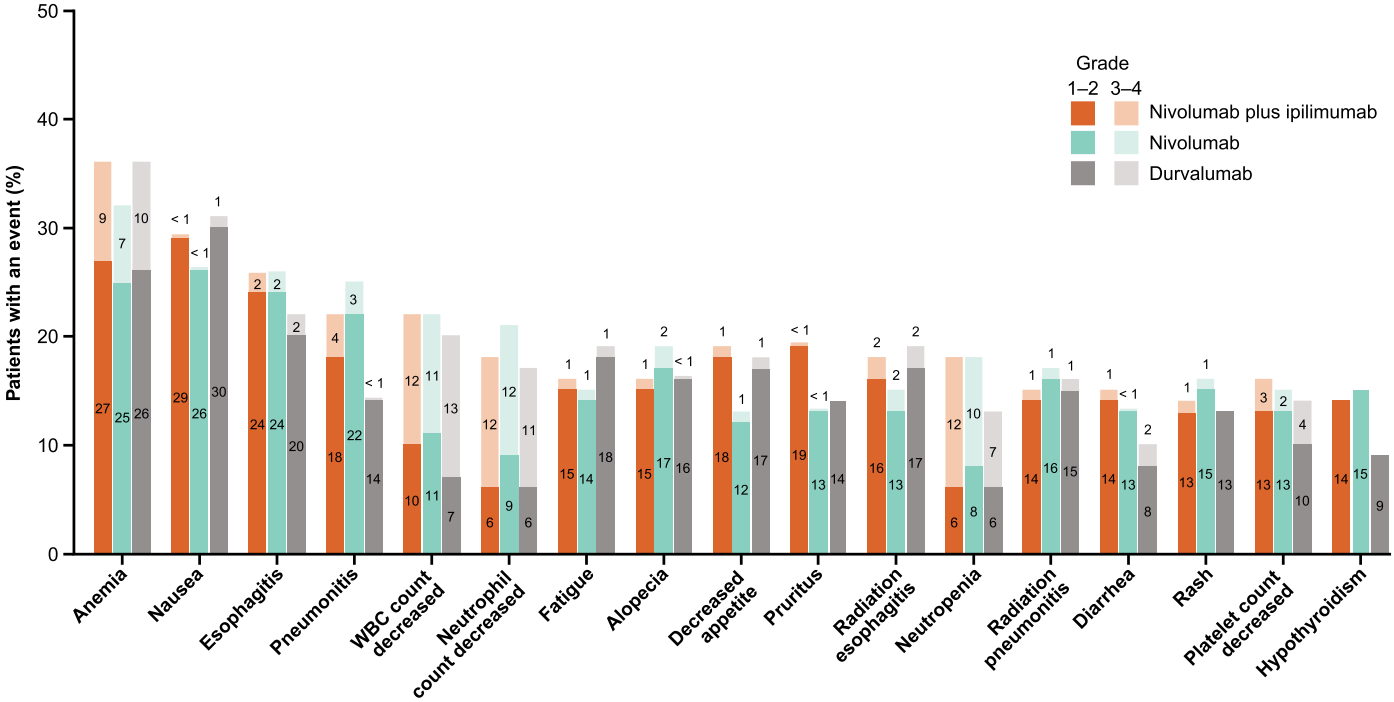
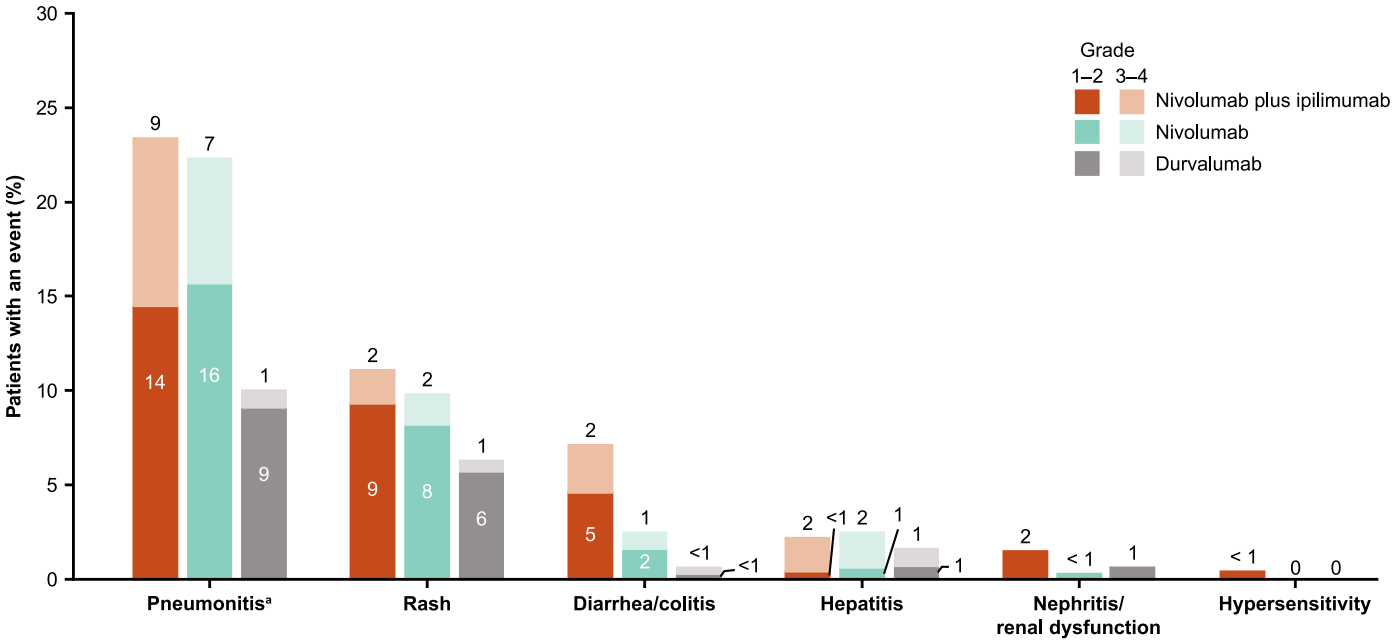


Extended Data Fig. 3 | Most common TRAEs[a] (≥15% in any arm). Nivolumab plus ipilimumab arm, n = 282; nivolumab arm, n = 318; durvalumab arm, n = 317. [a]Adverse events per CTCAE v4.0 and MedDRA v26.1. Includes events reported between the first dose and 30 days after the last dose of study therapy, excluding re-treatment. CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TRAE, treatment-related adverse event.

https://doi.org/10.1038/s43018-026-01161-y



Extended Data Fig. 4 | Immune-mediated adverse events. Nivolumab plus ipilimumab arm, n = 282; nivolumab arm, n = 318; durvalumab arm, n = 317. Immune-mediated AEs were AEs consistent with an immune-mediated mechanism or an immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) were ruled out. [a]All-cause pneumonitis included pneumonitis, immune-mediated lung diseases, and interstitial lung disease. One grade 5 pneumonitis event was reported in the nivolumab alone arm.

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☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	N/A
Data analysis	SAS software (Statistical Analysis System software, SAS Institute, North Carolina, USA, version 9.04.01M7P08062020).

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The remaining data are available within the Article, Supplementary Information, or Source Data file. The study protocol and statistical analysis plan are available in the Supplementary Information. Source data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Male and female (sex) patients, as based on self report, were eligible for enrollment. The number of patients enrolled by sex is reported in Table 1, and PFS analyses in key patient subgroups, including those defined by sex, are reported in Figure 3B.
Reporting on race, ethnicity, or other socially relevant groupings	The geographic region breakdown is reported in Table 1. There are no analyses based geographic region, or race or ethnicity reported in this manuscript.
Population characteristics	Baseline patient demographics and disease characteristics are reported in Table 1.
Recruitment	Between November 2019 and November 2022, a total of 1787 previously untreated patients with unresectable stage III NSCLC from 159 sites in 26 countries were screened, of whom 925 were randomized.
Ethics oversight	Data were collected by investigators (the list of investigators is provided in the Supplementary Information) and analyzed in collaboration with the sponsor, with an independent data monitoring committee providing oversight. The study was performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines, with independent ethics committees or institutional review boards at each study site approving the protocol (additional information provided in the Supplementary Information).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample size was determined based on the primary endpoint of PFS between the nivolumab plus ipilimumab and durvalumab arms. A total of 346 PFS events (ie, progression events or deaths) in the nivolumab plus ipilimumab and durvalumab arms would provide approximately 82% power to detect an HR of 1 during the first 3 months and an HR of 0.69 thereafter, with a 0.05 two-sided alpha. Based on the enrollment projection and the accrual duration, a total of 888 participants were planned for randomization across the three treatment groups in a 1:1:1 ratio.
Data exclusions	No data exclusions are reported.
Replication	CheckMate 73L is a clinical trial and no attempts at replication were conducted.
Randomization	925 were randomized 1:1:1 to the nivolumab plus ipilimumab arm (n = 287), nivolumab arm (n = 320), or durvalumab arm (n = 318).
Blinding	CheckMate 73L is an open-label trial.

Reporting for specific materials, systems and methods

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☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Nivolumab, a fully human anti–programmed death 1 (PD-1) antibody, Ipilumumab, a fully-human anti–cytotoxic T lymphocyte antigen-4 (CTLA-4) antibody, and Durvalumab, a human anti-programmed death ligand-1 (PD-L1) antibody were administered as the experimental treatments in this study which was provided by the study's sponsor (Bristol Myers Squibb).

Validation

Nivolumab has been validated as an effective immunotherapeutic agent for the treatment of advanced non-small cell lung (NSCLC). in the pivotal phase 3 CheckMate 017 and CheckMate 057 trials nivolumab significantly improved overall survival (OS) and objective response rates compared with docetaxel in previously treated patients with squamous and non-squamous NSCLC, respectively.

Nivolumab plus ipilimumab has been validated as an effective regimen for patients with advanced NSCLC. Clinical trials, including the phase 3 CheckMate 227 trial, demonstrated that the combination significantly improved OS compared with chemotherapy in treatment-naïve patients with advanced NSCLC.

Durvalumab has been clinically validated as a standard-of-care immunotherapy for patients with NSCLC, based on the landmark phase 3 PACIFIC trial, which demonstrated significant improvements in progression-free survival (PFS) and OS in patients with unresectable stage III NSCLC who had not progressed following concurrent chemoradiotherapy.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration

NCT04026412

Study protocol

The study protocol of CheckMate 73L is provided in the Supplementary Information.

Data collection

Between November 2019 and November 2022, a total of 1787 previously untreated patients with unresectable stage III NSCLC from 159 sites in 26 countries were screened, of whom 925 were randomized to the nivolumab plus ipilimumab arm (n = 287), nivolumab arm (n = 320), or durvalumab arm (n = 318).

Outcomes

The primary endpoint was PFS by Response Evaluation Criteria in Solid Tumors, v1.1 (RECIST v1.1) per BICR for the nivolumab plus ipilimumab arm versus the durvalumab arm. PFS was defined as the time between the date of randomization and the first date of documented progression (RECIST v1.1 per BICR), or death due to any cause, whichever occurred first, regardless of receipt of subsequent anticancer therapy prior to the documented progression per BICR.
Key secondary endpoints included OS for the nivolumab plus ipilimumab arm versus the durvalumab arm, PFS by RECIST v1.1 per BICR and per investigator assessment, and OS for the nivolumab arm versus the durvalumab arm, tumor response assessment for both nivolumab arms versus the durvalumab arm (included ORR, DOR, and time to response by RECIST v1.1 per BICR and per investigator assessment), and safety.
Additional exploratory analyses included patterns of progression and onset of pneumonitis after last dose of radiotherapy (≤3 months, ≤6 months, >6 months).

Plants

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Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
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