Supplemental Online Content

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. doi:10.1001/jamanetworkopen.2024.7542

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Flatiron Health database

The Flatiron database is one of the most comprehensive sources of longitudinal, electronic health record-derived data collected during the routine care of real-world patients with cancer. At the time the study was designed, this database included about 2.2 million patient records from 280 community practices and seven large academic research institutions, including approximately 64,000 patients with advanced NSCLC.

Despite the scale of the database, the sample size of this study was based on the fact that the two cohorts had to be manually curated (i.e., de-identified patient-level data had to be manually extracted). However, the sample was randomly generated from the database, during an initial selection process, in order to minimize the effects of selection bias and ensure representativeness of the patient population. In the end, the patients in this study were from 81 unique practices across the US.

Race and ethnicity data collection

Race and ethnicity information could be recorded in different ways by clinical teams after being reported by a patient (although ethnicity was not reported here due to excessive missing data). Practices documented the information within the electronic health record (EHR) or in the practice management system imported into the EHR. This information was often collected from patients via intake interviews and forms, but exact processes could vary greatly between practices.

Exploratory analyses

As a comparative analysis and to mirror patient eligibility in PACIFIC, exploratory analyses compared PFS and OS in patients who completed (without progressing during) chemotherapy administered concurrently with radiotherapy (cCRT). Complete cCRT was defined as CT with selected agents of interest occurring during the same period of the RT: received and completed platinum chemo doublet; for CT given every 21 days, CRT will be considered complete if the patient received at least 2 administrations of the same chemotherapy overlapping with RT; for CT given every week, CRT will be considered complete if the patient received at least 4 administrations of the same CT, overlapping with RT; total RT duration needs to be at least 5 weeks (start date of any RT to the last date of any RT); at least 4 weeks overlap of platinum-based CT and RT. These analyses counted time-to-event outcomes from the end of cCRT and only included the subset of patients who did not progress or die during cCRT, before the start of durvalumab (for the durvalumab group), or within 42 days from the end of cCRT (for the non-durvalumab group). The 42-day threshold was based on the PACIFIC trial,[1] which required study participants to start durvalumab within 42 days of ending CRT.

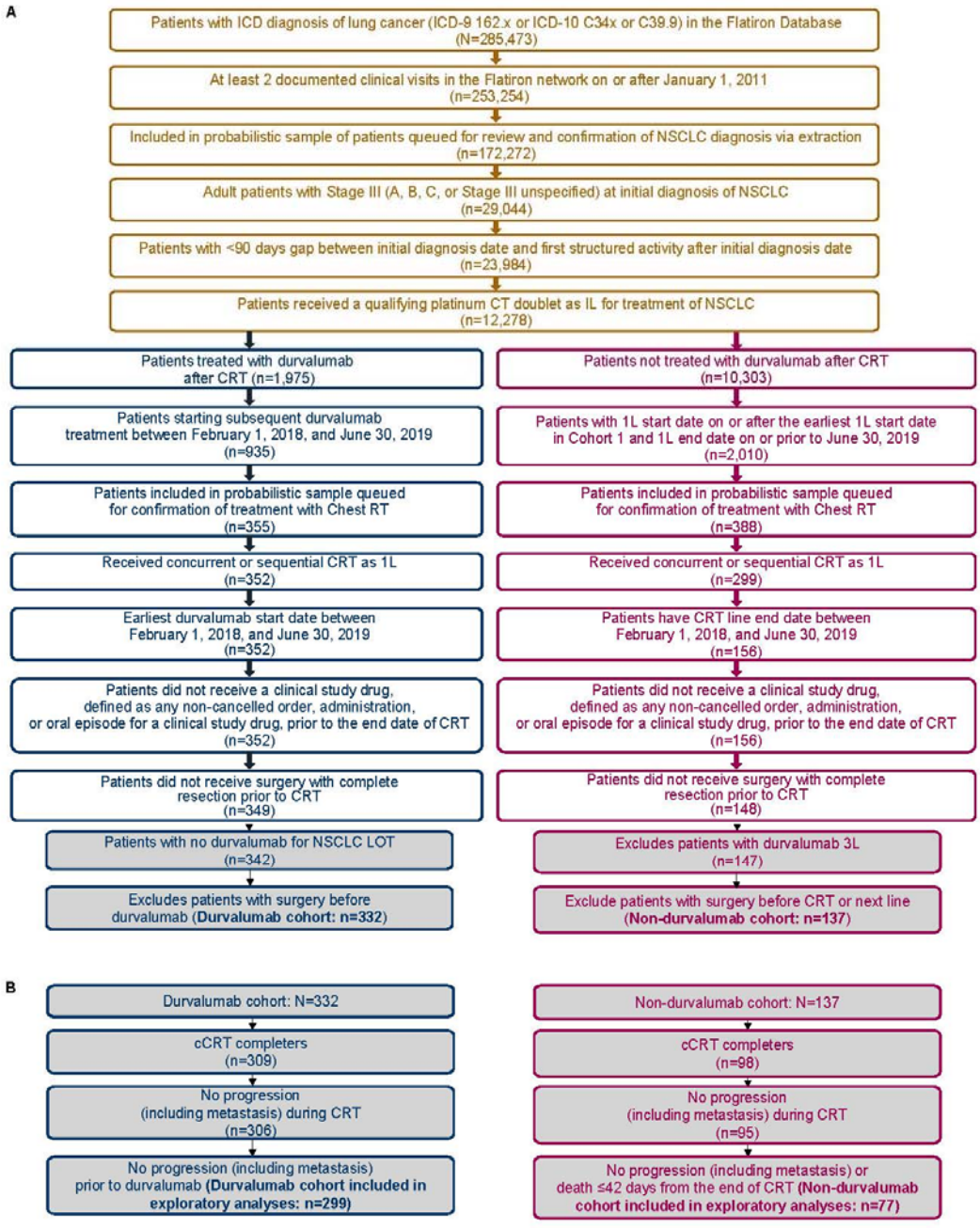
Sensitivity analyses

Sensitivity analyses were performed using treatment time-distribution matching, a different method to address immortal time bias.[2] With this method, time-to-event outcomes were counted from a different time origin, denoted as t0. For the durvalumab group, t0 was the durvalumab start date. For the non-durvalumab group, t0 was a simulated date such that the distribution of time intervals from the end of CRT to t0 was the same as the durvalumab group. To achieve this, random sampling with replacement was performed using the time intervals (between the end of CRT and the durvalumab start date) from the durvalumab group. Only those patients who completed cCRT without progression during CRT or between the end of CRT and t0 were included in this analysis. Similar to the main exploratory analyses, Cox regression analyses were used to evaluate the association of durvalumab with PFS and OS, separately, adjusting for prior platinum agent and the same set of patient characteristics but evaluated at t0 instead.

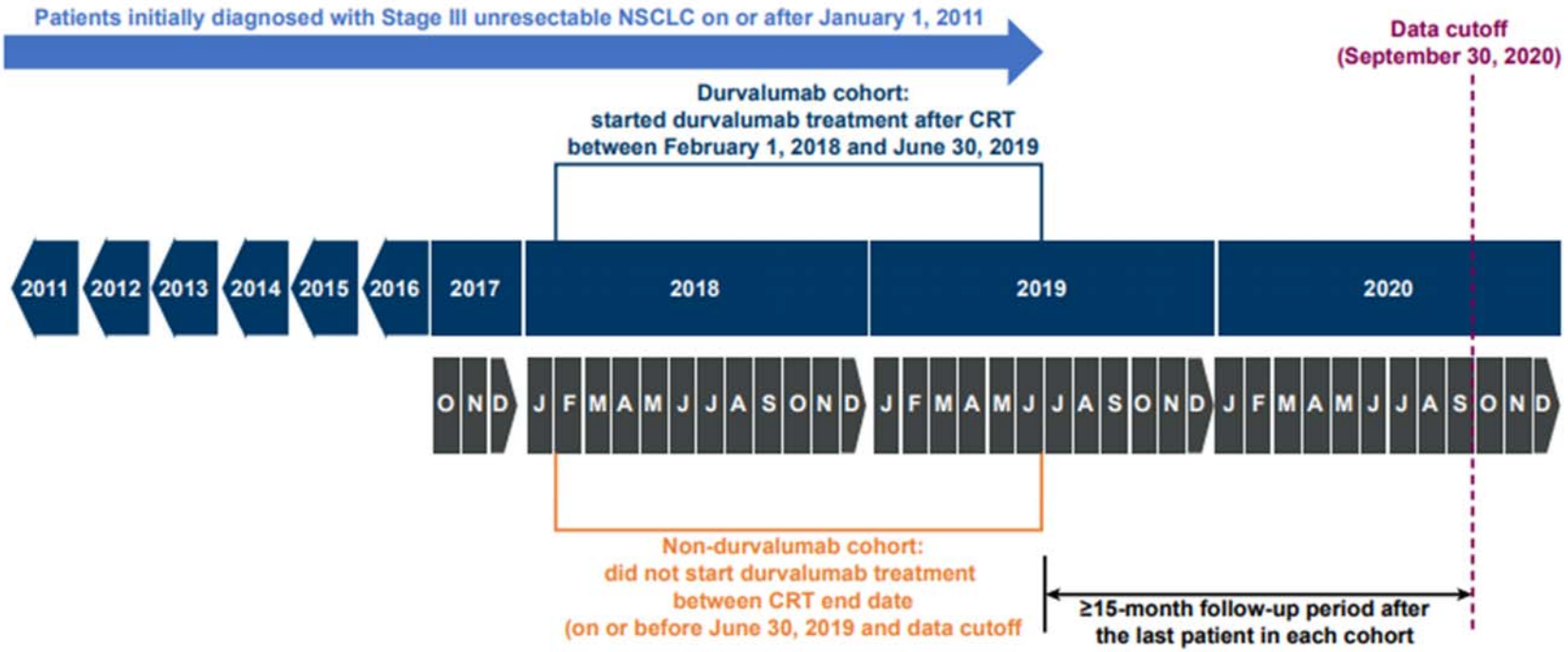
1. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919–1929. doi:10.1056/NEJMoa1709937.
2. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol*. 2005;162(10):1016–1023. doi: 10.1093/aje/kwi307.

eFigure 1. Selection of patients from Flatiron database: attrition flow chart.

Panel A outlines the attrition steps to reach the overall cohort of 469 patients who met all of the criteria for inclusion in the study (durvalumab cohort, n=332; non-durvalumab cohort, n=137). Panel B outlines the attrition steps to reach the subgroup of patients included in the main exploratory analyses. 1L, first-line; 3L, third-line; CRT, chemoradiotherapy; ICD, International Classification of Diseases; LOT, line of therapy; NSCLC, non-small-cell lung cancer; RT, radiotherapy.



eFigure 2. Study design.



eTable 1. Patient demographics and clinical characteristics at durvalumab initiation (durvalumab cohort).

	Durvalumab cohort (N=332)
Median age (range), years	67.5 (35–83)
Age ≥65 years, n (%)	210 (63.3)
Sex, n (%)	
Male	187 (56.3)
Female	145 (43.7)
Race, n (%)	
Asian	7 (2.3)
Black or African American	27 (8.7)
White	249 (80.6)
Other	26 (8.4)
Missing[a]	23
Smoking history, n (%)	
Current/prior smoker	316 (95.2)
Never-smoker	16 (4.8)
ECOG performance status, n (%)[b]	
0	100 (36.2)
1	151 (54.7)
2	23 (8.3)
3	2 (0.7)
Missing[a]	56
AJCC disease stage at initial diagnosis, n (%)	
IIIA	194 (58.4)
IIIB	128 (38.6)
IIIC	10 (3.0)
PD-L1 tumor cell expression, n (%)[b]	
≥1%	36 (65.5)
<1%	19 (34.5)
Missing[a]	277
EGFR mutation status, n (%)[b]	
Negative	56 (91.8)
Positive	3 (4.9)
Indeterminate or unsuccessful test	2 (3.3)
Missing[a]	271
Practice type, n (%)	
Academic	15 (4.5)
Community	317 (95.5)
Region, n (%)	
South	146 (46.6)
Midwest	76 (24.3)
Northeast	50 (16.0)
West	41 (13.1)
Missing[a]	19

[a]Missing values were not imputed; all reported percentages were calculated using the number of patients with available data as the denominator.
[b]Within 4 weeks before/after the start of durvalumab. If multiple records were available, the record closest to the start of durvalumab is reported. If a patient had values both before and after the start of durvalumab, with the same length of time from that date, then the value before was analyzed.

AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death-ligand 1.

eTable 2. Patient demographics and clinical characteristics at CRT start (non-durvalumab cohort).

	Non-durvalumab cohort (N=137)
Median age (range), years	70.0 (36–83)
Age ≥65 years, n (%)	101 (73.7)
Sex, n (%)	
Male	89 (65.0)
Female	48 (35.0)
Race, n (%)	
Asian	3 (2.4)
Black or African American	11 (8.9)
White	93 (75.6)
Other	16 (13.0)
Missing[a]	14
Smoking history, n (%)	
Current/prior smoker	132 (96.4)
Never-smoker	5 (3.6)
ECOG performance status, n (%)[b]	
0	39 (36.1)
1	49 (45.4)
2	15 (13.9)
3	5 (4.6)
Missing[a]	29
AJCC disease stage at initial diagnosis, n (%)	
IIIA	89 (65.0)
IIIB	45 (32.8)
IIIC	3 (2.2)
PD-L1 tumor cell expression, n (%)[b]	
≥1%	14 (56.0)
<1%	11 (44.0)
Missing[a]	112
EGFR mutation status, n (%)[b]	
Negative	27 (84.4)
Positive	1 (3.1)
Indeterminate or unsuccessful test	3 (9.4)
Unknown	1 (3.1)
Missing[a]	105
Practice type, n (%)	
Academic	7 (5.1)
Community	130 (94.9)
Region, n (%)	
South	75 (58.1)
Midwest	21 (16.3)
Northeast	23 (17.8)
West	10 (7.8)
Missing[a]	8

[a]Missing values were not imputed; all reported percentages are calculated using the number of patients with available data as the denominator.
[b]Within 4 weeks before/after the start of CRT. If multiple records were available, the record closest to the start of CRT is reported. If a patient had values both before and after the start of CRT, with the same length of time from that date, then the value before was analyzed.

AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death-ligand 1.

eTable 3. Type and duration of CRT and duration of durvalumab treatment (durvalumab cohort).

	Durvalumab cohort (N=332)
Type of CRT, n (%)	
Complete cCRT[a]	309 (93.1)
sCRT	2 (0.6)
Other[b]	21 (6.3)
Median duration of CRT (IQR), months[c]	1.6 (1.4–1.8)
Median time from end of CRT to start of durvalumab (IQR), days	42 (29–65)
Median duration of durvalumab treatment (95% CI), months[d]	9.5 (7.8–10.6)
Patients remaining on durvalumab treatment, % (95% CI)[d]	
3 months	75.7 (70.7–80.0)
6 months	64.2 (58.8–69.2)
9 months	50.7 (45.1–56.0)
11 months	40.5 (35.1–45.8)
12 months	18.2 (14.1–22.6)

[a]Complete cCRT is defined as CT with selected agents of interest occurring during the same period of the RT: received and completed platinum chemo doublet; for CT given every 21 days, CRT will be considered complete if the patient received at least 2 administrations of the same chemotherapy overlapping with RT; for CT given every week, CRT will be considered complete if the patient received at least 4 administrations of the same CT, overlapping with RT; total RT duration needs to be at least 5 weeks (start date of any RT to the last date of any RT); at least 4 weeks overlap of platinum-based CT and RT.
[b]Did not match the criteria used to define cCRT or sCRT.
[c]Total duration of CRT was calculated as: (CRT end date - CRT start date+1) /30.4375. The CRT start date was defined as the start date of radiation therapy, unless the patient had chemotherapy less than 10 days before the radiation start date. In that case, the first date of chemotherapy was used as the start of CRT. The CRT end date was defined as the last date of radiation therapy unless the patient had chemotherapy less than 10 days after radiation therapy. In that case, the last date of chemotherapy was used as the end of CRT.
[d]Calculated using the Kaplan-Meier method. Four patients remained on durvalumab treatment and 14 were lost to follow up at the time of data cutoff. Two patients discontinued durvalumab after completing 26 infusions, and restarted durvalumab 4 months later; the discontinuation date was the date that each completed their 26th infusion. One patient discontinued durvalumab due to disease progression and restarted durvalumab three months later after a second progression; the discontinuation date for this patient was the date of the last durvalumab administration after the first progression.
cCRT, concurrent chemoradiotherapy; CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; IQR, interquartile range; RT, radiotherapy; sCRT, sequential chemoradiotherapy.

eTable 4. Reasons for discontinuation of durvalumab by duration of treatment (durvalumab cohort).

	<3 months[a] (n=80)	**3 to <6 months[a] (n=37)**	**6 months to <360 days[a] (n=124)**	**≥360 days[a] (n=78)**	**Overall (N=332)**
Discontinued durvalumab, n (%)[b]	80 (100)	37 (100)	124 (100)	73 (93.6)	314 (94.6)
Completed treatment[c]	0	1 (2.7)	64 (51.6)	68 (87.2)	133 (40.1)
Progressive disease[d]	24 (30.0)	18 (48.6)	27 (21.8)	3 (3.8)	72 (21.7)
Toxicity	34 (42.5)	10 (27.0)	19 (15.3)	0	63 (19.0)
Non-cancer related medical issue	15 (18.8)	5 (13.5)	6 (4.8)	1 (1.3)	27 (8.1)
Cancer-related symptoms not due to therapy	6 (7.5)	1 (2.7)	3 (2.4)	0	10 (3.0)
Financial	0	1 (2.7)	2 (1.6)	1 (1.3)	4 (1.2)
Patient's request	0	1 (2.7)	2 (1.6)	0	3 (0.9)
No evidence of disease[e]	1 (1.3)	0	0	0	1 (0.3)
Other[f]	0	0	1 (0.8)	0	1 (0.3)

[a]Duration of treatment subgroup summaries exclude patients for whom time to discontinuation was censored before 360 days (13/332 patients could not be categorized); one month equates to 30.4375 days.
[b]Discontinuation reason is as reported from curated, unstructured data except as noted otherwise. Three patients discontinued durvalumab after completing 26 infusions or progressive disease but restarted durvalumab later; the reason for the first discontinuation is listed for these patients.
[c]Three patients were considered to have completed treatment because they had ≥26 infusions, even though not present in the curated discontinuation data. 'Completed treatment' as curated from unstructured data (physician notes included) does not always imply that a patient received ≥26 infusions or 12 months of durvalumab treatment.
[d]May include progressive disease that occurred shortly before durvalumab start.
[e]No evidence of disease; patient underwent surgery after durvalumab.
[f]Includes patients who may have discontinued due to death.

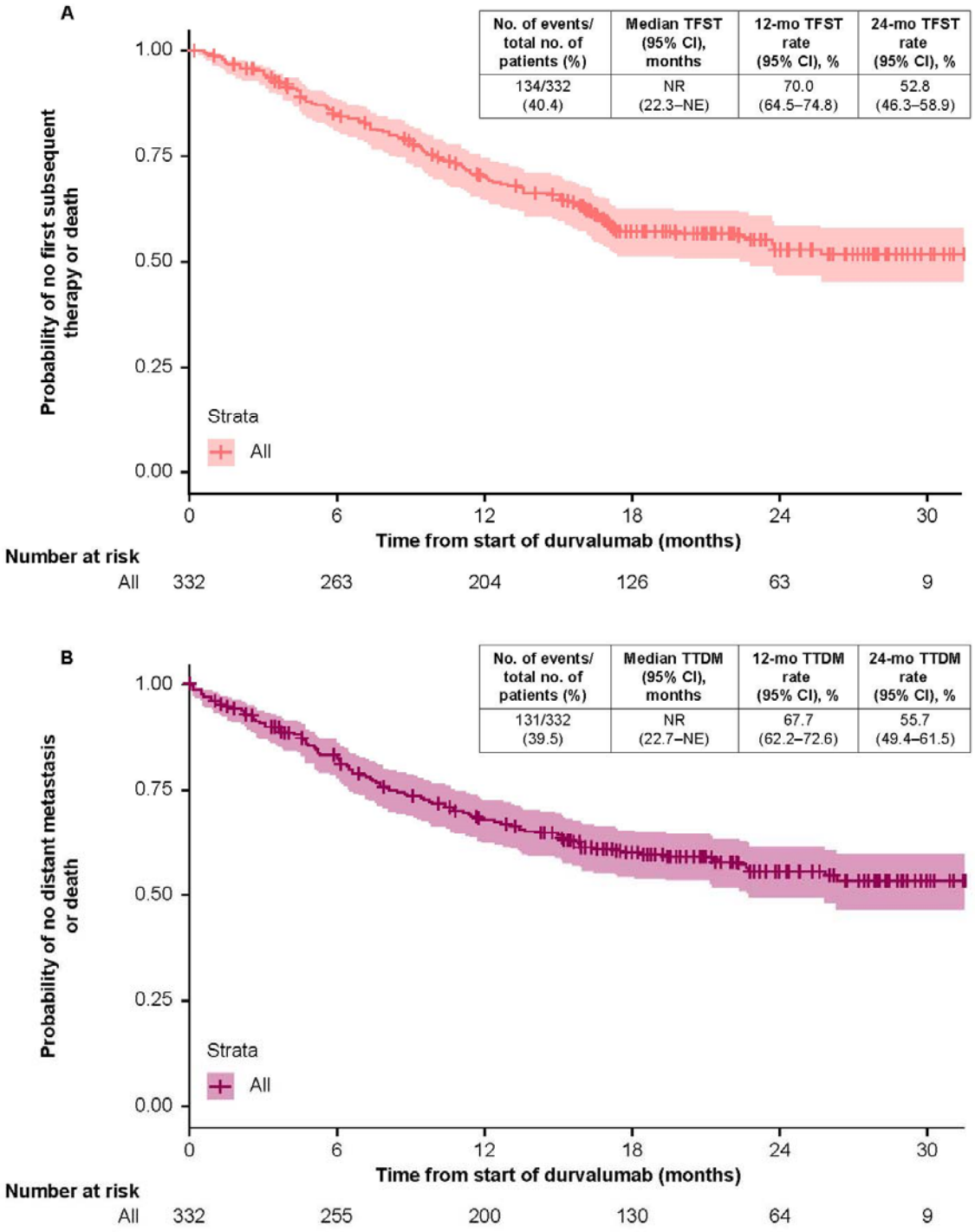
eTable 5. First subsequent therapy after discontinuation of durvalumab by duration of durvalumab treatment (durvalumab cohort).

	<3 months (n=37)	**3 to <6 months (n=21)**	**6 to <12 months (n=34)**	**≥12 months (n=11)**	**Overall (n=103)**
First subsequent therapy, n (%)[a]					
Chemotherapy	23 (62.2)	17 (81.0)	22 (64.7)	9 (81.8)	71 (68.9)
Immunotherapy	16 (43.2)	3 (14.3)	15 (44.1)	5 (45.5)	39 (37.9)
Targeted therapy	7 (18.9)	8 (38.1)	6 (17.6)	2 (18.2)	23 (22.3)
Surgery	1 (2.7)	0	1 (2.9)	1 (9.1)	3 (2.9)

[a]Patients could have more than one type of therapy, given in combination.

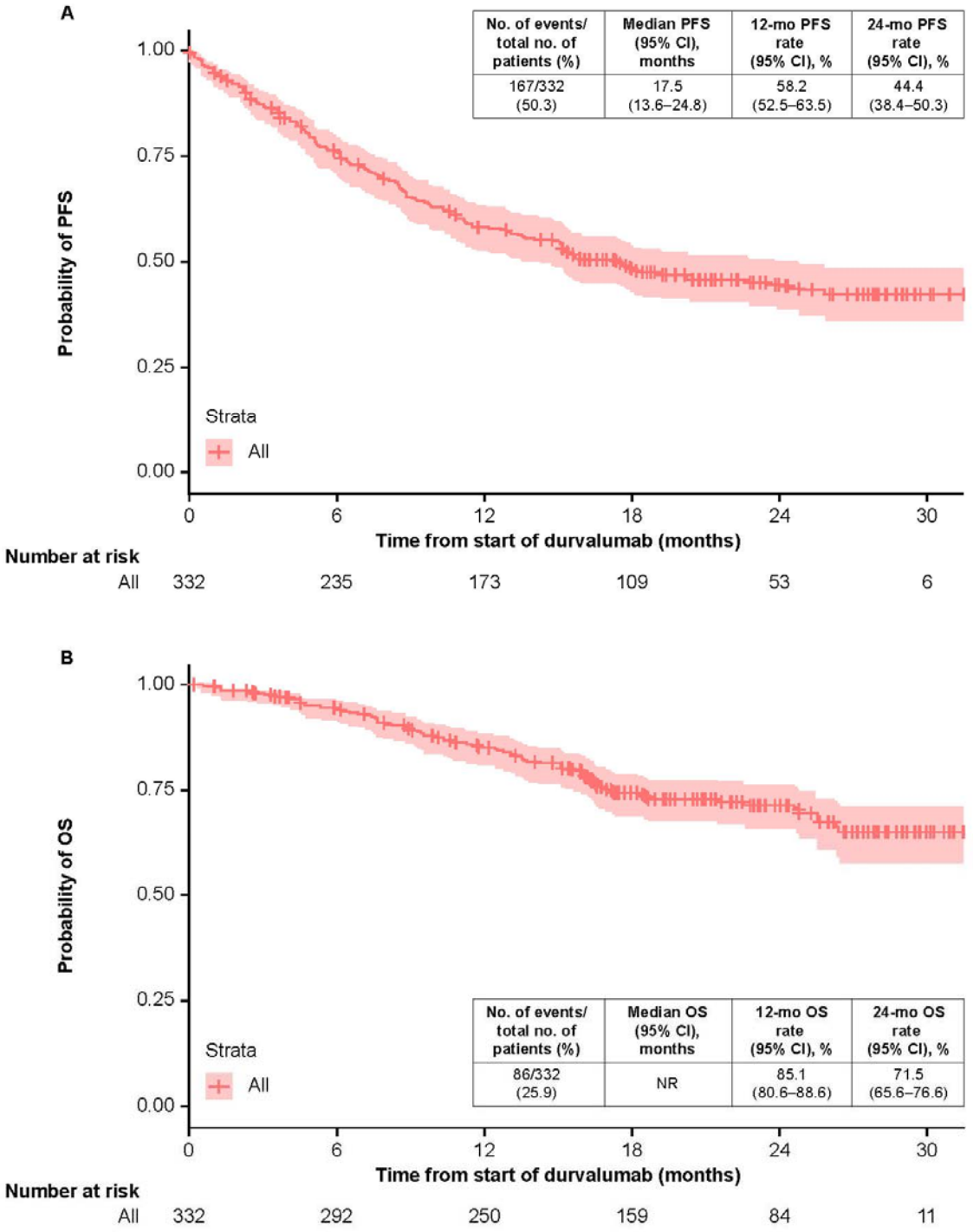
eFigure 3. Time to first subsequent therapy or death (TFST) (A) and time to distant metastasis or death (TTDM) (B) in the durvalumab cohort.

TFST was measured from the start of durvalumab to the earlier of either the start of first subsequent anticancer therapy, including surgery, or death, and TTDM was measured from the start of durvalumab to the earlier of either the first date of distant metastasis or death. Median follow-up in the durvalumab cohort was 17.5 months (range 0.2–32.0) from initiation of durvalumab. CI, confidence interval; NE, not estimable; NR, not reached.



eFigure 4. Progression-free survival (PFS) (A) and overall survival (OS) (B) in the durvalumab cohort.

PFS was measured from the start of durvalumab to progression or death from any cause, and OS was measured from start of durvalumab to death from any cause. Median follow-up in the durvalumab cohort was 17.5 months (range 0.2–32.0) from initiation of durvalumab. CI, confidence interval; NR, not reached.



eTable 6. Incidence and management of adverse events of interest occurring during CRT (durvalumab and non-durvalumab cohorts).

AE and action with treatment or outcome resulting from the AE[a]	Durvalumab cohort N=332	Non-durvalumab cohort N=137
Any AE of interest	275 (82.8)	103 (75.2)
Pain	218 (65.7)	89 (65.0)
Treatment for the AE	141 (42.5)	66 (48.2)
Hospitalization[b]	20 (6.0)	13 (9.5)
None[c]	119 (35.8)	38 (27.7)
Therapy discontinuation	1 (0.3)	0
Therapy hold or dose/schedule change	15 (4.5)	12 (8.8)
Esophagitis	144 (43.4)	47 (34.3)
Treatment for the AE	112 (33.7)	37 (27.0)
Hospitalization[b]	10 (3.0)	6 (4.4)
None[c]	32 (9.6)	8 (5.8)
Therapy discontinuation	5 (1.5)	2 (1.5)
Therapy hold or dose/schedule change	14 (4.2)	4 (2.9)
Pneumonitis	21 (6.3)	8 (5.8)
Treatment for the AE	15 (4.5)	8 (5.8)
Hospitalization[b]	0	4 (2.9)
None[c]	6 (1.8)	0
Therapy discontinuation	0	0
Therapy hold or dose/schedule change	3 (0.9)	1 (0.7)

Data are n (%) for all parameters.
[a]Categories other than "none" are not mutually exclusive; patients counted in the "none" category are not counted in any other category. An outcome can be attributed to multiple AEs and is listed with each AE.
[b]Including hospitalization with the admission date earlier than the AE onset date when the AE developed during hospitalization.
[c]No action was taken with the treatment and no related outcome is associated with the AE.
AE, adverse event; CRT, chemoradiotherapy.

eTable 7. Incidence and management of adverse events of interest occurring during durvalumab treatment (durvalumab cohort).

AE and action with durvalumab[a] or outcome resulting from the AE[b]	Durvalumab cohort N=332
Any AE of interest	270 (81.3)
Treatment for the AE	215 (64.8)
Hospitalization[c]	53 (16.0)
Durvalumab discontinuation	30 (9.0)
Durvalumab hold or dose/schedule change	74 (22.3)
Pain	252 (75.9)
Treatment for the AE	183 (55.1)
Hospitalization[c]	38 (11.4)
None[d]	153 (46.1)
Durvalumab discontinuation	8 (2.4)
Durvalumab hold or dose/schedule change	36 (10.8)
Pneumonitis	79 (23.8)
Treatment for the AE	63 (19.0)
Hospitalization[c]	15 (4.5)
None[d]	13 (3.9)
Durvalumab discontinuation	23 (6.9)
Durvalumab hold or dose/schedule change	41 (12.3)
Esophagitis	10 (3.0)
Treatment for the AE	9 (2.7)
Hospitalization[c]	3 (0.9)
None[d]	1 (0.3)
Durvalumab discontinuation	1 (0.3)
Durvalumab hold or dose/schedule change	3 (0.9)

Data are n (%) for all parameters.
[a]Two patients received durvalumab alongside other anti-cancer agents in the same therapy line; the action reported could be in relation to any treatment received in the same therapy line as durvalumab.
[b]Categories other than "none" are not mutually exclusive; patients counted in the "none" category are not counted in any other category. An outcome can be attributed to multiple AEs and is listed with each AE.
[c]Including hospitalization with the admission date earlier than the AE onset date when the AE developed during hospitalization.
[d]No action was taken with the treatment and no related outcome is associated with the AE.
AE, adverse event.

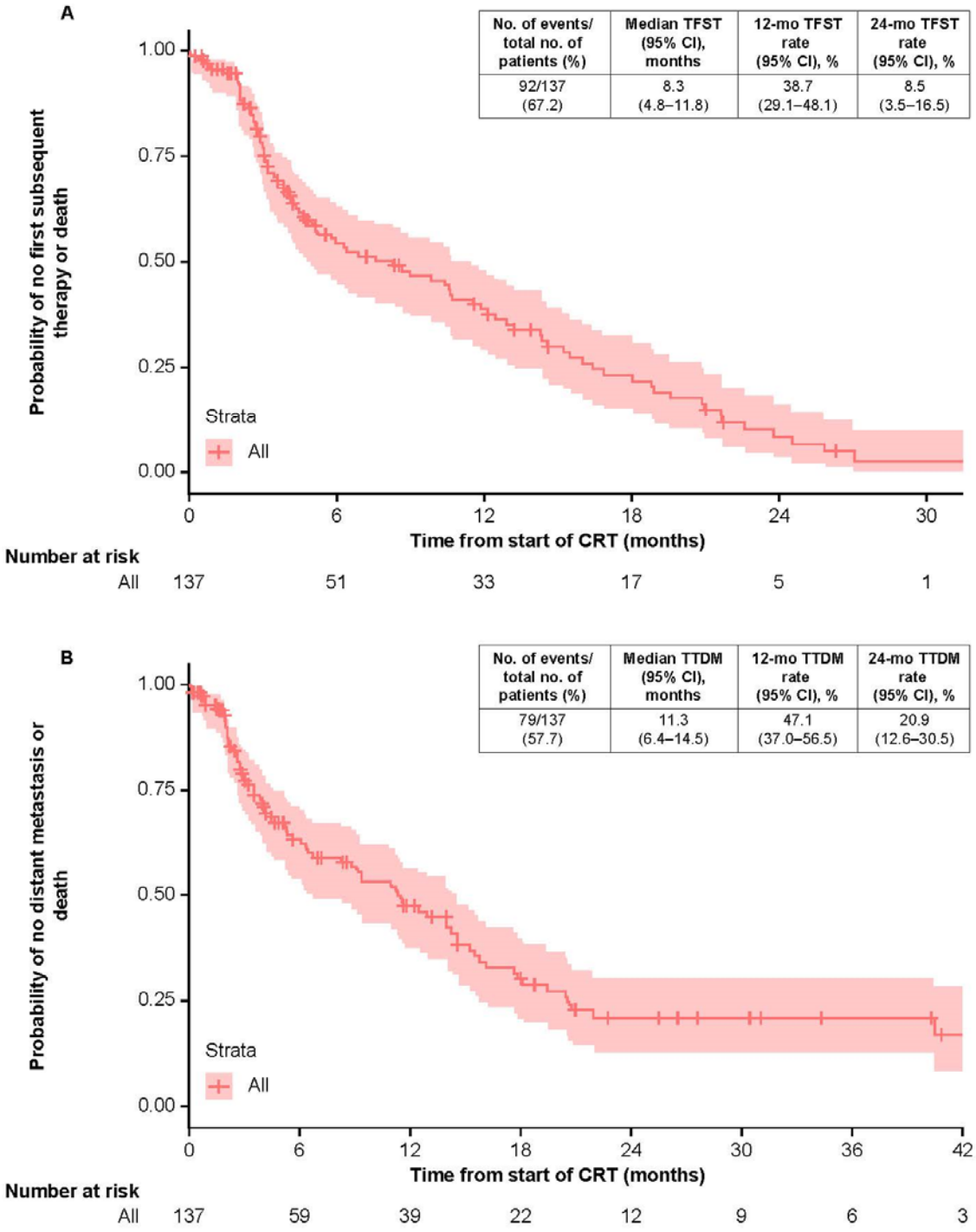
eTable 8. Type and duration of CRT (non-durvalumab cohort).

	Non-durvalumab cohort (N=137)
Type of CRT, n (%)	
Complete cCRT[a]	98 (71.5)
sCRT	2 (1.5)
Other[b]	37 (27.0)
Median duration of CRT (IQR), months[c]	1.5 (1.4–1.8)

[a]Complete cCRT is defined as CT with selected agents of interest occurring during the same period of the RT: received and completed platinum chemo doublet; for CT given every 21 days, CRT will be considered complete if the patient received at least 2 administrations of the same chemotherapy overlapping with RT; for CT given every week, CRT will be considered complete if the patient received at least 4 administrations of the same CT, overlapping with RT; total RT duration needs to be at least 5 weeks (start date of any RT to the last date of any RT); at least 4 weeks overlap of platinum-based CT and RT.
[b]Did not match the criteria used to define cCRT or sCRT
[c]Total treatment duration of CRT was calculated as: (CRT end date - CRT start date+1) /30.4375. The CRT start date was defined as the start date of radiation therapy, unless the patient had chemotherapy less than 10 days before the radiation start date. In that case, the first date of chemotherapy was used as the start of CRT. The CRT end date was defined as the last date of radiation therapy unless the patient had chemotherapy less than 10 days after radiation therapy. In that case, the last date of chemotherapy was used as the end of CRT.
cCRT, concurrent chemoradiotherapy; CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; IQR, interquartile range; RT, radiotherapy; sCRT, sequential chemoradiotherapy.

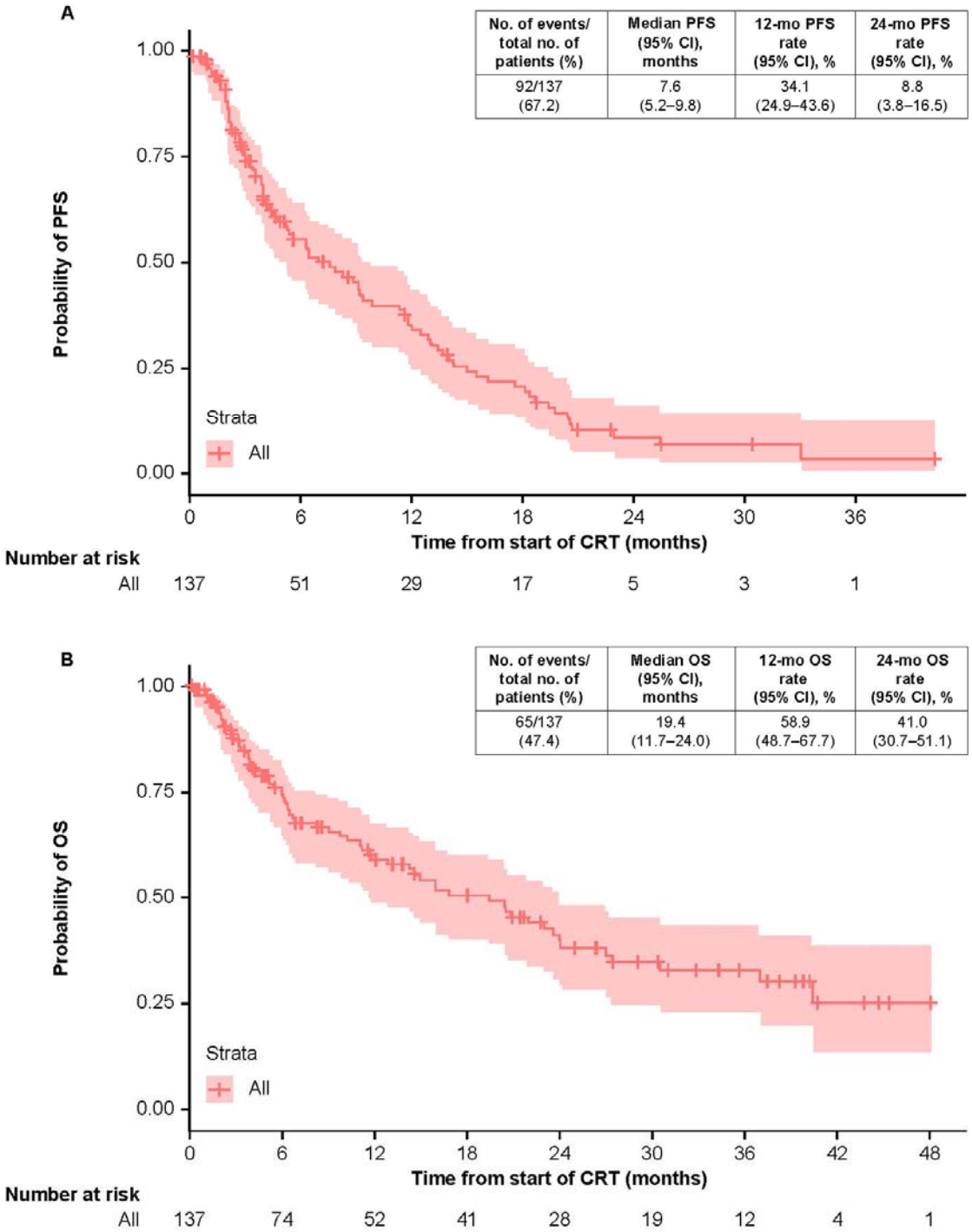
eFigure 5. Time to first subsequent therapy or death (TFST) (A) and time to distant metastasis or death (TTDM) (B) in the non-durvalumab cohort.

TFST was measured from the start of CRT to the earlier of either the start of first subsequent anticancer therapy, including surgery, or death, and TTDM was measured from the start of CRT to the earlier of either the first date of distant metastasis or death. In the non-durvalumab cohort, median follow-up from start of CRT was 6.1 months (range 0.2–48.2). CI, confidence interval; NE, not estimable; NR, not reached. CI, confidence interval.

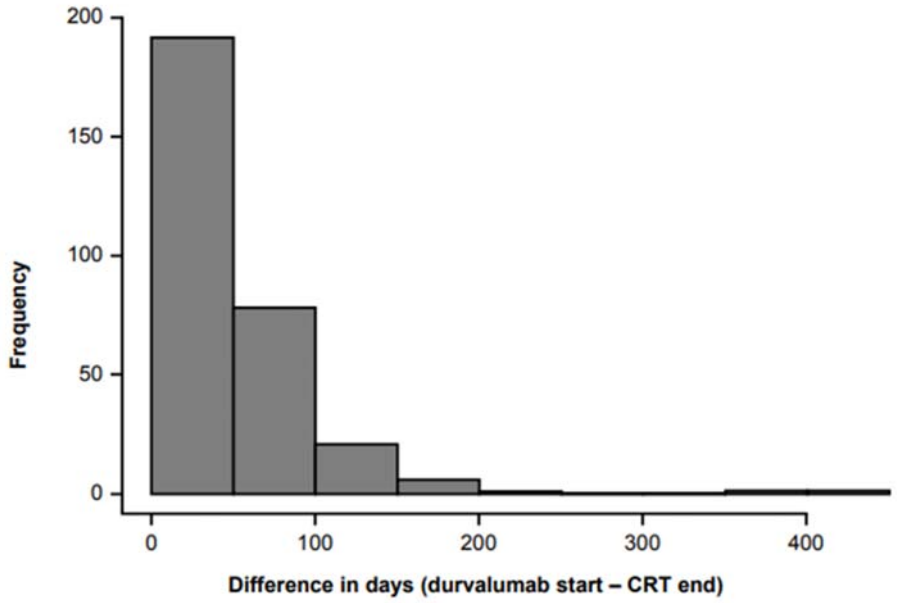


eFigure 6. Progression-free survival (PFS) (A) and overall survival (OS) (B) in the non-durvalumab cohort.

PFS was measured from the start of CRT to progression or death from any cause, and OS was measured from start of CRT to death from any cause. In the non-durvalumab cohort, median follow-up from start of CRT was 6.1 months (range 0.2–48.2). CI, confidence interval.

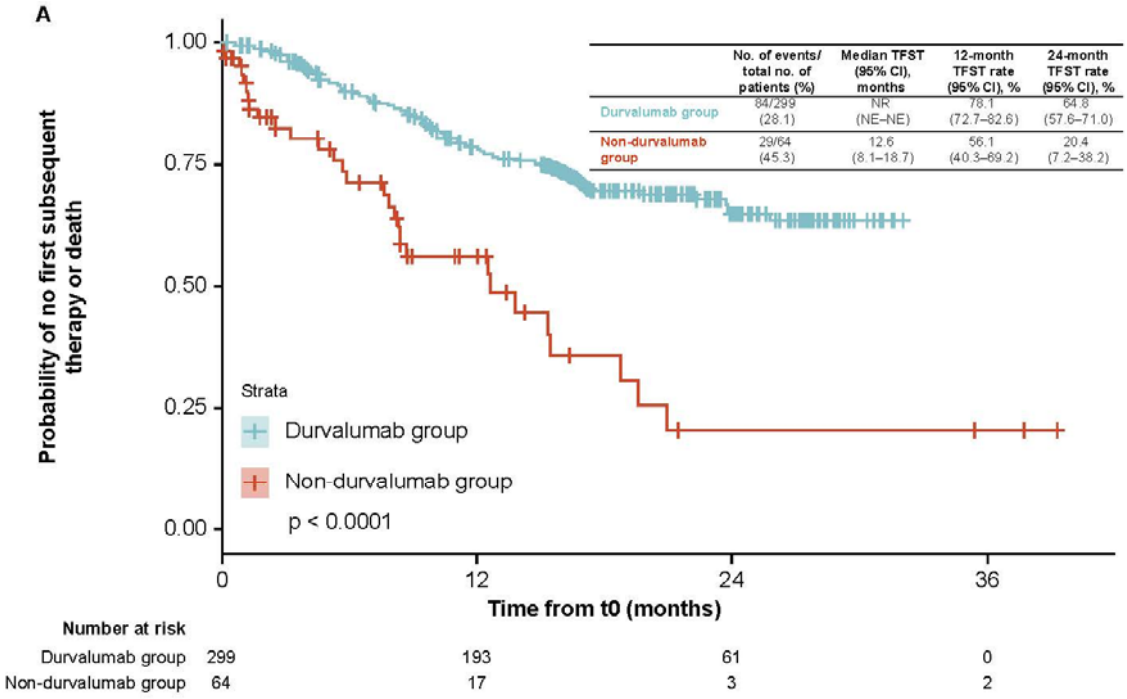


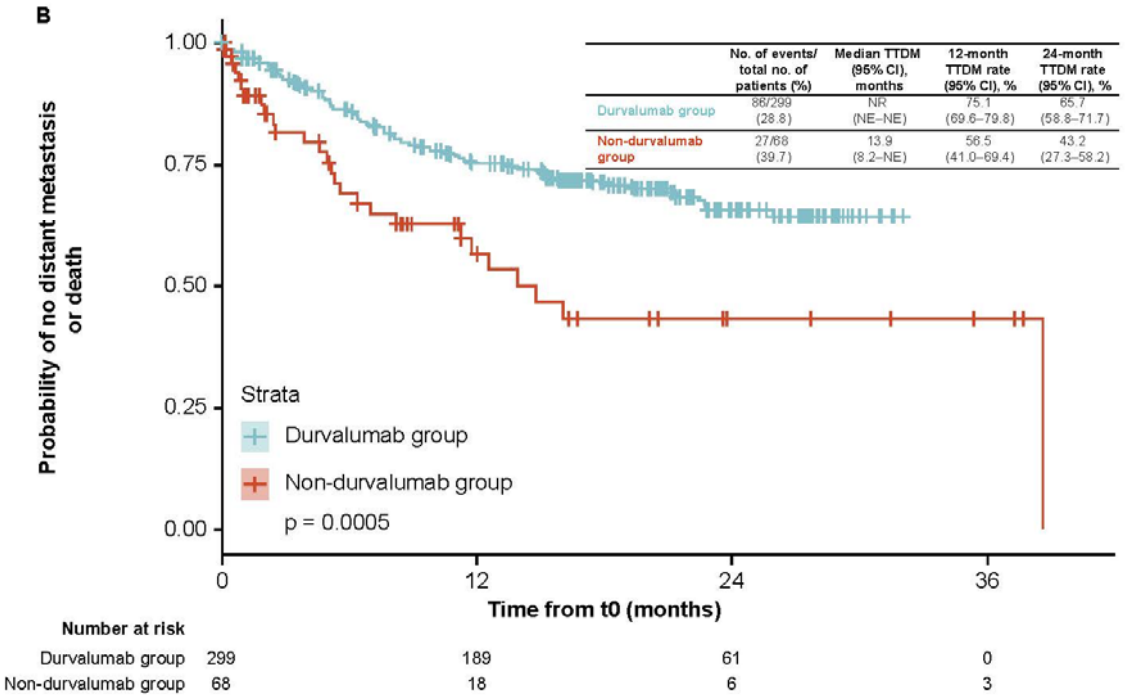
eFigure 7. Time to start of durvalumab from end of chemoradiotherapy (durvalumab group).



eFigure 8. Sensitivity analyses of time to first subsequent therapy or death (TFST) (A) and time to distant metastasis or death (TTDM) (B).

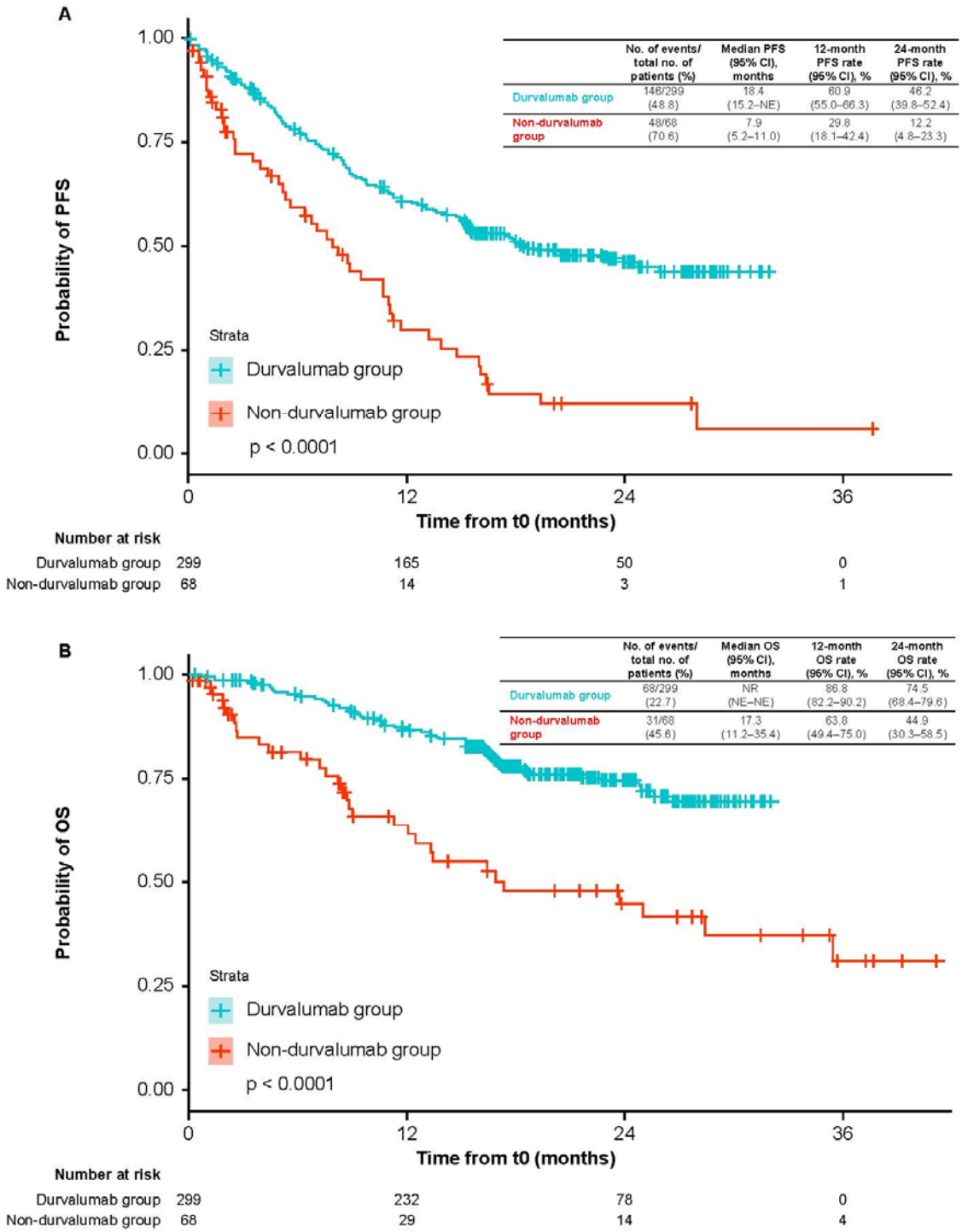
TFST was measured from t0 to the earlier of either the start of first subsequent anticancer therapy, including surgery, or death, and TTDM was measured from t0 to the earlier of either the first date of distant metastasis or death. For the durvalumab group, t0 was the durvalumab start date. For the non-durvalumab group, t0 was a simulated date such that the distribution of time intervals from the end of CRT to t0 was the same as the durvalumab group. CI, confidence interval; NE, not estimable; NR, not reached.





eFigure 9. Sensitivity analyses of progression-free survival (PFS) (A) and overall survival (OS) (B)**.**

PFS was measured from t0 to progression or death from any cause, and OS was measured from t0 to death from any cause. For the durvalumab group, t0 was the durvalumab start date. For the non-durvalumab group, t0 was a simulated date such that the distribution of time intervals from the end of CRT to t0 was the same as the durvalumab group. CI, confidence interval; NE, not estimable; NR, not reached.



eResults

Sensitivity analyses

The sensitivity analyses for the main exploratory analyses included all 299 patients from the durvalumab group and 68 patients from the non-durvalumab group as defined in the **eMethods**. The distribution of time intervals from CRT end to durvalumab start in the durvalumab group is shown in **eFigure 7**; median time from CRT end to durvalumab start was 41 days (range 0–447). The sensitivity analyses of TFST and TTDM are reported in **eFigure 8**, and the sensitivity analyses of PFS and OS are reported in **eFigure 9**. The Cox regression analysis adjusting for prior platinum agent and patient characteristics evaluated at t0 showed that durvalumab was associated with a lower risk of progression or death (HR 0.36; 95% CI 0.25–0.52), as well as a lower risk of death (HR 0.27; 95% CI 0.16–0.44). These results were consistent with those from the main exploratory analyses.