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ORIGINAL ARTICLE

ARCTIC: durvalumab with or without tremelimumab as third-line or later treatment of metastatic non-small-cell lung cancer☆

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Background: Many patients with metastatic non-small-cell lung cancer (mNSCLC) experience disease progression after first- and second-line treatment; more treatment options are required for these patients. ARCTIC, a phase III, randomized, open-label study, assessed durvalumab ± tremelimumab versus standard of care (SoC) as ≥ third-line treatment of mNSCLC.

Patients and methods: ARCTIC comprised two independent sub-studies. Study A: 126 patients with ≥25% of tumor cells (TCs) expressing programmed cell death ligand-1 (PD-L1) were randomized (1 : 1) to durvalumab [up to 12 months 10 mg/kg every 2 weeks (q2w)] or SoC. Study B: 469 patients with PD-L1 TC <25% were randomized (3 : 2 : 2 : 1) to durvalumab + tremelimumab (12 weeks durvalumab 20 mg/kg + tremelimumab 1 mg/kg q4w then 34 weeks durvalumab 10 mg/kg q2w), SoC, durvalumab (up to 12 months 10 mg/kg q2w), or tremelimumab (24 weeks 10 mg/kg q4w then 24 weeks q12w). Primary end points: overall survival (OS) and progression-free survival (PFS) for durvalumab versus SoC (study A; descriptive only) and durvalumab + tremelimumab versus SoC (study B).

Results: Study A: median OS 11.7 (durvalumab) versus 6.8 (SoC) months {hazard ratio (HR) 0.63 [95% confidence interval (CI), 0.42—0.93]}; median PFS 3.8 (durvalumab) versus 2.2 (SoC) months [HR 0.71 (95% CI, 0.49—1.04)]. Study B: median OS 11.5 (durvalumab + tremelimumab) versus 8.7 (SoC) months [HR 0.80 (95% CI, 0.61—1.05); $P = 0.109$]. Median PFS of 3.5 months for both groups [HR 0.77 (95% CI, 0.59—1.01); $P = 0.056$]. Treatment-related grade 3/4 adverse events: 9.7% (durvalumab) and 44.4% (SoC; study A) and 22.0% (durvalumab + tremelimumab) and 36.4% (SoC; study B).

Conclusions: In heavily pretreated patients with mNSCLC, durvalumab demonstrated clinically meaningful improvements in OS and PFS versus SoC (patients with PD-L1 TC ≥25%); numerical improvements in OS and PFS for durvalumab + tremelimumab versus SoC were observed (patients with PD-L1 TC <25%). Safety profiles were consistent with previous studies.

Trial registration: Clinicaltrials.gov identifier: NCT02352948.

Key words: ARCTIC, durvalumab, immunotherapy, metastatic non-small-cell lung cancer, tremelimumab

INTRODUCTION

Immune checkpoint inhibitors targeting programmed cell death-1 (PD-1) or its ligand programmed cell death ligand-1 (PD-L1), as monotherapy or in combination with other therapies, have reshaped the metastatic non-small-cell lung cancer (mNSCLC) treatment landscape.[1–5] Not all patients with mNSCLC receive immunotherapy in the first- or second-line setting (due to multiple factors including approval/availability of these products at that time in some countries). Thus, in patients with disease progression there is a need for more therapy options in the advanced treatment-line setting.

Durvalumab, a selective, high-affinity, human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, is indicated for the treatment of patients with unresectable, stage III NSCLC whose disease has not

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progressed following platinum-based chemotherapy and radiotherapy.[6,7] In the phase II ATLANTIC trial, durvalumab showed promising activity in heavily pretreated (third-line or higher) patients with mNSCLC with results consistent with those of other anti-PD-1/PD-L1 agents.[3] Across multiple trials, anti-PD-1/PD-L1 therapies have demonstrated clinical benefit in patients with varying PD-L1 expression levels on tumor cells (TCs), including those with PD-L1-negative tumors.[1,3,8–11] However, better efficacy outcomes with anti-PD-1/PD-L1 monotherapies have been reported in patients who have higher PD-L1 TC expression levels, with cut-offs of 1%, 25%, and 50% used most frequently to define high PD-L1 expression during the clinical development programs for immune checkpoint inhibitors in lung cancer.[3,9–14] The simultaneous blockade of the PD-1/PD-L1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) pathways has shown additive or synergistic antitumor activity in previous studies and may be a treatment option in patients with low/negative PD-L1 expression.[4,15–17]

Here, we report final results from ARCTIC (NCT02352948), a phase III, randomized, open-label, multicenter study (comprising two independent sub-studies) in patients with heavily pretreated stage IIIB/IV NSCLC. Study A assessed the efficacy and safety of durvalumab monotherapy versus standard of care (SoC), in patients with $\geq$25% of TCs expressing PD-L1 (PD-L1 TC $\geq$25%). Study B assessed the efficacy and safety of durvalumab + tremelimumab (anti-CTLA-4 antibody)[18] versus SoC or either agent as monotherapy, in patients with <25% of TCs expressing PD-L1 (PD-L1 TC <25%).

PATIENTS AND METHODS

Patients

Full eligibility criteria are provided in supplementary Table S1, available at *Annals of Oncology* online, and have been described previously.[19] Adult patients were eligible if they had histologically or cytologically documented stage IIIB/IV locally advanced or mNSCLC; disease progression or recurrence after both a platinum-doublet regimen and one or more additional systemic regimens for NSCLC; measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)[20]; World Health Organization performance status of 0/1; and adequate bone marrow and organ function. Patients were excluded if they had prior exposure to any anti-CTLA-4 or anti-PD-(L)1 antibody, known *EGFR* activating mutations or *ALK* rearrangements, brain metastases (unless asymptomatic, treated, and stable), any unresolved toxicity grade $\geq$2 from previous anticancer therapy, or current or prior use of immunosuppressive medication within 28 days of first study treatment. All patients provided written informed consent for participation in the study.

Study design and treatment

The ARCTIC study included patients from 205 study centers in 26 countries across North America, Latin America, Asia, and Europe between 13 January 2015 and 13 September 2016 (study design described previously[19]; supplementary Figure S1, available at *Annals of Oncology* online). Patients were assigned to study A or study B based on PD-L1 expression [newly acquired or archival tumor samples ($\leq$3 years)], which was centrally assessed using the VENTANA PD-L1 (SP263) immunohistochemistry assay.[21]

In study A, patients with PD-L1 TC $\geq$25% were randomized 1 : 1 to receive durvalumab [10 mg/kg every 2 weeks (q2w) for up to 12 months] or investigator's choice of one of three SoC regimens (erlotinib, gemcitabine, or vinorelbine). In study B, patients with PD-L1 TC <25% were randomized 3 : 2 : 2 : 1 to receive either durvalumab + tremelimumab (durvalumab 20 mg/kg q4w + tremelimumab 1 mg/kg q4w for up to 12 weeks, then durvalumab alone 10 mg/kg q2w for 34 weeks), investigator's choice of SoC (as in study A), durvalumab (as in study A), or tremelimumab (10 mg/kg q4w for 24 weeks then q12w for 24 weeks). The 25% cut-off for PD-L1 expression was based on a phase I/II study that demonstrated higher objective responses in patients with PD-L1 TC $\geq$25% versus <25%.[12] Randomization was stratified according to the planned SoC treatment (erlotinib versus gemcitabine/vinorelbine) and histology (squamous versus non-squamous). Additional treatment details and randomization methods are included in the supplementary Sections S1/S2, available at *Annals of Oncology* online.

The study was carried out in accordance with ethical principles of the Declaration of Helsinki and International Conference on Harmonisation/Good Clinical Practices. All protocols and amendments (detailed in supplementary Section S3, available at *Annals of Oncology* online) were approved by the Institutional Review Board or independent Ethics Committee at all participating centers.

Assessments

Efficacy. The primary end points in both studies were overall survival (OS) and progression-free survival (PFS), per investigator assessment according to RECIST v1.1. The primary comparison for study A was durvalumab versus SoC and for study B, durvalumab + tremelimumab versus SoC.

Key secondary end points for both studies included OS rate at 12 months, proportion of patients alive and progression-free at 6 and 12 months, objective response rate (ORR), and duration of response (DoR), all investigator-assessed according to RECIST v1.1. Time from randomization to second progression (PFS2) was assessed in study B only (additional details in supplementary Section S4, available at *Annals of Oncology* online). The primary comparison for the secondary end points was durvalumab versus SoC for study A and durvalumab + tremelimumab versus SoC for study B. In study B, in a contribution of components (CoC) analysis, durvalumab + tremelimumab was compared with the individual monotherapy components for OS and PFS as well as the other key secondary end points.

Safety. Adverse events (AEs), serious AEs (SAEs), deaths, physical examinations, vital signs and laboratory findings

were evaluated. AEs of special interest (AESIs) included, but were not limited to, events with a potential inflammatory or immune-mediated mechanism that may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy.

Statistical analysis

The study was powered to compare the efficacy of OS and PFS in study B, but not in study A. The planned number of patients to be randomized was approximately 610 [study A, $n = 126$; study B, $n = 480$ (initial plan was to randomize 250 and 600 patients to study A and study B, respectively; however, due to low recruitment, the protocol was amended)]. Thus, formal statistical comparisons were not carried out for study A; study B was powered for statistical analysis [hazard ratio (HR) = 0.63 for both OS and PFS; two-sided 5% alpha was allocated to study B (4% OS; 1% PFS)]. Sample size assumptions for the primary comparison in study B are detailed in supplementary Table S2, available at *Annals of Oncology* online.

All efficacy outcomes were analyzed using the full analysis set (all randomized patients regardless of treatment received) on an intention-to-treat basis. The safety population included all patients who received one or more doses of randomized treatment. Time-to-event end points were analyzed in the full analysis set using a stratified log-rank test [stratification by planned SoC (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other)]. HRs and confidence intervals (CIs) were estimated from a stratified Cox proportional hazards model. ORR was determined using logistic regression analysis. In study B, *post hoc* subgroup analyses according to PD-L1 expression level (<1% and ≥1% to <25%) were also carried out for OS and PFS with HRs and CIs estimated from an unstratified Cox proportional hazards model.

RESULTS

Patients and treatment

Between 13 January 2015 and 13 September 2016, 1293 patients entered the study, of whom 595 (46.0%) were

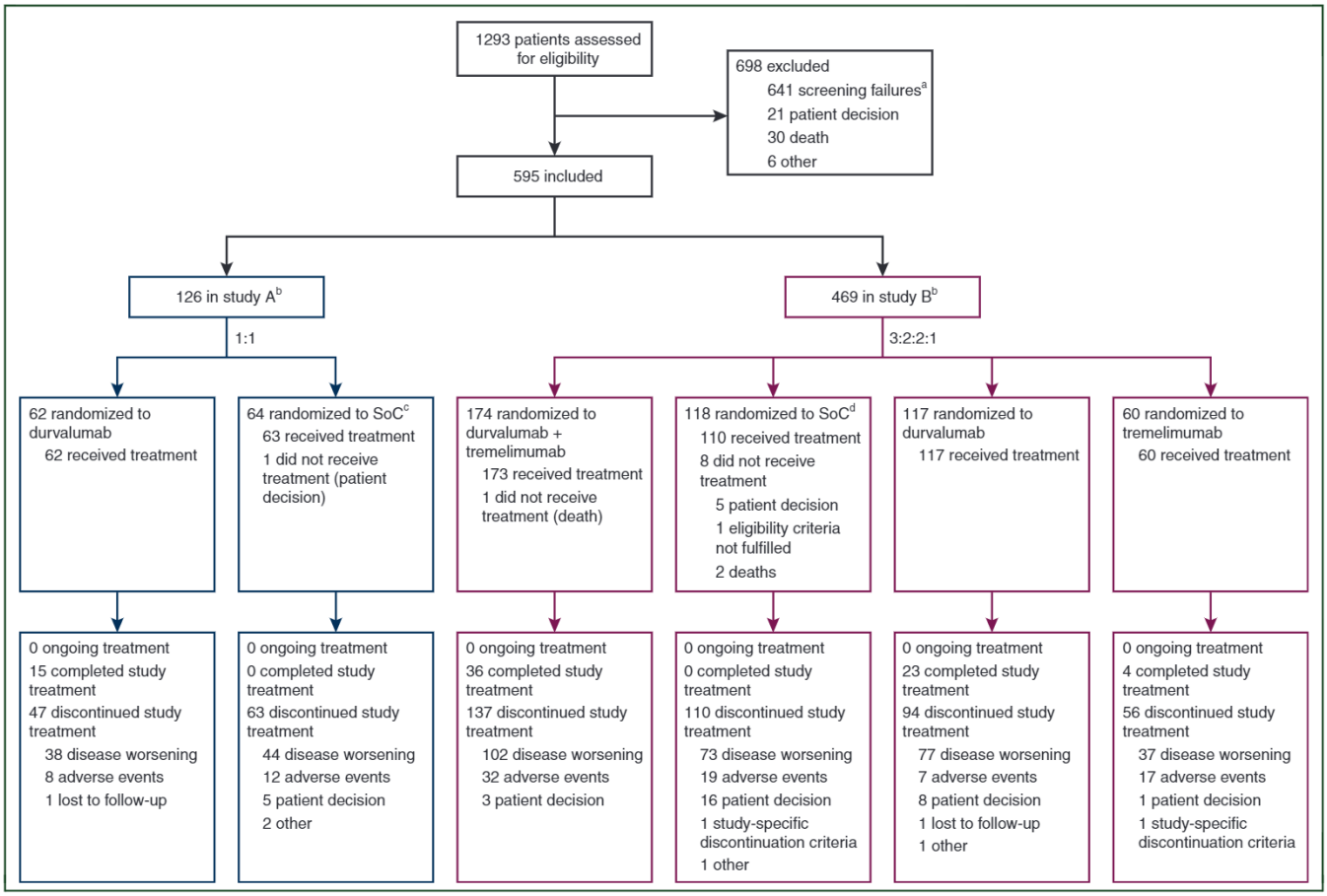

Figure 1. CONSORT diagram.

[a] The high screening failure rate was partly attributable to the operational complexities of the study. In some countries study A and study B were open at different times in different locations; this led to patients who did not meet the PD-L1 requirements for one of the studies being classified as screening failures, while they may have been eligible for the other study.

[b] One patient in study A had PD-L1 TC <25% and one patient in study B had PD-L1 TC ≥25%.

[c] Study A SoC arm: patients were treated with gemcitabine ($n = 22$) and vinorelbine ($n = 21$) or erlotinib ($n = 20$).

[d] Study B SoC arm: patients were treated with gemcitabine ($n = 49$) and vinorelbine ($n = 26$) or erlotinib ($n = 35$).

PD-L1, programmed cell death ligand-1; SoC, standard of care; TC, tumor cell.

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randomized (Figure 1); 126 entered study A and 469 entered study B. The data cut-off date for both studies A and B (9 February 2018) also represents the end of the study in terms of data collection for analyses.

Study A (PD-L1 TC ≥25%). Of 126 randomized patients (durvalumab, 62; SoC, 64), 125 (99.2%) received one or more doses of study drug (Figure 1). Median treatment duration was 21.1 (durvalumab) and 8.0 (SoC) weeks. At data cut-off (9 February 2018), no patients were receiving ongoing study treatment; 15 patients (12.0%) had completed 12 months of study treatment and 110 (88.0%) had discontinued treatment, mainly owing to disease worsening (Figure 1). Of the patients who completed 12 months of treatment, seven patients in the durvalumab monotherapy arm entered retreatment. Post-discontinuation anticancer therapy was received by 30 (48.4%) and 36 (56.3%) patients in the durvalumab and SoC arms, respectively; 8.1% and 42.2% in the corresponding groups received subsequent immunotherapy. Baseline characteristics were well balanced between the treatment arms (Table 1).

Study B (PD-L1 TC <25%). Of the 469 randomized patients (durvalumab + tremelimumab, 174; SoC, 118; durvalumab, 117; tremelimumab, 60), 460 (98.1%) received one or more doses of study drug (Figure 1). Median treatment duration was 18.0, 8.2, 16.0, and 9.9 weeks, respectively. At data cut-off (9 February 2018), no patients were receiving ongoing study treatment; of the 460 patients who had received treatment, 63 (13.7%) had completed 12 months of study treatment and 397 (86.3%) had discontinued treatment, mainly owing to disease worsening (Figure 1). Of the patients who completed 12 months of treatment, 14 patients in the durvalumab + tremelimumab arm and seven patients in the durvalumab monotherapy arm entered retreatment. Post-discontinuation anticancer therapy was received by 60 (34.5%), 51 (43.2%), 50 (42.7%), and 21 (35.0%) patients in the durvalumab + tremelimumab, SoC, durvalumab, and tremelimumab arms, respectively; 5.2%,

Table 1. Baseline characteristics of patients in study A and study B (full analysis set)

	Study A		Study B			
	Durvalumab (n = 62)	SoC (n = 64)	Durvalumab + tremelimumab (n = 174)	SoC (n = 118)	Durvalumab (n = 117)	Tremelimumab (n = 60)
Age, years						
Median (range)	63.5 (35–79)	62.0 (41–81)	62.5 (26–81)	65.0 (42–83)	63.0 (19–83)	63.5 (45–81)
≥65 years, n (%)	28 (45.2)	28 (43.8)	79 (45.4)	61 (51.7)	52 (44.4)	29 (48.3)
Sex, n (%)						
Male	42 (67.7)	48 (75.0)	115 (66.1)	81 (68.6)	73 (62.4)	39 (65.0)
Female	20 (32.3)	16 (25.0)	59 (33.9)	37 (31.4)	44 (37.6)	21 (35.0)
Race, n (%)						
White	40 (64.5)	40 (62.5)	129 (74.1)	74 (62.7)	79 (67.5)	43 (71.7)
Asian	22 (35.5)	23 (35.9)	41 (23.6)	41 (34.7)	34 (29.1)	16 (26.7)
Black or African American	0	1 (1.6)	3 (1.7)	2 (1.7)	2 (1.7)	1 (1.7)
Other	0	0	1 (0.6)	1 (0.8)	1 (0.9)	0
Missing	0	0	0	0	1 (0.9)	0
Disease status, n (%)						
Metastatic	59 (95.2)	60 (93.8)	158 (90.8)	111 (94.1)	111 (94.9)	57 (95.0)
Locally advanced	3 (4.8)	4 (6.3)	16 (9.2)	7 (5.9)	6 (5.1)	3 (5.0)
WHO performance status, n (%)						
0	21 (33.9)	30 (46.9)	58 (33.3)	40 (33.9)	34 (29.1)	19 (31.7)
1	41 (66.1)	34 (51.3)	116 (66.7)	78 (66.1)	82 (70.1)	41 (68.3)
Histology, n (%)						
Squamous	16 (25.8)	16 (25.0)	42 (24.1)	28 (23.7)	29 (24.8)	15 (25.0)
Non-squamous	46 (74.2)	48 (75.0)	132 (75.9)	90 (76.3)	88 (75.2)	45 (75.0)
SoC treatment at randomization, n (%)						
Gemcitabine/vinorelbine	41 (66.1)	43 (67.2)	120 (69.0)	82 (69.5)	81 (69.2)	41 (68.3)
Erlotinib	21 (33.9)	21 (32.8)	54 (31.0)	36 (30.5)	36 (30.8)	19 (31.7)
Smoking status, n (%)						
Current smoker	5 (8.1)	10 (15.6)	30 (17.2)	22 (18.6)	22 (18.8)	8 (13.3)
Former smoker	47 (75.8)	45 (70.3)	109 (62.6)	74 (62.7)	67 (57.3)	38 (63.3)
Never smoked	10 (16.1)	9 (14.1)	35 (20.1)	21 (17.8)	28 (23.9)	14 (23.3)
Number of prior anticancer therapies, median (range)	2.0 (2–9)	3.0 (2–7)	3.0 (2–10)	3.0 (2–12)	3.0 (2–9)	2.0 (2–8)
Patients with metastatic disease, n (%)						
Total patients	59 (95.2)	60 (93.8)	158 (90.8)	111 (94.1)	111 (94.9)	57 (95.0)
Patients with brain/CNS metastases[a]	6 (10.2)	7 (11.7)	16 (10.1)	14 (12.6)	13 (11.7)	9 (15.8)
Patients with liver metastases	23 (39.0)	21 (35.0)	32 (20.3)	26 (23.4)	26 (23.4)	11 (19.3)
Best response to prior treatment, n (%)						
CR/PR/SD	30 (48.4)	22 (34.4)	73 (42.0)	54 (45.8)	56 (47.9)	29 (48.3)
PD	31 (50.0)	40 (62.5)	94 (54.0)	57 (48.3)	56 (47.9)	30 (50.0)

CNS, central nervous system; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SoC, standard of care; WHO, World Health Organization.
[a] Per protocol, patients with brain metastases or spinal cord compression were included in the trial only if they were asymptomatic, treated, and stable off steroids and anticonvulsants for at least 1 month before entry into the study.

27.1%, 11.1%, and 13.3% of patients in the corresponding groups received subsequent immunotherapy. Again, baseline characteristics were well balanced between groups (Table 1).

Efficacy

Study A (PD-L1 TC ≥25%). Median duration of OS follow-up was 9.1 (range, 0.1−33.0) months. The OS HR (95% CI) for durvalumab versus SoC was 0.63 (0.42−0.93) (Figure 2A); median OS (mOS) was 11.7 and 6.8 months, respectively (Table 2). The PFS HR (95% CI) for durvalumab versus SoC was 0.71 (0.49−1.04) (Figure 2B); median PFS (mPFS) was 3.8 versus 2.2 months, respectively (Table 2). A total of 50 (80.6%) and 41 (64.1%) patients in the durvalumab and SoC arms, respectively, had objective disease progression per RECIST v1.1. Death in the absence of radiologic progression was reported in 8 (12.9%) and 17 (26.6%) patients in the durvalumab and SoC arms, respectively. The 12-month OS rate (49.3% versus 31.3%), 6- and 12-month PFS rates (35.5% versus 24.1% and 19.4% versus 9.9%), and response outcomes (ORR, 35.5% versus 12.5%; DoR, 9.5 versus 4.8 months; patients remaining in response at 12 months, 40.9% versus 18.8%) all favored durvalumab over SoC (Table 2).

Study B (PD-L1 TC <25%). Median duration of OS follow-up was 9.1 (range, 0−32.8) months. Durvalumab + tremelimumab did not statistically significantly improve OS compared with SoC [HR 0.80 (95% CI, 0.61−1.05); $P = 0.109$; Figure 3A]; mOS (95% CI) was 11.5 (8.7−14.1) and 8.7 (6.5−11.7) months, respectively (Table 3). OS in prespecified subgroups was generally consistent with OS in the overall population (supplementary Figure S2, available at *Annals of Oncology* online). Durvalumab + tremelimumab did not statistically significantly improve PFS compared with SoC [mPFS 3.5 months for both; HR 0.77 (95% CI, 0.59−1.01); $P = 0.056$] (Figure 3B). A total of 114 (65.5%) and 67 (56.8%) patients in the durvalumab + tremelimumab and SoC arms, respectively, had objective disease progression. Death in the absence of radiologic progression occurred in 32 (18.4%) and 25 (21.2%) patients in the durvalumab + tremelimumab and SoC arms, respectively.

The 12-month OS rates, 6- and 12-month PFS rates, and response outcomes (ORR, DoR, patients remaining in response at 12 months) are detailed in Table 3. mPFS2 was 9.1 (durvalumab + tremelimumab) and 6.7 months (SoC); HR 0.65 (95% CI, 0.49−0.85) (Table 3 and supplementary Figure S3, available at *Annals of Oncology* online).

Compared with the individual monotherapy components, outcomes of the CoC analysis suggested that combination therapy (durvalumab + tremelimumab) did not provide additional clinical benefit in terms of OS or PFS (Table 3). Additional results from the CoC analysis are presented in Figure 3C and D, and Table 3.

In an exploratory, *post hoc* analysis in the PD-L1 TC <1% subgroup, HRs (95% CI) for durvalumab + tremelimumab versus SoC were 0.59 (0.40−0.89) for OS, and 0.55 (0.37−0.83) for PFS. In the same subgroup, the HRs (95% CI) for durvalumab versus SoC were 0.80 (0.53−1.22) and 0.76 (0.51−1.15), respectively. In the PD-L1 TC ≥1% to <25% subgroup, the HRs (95% CI) for OS and PFS with durvalumab ± tremelimumab versus SoC were 1.00 (95% CI, 0.69−1.47) and 0.95 (0.66−1.35), respectively (supplementary Table S3, available at *Annals of Oncology* online).

Safety

Study A (PD-L1 TC ≥25%). A safety summary for study A is provided in Table 4. The number of patients experiencing an AE was 96.8% and 100% in the durvalumab and SoC arms, respectively. In the durvalumab and SoC arms, any-grade treatment-related AEs (TRAEs) occurred in 56.5% and 87.3% of patients; grade 3/4 TRAEs in 9.7% and 44.4% of patients (no grade 4 TRAEs in the durvalumab arm); treatment-related SAEs in 11.3% and 11.1% of patients; and discontinuations due to TRAEs in 6.5% and 6.3% of patients, respectively. No treatment-related deaths occurred in either treatment arm. TRAEs by grade and type of events are

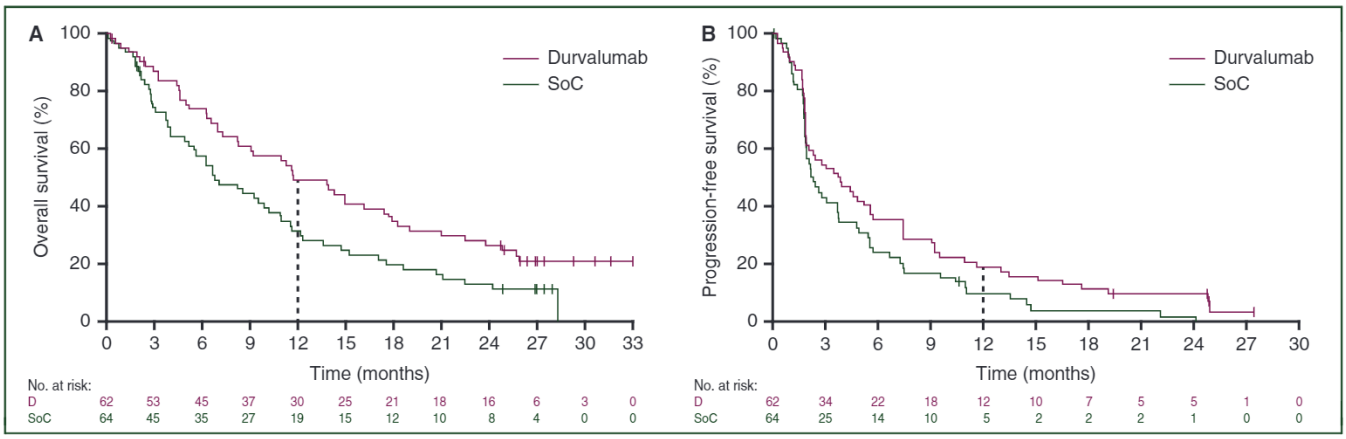

Figure 2. Study A (PD-L1 TC ≥25%) primary efficacy end points.
Overall survival (A) and progression-free survival (B) in patients treated with durvalumab versus SoC in the full analysis set.
Data cut-off date: 9 February 2018; Study A was not statistically powered for hypothesis testing.
D, durvalumab; PD-L1, programmed cell death ligand-1; SoC, standard of care; TC, tumor cell.

Table 2. Summary of efficacy outcomes in study A (full analysis set)

Assessments	Durvalumab (n = 62)	SoC (n = 64)
Overall survival		
Events, n (%)	48 (77.4)	55 (85.9)
Median overall survival (95% CI), months[a]	11.7 (8.2—17.4)	6.8 (4.9—10.2)
HR versus SoC (95% CI)[b]	0.63 (0.42—0.93)	—
Survival rate at 12 months (95% CI), %[a]	49.3 (36.3—61.0)	31.3 (20.2—43.0)
Progression-free survival		
Events, n (%)[c]	58 (93.5)	58 (90.6)
Median progression-free survival (95% CI), months[a]	3.8 (1.9—5.6)	2.2 (1.9—3.7)
HR versus SoC (95% CI)[b]	0.71 (0.49—1.04)	—
Progression-free survival rate at 6 months (95% CI), %[c]	35.5 (23.9—47.3)	24.1 (14.1—35.6)
Progression-free survival rate at 12 months (95% CI), %[c]	19.4 (10.7—30.0)	9.9 (3.8—19.3)
Objective response rate		
n (%)[c,d]	22 (35.5)	8 (12.5)
OR versus SoC (95% CI)[e]	3.87 (1.61—10.10)	—
Duration of response[a,f]		
Median (Q1, Q3), months	9.5 (3.0, 17.8)	4.8 (1.9, 7.6)
Patients remaining in response at 12 months, %[a]	40.9	18.8

CI, confidence interval; HR, hazard ratio; OR, odds ratio; SoC, standard of care.
[a] Calculated using the Kaplan—Meier technique.
[b] Estimated from a stratified Cox proportional hazards model with the Breslow method to control for ties and stratification factors [SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus non-squamous) in the strata statement; CI calculated using a profile likelihood approach].
[c] Progression and objective response rate determined by the site Investigator according to RECIST v1.1.
[d] Includes unconfirmed responses.
[e] Carried out using logistic regression adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus non-squamous); CI calculated using a profile likelihood approach.
[f] Time from the first documentation of complete response/partial response until the date of progression, death, or the last evaluable RECIST assessment for patients who have not progressed or for patients who progressed or died after two or more missed visits.

summarized in supplementary Table S4, available at *Annals of Oncology* online. All-cause AESIs grouped by grade are summarized in supplementary Table S5, available at *Annals of Oncology* online. Treatment-related AESIs were reported in 38.7% (durvalumab) and 38.1% (SoC) of patients.

Study B (PD-L1 TC <25%). Safety events during study B are summarized in Table 4. In the durvalumab + tremelimumab, SoC, durvalumab, and tremelimumab treatment arms, any AE was reported in 92.5%, 95.5%, 93.2%, and 85.0% of patients, respectively; any-grade TRAEs in 62.4%, 80.9%, 62.4%, and 63.3% of patients, respectively; grade 3/4 TRAEs in 22.0%, 36.4%, 12.0%, and 23.3% of patients, respectively; treatment-related SAEs in 16.2%, 7.3%, 6.8%, and 20.0% of patients, respectively; and discontinuations due to TRAEs in 13.9%, 8.2%, 1.7%, and 20.0% of patients, respectively. There were no treatment-related deaths in the durvalumab + tremelimumab or SoC arms, but one death each was reported in the durvalumab (0.9%; colitis) and tremelimumab (1.7%; respiratory failure) arms.

TRAEs by grade and type of events are summarized in supplementary Table S6, available at *Annals of Oncology* online. All-cause AESIs grouped by grades are summarized in supplementary Table S7, available at *Annals of Oncology* online. Treatment-related AESIs were reported in 45.7%, 35.5%, 35.0%, and 58.3% of patients in the durvalumab + tremelimumab, SoC, durvalumab, and tremelimumab arms, respectively.

DISCUSSION

In the ARCTIC study, durvalumab, with or without tremelimumab, showed clinical activity in heavily pretreated patients with mNSCLC and had a manageable safety profile consistent with known safety profiles for these treatments. In study A (PD-L1 TC ≥25%), improvements in OS were observed for durvalumab versus SoC (HR 0.63; mOS, 11.7 versus 6.8 months). These findings confirm and further support results seen with durvalumab monotherapy in patients with mNSCLC.[3,13] In study B (PD-L1 TC <25%), while statistical significance was not achieved, durvalumab + tremelimumab resulted in an OS HR versus SoC of 0.80 (P = 0.109), with mOS of 11.5 and 8.7 months, respectively. These results are consistent with previous reports for combination therapies targeting the PD-1/PD-L1 and CTLA-4 pathways.[4,15,17,22] Given the poor prognosis for heavily pretreated patients with mNSCLC and limited data in the third-line or higher setting, these results expand the body of evidence for advanced treatment lines and the predictive role of tumor PD-L1 expression in patients with mNSCLC.

Although study A was not powered to test for statistical significance, the analysis showed an overall clinically meaningful efficacy benefit with durvalumab monotherapy versus SoC, as reflected by the OS HR [0.63 (95% CI, 0.42—0.93)], the PFS HR [0.71 (95% CI, 0.49—1.04)], the ORR (35.5% versus 12.5%), and a longer DoR. These results were consistent with those from previous studies with durvalumab and other anti-PD-1/PD-L1 immunotherapies in heavily pretreated patients with mNSCLC.[3] In the phase II ATLANTIC study (third-line or higher), *EGFR*$^{-}$/*ALK*$^{-}$ patients with PD-L1 TC ≥25% who received durvalumab showed a mOS of 10.9 months, mPFS of 3.3 months, and ORR of 16.4%.[3] Similarly, in a phase I/II study of durvalumab in patients with PD-L1 TC ≥25% (third-line or higher cohort), a mOS of 13.4 months, a mPFS of 2.8 months, and an ORR of 23.2% were reported.[23] In the phase II CheckMate 063 study (third-line or higher), patients who received nivolumab had a mOS of 8.2 months, a mPFS of 1.9 months, and an ORR of 14.5%.[24] In the second-line or higher setting, mOS with nivolumab, pembrolizumab, and atezolizumab ranges from 9.2 to 13.8 months.[5,24—27]

Higher PD-L1 TC expression levels have been associated with better treatment outcomes with anti-PD-1/PD-L1 monotherapies.[3,9—11,28,29] Durvalumab + tremelimumab was hypothesized to result in additive or synergistic antitumor activity, which may have provided clinical benefit to patients with low/negative PD-L1 TC levels. In study B (PD-L1 TC <25%), the primary efficacy analysis showed higher OS HR [0.80 (95% CI, 0.61—1.05)] and PFS HR [0.77 (95% CI, 0.59—1.01)] with durvalumab + tremelimumab versus SoC, although statistical significance was not

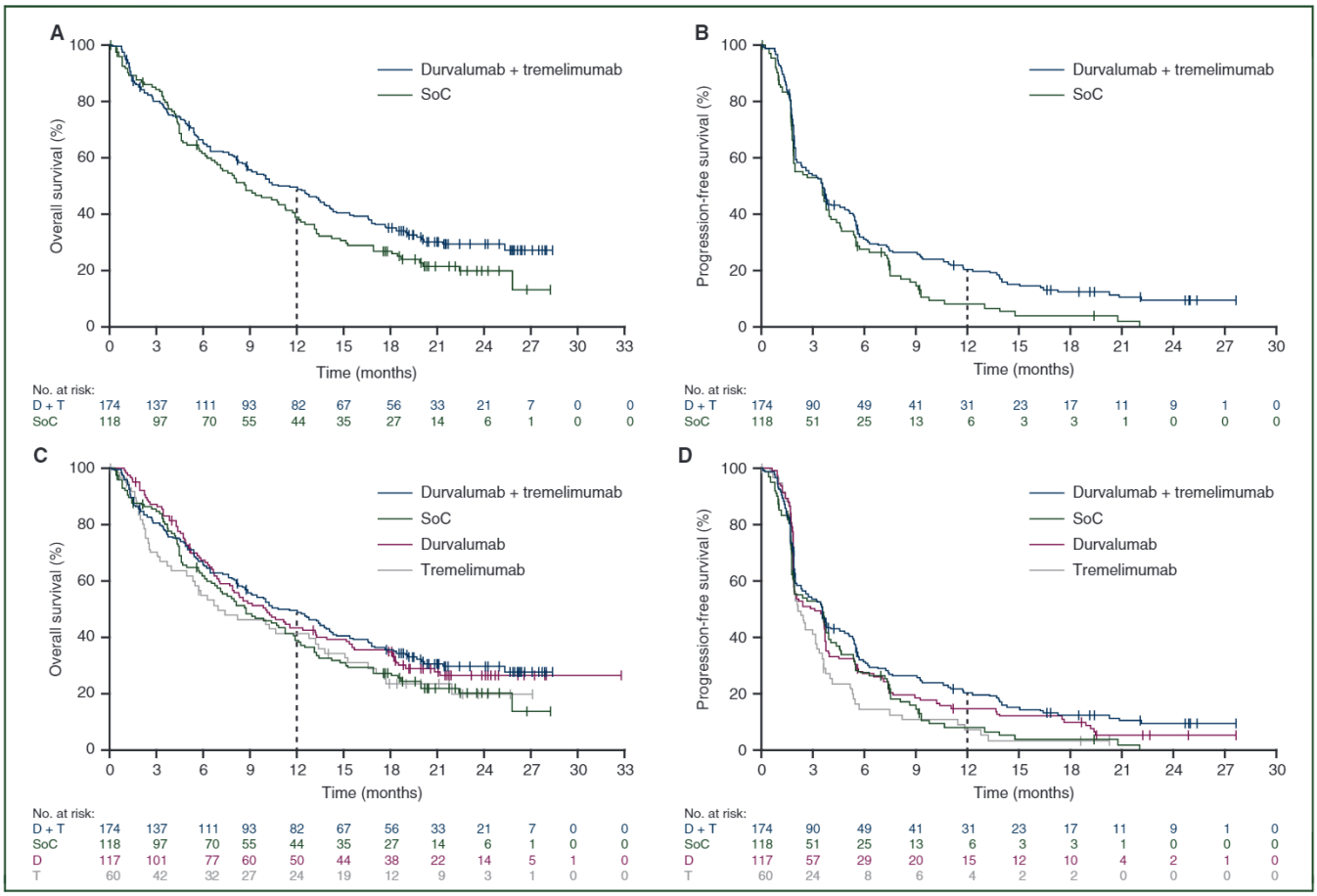

Figure 3. Study B (PD-L1 <25%) efficacy endpoints.
Overall survival (A) and progression-free survival (B) in patients treated with durvalumab + tremelimumab versus SoC (primary end point). Overall survival (C) and progression-free survival (D) for contribution of components analysis.
Data cut-off date: 9 February 2018.
D, durvalumab; PD-L1, programmed cell death ligand-1; SoC, standard of care; T, tremelimumab; TC, tumor cell.

achieved. The clinical benefit with durvalumab + tremelimumab was also reflected in the higher ORR, sustained clinical activity, and longer time to second progression versus SoC [mPFS2, 9.1 versus 6.7 months; HR 0.65 (95% CI, 0.49—0.85)]. Overall, these results are consistent with previous data for PD-L1/PD-1 and CTLA-4 combination therapies.[4,14,15,22]

In the secondary CoC analysis in study B, the efficacy of durvalumab + tremelimumab was comparable with that of durvalumab monotherapy, suggesting a limited contribution of tremelimumab to the combination regimen in this patient population. However, the improvement in OS with durvalumab versus SoC suggests that durvalumab monotherapy may have clinical activity in patients with PD-L1 TC <25%.

Of interest, exploratory analyses in the PD-L1 TC <1% subgroup revealed a favorable effect of durvalumab + tremelimumab versus SoC, in terms of OS (HR 0.59) and PFS (HR 0.55). This effect appeared to be more marked than with durvalumab monotherapy versus SoC (HRs for OS and PFS, 0.80 and 0.76, respectively). However, given the small sample sizes in the subgroups, these results should be interpreted with caution. Similar observations have also been made in the MYSTIC and CheckMate 227 studies. In the phase III MYSTIC study in patients with mNSCLC, first-line durvalumab + tremelimumab versus SoC resulted in an OS HR of 0.73 in the PD-L1 TC <1% subset, whereas the effects of durvalumab monotherapy versus SoC were less distinct.[17] In the CheckMate 227 study, OS benefit with nivolumab + ipilimumab versus chemotherapy was numerically greater in patients with PD-L1 TC <1% versus those with PD-L1 TC ≥1% (OS HR 0.62 versus 0.79).[22] Further investigation of durvalumab + tremelimumab in specific subsets of patients is warranted to identify and define the patient population specifically benefiting from this combination. Tumor mutational burden (TMB) may represent one potential strategy and has been shown to be predictive of survival benefits with immunotherapy.[16,17,30,31] Exploratory analyses from the MYSTIC trial suggest that blood TMB (bTMB) is predictive of OS and PFS for patients receiving durvalumab + tremelimumab versus chemotherapy.[17] Further investigation of bTMB as a predictive biomarker for immunotherapy in NSCLC is warranted.

The overall safety profiles of study A and study B were consistent with the known safety profiles of durvalumab + tremelimumab, durvalumab monotherapy, and tremelimumab monotherapy, and no new safety signals were identified.[3,4,18,23,32,33]

Table 3. Summary of efficacy outcomes in study B (full analysis set)

Assessments	Durvalumab + tremelimumab (*n* = 174)	SoC (*n* = 118)	Durvalumab (*n* = 117)	Tremelimumab (*n* = 60)
Overall survival				
Events, *n* (%)	118 (67.8)	90 (76.3)	83 (70.9)	46 (76.7)
Median overall survival (95% CI), months[a]	11.5 (8.7–14.1)	8.7 (6.5–11.7)	10.0 (7.1–13.2)	6.9 (3.9–13.2)
HR versus SoC (95% CI);[b] *P* value[c]	0.80 (0.61–1.05); 0.109	—	0.80 (0.59–1.08)	1.02 (0.71–1.46)
HR versus durvalumab (95% CI)[b]	0.98 (0.74–1.30)	—	—	—
HR versus tremelimumab (95% CI)[b]	0.78 (0.56–1.11)	—	—	—
Survival rate at 12 months (95% CI), %[a]	49.5 (41.7–56.7)	38.8 (29.9–47.7)	43.6 (34.4–52.4)	41.2 (28.7–53.3)
Progression-free survival				
Events, *n* (%)[d]	146 (83.9)	92 (78.0)	105 (89.7)	56 (93.3)
Median progression-free survival (95% CI), months[a]	3.5 (2.3–4.6)	3.5 (1.9–3.9)	3.1 (1.9–3.7)	2.1 (1.8–3.2)
HR versus SoC (95% CI);[b] *P* value[c]	0.77 (0.59–1.01); 0.056	—	0.87 (0.65–1.16)	1.25 (0.88–1.77)
HR versus durvalumab (95% CI)[b]	0.87 (0.68–1.12)	—	—	—
HR versus tremelimumab (95% CI)[b]	0.67 (0.49–0.92)	—	—	—
Progression-free survival rate at 6 months (95% CI), %[a]	31.5 (24.6–38.7)	27.6 (19.0–36.7)	27.2 (19.4–35.6)	14.5 (6.9–24.9)
Progression-free survival rate at 12 months (95% CI), %[a]	20.6 (14.7–27.1)	8.0 (3.4–15.2)	15.0 (9.1–22.3)	7.3 (2.4–16.0)
Progression-free survival 2				
Median time to second progression (95% CI), months[a]	9.1 (6.6–12.3)	6.7 (4.7–8.9)	8.0 (6.3–10.0)	5.7 (3.2–10.0)
HR versus SoC (95% CI)[b]	0.65 (0.49–0.85)	—	—	—
Objective response rate				
n (%)[d,e]	26 (14.9)	8 (6.8)	18 (15.4)	4 (6.7)
OR versus SoC (95% CI)[e]	2.43 (1.10–5.94)	—	2.49 (1.07–6.33)	0.98 (0.25–3.28)
Duration of response				
Median (Q1, Q3), months[a,f]	12.2 (6.5, NR)	10.8 (5.6, 12.2)	10.0 (4.0, NR)	4.7 (2.9, NR)
Patients remaining in response at 12 months, %[a]	50.0	38.1	47.7	NR

CI, confidence interval; HR, hazard ratio; NR, not reached; OR, odds ratio; SoC, standard of care.
[a] Calculated using the Kaplan–Meier technique.
[b] Estimated from a stratified Cox proportional hazards model with the Breslow method to control for ties and stratification factors [SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus non-squamous) in the strata statement; CI calculated using a profile likelihood approach].
[c] Carried out using a stratified log-rank test adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus non-squamous) with ties handled by the Breslow method.
[d] Progression and objective response rate determined by the site Investigator according to RECIST v1.1.
[e] Includes unconfirmed responses.
[f] Time from the first documentation of complete response/partial response until the date of progression, death, or the last evaluable RECIST assessment for patients who have not progressed or for patients who progressed or died after two or more missed visits.

Limitations of our study include the recruitment challenges experienced in both study A and study B arising from the changing treatment landscape (including approval of anti-PD-1/PD-L1 treatments across treatment lines and extensive clinical trial programs) that made it difficult to recruit immunotherapy-naïve patients in the third-line or higher setting.[34] When ARCTIC was designed in 2014, there were no immunotherapy agents approved in any treatment line in mNSCLC; midway through the study enrolment in 2015–2016, anti-PD-1/PD-L1 products were being approved in the second-line or higher setting, thus limiting the accrual of patients, especially those with high PD-L1 into study A. Therefore, the planned patient number was reduced and fewer patients than planned were enrolled

Table 4. Safety summary—study A and study B

n (%)	Study A		Study B			
	Durvalumab (*n* = 62)	SoC (*n* = 63)	Durvalumab + tremelimumab (*n* = 173)	SoC (*n* = 110)	Durvalumab (*n* = 117)	Tremelimumab (*n* = 60)
Any AE	60 (96.8)	63 (100.0)	160 (92.5)	105 (95.5)	109 (93.2)	51 (85.0)
Any grade 3/4 AE	25 (40.3)	41 (65.1)	74 (42.8)	57 (51.8)	43 (36.8)	25 (41.7)
Any deaths	6 (9.7)	2 (3.2)	13 (7.5)	6 (5.5)	7 (6.0)	3 (5.0)
Any SAE	23 (37.1)	16 (25.4)	65 (37.6)	28 (25.5)	36 (30.8)	23 (38.3)
Any AE leading to discontinuation	8 (12.9)	12 (19.0)	32 (18.5)	19 (17.3)	7 (6.0)	17 (28.3)
Any treatment-related AE[a]	35 (56.5)	55 (87.3)	108 (62.4)	89 (80.9)	73 (62.4)	38 (63.3)
Any treatment-related grade 3/4 AE[a]	6 (9.7)	28 (44.4)	38 (22.0)	40 (36.4)	14 (12.0)	14 (23.3)
Any treatment-related death[a]	0	0	0	0	1 (0.9)	1 (1.7)
Any treatment-related SAE[a]	7 (11.3)	7 (11.1)	28 (16.2)	8 (7.3)	8 (6.8)	12 (20.0)
Any treatment-related AE leading to discontinuation[a]	4 (6.5)	4 (6.3)	24 (13.9)	9 (8.2)	2 (1.7)	12 (20.0)

AEs were summarized by maximum reported grade. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
AE, adverse event; SAE, serious adverse event; SoC, standard of care.
[a] Investigator assessed.

[study A, $N = 126$; study B, $N = 480$ (initial plan was to randomize 250 and 600 patients, respectively)]. In both study A and study B, the proportion of patients who received subsequent immunotherapy was markedly higher in the SoC arms (42.2% and 27.1%, respectively) than in the durvalumab and tremelimumab monotherapy and combination therapy arms (study A, 8.1%; study B, 5.2% to 13.3%), which may have confounded OS results.

In conclusion, in heavily pretreated patients with mNSCLC, a clinically meaningful improvement in OS was observed with durvalumab monotherapy versus SoC in patients with PD-L1 TC $\geq$25%. Furthermore, durvalumab monotherapy showed some activity in patients with PD-L1 TC $<$25% versus SoC. While statistical significance was not achieved, numerical improvements in OS and PFS were observed with durvalumab + tremelimumab versus SOC in patients with PD-L1 TC $<$25%. For all treatment arms, the safety profiles were consistent with known safety profiles for these treatment regimens.

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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