



Durvalumab With or Without Tremelimumab in Combination With Chemotherapy in First-Line Metastatic NSCLC: Five-Year Overall Survival Outcomes From the Phase 3 POSEIDON Trial

Solange Peters, MD, PhD,^{a,*} Byoung Chul Cho, MD, PhD,^b Alexander V. Luft, MD,^c Jorge Alatorre-Alexander, MD,^d Sarayut Lucien Geater, MD, PhD,^e Konstantin Laktionov, MD,^f Dmytro Trukhin, MD,^g Sang-We Kim, MD, PhD,^h Grygorii M. Ursol, MD,ⁱ Maen Hussein, MD,^j Farah Louise Lim, M.B.B.S., MRCP,^k Cheng-Ta Yang, MD,^l Luiz Henrique Araujo, MD, PhD,^m Haruhiro Saito, MD, PhD,ⁿ Niels Reinmuth, MD, PhD,^o Caitlin Lowery, PhD,^p Helen Mann, MSc,^q Ross Stewart, PhD,^q Haiyi Jiang, MD,^p Edward B. Garon, MD,^r Tony Mok, MD,^s Melissa L. Johnson, MD^t

^aCentre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland

^bYonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

^cLeningrad Regional Clinical Hospital, St Petersburg, Russia

^dHealth Pharma Professional Research, Mexico City, Mexico

^ePrince of Songkla University, Songkhla, Thailand

^fFederal State Budgetary Institution “N.N. Blokhin National Medical Research Center of Oncology” of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia

^gOdessa National Medical University, Odessa, Ukraine

^hAsan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

ⁱAcinus, Kropyvnytskyi, Ukraine

^jFlorida Cancer Specialists - Sarah Cannon Research Institute, Leesburg, Florida

^kQueen Mary University of London, London, United Kingdom

^lChang Gung Memorial Hospital, Taoyuan City, Taiwan

^mInstituto Nacional de Cancer-INCA, Rio de Janeiro, Brazil

ⁿKanagawa Cancer Center, Yokohama, Japan

^oAsklepios Lung Clinic, member of the German Centre for Lung Research (DZL), Munich-Gauting, Germany

^pAstraZeneca, Gaithersburg, Maryland

^qAstraZeneca, Cambridge, United Kingdom

^rDavid Geffen School of Medicine at UCLA, Los Angeles, California

^sChinese University of Hong Kong, Hong Kong, People's Republic of China

^tSarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, Tennessee

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ABSTRACT

Introduction: The primary analysis (median follow-up 34.9 mo across all arms) of the phase 3 POSEIDON study revealed a statistically significant overall survival (OS) improvement with first-line tremelimumab plus durvalumab and chemotherapy (T+D+CT) versus CT in patients with *EGFR* and *ALK* wild-type metastatic NSCLC (mNSCLC). D+CT had a trend for OS improvement versus CT that did not reach statistical significance. This article reports prespecified OS analyses after long-term follow-up (median >5 y).

Methods: A total of 1013 patients were randomized (1:1:1) to T+D+CT, D+CT, or CT, stratified by tumor cell

*Corresponding author.

Address for correspondence: Solange Peters, MD, PhD, Centre Hospitalier Universitaire Vaudois, Lausanne University, Bugnon 46, Lausanne 1011, Switzerland. E-mail: solange.peters@chuv.ch

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programmed cell death ligand-1 (PD-L1) expression ($\geq 50\%$ versus $< 50\%$), disease stage (IVA versus IVB), and tumor histologic type (squamous versus nonsquamous). Serious adverse events were collected during follow-up.

Results: After a median follow-up of 63.4 months across all arms, T+D+CT had sustained OS benefit versus CT (hazard ratio [HR] = 0.76, 95% confidence interval [CI]: 0.64–0.89; 5-y OS: 15.7% versus 6.8%). OS improvement with D+CT versus CT (HR = 0.84, 95% CI: 0.72–1.00; 5-y OS: 13.0%) was consistent with the primary analysis. OS benefit with T+D+CT versus CT remained more pronounced in nonsquamous (HR = 0.69, 95% CI: 0.56–0.85) versus squamous (HR = 0.85, 95% CI: 0.65–1.10) mNSCLC. OS benefit with T+D+CT versus CT was still evident regardless of PD-L1 expression, including patients with PD-L1 tumor cell less than 1%, and remained evident in *STK11*-mutant (nonsquamous), *KEAP1*-mutant, and *KRAS*-mutant (nonsquamous) mNSCLC. No new safety signals were identified.

Conclusions: After a median follow-up of more than 5 years, T+D+CT had durable long-term OS benefit versus CT, supporting its use as first-line treatment in mNSCLC, including in patient subgroups with harder-to-treat disease.

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Keywords: Tremelimumab; Durvalumab; POSEIDON; Metastatic NSCLC; Five-year overall survival

Introduction

Inhibitors targeting the programmed cell death protein 1 (PD-1) or programmed cell death ligand-1 (PD-L1) pathway, alone or in combination with CTLA-4 inhibitors, and with or without chemotherapy, improve survival outcomes compared with chemotherapy alone as first-line treatment for metastatic NSCLC (mNSCLC) lacking *EGFR* or *ALK* alterations.^{1–7} These immunotherapy-based regimens are now guideline-recommended standards of care.^{8,9} Nevertheless, patients do not respond equally to this treatment strategy. Although an overall survival (OS) benefit versus chemotherapy is found, estimated 5-year OS rates range from only 10.0% to 31.9% across various mNSCLC populations defined by one or both of PD-L1 expression level and tumor histologic type,^{10–14} highlighting the need to identify patients most likely to benefit from treatment and to optimize regimens for subgroups with harder-to-treat disease.

In the global, randomized, phase 3 POSEIDON study (NCT03164616), a limited course of tremelimumab plus durvalumab and chemotherapy (T+D+CT) significantly

improved OS (hazard ratio [HR] = 0.77, 95% confidence interval [CI]: 0.65–0.92, $p = 0.0030$; median follow-up 34.9 mo) and progression-free survival (PFS; HR = 0.72, 95% CI: 0.60–0.86, $p = 0.0003$; median follow-up 10.3 mo) compared with CT in patients with *EGFR/ALK* wild-type mNSCLC.³ On the basis of these findings, T+D+CT was approved for first-line treatment of mNSCLC.⁸ D+CT significantly improved PFS (HR = 0.74, 95% CI: 0.62–0.89, $p = 0.0009$), with a trend for improved OS that did not reach statistical significance (HR = 0.86, 95% CI: 0.72–1.02, $p = 0.0758$).³

Prespecified subgroup analyses from POSEIDON indicated that T+D+CT had more pronounced OS improvement versus CT in patients with nonsquamous compared with squamous tumor histologic type and improved OS in both patients with PD-L1 tumor cell (TC) expression more than or equal to 1% and those with PD-L1 TC less than 1%,³ the latter a subgroup characterized by relative resistance to anti-PD-1/PD-L1 treatment.^{15,16} Exploratory analyses have suggested that tremelimumab is key to OS benefit in patients with tumors harboring mutations in either *STK11* (*STK11m*) or *KEAP1* (*KEAP1m*) or in *KRAS* (*KRASm*).^{17,18} *STK11m* and *KEAP1m* tumors are associated with poor prognosis in NSCLC and the absence of meaningful benefit after PD-1/PD-L1 inhibitor therapy,^{19–24} being immunologically “cold” and lacking T-cell infiltration. The *KRASm* subgroup is heterogeneous, with certain mutation types (e.g., *KRAS*^{G12C})²⁵ being responsive to immunotherapy, whereas others (e.g., *KRAS*^{G12D})²⁵ and the presence of co-mutations such as *STK11m* and *KEAP1m* preclude meaningful impact of anti-PD-1/PD-L1 therapy.^{22,26}

We report updated OS analyses from POSEIDON after a median follow-up of more than 5 years, including updated subgroup analyses of OS by tumor histologic type, PD-L1 expression, and *STK11*, *KEAP1*, and *KRAS* mutation status.

Materials and Methods

Study Design and Patients

The POSEIDON study design, patient eligibility, and treatment have been described previously.³ In brief, eligible patients were aged above or equal to 18 years and had previously untreated stage IV NSCLC without *EGFR/ALK* alterations, Eastern Cooperative Oncology Group performance status 0 or 1, and measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1. Patients were randomized (1:1:1) to receive: tremelimumab 75 mg plus durvalumab 1500 mg and chemotherapy every 3 weeks for up to four cycles, followed by durvalumab 1500 mg once every 4 weeks, with one additional (fifth) tremelimumab dose after chemotherapy at week 16 (T+D+CT); durvalumab 1500 mg

plus chemotherapy every 3 weeks for up to four cycles, followed by durvalumab 1500 mg every 4 weeks (D+CT); or chemotherapy every 3 weeks for up to six cycles (CT). Chemotherapy in all arms comprised a platinum-doublet; patients with nonsquamous tumor histologic type who received pemetrexed-platinum could receive pemetrexed maintenance therapy if eligible. Randomization was stratified by PD-L1 expression (TC $\geq 50\%$ versus $< 50\%$), disease stage (IVA versus IVB; International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology version 8),²⁷ and tumor histologic type (squamous versus nonsquamous). Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal, or until maximum duration had been reached (CT arm only). POSEIDON was run in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol and amendments were approved by the relevant ethics committees and regulatory authorities. All patients gave written informed consent.

End Points and Assessments

The primary end points were PFS and OS with D+CT versus CT. If either primary end point were positive (as PFS was), the alpha was recycled to sequentially evaluate key secondary end points of PFS and OS with T+D+CT versus CT using a gatekeeping approach. These results have been reported previously.³ Long-term follow-up analyses of OS were prespecified; serious adverse events (SAEs), including adverse event (AEs) leading to death, were collected during long-term follow-up, but no other safety data were collected after the final analysis for OS superiority. Post-discontinuation anticancer treatment received was also collected. This analysis evaluated OS, SAEs, and AEs leading to death through a cutoff of August 24, 2023, plus OS in subgroups defined by prespecified baseline demographic and disease characteristics, including PD-L1 status, and in subgroups defined according to *STK11*, *KEAP1*, and *KRAS* mutation status.

For assessment of PD-L1 and mutation status, all patients were required to provide formalin-fixed, paraffin-embedded tumor tissue samples (tissue block or 20 unstained sections) collected within 3 months before enrollment. Plasma samples for genome profiling were obtained before the start of treatment. As PD-L1 data were required for stratification, tissue samples were assessed centrally before randomization for PD-L1 TC expression level using the VENTANA PD-L1 (SP263) immunohistochemistry assay (VENTANA Medical Systems, Tucson, AZ), using positivity cutoffs of 1% and 50%. *STK11*, *KEAP1*, and *KRAS* mutation status was assessed in tumor tissue samples using the

FoundationOne CDx panel (Foundation Medicine Inc.) or circulating tumor DNA (ctDNA) using the GuardantOMNI panel (Guardant Health), or both. Patients who had both blood and tissue samples were considered mutation positive for a specific gene if a mutation was identified in that gene by either method.²⁸ All confirmed gain/loss-of-function mutations or amplifications/deletions were included, whereas variants of unknown significance were not considered mutations. For *STK11* and *KEAP1*, “altered” status was defined by detection of any truncating mutation, including frameshift insertions/deletions, homozygous deletions of one or more exons, splice site mutations within two base-pairs of exon, and nonsynonymous somatic mutations documented in OncoKB (<https://www.oncokb.org/>)²⁹ as of March 2020. For *KRAS*, “altered” status was defined only by documentation of a known missense somatic hotspot mutation; amplification of *KRAS* was considered a variant of unknown significance.

Statistical Analysis

These updated OS analyses were not alpha controlled. Consistent with the primary analyses,³ updated OS analyses in the intention-to-treat (ITT) population (all randomized patients) for T+D+CT versus CT and D+CT versus CT used a stratified Cox proportional hazards model adjusted for PD-L1 expression status, tumor histologic type, and disease stage to estimate HRs and 95% CIs (with the Efron method to control for ties; CI calculated using a profile likelihood approach). For patient subgroup analyses based on the ITT population, HRs and 95% CIs were estimated using an unstratified Cox proportional hazards model, with treatment as the only covariate. OS analyses by mutation status were done in all patients with an evaluable sample to determine mutational status (herein termed the “mutation-evaluable population”), using the same methodology as for ITT population subgroup analyses. *STK11* and *KRAS* subgroup analyses are presented in patients with nonsquamous tumor histologic type only; *KEAP1* subgroup analysis is presented in all patients and in patients with nonsquamous tumor histologic type only. Median OS and landmark OS rates were estimated using Kaplan–Meier methodology.

Results

Patients

Among 1013 patients randomized to T+D+CT (n = 338), D+CT (n = 338), and CT (n = 337), 997 received at least one dose of the study treatment, 331 (97.9%), 335 (99.1%), and 331 (98.2%) in the respective arms (Fig. 1). As reported previously,³ baseline demographics and disease characteristics were generally

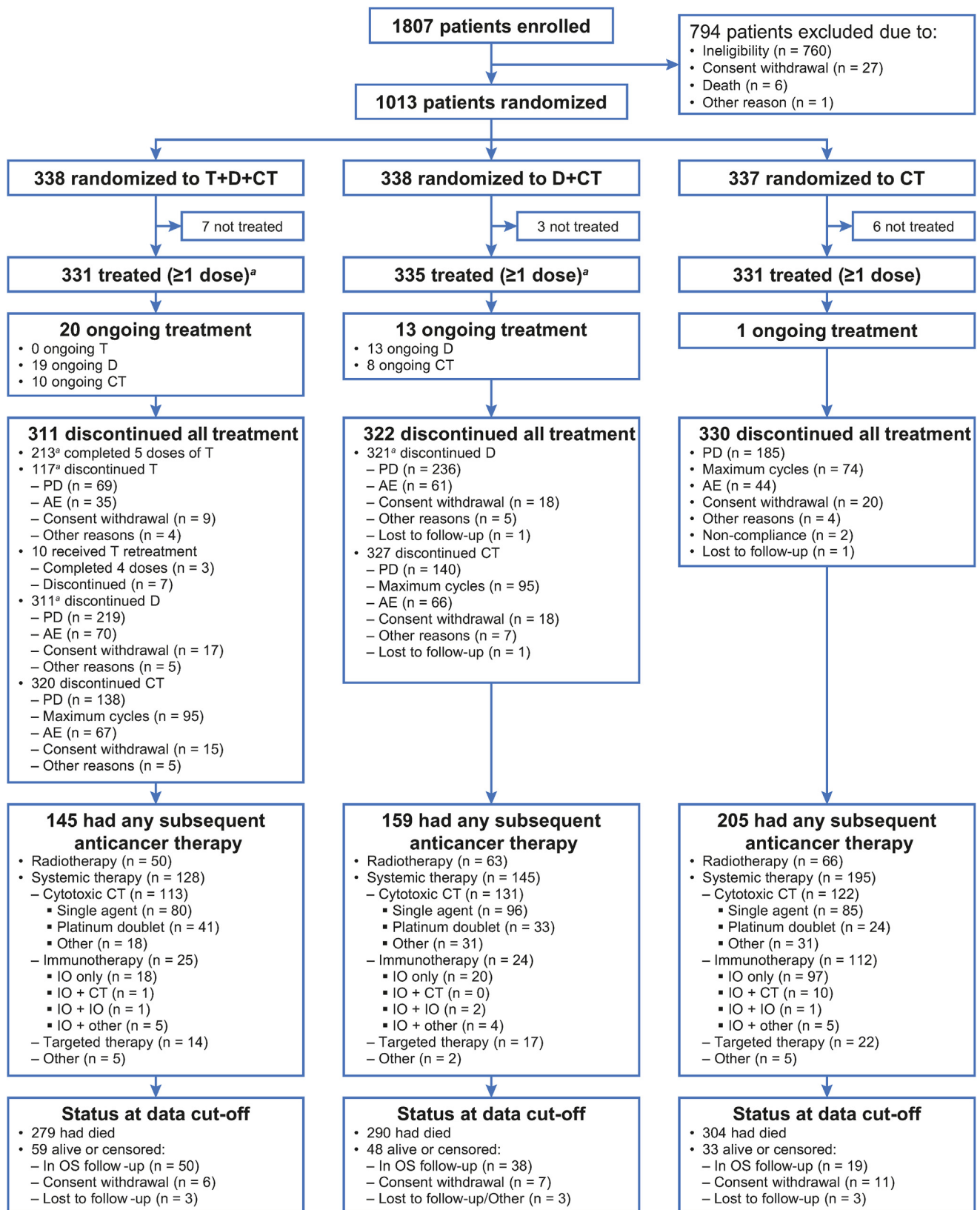


Figure 1. Patient disposition at data cutoff for this analysis (August 24, 2023). ^aTwo patients randomized to the T+D+CT (n = 1) and D+CT (n = 1) arms did not receive immunotherapy and were included in the CT safety population. One patient randomized to T+D+CT received T + D but not CT. AE, adverse event; CT, chemotherapy; D, durvalumab; IO, immunotherapy; OS, overall survival; PD, progressive disease; T, tremelimumab.

balanced between treatment arms. At data cutoff (August 24, 2023), 19 of 330 (5.8%) and 13 of 334 patients (3.9%) in the T+D+CT and D+CT arms, respectively, were still receiving durvalumab treatment (Fig. 1 and Table 1). In both durvalumab-containing arms, the median number of durvalumab doses received was eight (range: 1–80). Among 330 patients in the T+D+CT arm who received immunotherapy, 218 (66.1%) received more than or equal to five doses of tremelimumab; 10 (3.0%) of whom received retreatment with tremelimumab (in combination with durvalumab) on progression, as permitted per protocol (an additional 1–4 tremelimumab doses, i.e., doses 6–9 overall). Among the patients who received pemetrexed–platinum chemotherapy, 10 of 198 (5.1%), eight of 198 (4.0%), and one of 204 (0.5%) in the T+D+CT, D+CT, and CT arms, respectively, were ongoing on maintenance pemetrexed at data cutoff (Table 1).

Of the ITT population, 145 of 338 (42.9%), 159 of 338 (47.0%), and 205 of 337 patients (60.8%) had received subsequent anticancer treatment after T+D+CT, D+CT, and CT, respectively (Fig. 1 and Table 1). In the T+D+CT, D+CT, and CT arms, 50

(14.8%), 63 (18.6%), and 66 patients (19.6%) had received subsequent radiotherapy and 128 (37.9%), 145 (42.9%), and 195 (57.9%) had received any subsequent systemic anticancer therapy, including subsequent immunotherapy in 25 (7.4%), 24 (7.1%), and 112 patients (33.2%), respectively. Five patients, six patients, and one additional patient, respectively, had received subsequent systemic therapy since the primary analysis of OS.³

OS (ITT Population)

As of August 24, 2023, the median duration of follow-up across all treatment arms was 63.4 months (interquartile range: 59.4–67.2; range: 0.0–73.9) in censored patients. Overall, 73 additional deaths had been reported since the primary analysis of OS (data cutoff: March 12, 2021; median follow-up: 34.9 mo),³ including 32 deaths since a previously presented OS update (data cutoff: March 11, 2022; median follow-up: 46.5 mo).¹⁷

The updated OS analysis revealed an average 24% reduction in the risk of death with T+D+CT versus CT (HR = 0.76, 95% CI: 0.64–0.89) (Fig. 2A). The estimated

Table 1. Treatment Exposure on Study and Subsequent Anticancer Therapy

	T+D+CT n = 330	D+CT n = 334	CT n = 333
Treatment exposure, safety population			
Received ≥5 doses of tremelimumab, n (%)	218 (66.1)	n/a	n/a
Received tremelimumab retreatment, n (%) ^a	10 (3.0)	n/a	n/a
Median number of durvalumab doses (range)	8 (1–80)	8 (1–80)	n/a
Median total duration of durvalumab, wk (range)	29.8 (1.1–317.4)	28.7 (0.1–315.6)	n/a
Total duration of durvalumab exposure, n (%)			
≥156 wk (approximately 3 y)	36 (10.9)	28 (8.4)	n/a
≥208 wk (approximately 4 y)	27 (8.2)	19 (5.7)	n/a
≥260 wk (approximately 5 y)	20 (6.1)	15 (4.5)	n/a
Ongoing durvalumab at data cutoff, n (%)	19 (5.8)	13 (3.9)	n/a
Received pemetrexed + carboplatin/cisplatin, n (%)	198/329 ^b (60.2)	198 (59.3)	204 (61.3)
Received pemetrexed doublet and proceeded to maintenance pemetrexed, n (%)	149/198 (75.3)	159/198 (80.3)	131/204 (64.2)
Received pemetrexed doublet and ongoing maintenance pemetrexed at data cutoff, n (%)	10/198 (5.1)	8/198 (4.0)	1/204 (0.5)
Subsequent therapy, ITT population	n = 338	n = 338	n = 337
Received any subsequent anticancer therapy, n (%)	145 (42.9)	159 (47.0)	205 (60.8)
Received radiotherapy, n (%)	50 (14.8)	63 (18.6)	66 (19.6)
Received any systemic therapy, n (%)	128 (37.9)	145 (42.9)	195 (57.9)
Cytotoxic chemotherapy	113 (33.4)	131 (38.8)	122 (36.2)
Immunotherapy	25 (7.4)	24 (7.1)	112 (33.2)
Targeted therapy	14 (4.1)	17 (5.0)	22 (6.5)
Other	5 (1.5)	2 (0.6)	5 (1.5)

Note: Data cutoff: August 24, 2023.

^aPatients who received five cycles of tremelimumab plus durvalumab and subsequently had PD during durvalumab monotherapy could receive retreatment with up to four additional cycles of tremelimumab alongside durvalumab. At data cutoff, two patients who received tremelimumab retreatment remained alive. One of these patients had PD-L1 tumor cell expression of less than 1% and had not received any subsequent therapy.

^bOne patient did not receive CT in the T+D+CT arm.

CT, chemotherapy; D, durvalumab; ITT, intention-to-treat; n/a, not applicable; PD, progressive disease; PD-L1, programmed cell death ligand-1; T, tremelimumab.

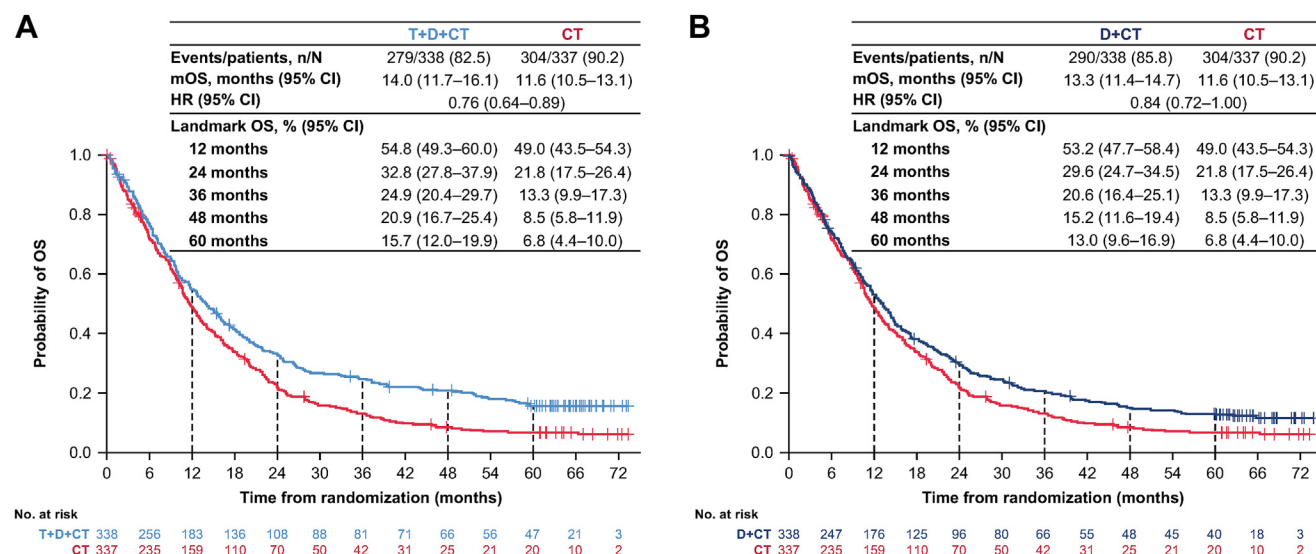


Figure 2. OS with (A) T+D+CT versus CT and (B) D+CT versus CT in the ITT population (data cutoff: August 24, 2023). Vertical tick marks indicate censored data, and dashed vertical lines indicate times of landmark analyses of OS. HR <1 favors (T)+D+CT versus CT. CI, confidence interval; CT, chemotherapy; D, durvalumab; HR, hazard ratio; ITT, intention-to-treat; (m)OS, (median) overall survival; T, tremelimumab.

5-year OS rate was 15.7% (95% CI: 12.0–19.9) with T+D+CT and 6.8% (95% CI: 4.4–10.0) with CT. For D+CT versus CT, the OS HR was 0.84 (95% CI: 0.72–1.00); estimated 5-year OS rate was 13.0% (95% CI: 9.6–16.9) with D+CT (Fig. 2B).

OS (Subgroup Analyses)

Updated OS subgroup analyses were consistent with earlier reports^{3,17,30} for T+D+CT versus CT (Fig. 3A) and D+CT versus CT (Fig. 3B). For T+D+CT versus CT, OS HRs across subgroups were broadly similar to that in the ITT population, with HR point estimates generally within the 95% CI for the ITT analysis (Fig. 3A). As previously reported, the OS HR seemed more in favor of T+D+CT versus CT in patients with nonsquamous tumor histologic type (HR = 0.69, 95% CI: 0.56–0.85) than with squamous tumor histologic type (HR = 0.85, 95% CI: 0.65–1.10) (Fig. 3A). In the T+D+CT and CT arms, estimated 5-year OS rates were 20.5% (95% CI: 15.3–26.2) and 9.1% (95% CI: 5.6–13.6) in patients with nonsquamous tumor histologic type and 7.3% (95% CI: 3.4–13.1) and 2.9% (95% CI: 0.8–7.3) in those with squamous tumor histologic type, respectively (Fig. 4A and B). Consistent with earlier reports,^{3,17,30} HRs for OS with D+CT versus CT were 0.81 (95% CI: 0.66–1.00) and 0.82 (95% CI: 0.64–1.07) in patients with nonsquamous and squamous tumor histologic type, respectively (Fig. 3B); 5-year rates in the D+CT arm were 16.4% (95% CI: 11.6–21.8) and 7.6% (95% CI: 3.8–13.2), respectively (Fig. 4A and B).

Consistent with the ITT population, OS HRs were in favor of T+D+CT versus CT in both patients with PD-L1 TC greater than or equal to 1% (HR = 0.71, 95% CI: 0.58–0.88; D+CT versus CT: HR = 0.78, 95% CI: 0.63–0.95; Supplementary Fig. 1A) and those with PD-L1 TC less than 1% (HR = 0.81, 95% CI: 0.62–1.05; D+CT versus CT: HR = 0.98, 95% CI: 0.75–1.27; Supplementary Fig. 1B), with the difference between OS HRs for T+D+CT versus CT and D+CT versus CT appearing somewhat more pronounced in the latter subgroup. OS HRs in favor of T+D+CT versus CT across PD-L1 subgroups were still evident after long-term follow-up, although numbers of patients remaining at risk at later landmark time points in these subgroups were low across arms, resulting in greater uncertainty in the Kaplan–Meier estimates. Estimated 5-year OS rates for T+D+CT and CT were 20.8% (95% CI: 15.6–26.6) and 8.6% (95% CI: 5.2–13.1) in the PD-L1 TC greater than or equal to 1% subgroup and 6.1% (95% CI: 2.6–11.8) and 4.0% (95% CI: 1.5–8.6) in the PD-L1 TC less than 1% subgroup, respectively; 5-year OS rates in the D+CT arm were 16.2% (95% CI: 11.6–21.4) and 6.5% (95% CI: 2.9–12.2) in patients with PD-L1 TC greater than or equal to 1% and less than 1%, respectively (Supplementary Fig. 1A and B).

Consistent with previous analyses,³⁰ OS HRs were in favor of T+D+CT versus CT in subgroups defined by tumor histologic type and PD-L1 TC. As with PD-L1 subgroup analyses, the numbers of patients remaining at risk at later landmark time points were very low, limiting interpretability of these landmark data. In patients with nonsquamous tumor histologic type and

A

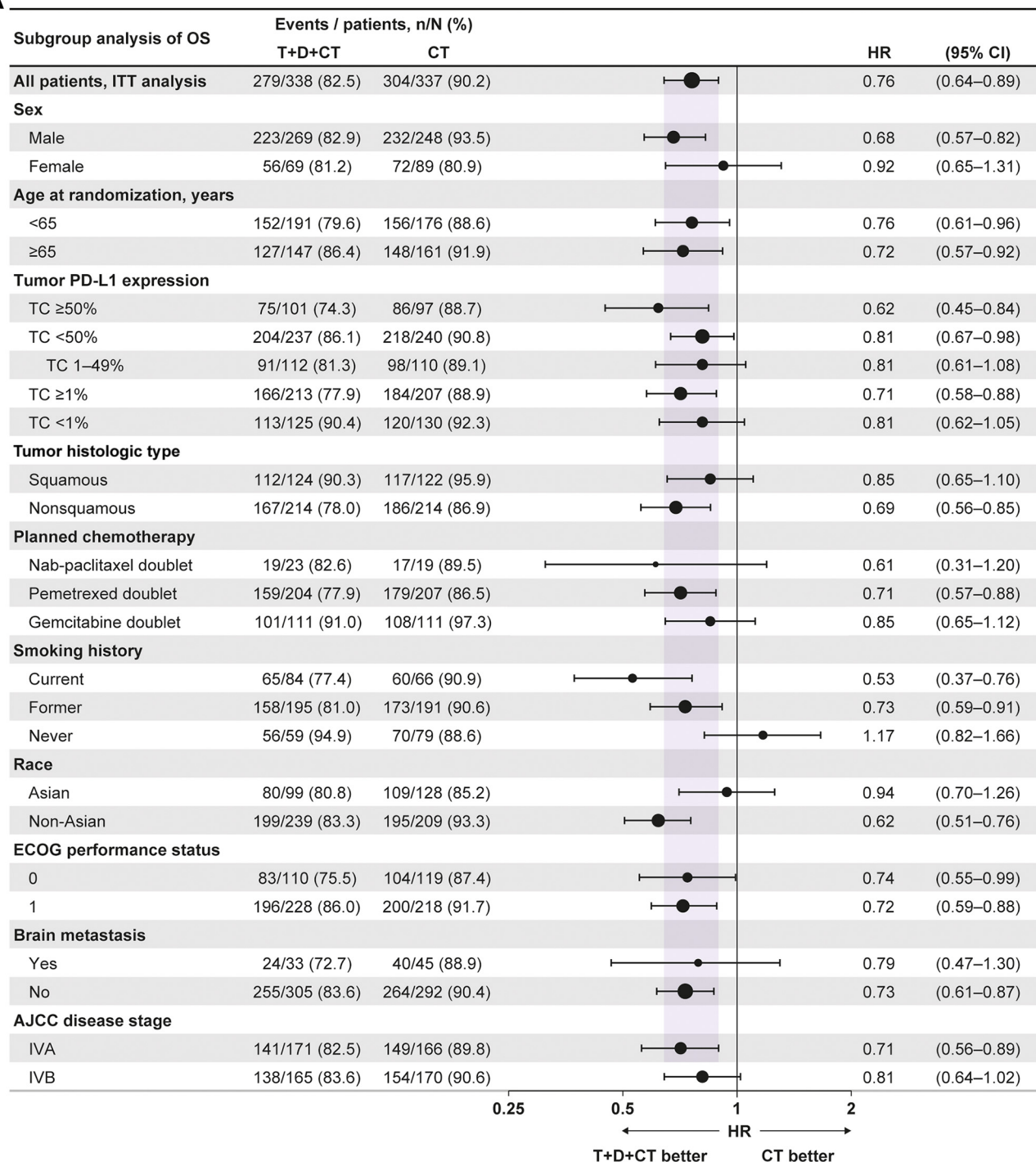


Figure 3. OS in patient subgroups with (A) T+D+CT versus CT and (B) D+CT versus CT (data cutoff: August 24, 2023). Circle sizes are proportional to the number of events across both treatment groups. All subgroups were prespecified except for the TC 1% to 49% subgroup. AJCC, American Joint Committee on Cancer; CI, confidence interval; CT, chemotherapy; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PD-L1, programmed cell death ligand-1; T, tremelimumab; TC, tumor cell.

PD-L1 TC greater than or equal to 1% or less than 1%, respective HRs were 0.63 (95% CI: 0.48–0.83) and 0.81 (95% CI: 0.59–1.13), whereas in those with squamous tumor histologic type and PD-L1 TC greater than or

equal to 1% or less than 1%, respective HRs were 0.89 (95% CI: 0.64–1.25) and 0.80 (95% CI: 0.53–1.23). With D+CT versus CT in these four subgroups, respective HRs for OS were 0.75 (95% CI: 0.57–0.98), 0.94 (95% CI:

B

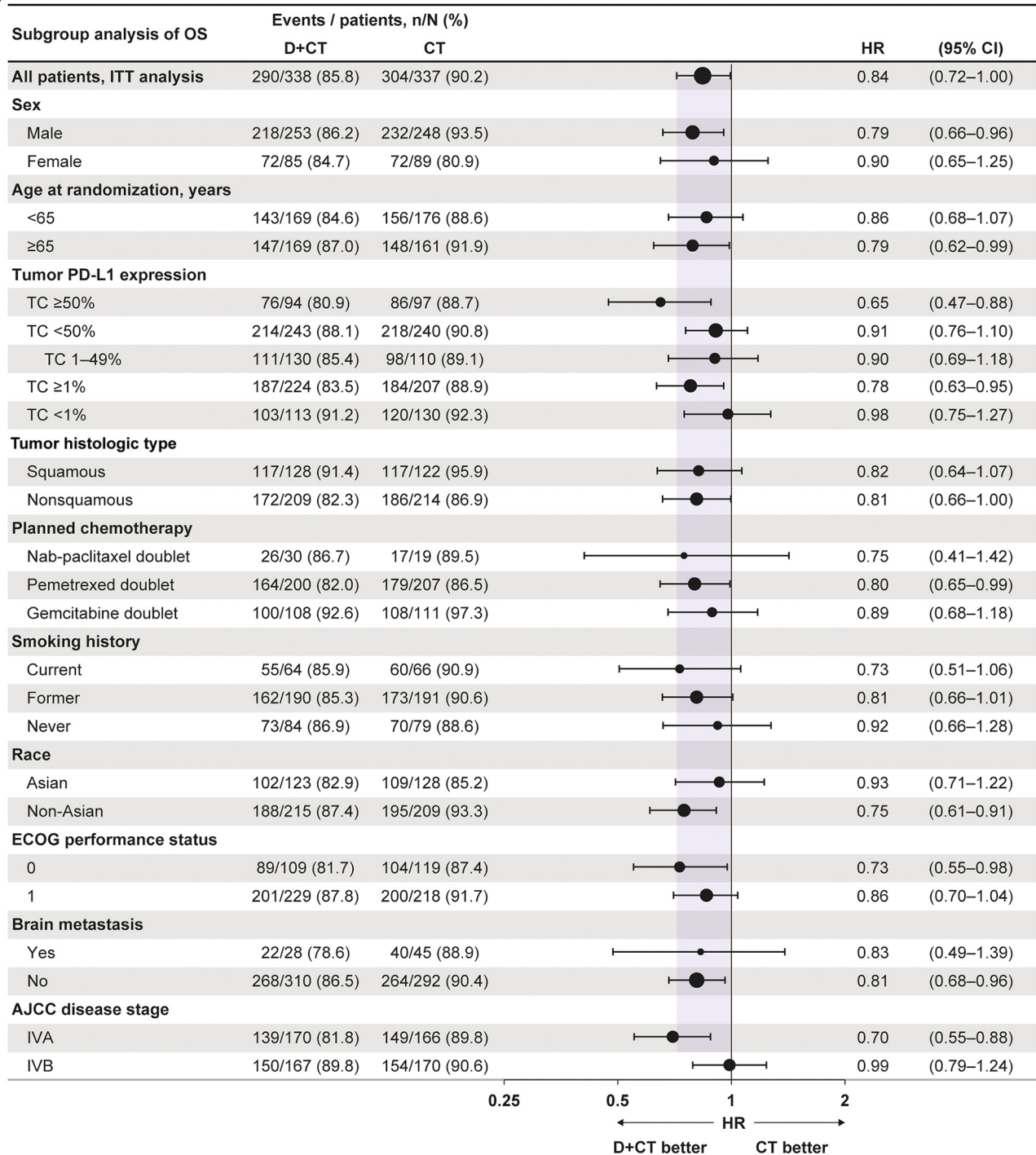


Figure 3. (continued).

0.68–1.31), 0.76 (95% CI: 0.56–1.05), and 1.28 (95% CI: 0.80–2.03).

OS by STK11, KEAP1, and KRAS Mutation Status

Among 1013 randomized patients, 973 (96.1%) had evaluable tissue or ctDNA samples, including 612 of 637

(96.1%) with nonsquamous tumor histologic type (Supplementary Table 1). In the nonsquamous population, baseline characteristics for which are summarized in Supplementary Table 2, 38 of 637 (6.0%), 240 of 637 (37.7%), and 334 of 637 (52.4%) had evaluable tissue samples only, ctDNA samples only, and tissue and ctDNA samples, respectively (Supplementary Table 1). Within

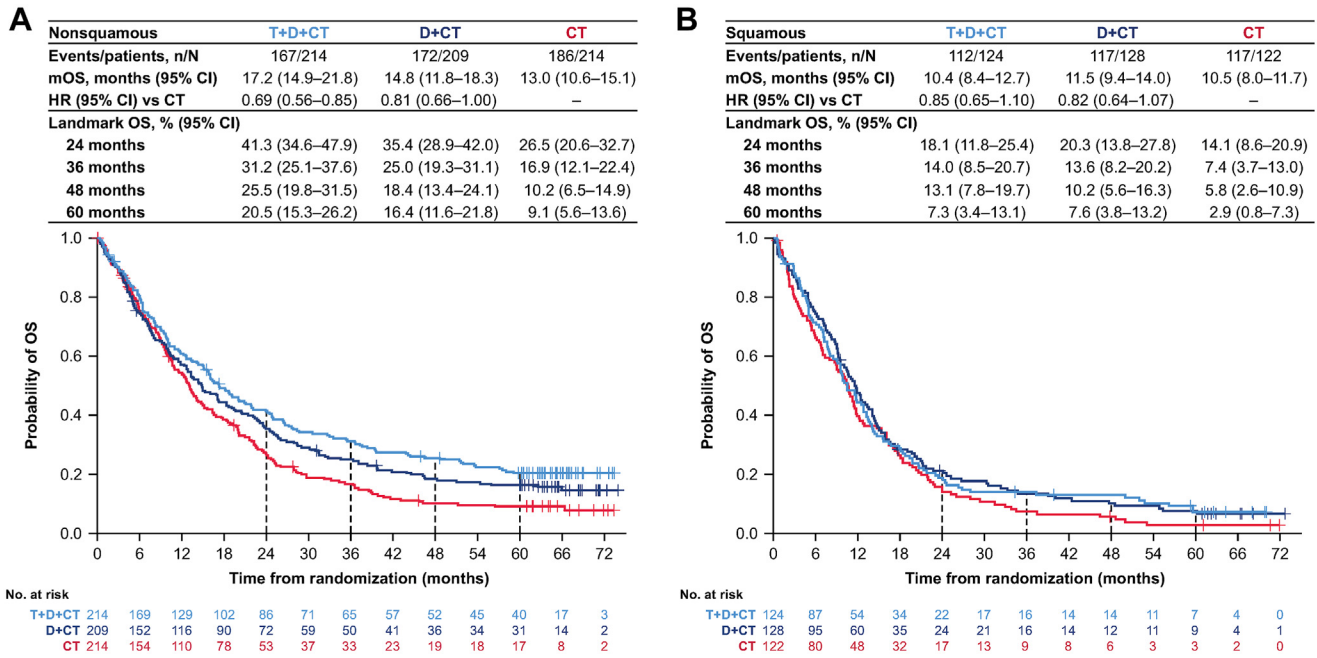


Figure 4. Updated OS by tumor histologic type. Kaplan-Meier curves of OS in patients with (A) nonsquamous tumor histologic type, (B) squamous tumor histologic type (data cutoff: August 24, 2023). Vertical tick marks indicate censored data, and dashed vertical lines indicate times of landmark analyses of OS. HR <1 favors (T)+D+CT versus CT. CI, confidence interval; CT, chemotherapy; D, durvalumab; HR, hazard ratio; ITT, intention-to-treat; (m)OS, (median) overall survival; T, tremelimumab.

this mutation-evaluable population, OS was assessed according to *STK11* or *KRAS* mutation status in patients with nonsquamous tumor histologic type and according to *KEAP1* mutation status in all patients, regardless of tumor histologic type, due to the limited number of patients with *KEAP1* mutations, including in patients with nonsquamous tumor histologic type. In the nonsquamous mutation-evaluable population overall, 87 of 612 (14.2%), 182 of 612 (29.7%), and 37 of 612 (6.0%) had *STK11*, *KRAS*, and *KEAP1* mutations, and in the overall mutation-evaluable population, 51 of 973 (5.2%) had *KEAP1* mutations.

Consistent with earlier analyses,^{17,18} OS HRs were in favor of T+D+CT compared with CT in all mutation subgroups (Fig. 5). OS HRs favored T+D+CT versus CT in patients with nonsquamous tumor histologic type and *STK11*m (5-y OS 12.9% versus 0%; HR = 0.57, 95% CI: 0.32–1.04; Fig. 5A) or wild-type *STK11* (22.0% versus 10.4%; HR = 0.71, 95% CI: 0.56–0.90; Fig. 5B). OS HRs also favored T+D+CT versus CT in patients with any tumor histologic type and *KEAP1*m (10.0% versus 0%; HR = 0.43, 95% CI: 0.16–1.25; Fig. 5C) or wild-type *KEAP1* (16.2% versus 7.0%; HR = 0.76, 95% CI: 0.64–0.90; Fig. 5D), including in the smaller number of patients with nonsquamous tumor histologic type and *KEAP1*m (HR = 0.33, 95% CI: 0.10–1.15). Similarly, OS HRs favored T+D+CT versus CT in patients with nonsquamous tumor histologic type and *KRAS*m (21.7%

versus 8.1%; HR = 0.55, 95% CI: 0.36–0.83; Fig. 5E) or wild-type *KRAS* (20.3% versus 9.5%; HR = 0.78, 95% CI: 0.61–1.00; Fig. 5F).

HRs for OS with D+CT versus CT were 1.02 (95% CI: 0.59–1.80) and 0.79 (95% CI: 0.63–1.00) in patients with nonsquamous tumor histologic type and *STK11*m or wild-type *STK11* (Fig. 5A and B), 0.77 (95% CI: 0.31–2.15) and 0.83 (95% CI: 0.70–0.98) in patients with any tumor histologic type and *KEAP1*m or wild-type *KEAP1* (Fig. 5C and D), 0.67 (95% CI: 0.23–2.17) in patients with nonsquamous tumor histologic type and *KEAP1*m, and 0.74 (95% CI: 0.50–1.09) and 0.87 (95% CI: 0.68–1.12) in patients with nonsquamous tumor histologic type and *KRAS*m or wild-type *KRAS*, respectively (Fig. 5E and F).

Among patients with nonsquamous tumor histologic type and *KRAS* mutations, 62 of 182 (34%) had *KRAS*m^{G12C} and 120 of 182 (66%) had *KRAS*m^{non-G12C} (including 35 of 182 [19%] with G12D mutations). OS HRs favored T+D+CT versus CT in patients with nonsquamous tumor histologic type and either *KRAS*m^{G12C} (HR = 0.63, 95% CI: 0.33–1.23; D+CT versus CT: HR = 0.71, 95% CI: 0.37–1.37; Supplementary Fig. 2A) or *KRAS*m^{non-G12C} (HR = 0.52, 95% CI: 0.30–0.88; D+CT versus CT: HR = 0.78, 95% CI: 0.48–1.28; Supplementary Fig. 2B). In both the *KRAS*m^{G12C} and *KRAS*m^{non-G12C} subgroups, the magnitude of OS benefit with T+D+CT versus CT was numerically greater than

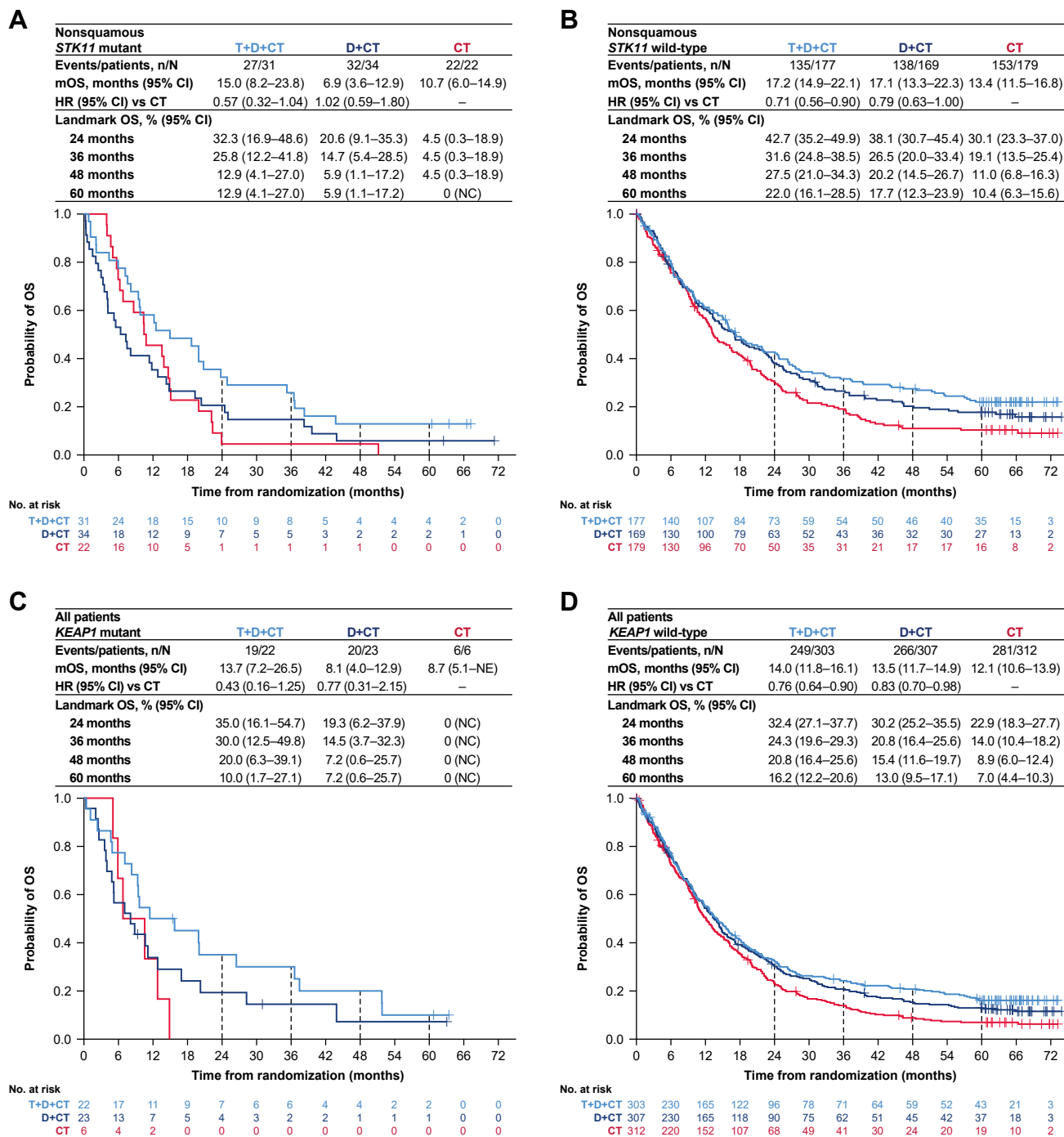


Figure 5. Updated OS by mutation status. Illustrated are Kaplan-Meier curves of OS in the (A) *STK11*m (nonsquamous tumor histologic type), (B) wild-type *STK11* (nonsquamous tumor histologic type), (C) *KEAP1*m (all patients), (D) wild-type *KEAP1* (all patients), (E) *KRAS*m (nonsquamous tumor histologic type), and (F) wild-type *KRAS* (nonsquamous tumor histologic type) populations. Data cutoff: August 24, 2023. Vertical tick marks indicate censored data, and the dashed vertical lines indicate the times of landmark analyses of OS. CI, confidence interval; CT, chemotherapy; D, durvalumab; HR, hazard ratio; (m)OS, (median) overall survival; T, tremelimumab.

that with D+CT versus CT. In the small nonsquamous *KRAS*m^{G12D} subgroup, the HR for OS versus CT was 0.61 (95% CI: 0.21–1.78) with T+D+CT and 0.94 (95% CI: 0.42–2.10) with D+CT.

Safety

Updated rates of SAEs and AEs leading to death at data cutoff are summarized in [Supplementary Table 3](#). Compared with the primary analysis of OS³: seven

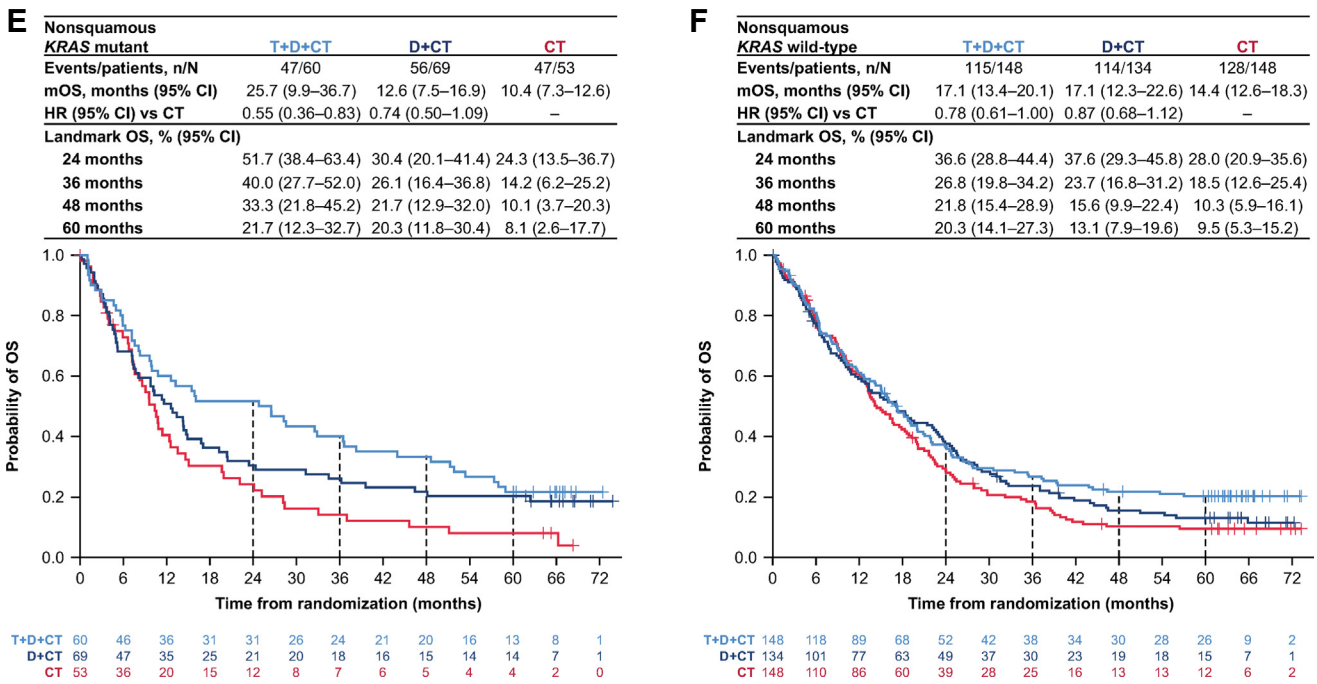


Figure 5. (continued).

additional patients had experienced an SAE (none considered related to treatment by the investigator), five and two in the T+D+CT and D+CT arms, respectively; one additional patient in the D+CT arm had experienced an SAE assessed by the investigator as possibly related to CT (anemia); and two additional patients in each of the T+D+CT and D+CT arms had AEs leading to death (not considered related to treatment by the investigator). No additional patients in the CT arm had experienced SAEs or AEs leading to death.

Discussion

These results from prespecified updated analyses of the phase 3 POSEIDON trial,³ after a median follow-up of more than 5 years, reveal the durable long-term OS benefit from adding a limited course of tremelimumab, plus durvalumab, to four cycles of chemotherapy. The OS HR for T+D+CT versus CT was consistent with previous analyses,^{3,17} revealing an average 24% reduction in the risk of death, and the 5-year OS rate with T+D+CT was more than two times greater than with CT, at 15.7% versus 6.8%, indicating that OS benefit was still evident after long-term follow-up. This was found despite the higher rate of subsequent immunotherapy in the CT arm (33.2%) compared with the T+D+CT arm (7.4%). The rate of subsequent immunotherapy use in the CT arm was comparable to other trials in this setting that did not permit crossover.^{31–35} Notably, OS benefit with T+D+CT

versus CT was found regardless of PD-L1 expression, including in patients with PD-L1 TC less than 1%, and was also found in patients with *STK11m* (nonsquamous), *KEAP1m*, and *KRASm* (nonsquamous) mNSCLC. Importantly, no new safety signals were identified based on SAEs collected during long-term follow-up; compared with the primary analysis of OS,³ four additional patients had AEs leading to death, none of which were considered related to treatment. These results support the use of T+D+CT as a first-line treatment option for patients with mNSCLC, including subgroups with harder-to-treat disease.

The long-term OS benefit with T+D+CT versus CT reflects the relative magnitude of benefit found at the final OS analysis after a median follow-up of approximately 3 years, which was the final alpha-controlled and statistically powered analysis for OS. At that analysis, the incremental benefit conferred by a short course of tremelimumab was necessary to achieve a significant OS gain versus CT alone, whereas a positive trend for OS that did not reach statistical significance with D+CT versus CT was reported.³ These updated findings from POSEIDON are consistent with other studies of immunotherapy with or without CT versus CT in mNSCLC,^{10–14,36,37} which have similarly revealed significant OS benefit and improved long-term OS rates after more than or equal to 4 to 6 years, including the CheckMate 227^{10,37} and CheckMate 9LA³⁶ trials of nivolumab and ipilimumab, and the KEYNOTE-189¹² and KEYNOTE-407¹³ trials of pembrolizumab. Cross-study comparisons of OS rates

are confounded due to differences in study designs including duration and components of treatment received, participating countries, patient populations, tumor histologic type, and PD-L1 expression, plus availability of subsequent treatment during the study. Such differences may explain differential OS rates in CT control arms across studies and serve to highlight the potential variability of landmark point estimates in the context of reduced numbers of patients remaining at risk. For this reason, OS HRs provide a more reliable evaluation of the added benefit of immunotherapy.

In POSEIDON, long-term OS benefit with T+D+CT versus CT across most patient subgroups, including those defined by tumor histologic type or PD-L1 status, was generally consistent with that in the ITT population, as were OS HRs for D+CT versus CT in patient subgroups. Patterns of OS benefit in histologic subgroups were consistent with those at earlier data cutoffs^{3,17}; OS benefit with T+D+CT versus CT was more pronounced in patients with nonsquamous (HR = 0.69, 95% CI: 0.56–0.85) versus squamous (HR = 0.85, 95% CI: 0.65–1.10) tumor histologic type, with 5-year rates being more than twice as high with T+D+CT versus CT in the nonsquamous subgroup (20.5% versus 9.1%). Although squamous tumor histologic type can be associated with a poorer prognosis in mNSCLC, as evidenced across historical data and by lower 5-year OS rates in both the nivolumab plus ipilimumab and chemotherapy arms in CheckMate 227,¹⁰ median and landmark OS in POSEIDON seemed particularly poor in patients with squamous tumor histologic type in all arms compared with outcomes in patients with nonsquamous tumor histologic type. In addition, in most immunotherapy trials, squamous tumor histologic type has not typically been associated with lower benefit from immunotherapy. A possible explanation for the difference found in POSEIDON could be that 330 of 374 (88%)³ patients with squamous tumor histologic type received gemcitabine doublet chemotherapy (possibly influenced by geographic distribution of enrolled patients), which may be associated with worse outcomes than nab-paclitaxel plus carboplatin in squamous NSCLC (potentially also when used in combination with immunotherapy).^{38,39} Similarly consistent with earlier analyses,^{17,30} T+D+CT provided OS benefit versus CT regardless of PD-L1 expression, including in patients with PD-L1 TC less than 1%. In this subgroup, the OS HR for T+D+CT versus CT was 0.81 (95% CI: 0.62–1.05), a difference that was sustained per previous analyses.^{17,30} For D+CT versus CT, the HR was 0.98 (95% CI: 0.75–1.27). Although the T+D+CT and D+CT Kaplan–Meier OS curves seemed to converge at the 5-year time point, these data are less reliable for comparison as there were

fewer than 10 patients at risk in each arm after the 54-month time point, resulting in increased uncertainty for the landmark OS estimates at 5 years. Overall, HRs and 95% CIs provide a more reliable interpretation of these data.

A strength of POSEIDON was that plasma samples for ctDNA analysis in addition to tissue samples for PD-L1 testing were prospectively collected, resulting in a mutation-evaluable population comprising 96.1% of the ITT population, which compares favorably with other studies in which such analyses have been conducted.^{24,33,35,40} This population was used to analyze OS by mutation status in subgroups with harder-to-treat disease, including those with *STK11m*, *KEAP1m*, or *KRASm*, the prevalences of which in the nonsquamous population were 14.2%, 6.0%, and 29.7%, respectively, broadly within previously reported ranges for these mutations.^{23,24,33,35,40,41} OS analysis by *STK11* and *KRAS* mutation status was restricted to patients with nonsquamous tumor histologic type, consistent with previous analyses from phase 3 trials^{33,35,40} and associated with the higher prevalence of these mutations in nonsquamous versus squamous NSCLC.^{42,43} OS analysis by *KEAP1* mutation status was conducted in all patients, regardless of tumor histologic type, due to the relatively low total number with *KEAP1m*, including in the nonsquamous population. Consistent with broader data on greater mutation frequency in nonsquamous NSCLC, numbers of patients with mutations in the squamous subgroups in POSEIDON were very small, preventing meaningful analysis of outcomes.

The tumor microenvironment associated with *STK11m* and *KEAP1m* is known to be immunosuppressive.⁴⁴ *STK11m* results in the production of immunosuppressive cytokines, which leads to neutrophil mobilization; the neutrophils then contribute to suppression of T cell activity, resulting in an immune-cold microenvironment.⁴⁵ In this context, addition of anti-CTLA-4 therapy, which lowers the threshold for T cell activation,⁴⁶ may be of particular benefit for improving clinical activity. The *KRASm* subgroup is heterogeneous; it is considered generally responsive to PD-(L)1-based therapy, unless associated with co-mutations such as *STK11m* and *KEAP1m*.²⁶ Nevertheless, *KRASm*^{G12D} NSCLC is a distinct subtype harboring different co-mutations compared with *KRASm*^{G12C} and *KRASm*^{G12V} and is associated with a more immune-cold tumor microenvironment and poorer outcomes to single-agent PD-(L)1 inhibition.²⁵ Results of analyses by *KRAS* mutation type in patients from POSEIDON with nonsquamous tumor histologic type were in line with expectations based on these previous findings; whereas OS benefit was observed for D+CT versus CT

in *KRAS*^{G12C}, no clear trend was found in *KRAS*^{G12D}. In contrast, OS benefit for T+D+CT versus CT was found in both subgroups. The updated OS data from POSEIDON suggest, first, the prognostic impact of *STK11*m and *KEAP1*m across treatment arms, which is consistent with data from other phase 3 trials^{35,47} and with real-world data²⁰ revealing poorer outcomes in patients with advanced NSCLC with these mutations. Second, addition of tremelimumab and durvalumab to CT extended long-term clinical benefit in patients with *STK11*m, *KEAP1*m, and *KRAS*m (irrespective of mutation type), subgroups for which outcomes can be suboptimal in clinical practice,^{20,22} suggesting a specific mechanistic rationale associated with added CTLA-4 inhibition.

Tolerability is an important factor when considering the use of any combination regimen, including those such as T+D+CT which incorporate dual checkpoint inhibition (anti-CTLA-4 and anti-PD-[L]1). Overall, previous analyses revealed that T+D+CT was well tolerated³ and that the addition of tremelimumab to durvalumab and chemotherapy did not compromise patient-reported global health status/quality of life, functioning, or symptom burden.⁴⁸ Safety results at the present data cutoff were consistent with the general pattern observed in these more comprehensive earlier analyses. This is in line with expectations; in particular, new safety signals related to tremelimumab were not expected to develop during longer-term follow-up as it was only given during the initial cycles of treatment.

As treatment of mNSCLC transitions to an increasingly individualized approach, it will be important to evaluate the impact of individual mutations and frequent co-mutations of *STK11*, *KRAS*, and *KEAP1*, as studies have suggested that mutations in two or more of these genes are associated with even worse outcomes than mutations in a single gene.^{19,26,49–51} Nevertheless, due to the small numbers of patients with co-mutations, it was not feasible to explore outcomes in these subgroups in POSEIDON. The upcoming randomized phase 3B TRITON study (NCT06008093), a dedicated trial specifically evaluating outcomes in approximately 280 patients with nonsquamous mNSCLC who have mutations or co-mutations in *STK11*, *KEAP1*, or *KRAS*, will further explore the efficacy of T+D+CT (versus pembrolizumab+CT) in this population.

In conclusion, after a median follow-up of more than 5 years across all arms, T+D+CT was found to have durable long-term OS benefit versus CT, supporting its use as first-line treatment in mNSCLC, including in patient subgroups with harder-to-treat disease.

CRediT Authorship Contribution Statement

Solange Peters: Formal analysis; Investigation; Writing – Review & Editing.

Byoung Chul Cho: Conceptualization; Methodology; Formal analysis; Investigation; Resources; Data Curation; Writing – Review & Editing.

Alexander V. Luft: Investigation; Writing – Review & Editing.

Jorge Alatorre-Alexander: Investigation; Writing – Review & Editing.

Sarayut Lucien Geater: Investigation; Writing – Review & Editing.

Konstantin Laktionov: Investigation; Writing – Review & Editing.

Dmytro Trukhin: Investigation; Writing – Review & Editing.

Sang-We Kim: Investigation; Writing – Review & Editing.

Grygorii M. Ursol: Investigation; Writing – Review & Editing.

Maen Hussein: Investigation; Writing – Review & Editing.

Farah Louise Lim: Investigation; Writing – Review & Editing.

Cheng-Ta Yang: Investigation; Writing – Review & Editing.

Luiz H. Araujo: Investigation; Writing – Review & Editing.

Haruhiro Saito: Investigation; Writing – Review & Editing.

Niels Reinmuth: Investigation; Writing – Review & Editing.

Caitlin Lowery: Formal analysis; Writing – Review & Editing; Supervision.

Helen Mann: Validation; Formal analysis; Writing – Review & Editing.

Ross Stewart: Formal analysis; Writing – Review & Editing.

Haiyi Jiang: Writing – Review & Editing; Supervision.

Edward B. Garon: Investigation; Writing – Review & Editing.

Tony Mok: Investigation; Writing – Review & Editing.

Melissa L. Johnson: Investigation; Writing – Review & Editing.

Data Sharing Statement

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>.

Data for studies directly listed on Vivli can be requested through Vivli at: www.vivli.org.

Data for studies not listed on Vivli could be requested through Vivli at: <https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/>.

The AstraZeneca Vivli member page is also available outlining further details: <https://vivli.org/ourmember/astrazeneca/>.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at <https://doi.org/10.1016/j.jtho.2024.09.1381>.

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