original reports

# Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study

**Melissa L. Johnson, MD[1]; Byoung Chul Cho, MD, PhD[2]; Alexander Luft, MD[3]; Jorge Alatorre-Alexander, MD[4]; Sarayut Lucien Geater, MD[5]; Konstantin Laktionov, MD[6]; Sang-We Kim, MD, PhD[7]; Grygorii Ursol, MD[8]; Maen Hussein, MD[9]; Farah Louise Lim, MBBS, MRCP[10]; Cheng-Ta Yang, MD[11]; Luiz Henrique Araujo, MD, PhD[12]; Haruhiro Saito, MD, PhD[13]; Niels Reinmuth, MD, PhD[14]; Xiaojin Shi, MD[15]; Lynne Poole, MSc[16]; Solange Peters, MD, PhD[17]; Edward B. Garon, MD[18]; and Tony Mok, MD[19] for the POSEIDON investigators**

abstract

**PURPOSE** The open-label, phase III POSEIDON study evaluated tremelimumab plus durvalumab and chemotherapy (T + D + CT) and durvalumab plus chemotherapy (D + CT) versus chemotherapy alone (CT) in first-line metastatic non–small-cell lung cancer (mNSCLC).

**METHODS** Patients (n = 1,013) with *EGFR*/*ALK* wild-type mNSCLC were randomly assigned (1:1:1) to tremelimumab 75 mg plus durvalumab 1,500 mg and platinum-based chemotherapy for up to four 21-day cycles, followed by durvalumab once every 4 weeks until progression and one additional tremelimumab dose; durvalumab plus chemotherapy for up to four 21-day cycles, followed by durvalumab once every 4 weeks until progression; or chemotherapy for up to six 21-day cycles (with or without maintenance pemetrexed; all arms). Primary end points were progression-free survival (PFS) and overall survival (OS) for D + CT versus CT. Key alpha-controlled secondary end points were PFS and OS for T + D + CT versus CT.

**RESULTS** PFS was significantly improved with D + CT versus CT (hazard ratio [HR], 0.74; 95% CI, 0.62 to 0.89; $P = .0009$; median, 5.5 *v* 4.8 months); a trend for improved OS did not reach statistical significance (HR, 0.86; 95% CI, 0.72 to 1.02; $P = .0758$; median, 13.3 *v* 11.7 months; 24-month OS, 29.6% *v* 22.1%). PFS (HR, 0.72; 95% CI, 0.60 to 0.86; $P = .0003$; median, 6.2 *v* 4.8 months) and OS (HR, 0.77; 95% CI, 0.65 to 0.92; $P = .0030$; median, 14.0 *v* 11.7 months; 24-month OS, 32.9% *v* 22.1%) were significantly improved with T + D + CT versus CT. Treatment-related adverse events were maximum grade 3/4 in 51.8%, 44.6%, and 44.4% of patients receiving T + D + CT, D + CT, and CT, respectively; 15.5%, 14.1%, and 9.9%, respectively, discontinued treatment because of treatment-related adverse events.

**CONCLUSION** D + CT significantly improved PFS versus CT. A limited course of tremelimumab added to durvalumab and chemotherapy significantly improved OS and PFS versus CT, without meaningful additional tolerability burden, representing a potential new option in first-line mNSCLC.

**J Clin Oncol 41:1213-1227. © 2022 by American Society of Clinical Oncology**



**ASSOCIATED CONTENT**

**See accompanying editorial on page 1176**

**Appendix**

**Data Supplement**

**Protocol**

Author affiliations and support information (if applicable) appear at the end of this article.

**Accepted on August 29, 2022 and published at ascopubs.org/journal/jco on November 3, 2022: DOI https://doi.org/10.1200/JCO.22.00975**

## INTRODUCTION

Immunotherapies targeting programmed cell death-1 (PD-1) and its ligand (PD-L1), administered as monotherapy or in combination with established chemotherapies, have transformed the first-line treatment of metastatic non–small-cell lung cancer (mNSCLC).[1-7] Although some patient subsets, such as those with higher levels of tumor PD-L1 expression, derive favorable long-term outcomes with anti–PD-(L)1 therapy,[8] the unmet needs of others are becoming better understood with clinical experience. For example, patients with PD-L1–low or PD-L1–negative tumors are less likely to respond to anti–PD-(L)1 therapy,[3,9-11] underlining the need for new therapeutic strategies with immunotherapy combinations in this setting.

Durvalumab is a selective, high-affinity human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80.[12] Tremelimumab is a human immunoglobulin G2 monoclonal antibody that targets cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4),

## CONTEXT

### Key Objective

The phase III three-arm POSEIDON trial of patients with first-line metastatic non–small-cell lung cancer evaluated the efficacy of tremelimumab plus durvalumab and chemotherapy (T + D + CT) and durvalumab plus chemotherapy (D + CT) versus chemotherapy alone (CT). Addition of a limited course of anti–cytotoxic T-lymphocyte–associated antigen 4 to anti–programmed cell death ligand-1 (PD-L1) and chemotherapy provides insights into long-term efficacy and tolerability in the context of commonly used treatment strategies in this setting.

### Knowledge Generated

D + CT significantly improved progression-free survival versus CT, with a positive trend for improved overall survival that did not reach statistical significance. T + D + CT significantly improved progression-free survival and overall survival versus CT, without clinically meaningful increase in tolerability burden; addition of anti–cytotoxic T-lymphocyte–associated antigen 4 extended clinical benefit to patients with PD-L1–negative tumors.

### Relevance

T + D + CT may represent a new first-line treatment option in metastatic non–small-cell lung cancer. Observations in the PD-L1–negative subgroup have particular clinical relevance as these patients can have suboptimal outcomes in clinical practice with currently available treatments.

enhancing binding of CD80 and CD86 to CD28.[13] A limited early course of tremelimumab can diversify T-cell responses and lead to increased tumor infiltration,[14-17] whereas continuous durvalumab treatment may enhance T-cell function and support a sustained antitumor response.[14,18] Given their complementary mechanisms of action, the addition of tremelimumab to a durvalumab-based regimen is expected to broaden clinical activity, potentially overcoming primary resistance to PD-(L)1 blockade by enabling novel T-cell responses. The concurrent addition of chemotherapy, which causes tumor cell (TC) death and release of neoantigens,[19] may increase immune priming and, on the basis of clinical experience, can be important for early disease control.[1,2,20]

POSEIDON (ClinicalTrials.gov identifier: NCT03164616) is a phase III, global, randomized, open-label study with a three-arm design, which evaluated the efficacy of tremelimumab plus durvalumab and chemotherapy (T + D + CT) and durvalumab plus chemotherapy (D + CT) versus chemotherapy alone (CT) in first-line mNSCLC. The addition of a limited course of anti–CTLA-4 to anti–PD-L1 and chemotherapy provides insights into both long-term efficacy and tolerability in the context of common treatment strategies used in the first-line *EGFR*/*ALK* wild-type mNSCLC setting. Here, we report results from the primary and secondary analyses.

## METHODS

### Patients

Patients age ≥ 18 years with stage IV NSCLC[21] were eligible for inclusion, provided they had not previously received systemic therapy for mNSCLC; had Eastern Cooperative Oncology Group performance status 0 or 1; and had measurable disease according to RECIST v1.1.[22] The patients' tumors were to have no sensitizing *EGFR* mutations or *ALK* rearrangements (by local assessment) and PD-L1 expression status that was assessed at a central laboratory using the VENTANA PD-L1 (SP263) immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ)[23] before random assignment. Patients with treated and stable brain metastases were eligible. Complete eligibility criteria are provided in the Data Supplement (online only).

### Study Design and Treatment

Patients were randomly assigned (1:1:1) with stratification by PD-L1 expression (≥ 50% *v* < 50% of TCs), disease stage (IVA *v* IVB, per International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology version 8),[21] and histology (squamous *v* nonsquamous) to tremelimumab 75 mg plus durvalumab 1,500 mg and chemotherapy for up to four 21-day cycles, followed by durvalumab 1,500 mg once every 4 weeks until disease progression (PD), with one additional tremelimumab dose after chemotherapy at week 16/cycle 6 (fifth dose); durvalumab 1,500 mg plus chemotherapy for up to four 21-day cycles, followed by durvalumab 1,500 mg once every 4 weeks until PD; or chemotherapy for up to six 21-day cycles (Data Supplement). Chemotherapy options for all arms included carboplatin plus nab-paclitaxel regardless of histology, cisplatin or carboplatin plus gemcitabine for patients with squamous histology, and cisplatin or carboplatin plus pemetrexed for patients with nonsquamous histology. Patients with nonsquamous histology who received pemetrexed-platinum doublet could receive pemetrexed maintenance therapy if eligible. Patients continued treatment until PD, unacceptable toxicity, or consent withdrawal.

Patients who continued to receive benefit and met the criteria to remain on treatment could continue durvalumab monotherapy beyond PD. In addition, patients 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 (Data Supplement). Full details of criteria for treatment through progression, which was at the investigator's discretion, are provided in the Protocol (online only). In-study crossover was not allowed.

The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol and all modifications were approved by relevant ethics committees and regulatory authorities. All patients provided written informed consent.

### End Points and Assessments

The primary end points were progression-free survival (PFS), evaluated by blinded independent central review (BICR) per RECIST v1.1, and overall survival (OS) for D + CT versus CT. PFS was defined as the time from random assignment to objective PD or death from any cause in the absence of progression and OS as the time from random assignment to death from any cause. Key alpha-controlled secondary end points were PFS and OS for T + D + CT versus CT. Other prespecified secondary end points included 12-month PFS rate, unconfirmed objective response rate (proportion of patients with a complete or partial response on ≥ 1 visit; ORR) by BICR, duration of response (DoR), and safety and tolerability. Additional analyses of efficacy by PD-L1 expression level and by blood tumor mutational burden (also secondary end points) will be reported separately. Further details of end points and assessments, including history of amendments to the primary end points, are provided in the Data Supplement.

### Statistical Analysis

The study planned to randomly assign approximately 1,000 patients to obtain approximately 497 PFS events and 532 OS events across the D + CT and CT arms for the final (primary) analyses of PFS and OS, planned at approximately 75% and 80% maturity, respectively. One interim analysis of PFS and three interim analyses of OS were planned. The alpha was split between the interim and final analyses using the Lan-DeMets spending function that approximates an O'Brien-Fleming approach to account for multiple time point assessments and treatment comparisons.[24] Sample size assumptions are described in the Data Supplement.

To strongly control the type I error at 5% (two-sided), a hierarchical multiple testing procedure with gatekeeping strategy was used across the primary end points and alpha-controlled secondary end points (Data Supplement). Initially, 1% alpha and 4% alpha were allocated to PFS and OS, respectively, for the D + CT versus CT comparison. Positivity for either primary end point enabled alpha recycling to the key secondary PFS and OS end points (T + D + CT *v* CT). If either of the key secondary PFS or OS end points was met, the alpha could be recycled to the other key secondary end point.

The primary and key secondary PFS and OS analyses were performed using a stratified log-rank test adjusted for the stratification variables of tumor PD-L1 expression, disease stage, and histology, with hazard ratios (HRs) and 95% CIs estimated using a stratified Cox proportional hazards model. A sensitivity analysis additionally adjusted for further prespecified covariates (age at random assignment, sex, smoking history, and race). HRs and 95% CIs for patient subgroups were calculated using an unstratified Cox proportional hazards model with treatment as the only covariate. ORR was analyzed using a logistic regression model, adjusted for the same factors as the primary end points, and odds ratios (ORs) and 95% CIs calculated. HRs, ORs, and corresponding 95% CIs were rounded to two decimal places. The Kaplan-Meier method was used to calculate median OS, PFS, and DoR. Efficacy data were analyzed in all randomly assigned patients (intention-to-treat [ITT] population). All patients who received ≥ 1 dose of study treatment (safety population) were included in safety analyses.

## RESULTS

### Patients and Treatment

Between June 27, 2017, and September 19, 2018, 1,013 patients from 142 sites in 18 countries were randomly assigned to T + D + CT (n = 338), D + CT (n = 338), or CT (n = 337; Fig 1). Of those, 997 (98.4%) patients received ≥ 1 dose of study treatment: 331 in the T + D + CT arm, 335 in the D + CT arm, and 331 in the CT arm. One patient randomly assigned to each of the T + D + CT and D + CT arms did not receive immunotherapy; the safety population therefore included 330, 334, and 333 patients in the T + D + CT, D + CT, and CT arms, respectively.

Baseline demographics were generally balanced between the treatment arms (Table 1). Overall, 292 (28.8%) patients had PD-L1 TC ≥ 50%, 502 (49.6%) had stage IVB disease, and 374 (36.9%) had squamous histology. 340 (33.6%) patients were randomly assigned from Asia and 320 (31.6%) from Eastern Europe. The data cutoff was July 24, 2019, for PFS and other RECIST-related end points, and March 12, 2021, for OS, safety, and all other data. As of these dates, the median (range) follow-up in censored patients was 10.3 (0.0-23.1) months for PFS and 34.9 (0.0-44.5) months for OS.

As of March 12, 2021, patients in the T + D + CT and D + CT arms had received a median (range) of 8 (1-49) and 8 (1-48) durvalumab doses, respectively (Data Supplement). In the T + D + CT arm, 218 (66.1%) of 330 treated patients received the planned five tremelimumab doses; the most common reason for tremelimumab discontinuation was PD.

The distribution of chemotherapy regimens across arms was generally balanced. Among patients who received chemotherapy, the most common regimens were pemetrexed-platinum for patients with nonsquamous histology (598/626 [95.5%]) and gemcitabine-platinum for those with squamous

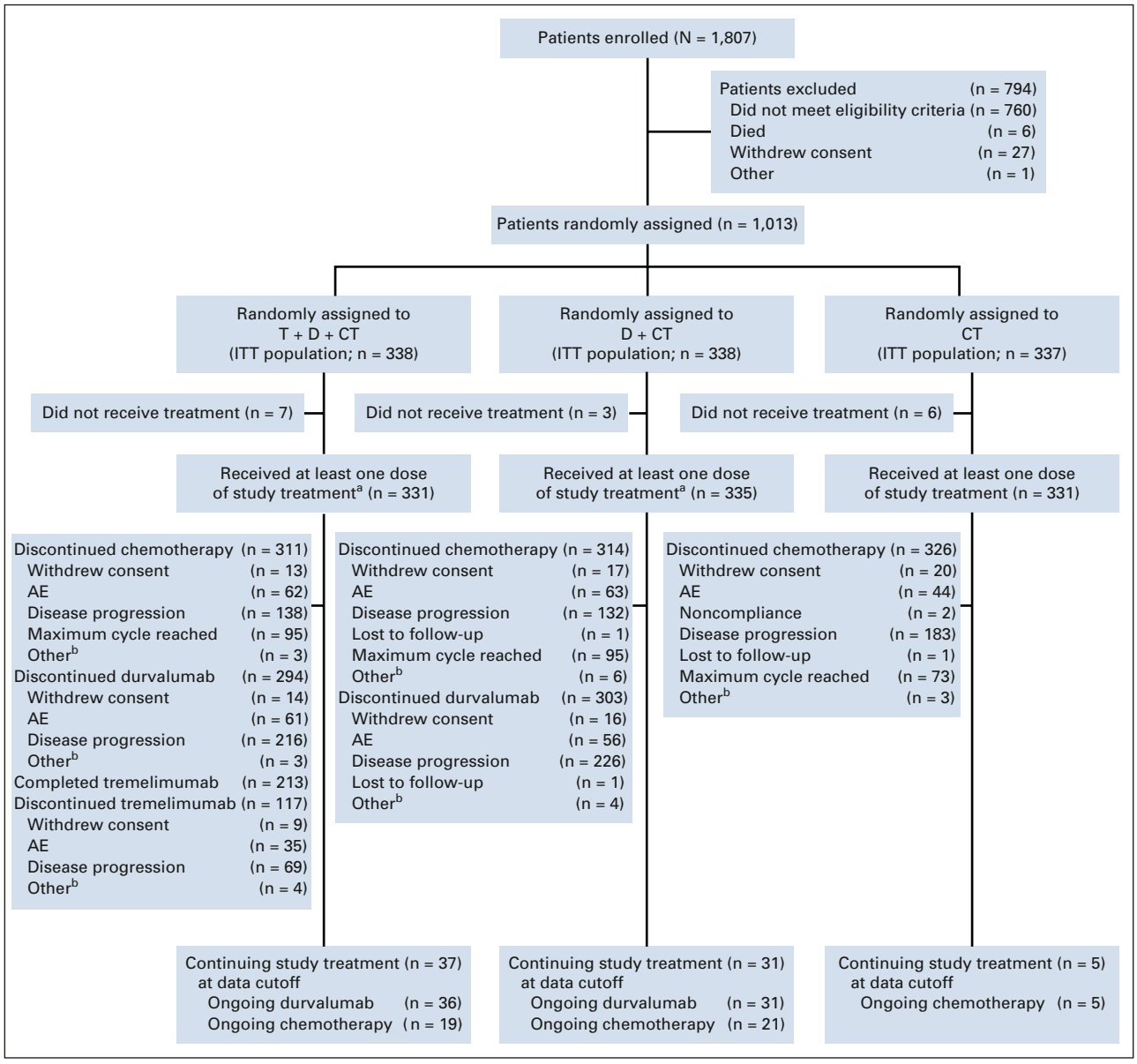


**FIG 1.** CONSORT diagram. Data cutoff date: March 12, 2021. [a]Among these patients, one patient each randomly assigned to the T + D + CT arm and the D + CT arm did not receive immunotherapy and were included in the CT arm of the safety population; one patient randomly assigned to the T + D + CT arm received durvalumab and tremelimumab but not chemotherapy. [b]The most common cause of treatment discontinuations classified as other was investigator's decision (39%). AE, adverse event; CT, chemotherapy; D, durvalumab; ITT, intention-to-treat; T, tremelimumab.

histology (326/369 [88.3%]). In the safety population, 259 (78.5%) patients in the T + D + CT arm and 273 (81.7%) in the D + CT arm received at least four cycles of platinum-based induction chemotherapy. In the CT arm, 247 (74.2%) patients received at least four cycles and 77 (23.1%) received the maximum permitted six cycles of platinum-based induction chemotherapy. Among the patients who received pemetrexed-platinum doublet, fewer patients went on to receive maintenance pemetrexed in the CT versus T + D + CT and D + CT arms (131 [64.2%] *v* 149 [75.3%] and 159 [80.3%], respectively), primarily because of PD.

At the OS data cutoff, 37 patients in the T + D + CT arm and 31 in the D + CT arm remained on durvalumab and/or pemetrexed treatment; five patients in the CT arm remained on pemetrexed (Fig 1).

In the ITT population, 123 (36.4%), 139 (41.1%), and 194 (57.6%) patients received subsequent systemic anticancer therapy in the T + D + CT, D + CT, and CT arms, respectively (Data Supplement). The higher rate of subsequent therapy in the CT arm was driven by immunotherapy administration (22 [6.5%] patients in each of the T + D + CT and D + CT arms *v* 112 [33.2%] in the CT arm), whereas the

**TABLE 1.** Baseline Patient Demographics and Disease Characteristics (ITT population)

| Characteristic | T + D + CT (n = 338) | D + CT (n = 338) | CT (n = 337) |
|---|---|---|---|
| Age, years, median (range) | 63.0 (27-87) | 64.5 (32-87) | 64.0 (32-84) |
| Sex, No. (%) | | | |
| Male | 269 (79.6) | 253 (74.9) | 248 (73.6) |
| Female | 69 (20.4) | 85 (25.1) | 89 (26.4) |
| Race, No. (%) | | | |
| White | 205 (60.7) | 182 (53.8) | 179 (53.1) |
| Asian | 99 (29.3) | 123 (36.4) | 128 (38.0) |
| American Indian/Alaska Native | 12 (3.6) | 17 (5.0) | 9 (2.7) |
| Black/African American | 8 (2.4) | 4 (1.2) | 8 (2.4) |
| Other | 14 (4.1) | 12 (3.6) | 13 (3.9) |
| Geographic region, No. (%) | | | |
| Eastern Europe | 122 (36.1) | 103 (30.5) | 95 (28.2) |
| Asia | 96 (28.4) | 120 (35.5) | 124 (36.8) |
| North America | 44 (13.0) | 46 (13.6) | 40 (11.9) |
| Western Europe | 29 (8.6) | 26 (7.7) | 28 (8.3) |
| South America | 34 (10.1) | 32 (9.5) | 41 (12.2) |
| Africa | 13 (3.8) | 11 (3.3) | 9 (2.7) |
| ECOG PS, No. (%) | | | |
| 0 | 110 (32.5) | 109 (32.2) | 119 (35.3) |
| 1 | 228 (67.5) | 229 (67.8) | 217 (64.4) |
| Missing | 0 | 0 | 1 (0.3) |
| Histology, No. (%) | | | |
| Squamous | 124 (36.7) | 128 (37.9) | 122 (36.2) |
| Nonsquamous | 214 (63.3) | 209 (61.8) | 214 (63.5) |
| Other or missing | 0 | 1 (0.3) | 1 (0.3) |
| AJCC disease stage, No. (%) | | | |
| IVA | 171 (50.6) | 170 (50.3) | 166 (49.3) |
| IVB | 165 (48.8) | 167 (49.4) | 170 (50.4) |
| Other or missing[a] | 2 (0.6) | 1 (0.3) | 1 (0.3) |
| Smoking history, No. (%) | | | |
| Current smoker | 84 (24.9) | 64 (18.9) | 66 (19.6) |
| Former smoker | 195 (57.7) | 190 (56.2) | 191 (56.7) |
| Never smoker | 59 (17.5) | 84 (24.9) | 79 (23.4) |
| Missing | 0 | 0 | 1 (0.3) |
| PD-L1 expression status, No. (%) | | | |
| TC ≥ 50% | 101 (29.9) | 94 (27.8) | 97 (28.8) |
| TC < 50% | 237 (70.1) | 243 (71.9) | 240 (71.2) |
| TC ≥ 1% | 213 (63.0) | 224 (66.3) | 207 (61.4) |
| TC < 1% | 125 (37.0) | 113 (33.4) | 130 (38.6) |
| Missing | 0 | 1 (0.3) | 0 |
| CNS metastases, No. (%) | 33 (9.8) | 28 (8.3) | 45 (13.4) |
| Liver metastases, No. (%) | 69 (20.4) | 62 (18.3) | 80 (23.7) |

Abbreviations: AJCC, American Joint Committee on Cancer; CT, chemotheraphy; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; PD-L1, programmed cell death ligand-1; T, tremelimumab; TC, tumor cell.

[a]Two patients in the tremelimumab plus durvalumab and chemotherapy arm and one in the durvalumab plus chemotherapy arm were incorrectly randomly assigned with stage III disease; these were reported as protocol deviations.

rate of second-line chemotherapy use was similar across the arms.

### Efficacy

***PFS/OS With D + CT Versus CT.*** Five hundred eleven of 675 patients experienced PD or died across the D + CT and CT arms (75.7% maturity). PFS was significantly improved with D + CT versus CT (HR, 0.74; 95% CI, 0.62 to 0.89; $P = .0009$; Fig 2A). The median PFS was 5.5 (95% CI, 4.7 to 6.5) versus 4.8 (95% CI, 4.6 to 5.8) months in the D + CT and CT arms, respectively, with 12-month PFS rates of 24.4% versus 13.1%.

Five hundred forty-nine of 675 patients died across the D + CT and CT arms (81.3% maturity). Although a trend for improvement in OS was observed for D + CT versus CT, this was not statistically significant (HR, 0.86; 95% CI, 0.72 to 1.02; $P = .0758$; Fig 2B). The median OS was 13.3 (95% CI, 11.4 to 14.7) versus 11.7 (95% CI, 10.5 to 13.1) months with D + CT versus CT, respectively, and 24-month OS rates were 29.6% versus 22.1%. PFS and OS benefit with D + CT versus CT was generally consistent with the ITT population across patient subgroups (Fig 3A and Data Supplement). A sensitivity analysis showed minimal impact of prespecified covariates on

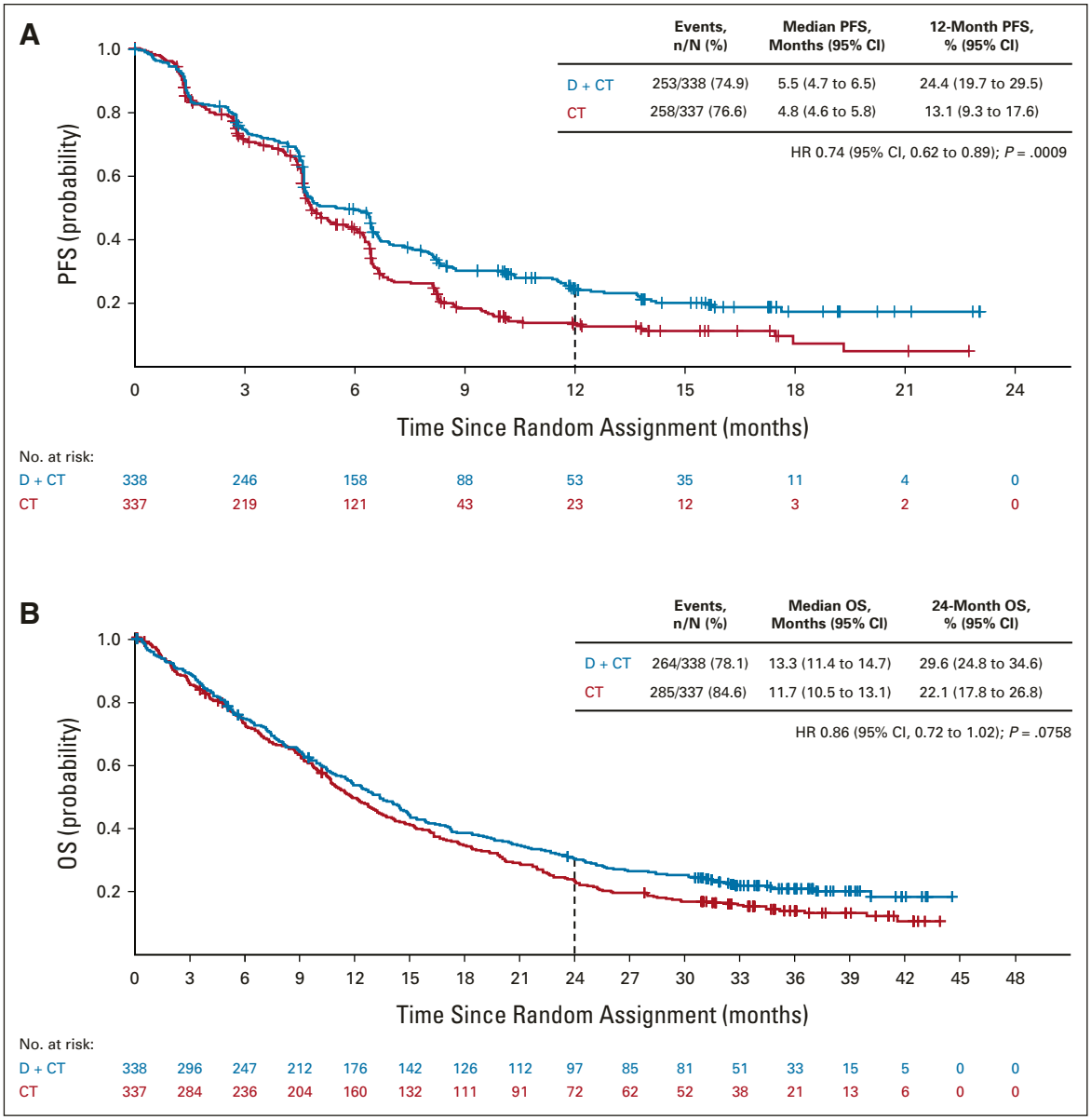


**FIG 2.** (A) PFS and (B) OS (ITT) with D + CT versus CT. (C) PFS and (D) OS (ITT) with T + D + CT versus CT. Data cutoff date for PFS: July 24, 2019. Data cutoff date for OS: March 12, 2021. One patient died 1 day before random assignment and was censored at day 1. CT, chemotherapy; D, durvalumab; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; T, tremelimumab. (continued on following page)

  

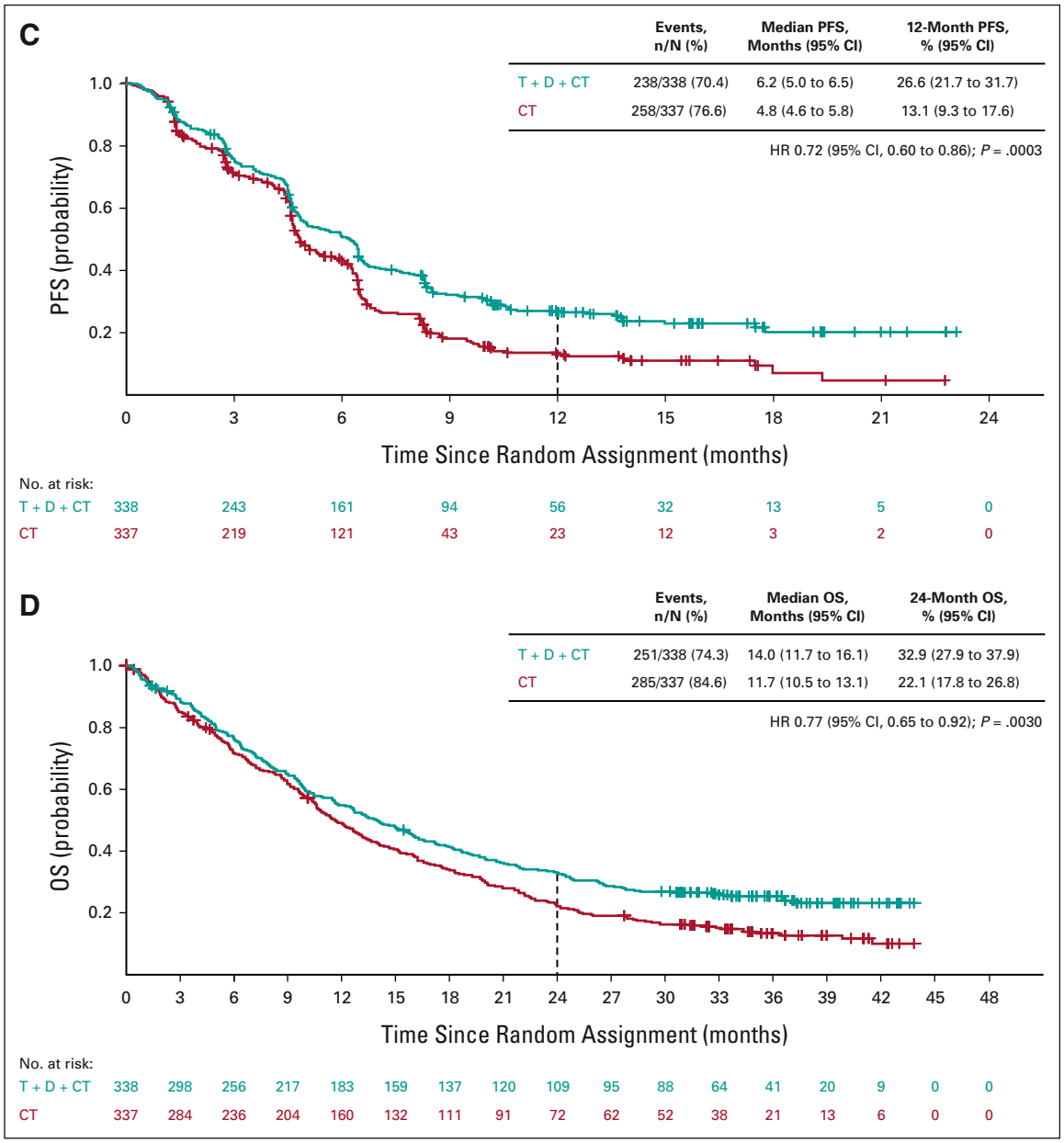


**FIG 2.** (Continued).

the HR estimates for PFS (0.75; 95% CI, 0.63 to 0.90) and OS (0.83; 95% CI, 0.70 to 0.99).

***PFS/OS With T + D + CT Versus CT.*** PFS for T + D + CT versus CT could be formally assessed as the primary PFS end point for D + CT versus CT had been met. As this key secondary end point was also met, the comparison of OS for T + D + CT versus CT was also formally assessed.

Both PFS (HR, 0.72; 95% CI, 0.60 to 0.86; $P = .0003$) and OS (HR, 0.77; 95% CI, 0.65 to 0.92; $P = .0030$) showed statistically significant improvement for T + D + CT versus CT (Figs 2C and 2D). The median PFS was 6.2 months (95% CI, 5.0 to 6.5) versus 4.8 months (95% CI, 4.6 to 5.8), with 12-month PFS rates of 26.6% versus 13.1%, in the T + D + CT arm versus CT arm, respectively. The median OS was 14.0 months (95% CI, 11.7 to 16.1) with T + D + CT versus 11.7 months (95% CI, 10.5 to 13.1) with CT; 24-month OS rates were 32.9% versus 22.1%.

The PFS and OS benefit with T + D + CT versus CT was generally consistent with the ITT population across patient subgroups, including all those defined by PD-L1 expression levels (Fig 3B and Data Supplement). PFS and OS benefit appeared more prominent in the subgroup with nonsquamous (than squamous) histology (Fig 4). A sensitivity analysis showed minimal impact of prespecified covariates on the HR estimates

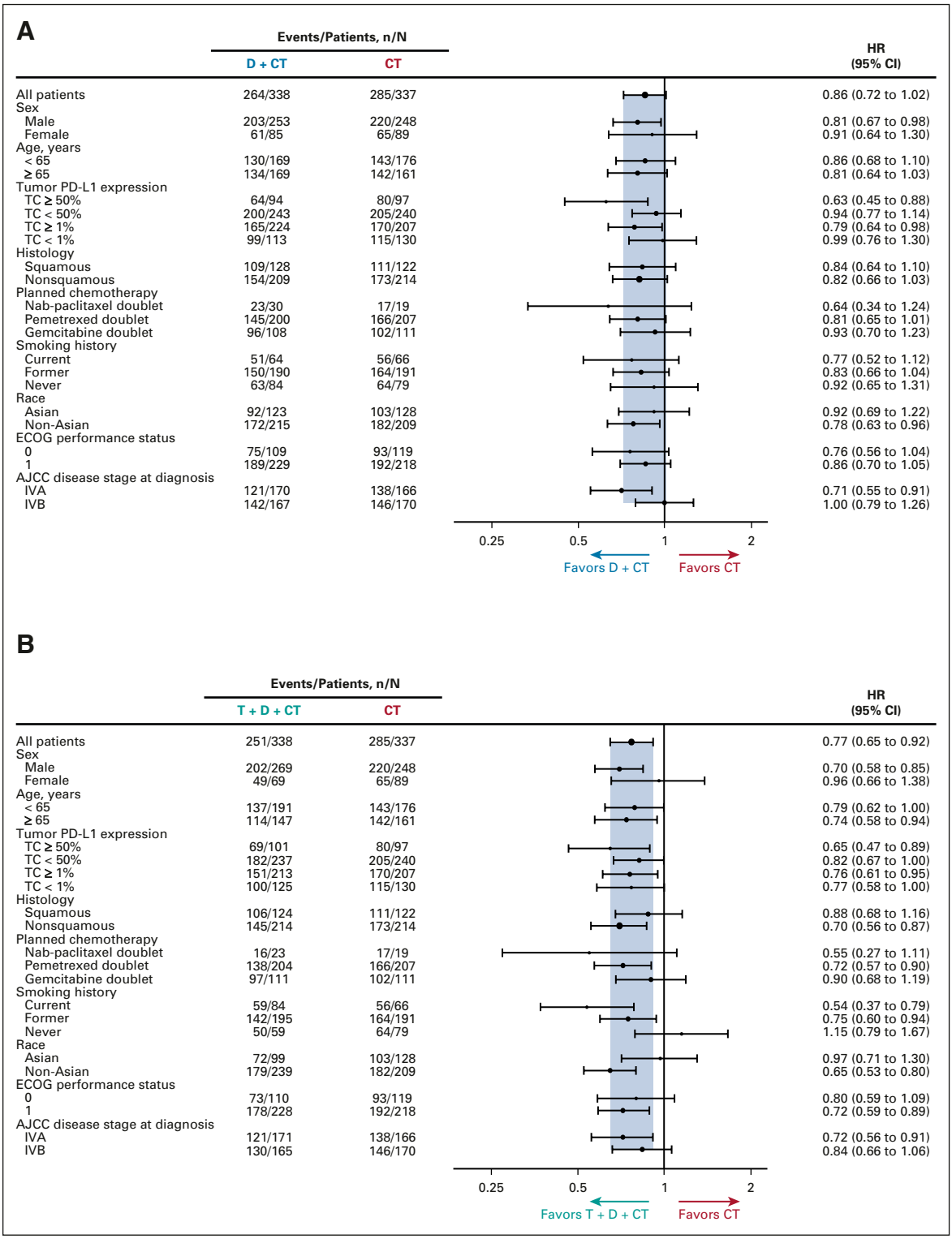


**FIG 3.** OS in patient subgroups with (A) D + CT versus CT or (B) T + D + CT versus CT. Data cutoff date: March 12, 2021. The size of circle in the forest plot is proportional to the number of events across both treatment groups. HRs and 95% CIs in the ITT population were estimated using a Cox proportional hazards model stratified by PD-L1 expression status, histology, and disease stage; HRs and 95% CIs in subgroups were estimated using an unstratified Cox proportional hazards model. AJCC, American Joint Committee on Cancer; 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; PFS, progression-free survival; T, tremelimumab; TC, tumor cell.

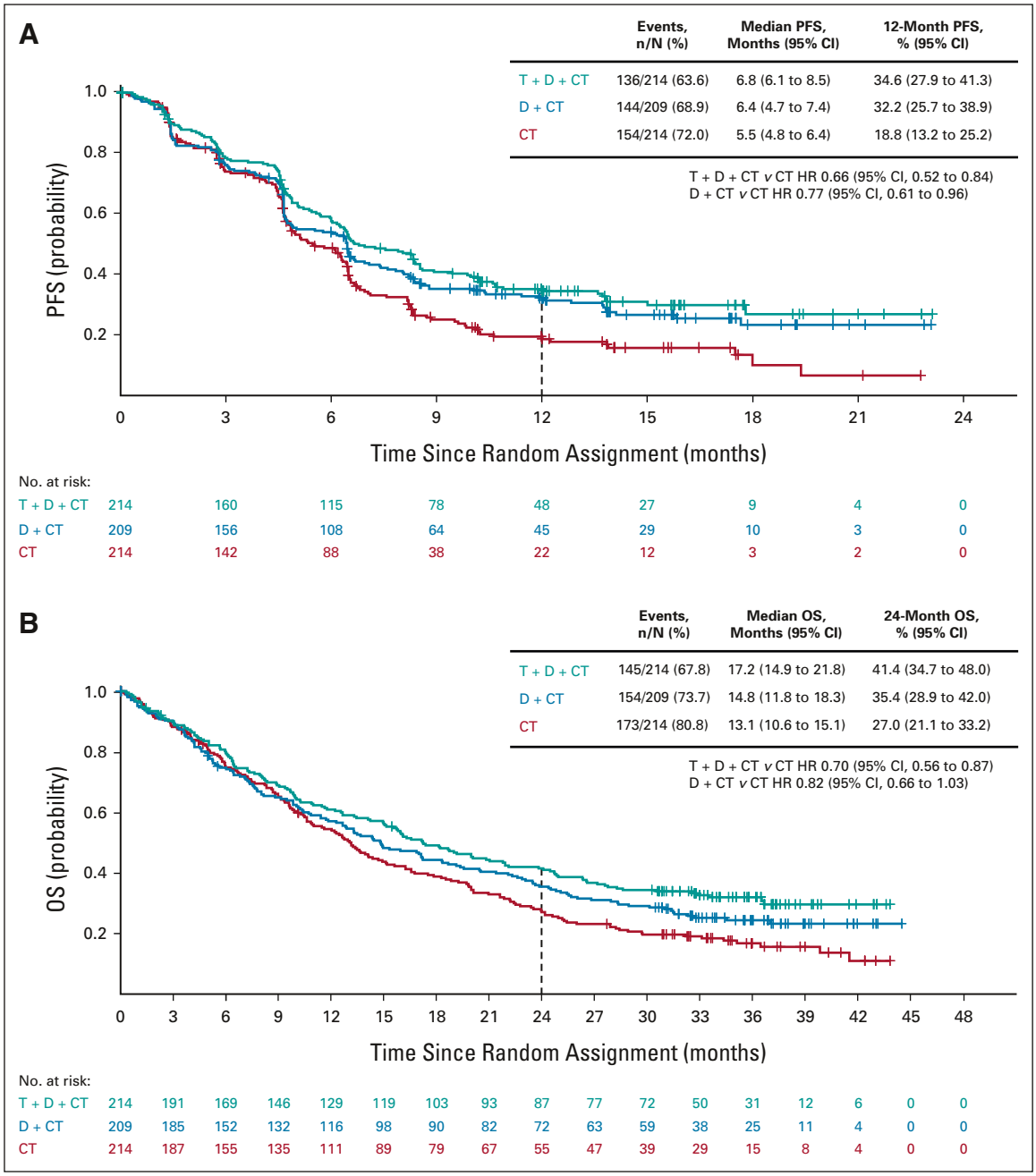


**FIG 4.** (A) PFS and (B) OS in patients with nonsquamous histology. (C) PFS and (D) OS in patients with squamous histology. Data cutoff date for PFS: July 24, 2019. Data cutoff date for OS: March 12, 2021. HRs and 95% CIs were calculated using an unstratified Cox proportional hazards model. CT, chemotherapy; D, durvalumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; T, tremelimumab. (continued on following page)

for PFS (0.70; 95% CI, 0.59 to 0.84) and OS (0.76; 95% CI, 0.63 to 0.90).

***ORR and DoR.*** Unconfirmed ORR was 46.3% with T + D + CT (OR *v* CT, 1.72; 95% CI, 1.26 to 2.37), 48.5% with D + CT (OR *v* CT, 1.90; 95% CI, 1.38 to 2.62), and 33.4% with CT. In a post hoc analysis, the confirmed ORR was 38.8% with T + D + CT (OR *v* CT, 2.00; 95% CI, 1.43 to 2.81), 41.5% with D + CT (OR *v* CT, 2.26; 95% CI, 1.61 to 3.19), and 24.4% with CT.

Among patients with a confirmed response, the median DoR was 9.5 months (95% CI, 7.2 to not estimable) with T + D + CT, 7.0 months (95% CI, 5.7 to 9.9) with D + CT, and 5.1 months (95% CI, 4.4 to 6.0) with CT (Fig 5). Post

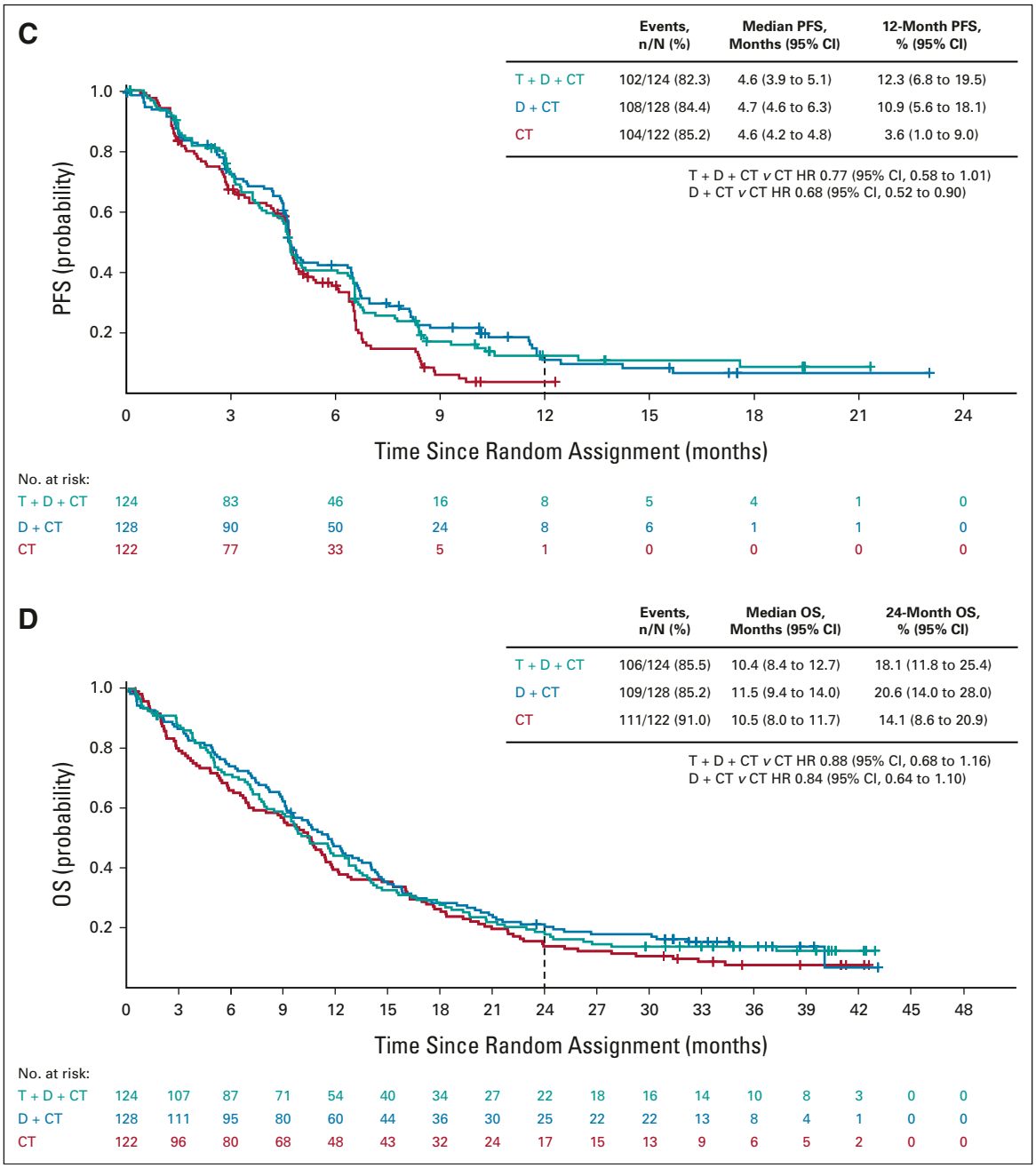


**FIG 4.** (Continued).

hoc analyses of ORR and DoR by histology are included in the Data Supplement.

## Safety

Any-grade adverse events (AEs) considered by the investigator to be treatment-related (TRAEs) were reported in 306 (92.7%), 296 (88.6%), and 298 (89.5%) of patients treated with T + D + CT, D + CT, and CT, respectively (Table 2). The incidence of TRAEs with maximum grade 3/4 severity was numerically higher in the T + D + CT arm (51.8%) compared with the other arms (44.6% for D + CT and 44.4% for CT); a similar pattern was observed for serious TRAEs (27.6% *v* 19.5% and 17.7%). The most common TRAEs of maximum grade 3/4 were anemia and neutropenia.

Treatment-related deaths occurred in 11 (3.3%), 7 (2.1%), and 8 (2.4%) patients treated with T + D + CT, D + CT, and CT, respectively. The incidence of TRAEs leading to treatment discontinuation was similar in the T + D + CT and D + CT arms (15.5% and 14.1%) and numerically lower in the CT arm (9.9%).

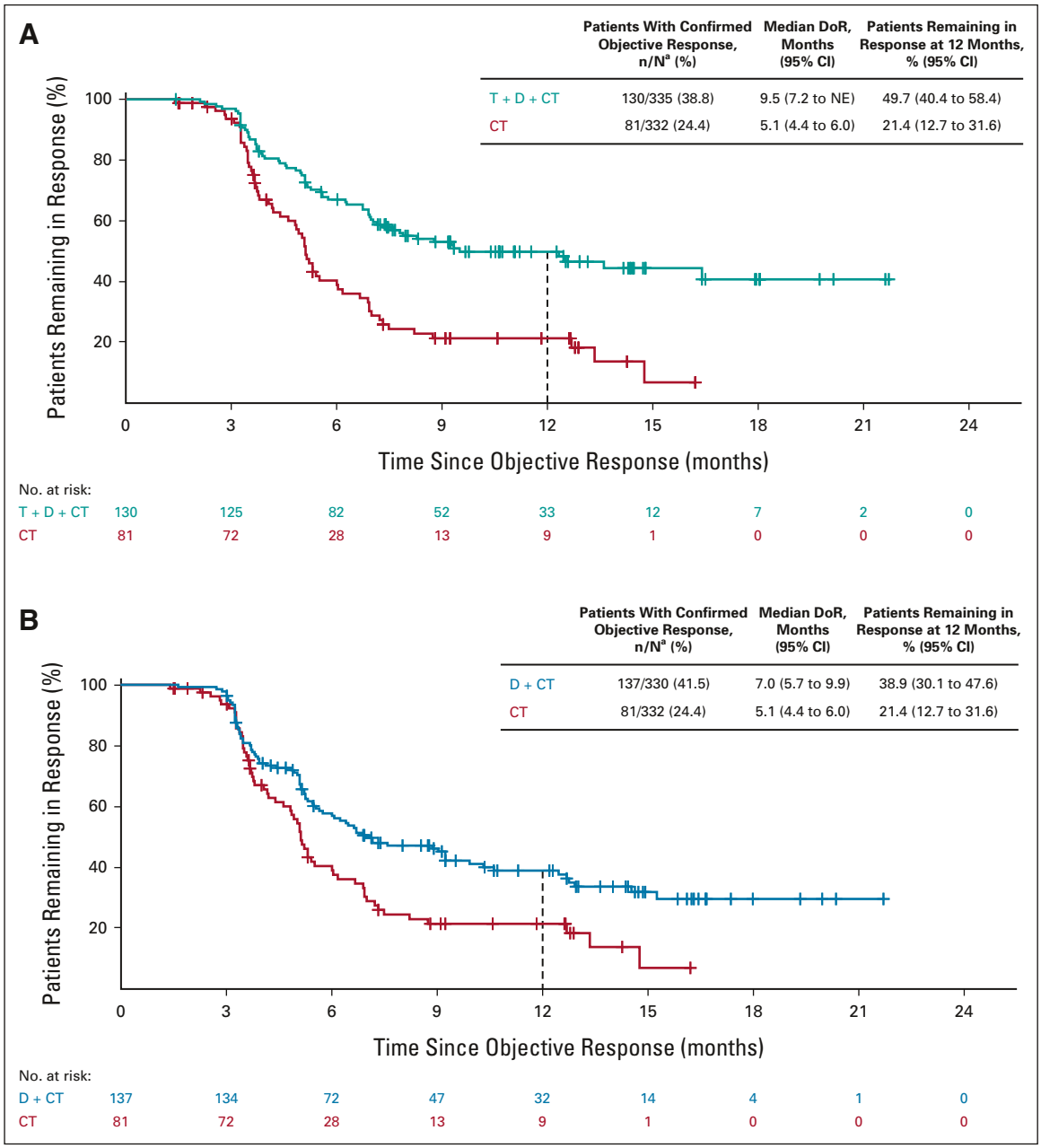


**FIG 5.** Duration of response with (A) T + D + CT versus CT and (B) D + CT versus CT. Data cutoff date: July 24, 2019. Data included are for confirmed response (at least one visit response of complete response or partial response and a confirmatory scan no sooner than 4 weeks after the initial response) by BICR per RECIST v1.1; confirmation was not required per protocol (post hoc analysis). DoR was defined as the time from the first documentation of complete response/partial response until the date of progression, death in absence of progression, or the last evaluable RECIST assessment for patients who progressed or died after two or more missed visits. [a]N = patients with measurable disease at baseline. BICR, blinded independent central review; CT, chemotherapy; D, durvalumab; DoR, duration of response; NE, not estimable; T, tremelimumab.

Immune-mediated AEs occurred in 33.6%, 19.2%, and 5.1% of patients treated with T + D + CT, D + CT, and CT, respectively (Table 2 and Data Supplement). Immune-mediated AEs were maximum grade 3/4 in 10.0%, 6.9%, and 1.5% of patients in the T + D + CT, D + CT, and CT arms, serious in 9.7%, 6.0%, and 1.2%, led to treatment discontinuation in 5.8%, 4.2%, and 0.6%, and led to death in 0.6%, 0.3%, and 0% in the T + D + CT, D + CT, and CT arms, respectively.

Details of any-cause AEs, serious TRAEs, and discontinuations because of TRAEs are reported in the Data Supplement.

**TABLE 2.** Adverse Events in the Safety Population

| | T + D + CT (n = 330) | | D + CT (n = 334) | | CT (n = 333) | |
|---|---|---|---|---|---|---|
| **Event** | **Any Grade** | **Maximum Grade 3/4** | **Any Grade** | **Maximum Grade 3/4** | **Any Grade** | **Maximum Grade 3/4** |
| Treatment-related[a] | | | | | | |
| Any event, No. (%) | 306 (92.7) | 171 (51.8) | 296 (88.6) | 149 (44.6) | 298 (89.5) | 148 (44.4) |
| Any serious event, No. (%) | 91 (27.6) | 70 (21.2) | 65 (19.5) | 48 (14.4) | 59 (17.7) | 44 (13.2) |
| Any event leading to discontinuation,[b] No. (%) | 51 (15.5) | 31 (9.4) | 47 (14.1) | 24 (7.2) | 33 (9.9) | 14 (4.2) |
| Any event leading to death,[c] No. (%) | 11 (3.3) | — | 7 (2.1) | — | 8 (2.4) | — |
| Event occurring in ≥ 10% of patients in any group,[d] No. (%) | | | | | | |
| Anemia | 144 (43.6) | 57 (17.3) | 122 (36.5) | 51 (15.3) | 145 (43.5) | 68 (20.4) |
| Nausea | 124 (37.6) | 4 (1.2) | 104 (31.1) | 1 (0.3) | 115 (34.5) | 5 (1.5) |
| Neutropenia | 96 (29.1) | 53 (16.1) | 74 (22.2) | 42 (12.6) | 75 (22.5) | 40 (12.0) |
| Decreased appetite | 69 (20.9) | 5 (1.5) | 56 (16.8) | 1 (0.3) | 70 (21.0) | 4 (1.2) |
| Fatigue | 65 (19.7) | 5 (1.5) | 67 (20.1) | 7 (2.1) | 62 (18.6) | 7 (2.1) |
| Thrombocytopenia | 53 (16.1) | 18 (5.5) | 39 (11.7) | 15 (4.5) | 53 (15.9) | 17 (5.1) |
| Neutrophil count decreased | 35 (10.6) | 24 (7.3) | 42 (12.6) | 24 (7.2) | 57 (17.1) | 25 (7.5) |
| Vomiting | 47 (14.2) | 4 (1.2) | 39 (11.7) | 1 (0.3) | 40 (12.0) | 4 (1.2) |
| ALT increased | 34 (10.3) | 4 (1.2) | 40 (12.0) | 7 (2.1) | 41 (12.3) | 7 (2.1) |
| Diarrhea | 46 (13.9) | 5 (1.5) | 34 (10.2) | 4 (1.2) | 35 (10.5) | 4 (1.2) |
| Constipation | 27 (8.2) | 0 | 33 (9.9) | 0 | 49 (14.7) | 2 (0.6) |
| Leukopenia | 42 (12.7) | 9 (2.7) | 28 (8.4) | 8 (2.4) | 36 (10.8) | 12 (3.6) |
| Rash | 52 (15.8) | 4 (1.2) | 39 (11.7) | 3 (0.9) | 10 (3.0) | 0 |
| AST increased | 32 (9.7) | 1 (0.3) | 34 (10.2) | 3 (0.9) | 31 (9.3) | 0 |
| Asthenia | 41 (12.4) | 8 (2.4) | 20 (6.0) | 3 (0.9) | 26 (7.8) | 5 (1.5) |
| Alopecia | 31 (9.4) | 0 | 35 (10.5) | 0 | 20 (6.0) | 0 |
| Hypothyroidism | 35 (10.6) | 0 | 16 (4.8) | 0 | 3 (0.9) | 0 |
| Immune-mediated (grouped terms)[e] | | | | | | |
| Any event, No. (%) | 111 (33.6) | 33 (10.0) | 64 (19.2) | 23 (6.9) | 17 (5.1) | 5 (1.5) |
| Any serious event, No. (%) | 32 (9.7) | 25 (7.6) | 20 (6.0) | 16 (4.8) | 4 (1.2) | 3 (0.9) |
| Any event leading to discontinuation,[b] No. (%) | 19 (5.8) | 12 (3.6) | 14 (4.2) | 10 (3.0) | 2 (0.6) | 2 (0.6) |
| Any event leading to death, No. (%) | 2 (0.6) | — | 1 (0.3) | — | 0 | — |
| Event occurring in ≥ 2% of patients in any group,[d] No. (%) | | | | | | |
| Hypothyroid events | 27 (8.2) | 0 | 20 (6.0) | 0 | 3 (0.9) | 0 |
| Pneumonitis | 12 (3.6) | 3 (0.9) | 10 (3.0) | 4 (1.2) | 2 (0.6) | 2 (0.6) |
| Rash | 13 (3.9) | 3 (0.9) | 5 (1.5) | 2 (0.6) | 6 (1.8) | 2 (0.6) |
| Hepatic events | 12 (3.6) | 7 (2.1) | 11 (3.3) | 8 (2.4) | 0 | 0 |
| Dermatitis | 14 (4.2) | 1 (0.3) | 4 (1.2) | 1 (0.3) | 1 (0.3) | 0 |
| Colitis | 13 (3.9) | 5 (1.5) | 4 (1.2) | 1 (0.3) | 0 | 0 |
| Hyperthyroid events | 9 (2.7) | 0 | 4 (1.2) | 1 (0.3) | 1 (0.3) | 0 |
| Adrenal insufficiency | 8 (2.4) | 2 (0.6) | 4 (1.2) | 1 (0.3) | 0 | 0 |

NOTE. Data cutoff date: March 12, 2021. Includes adverse events that occurred during the treatment period and up to 90 days after the last dose of study treatment or up to the start of any subsequent therapy (whichever occurred first).

Abbreviations: CT, chemotherapy; D, durvalumab; T, tremelimumab.

[a]Adverse events assessed by the investigator as possibly related to any study treatment.

[b]Includes patients who permanently discontinued at least one study drug.

[c]Treatment-related adverse events leading to death were autoimmune hepatitis, autoimmune myocarditis, autoimmune nephritis, and autoimmune pancreatitis (all in the same patient), sepsis in two patients, and acute kidney injury, COVID-19, death, febrile neutropenia, gastric ulcer perforation, ischemic stroke, pneumonitis, and renal failure in one patient each in the tremelimumab plus durvalumab and chemotherapy arm; acute cardiac failure, acute kidney injury, acute myocardial infarction, death, febrile neutropenia, pneumonia, and pulmonary embolism in one patient each in the durvalumab plus chemotherapy arm; and pancytopenia and pneumonia (in the same patient), febrile neutropenia and pulmonary embolism in two patients each, and acute myocardial infarction, pneumonia, and pulmonary artery thrombosis in one patient each in the chemotherapy arm.

[d]The events are listed in descending order of frequency across all three treatment groups.

[e]An adverse event of special interest consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology, and requiring the use of systemic steroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy.

## DISCUSSION

In POSEIDON, first-line D + CT significantly improved PFS versus CT in patients with mNSCLC, with a positive trend for OS improvement that did not reach statistical significance. First-line T + D + CT demonstrated statistically significant and clinically meaningful improvements in both PFS and OS versus CT. Both T + D + CT and D + CT demonstrated higher 12-month PFS and 24-month OS rates compared with CT. The delayed separation of the Kaplan-Meier curves for each experimental arm versus CT suggests the HRs should be considered as an average estimate of treatment benefit, with survival landmarks as well as durability of responses being an important component of efficacy assessment for this class of therapies. Although not formally assessed in the statistical analysis plan, the addition of tremelimumab to durvalumab and chemotherapy led to more durable responses than were observed with D + CT, and a notable separation of the survival curves, particularly at later landmarks.

Overall, the four-drug T + D + CT regimen was well tolerated. The most common AEs across all arms were those typically associated with chemotherapy. Although more frequent with T + D + CT than with D + CT, immune-mediated AEs were generally low grade and manageable within current guidelines. Treatment discontinuations because of TRAEs were similar in the T + D + CT and D + CT arms, with similar exposure to chemotherapy and durvalumab achieved in both arms.

POSEIDON is a three-arm trial comparing two experimental regimens—anti–CTLA-4 plus anti–PD-(L)1 and chemotherapy, and anti–PD-(L)1 plus chemotherapy—with a chemotherapy control arm, allowing the optimal use of anti–CTLA-4 therapy with commonly used treatment strategies to be considered. Among patients with PD-L1 TC ≥ 1% mNSCLC, survival benefit with T + D + CT, and especially D + CT, versus CT appeared to be greatest in the PD-L1 TC ≥ 50% subgroup; notably, patients with PD-L1 TC < 1% mNSCLC, in particular, appeared to gain improved survival benefit from the addition of tremelimumab to durvalumab and chemotherapy, consistent with the role of CTLA-4 and PD-(L)1 checkpoints in the immune response. This observation has particular clinical relevance, given that patients with PD-L1–low or PD-L1–negative (*v* PD-L1–high) tumors are more likely to show primary resistance to anti–PD-(L)1 therapy.[9] Real-world data suggest that the treatment benefit observed in patients with PD-L1–low or PD-L1–negative NSCLC in a clinical trial setting does not necessarily translate into optimal outcomes in clinical practice with the treatment options currently available.[8] Consistent with our observations, CTLA-4 (ipilimumab) plus PD-1 (nivolumab) and chemotherapy also seemed to confer benefit versus chemotherapy for patients with PD-L1 TC < 1% mNSCLC in CheckMate 9LA.[20] Further analysis of the POSEIDON data set will help to characterize those patients most likely to gain maximum benefit from the combination of tremelimumab with durvalumab and chemotherapy.

PFS and OS benefit with T + D + CT versus CT appeared to be more prominent among patients with nonsquamous (than squamous) histology. Although squamous histology is generally associated with a worse prognosis, median and landmark PFS, OS, and DoR values were particularly poor for this subgroup across all treatment arms. There was no obvious explanation for this finding; however, we note that, in POSEIDON, most patients with squamous histology received gemcitabine-platinum (88.3%; others received nab-paclitaxel-carboplatin) doublet chemotherapy, unlike most other studies of immunotherapy in combination with chemotherapy. In CheckMate-9LA, patients with squamous histology received paclitaxel plus carboplatin.[20] Although patients receiving nab-paclitaxel-carboplatin in POSEIDON had improved treatment benefit with T + D + CT or D + CT versus CT compared with those receiving gemcitabine-platinum, the results of the subgroup analysis should be interpreted with caution because of small sample sizes. Whether some chemotherapy regimens are superior to others in engaging the immune response in combination with immunotherapies is an important area for clinical research as these treatments become established standards of care in lung cancer. There are currently only limited data for gemcitabine from trials of immunotherapy plus chemotherapy in NSCLC; subgroup data from IMpower010 suggested a lack of benefit for atezolizumab versus best supportive care following gemcitabine-cisplatin adjuvant chemotherapy in resected stage IB–IIIA NSCLC.[25]

POSEIDON was a multiregional study with a design intended to reflect broad clinical practice patterns across mNSCLC globally, encompassing patients with both squamous and nonsquamous histology and permitting the use of multiple chemotherapy regimens and up to six cycles of platinum-based induction chemotherapy in the control arm (patients in the T + D + CT and D + CT arms could receive up to four cycles). The inclusion of the D + CT arm allowed assessment of the contribution of a limited course of anti–CTLA-4 within the study, although the two experimental arms were not formally compared. The broad study remit is both a strength and a weakness, ensuring the results have real-world applicability but leading to a more heterogeneous patient population, which complicates interpretation. Although chemotherapy was the standard of care in this setting at the time of starting the trial, this is now no longer the case in many regions because of advances in the treatment landscape during the trial. The open-label design means that patient withdrawals and attribution of causality for AEs may have been affected by open-label bias, although the RECIST-related end points assessed by BICR and OS should not have been.

In conclusion, D + CT significantly improved PFS and T + D + CT significantly improved OS and PFS versus CT. Adding a limited course of tremelimumab to durvalumab and four cycles of chemotherapy provided long-term

survival benefit for patients with mNSCLC, alongside early disease control and a manageable tolerability profile, without compromising treatment exposure. The addition of anti–CTLA-4 extended clinical benefit to patients with PD-L1 TC < 1%: a subgroup with hard-to-treat disease and outcomes that can be suboptimal in clinical practice with currently available treatments. T + D + CT may represent a new first-line treatment option in mNSCLC.


## AFFILIATIONS

[1]Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN
[2]Yonsei Cancer Center, Seoul, South Korea
[3]Leningrad Regional Clinical Hospital, St Petersburg, Russia
[4]Health Pharma Professional Research, Mexico City, Mexico
[5]Prince of Songkla University, Songkhla, Thailand
[6]Federal 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
[7]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea
[8]Acinus, Kropyvnytskyi, Ukraine
[9]Florida Cancer Specialists—Sarah Cannon Research Institute, Leesburg, FL
[10]Queen Mary University of London, London, United Kingdom
[11]Chang Gung Memorial Hospital, Taoyuan City, Taiwan
[12]Instituto Nacional de Cancer-INCA, Rio de Janeiro, Brazil
[13]Kanagawa Cancer Center, Yokohama, Japan
[14]Asklepios Lung Clinic, member of the German Center for Lung Research (DZL), Munich-Gauting, Germany
[15]AstraZeneca, Gaithersburg, MD
[16]AstraZeneca, Cambridge, United Kingdom
[17]Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland
[18]David Geffen School of Medicine at UCLA, Los Angeles, CA
[19]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong, China

## CORRESPONDING AUTHOR

Melissa L. Johnson, MD, Sarah Cannon Research Institute—Tennessee Oncology, 250 25th Ave North, Suite 100, Nashville, TN 37203; e-mail: mjohnson@tnonc.com.



## PRIOR PRESENTATION

Presented in part as an oral presentation at the World Conference on Lung Cancer, virtual, September 8-14, 2021.

## SUPPORT

Supported by AstraZeneca.

## CLINICAL TRIAL INFORMATION

NCT03164616


## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.00975.

## 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.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Melissa L. Johnson, Byoung Chul Cho, Maen Hussein, Xiaojin Shi, Solange Peters, Edward B. Garon, Tony Mok
**Provision of study materials or patients:** Alexander Luft, Sang-We Kim, Grygorii Ursol, Cheng-Ta Yang, Luiz Henrique Araujo, Haruhiro Saito, Niels Reinmuth, Edward B. Garon, Tony Mok
**Collection and assembly of data:** Melissa L. Johnson, Byoung Chul Cho, Alexander Luft, Jorge Alatorre-Alexander, Sarayut Lucien Geater, Konstantin Laktionov, Sang-We Kim, Grygorii Ursol, Farah Louise Lim, Cheng-Ta Yang, Luiz Henrique Araujo, Haruhiro Saito, Xiaojin Shi, Solange Peters, Edward B. Garon, Tony Mok
**Data analysis and interpretation:** Melissa L. Johnson, Byoung Chul Cho, Jorge Alatorre-Alexander, Sarayut Lucien Geater, Konstantin Laktionov, Sang-We Kim, Cheng-Ta Yang, Luiz Henrique Araujo, Haruhiro Saito, Niels Reinmuth, Xiaojin Shi, Lynne Poole, Solange Peters, Edward B. Garon, Tony Mok
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors


## ACKNOWLEDGMENT

The authors would like to thank the patients, their families and caregivers, and all investigators involved in this study. Medical writing support, under the direction of the authors, was provided by James Holland, PhD, and Samantha Holmes, DPhil, of Ashfield MedComms (Macclesfield, United Kingdom), an Inizio company, and was funded by AstraZeneca.

A complete list of investigators who enrolled patients in POSEIDON is provided in Appendix 1 (online only).


## REFERENCES


1. Paz-Ares L, Luft A, Vicente D, et al: Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 379:2040-2051, 2018
2. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378:2078-2092, 2018
3. Mok TSK, Wu YL, Kudaba I, et al: Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. Lancet 393:1819-1830, 2019
4. Socinski MA, Jotte RM, Cappuzzo F, et al: Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 378:2288-2301, 2018
5. West H, McCleod M, Hussein M, et al: Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 20:924-937, 2019
6. Herbst RS, Giaccone G, de Marinis F, et al: Atezolizumab for first-line treatment of PD-L1–selected patients with NSCLC. N Engl J Med 383:1328-1339, 2020
7. Sezer A, Kilickap S, Gümüş M, et al: Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: A multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet 397:592-604, 2021

8. Waterhouse D, Lam J, Betts KA, et al: Real-world outcomes of immunotherapy-based regimens in first-line advanced non-small cell lung cancer. Lung Cancer 156:41-49, 2021
9. Chocarro de Erauso L, Zuazo M, Arasanz H, et al: Resistance to PD-L1/PD-1 blockade immunotherapy. A tumor-intrinsic or tumor-extrinsic phenomenon? Front Pharmacol 11:441, 2020
10. Sun J-Y, Zhang D, Wu S, et al: Resistance to PD-1/PD-L1 blockade cancer immunotherapy: Mechanisms, predictive factors, and future perspectives. Biomarker Res 8:35, 2020
11. Garon EB, Rizvi NA, Hui R, et al: Pembrolizumab for the treatment of non–small-cell lung cancer. N Engl J Med 372:2018-2028, 2015
12. Stewart R, Morrow M, Hammond SA, et al: Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 3:1052-1062, 2015
13. Tarhini AA, Kirkwood JM: Tremelimumab (CP-675,206): A fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. Expert Opin Biol Ther 8:1583-1593, 2008
14. Buchbinder EI, Desai A: CTLA-4 and PD-1 pathways: Similarities, differences, and implications of their inhibition. Am J Clin Oncol 39:98-106, 2016
15. Huang RR, Jalil J, Economou JS, et al: CTLA4 blockade induces frequent tumor infiltration by activated lymphocytes regardless of clinical responses in humans. Clin Cancer Res 17:4101-4109, 2011
16. Cha E, Klinger M, Hou Y, et al: Improved survival with T cell clonotype stability after anti-CTLA-4 treatment in cancer patients. Sci Transl Med 6:238ra70, 2014
17. Robert L, Tsoi J, Wang X, et al: CTLA4 blockade broadens the peripheral T-cell receptor repertoire. Clin Cancer Res 20:2424-2432, 2014
18. Akinleye A, Rasool Z: Immune checkpoint inhibitors of PD-L1 as cancer therapeutics. J Hematol Oncol 12:92, 2019
19. Asadzadeh Z, Safarzadeh E, Safaei S, et al: Current approaches for combination therapy of cancer: The role of immunogenic cell death. Cancers 12:1047, 2020
20. Paz-Ares L, Ciuleanu T-E, Cobo M, et al: First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): An international, randomised, open-label, phase 3 trial. Lancet Oncol 22:198-211, 2021
21. Rami-Porta R: IASLC Staging Manual in Thoracic Oncology, 2nd ed. North Fort Myers, FL, Editorial Rx Press, 2016
22. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009
23. Rebelatto MC, Midha A, Mistry A, et al: Development of a programmed cell death ligand-1 immunohistochemical assay validated for analysis of non-small cell lung cancer and head and neck squamous cell carcinoma. Diagn Pathol 11:95, 2016
24. Lan KKG, DeMets DL: Discrete sequential boundaries for clinical trials. Biometrika 70:659-663, 1983
25. Felip E, Altorki N, Zhou C, et al: Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase 3 trial. Lancet 398:1344-1357, 2021

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

**Melissa L. Johnson**
**Consulting or Advisory Role:** Genentech/Roche (Inst), Boehringer Ingelheim (Inst), AstraZeneca (Inst), Calithera Biosciences (Inst), Merck (Inst), Sanofi (Inst), Mirati Therapeutics (Inst), Ribon Therapeutics (Inst), AbbVie (Inst), GlaxoSmithKline (Inst), Gritstone Bio (Inst), Janssen Oncology (Inst), Lilly (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Daiichi Sankyo (Inst), EMD Serono (Inst), G1 Therapeutics (Inst), WindMIL (Inst), Eisai (Inst), Axelia Oncology (Inst), Black Diamond Therapeutics (Inst), CytomX Therapeutics (Inst), EcoR1 Capital (Inst), Editas Medicine (Inst), Genmab (Inst), IDEAYA Biosciences (Inst), ITeos Therapeutics (Inst), Oncorus (Inst), Regeneron (Inst), Turning Point Therapeutics (Inst), Astellas Pharma (Inst)
**Research Funding:** EMD Serono (Inst), Kadmon (Inst), Janssen (Inst), Mirati Therapeutics (Inst), Genmab (Inst), Pfizer (Inst), AstraZeneca (Inst), Stem CentRx (Inst), Novartis (Inst), Checkpoint Therapeutics (Inst), Array BioPharma (Inst), Regeneron (Inst), Merck (Inst), Hengrui Pharmaceutical (Inst), Lycera (Inst), BeiGene (Inst), Tarveda Therapeutics (Inst), Loxo (Inst), AbbVie (Inst), Boehringer Ingelheim (Inst), Guardant Health (Inst), Daiichi Sankyo (Inst), Sanofi (Inst), CytomX Therapeutics (Inst), Dynavax Technologies (Inst), Corvus Pharmaceuticals (Inst), Incyte (Inst), Genocea Biosciences (Inst), Gritstone Bio (Inst), Amgen (Inst), Genentech/Roche (Inst), Adaptimmune (Inst), Syndax (Inst), Neovia Oncology (Inst), Acerta Pharma (Inst), Takeda (Inst), Shattuck Labs (Inst), GlaxoSmithKline (Inst), Apexigen (Inst), Atreca (Inst), OncoMed (Inst), Lilly (Inst), Immunocore (Inst), Jounce Therapeutics (Inst), University of Michigan (Inst), WindMIL (Inst), TCR2 Therapeutics (Inst), Arcus Biosciences (Inst), Ribon Therapeutics (Inst), BerGenBio (Inst), Calithera Biosciences (Inst), Tmunity Therapeutics, Inc (Inst), Seven and Eight Biopharmaceuticals (Inst), Rubius Therapeutics (Inst), Curis (Inst), Silicon Therapeutics (Inst), Dracen (Inst), PMV Pharma (Inst), Artios (Inst), BioAtla (Inst), Elicio Therapeutics (Inst), Erasca, Inc (Inst), Harpoon (Inst), Helsinn Healthcare (Inst), Hutchison MediPharma (Inst), IDEAYA Biosciences (Inst), IGM Biosciences (Inst), Memorial Sloan-Kettering Cancer Center (Inst), NeoImmuneTech (Inst), Numab (Inst), RasCal (Inst), Relay Therapeutics (Inst), Revolution Medicines (Inst), Tempest Therapeutics (Inst), Tizona Therapeutics, Inc (Inst), Turning Point Therapeutics (Inst), Vyriad (Inst), Y-mAbs Therapeutics (Inst), Exelixis (Inst), Fate Therapeutics (Inst), Merus (Inst), Black Diamond Therapeutics (Inst), Kartos Therapeutics (Inst), Carisma Therapeutics (Inst), Rain Therapeutics (Inst), Nuvalent, Inc (Inst), Palleon Pharmaceuticals (Inst), Impact Therapeutics (Inst)
**Travel, Accommodations, Expenses:** AbbVie, AstraZeneca, Genentech, Incyte, Merck, Pfizer, Sanofi

**Byoung Chul Cho**
**Leadership:** Interpark Bio, J Ints Bio
**Stock and Other Ownership Interests:** Theravance, Gencurix, Bridgebio, Kanaph Therapeutics, Cyrus Therapeutics, Interpark Bio
**Consulting or Advisory Role:** Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Bristol Myers Squibb, Yuhan, Pfizer, Janssen, Takeda, Merck Sharp & Dohme, Ono Pharmaceutical, Lilly, Medpacto, Blueprint Medicines, Kanaph Therapeutics, Bridgebio, Cyrus Therapeutics, Guardant Health, J INTS BIO
**Research Funding:** Novartis, Bayer, AstraZeneca, Mogam Biotechnology Research Institue, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, Merck Sharp & Dohme, AbbVie, Medpacto, GI Innovation, Lilly, Blueprint Medicines, Interpark Bio
**Patents, Royalties, Other Intellectual Property:** Champions Oncology
**Other Relationship:** DAAN Biotherapeutics

**Sarayut Lucien Geater**
**Honoraria:** AstraZeneca, Boehringer Ingelheim
**Consulting or Advisory Role:** Pfizer
**Research Funding:** AstraZeneca (Inst), Boehringer Ingelheim (Inst), Roche (Inst)

**Maen Hussein**
**Consulting or Advisory Role:** IntegraConnect, Coherus Biosciences, Athenex, Karyopharm Therapeutics, Bristol Myers Squibb, AstraZeneca, Mirati Therapeutics, Exelixis, Biopharma, AbbVie, AstraZeneca, Oncocyte, Aptitude Health

**Luiz Henrique Araujo**
**Consulting or Advisory Role:** Merck Sharp & Dohme, Bristol Myers Squibb, AstraZeneca, Pfizer, Boehringer Ingelheim, Merck, Roche
**Speakers' Bureau:** AstraZeneca, Pfizer, Merck, Roche, Merck Sharp & Dohme, Bristol Myers Squibb, Boehringer Ingelheim
**Research Funding:** Merck Sharp & Dohme (Inst), Bristol Myers Squibb (Inst), AstraZeneca (Inst), Pfizer (Inst), Merck (Inst), Roche (Inst), Boehringer Ingelheim (Inst)

**Haruhiro Saito**
**Speakers' Bureau:** AstraZeneca, Ono Pharmaceutical, Boehringer Ingelheim, Bristol Myers Squibb Japan, Pfizer, Chugai Pharma, Taiho Pharmaceutical
**Research Funding:** AstraZeneca (Inst), Chugai Pharma (Inst), Ono Pharmaceutical (Inst)

**Niels Reinmuth**
**Consulting or Advisory Role:** Bristol Myers Squibb, AstraZeneca, Pfizer, Boehringer Ingelheim, Merck Sharp & Dohme Oncology, Takeda, Amgen
**Speakers' Bureau:** AstraZeneca, Bristol Myers Squibb, Roche, Merck Sharp & Dohme, Pfizer, Boehringer Ingelheim, Takeda, Amgen, Lilly, AbbVie, Merck KGaA
**Travel, Accommodations, Expenses:** Janssen

**Xiaojin Shi**
**Employment:** AstraZeneca
**Stock and Other Ownership Interests:** AstraZeneca

**Lynne Poole**
**Employment:** AstraZeneca
**Stock and Other Ownership Interests:** Lilly, Takeda, AstraZeneca
**Consulting or Advisory Role:** Lilly

**Solange Peters**
**Honoraria:** Roche (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Pfizer (Inst), Merck Sharp & Dohme (Inst), AstraZeneca (Inst), Takeda (Inst), Illumina (Inst), Medscape (Inst), Prime Oncology (Inst), RMEI Medical Education (Inst), Research to Practice (Inst), PER (Inst), Imedex (Inst), Ecancer (Inst), OncologyEducation (Inst), Fishawack Facilitate (Inst)
**Consulting or Advisory Role:** Roche/Genentech (Inst), Novartis (Inst), Bristol Myers Squibb (Inst), Pfizer (Inst), Merck Sharp & Dohme (Inst), Amgen (Inst), AstraZeneca (Inst), Janssen (Inst), Regeneron (Inst), Merck Serono (Inst), Boehringer Ingelheim (Inst), Takeda (Inst), Lilly (Inst), AbbVie (Inst), Bayer (Inst), Biocartis (Inst), Debiopharm Group (Inst), Illumina (Inst), PharmaMar (Inst), Sanofi (Inst), Seattle Genetics (Inst), Blueprint Medicines (Inst), Daiichi Sankyo (Inst), Incyte (Inst), Bioinvent (Inst), Clovis Oncology (Inst), Vaccibody (Inst), Phosplatin Therapeutics (Inst), Foundation Medicine (Inst), Arcus Biosciences (Inst), F-Star Biotechnology (Inst), Genzyme (Inst), Gilead Sciences (Inst), GlaxoSmithKline (Inst)
**Research Funding:** Roche (Inst), Bristol Myers Squibb (Inst), Merck Sharp & Dohme (Inst), Amgen (Inst), Lilly (Inst), AstraZeneca (Inst), Pfizer (Inst), Illumina (Inst), Merck Serono (Inst), Novartis (Inst), Biodesix (Inst), Boehringer Ingelheim (Inst), Iovance Biotherapeutics (Inst), Phosplatin Therapeutics (Inst)
**Travel, Accommodations, Expenses:** Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi, Incyte
**Uncompensated Relationships:** Journal of Thoracic Oncology, ESMO, European Thoracic Oncology Platform (ETOP), Annals of Oncology

**Edward B. Garon**
**Consulting or Advisory Role:** Novartis, GlaxoSmithKline, Merck, Boehringer Ingelheim, Shionogi, Eisai, Bristol Myers Squibb, ABL Bio, Xilio Therapeutics, Natera, Sanofi/Regeneron, Lilly, Personalis, Gilead Sciences, AstraZeneca, AbbVie/ABBOTT
**Research Funding:** Merck (Inst), Genentech (Inst), AstraZeneca (Inst), Novartis (Inst), Lilly (Inst), Bristol Myers Squibb (Inst), Mirati Therapeutics (Inst), Dynavax Technologies (Inst), Iovance Biotherapeutics (Inst), Neon Therapeutics (Inst), EMD Serono (Inst), ABL Bio (Inst)
**Patents, Royalties, Other Intellectual Property:** Diagnostic and therapeutic use of Motif Neoepitopes as defined by Cummings et al in Nature Cancer (Inst)

**Tony Mok**
**Employment:** The Chinese University of Hong Kong
**Leadership:** AstraZeneca, Aurora Tele-Oncology Platform, Lunit, ACT Genomics-Sanomics Group, HUTCHMED
**Stock and Other Ownership Interests:** Aurora Tele-Oncology Platform, HUTCHMED, ACT Genomics-Sanomics Group
**Honoraria:** AstraZeneca, Alpha Biopharma, ACEA Pharmaceutical Research, Amgen, Amoy Diagnostics, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo/UCB Japan, Fishawack Facilitate, InMed, Lilly, Merck Sharp & Dohme, Novartis, Origimed, Pfizer, Prime Oncology, Roche, Sanofi Aventis GmbH, Taiho Pharmaceutical, Takeda, Lucence, Medscape, Permanyer Publications, PeerVoice, Physicans' Education Resource, Research to Practice, Shanghai BeBirds Translation & Consulting, Liangyihui Network Technology Co, Ltd, AbbVie, Berry Oncology, Blueprint Medicines, C4 Therapeutics, CStone Pharmaceuticals, Curio Science, D3, Eisai, Gilead Sciences, Gritstone Bio, Guardant Health, touchIME
**Consulting or Advisory Role:** AbbVie, ACEA Pharmaceutical Research, Alpha Biopharma, Amgen, Amoy Diagnostics, AstraZeneca, BeiGene, Berry Oncology, Boehringer Ingelheim, Blueprint Medicines, Bristol Myers Squibb, CStone Pharmaceuticals, Curio Science, Daiichi Sankyo/UCB Japan, Eisai, Fishawack Facilitate, Gritstone Bio, Guardant Health, Hengrui Therapeutics, Ignyta, Incyte, Inivata, IQvia, Lilly, Loxo, Lunit, Merck Serono, Merck Sharp & Dohme, Mirati Therapeutics, Novartis, Pfizer, Puma Biotechnology, Roche, SFJ Pharmaceuticals Group, Takeda, Vertex, Yuhan, Qiming Development (HK) Ltd, D3, C4 Therapeutics, G1 Therapeutics, Gilead Sciences, Janssen, geneDecode
**Research Funding:** AstraZeneca (Inst), Boehringer Ingelheim (Inst), Pfizer (Inst), Novartis (Inst), SFJ Pharmaceuticals Group (Inst), Roche (Inst), Merck Sharp & Dohme (Inst), Bristol Myers Squibb (Inst), Xcovery (Inst), G1 Therapeutics (Inst), Merck Serono (Inst), Takeda (Inst)

No other potential conflicts of interest were reported.

## APPENDIX 1. LIST OF POSEIDON INVESTIGATORS

**Brazil:** Gustavo Girotto, Luiz Henrique Araujo, Gustavo Pinto, Pedro Marchi, Brigitte M. R. H. Adam van Eyll, Gilberto de Castro, Claudia Sette, Ana Gelatti, Ellias Lima, Juliana de Menezes, Nils Skare, Amanda Faulhaber, Felipe Cruz, Adilson Faccio, Sérgio de Azevedo; **Bulgaria:** Margarita Georgieva, Violetka Venkova, Krassimir Koynov, Ivan Tonev, Rumyana Ilieva, Nadezhda Miteva-Jovcheva, Spartak Valev, Georgi Zhbantov, Asen Dudov; **Germany:** Jens Kern, Niels Reinmuth, Christian Grohe, Eckart Laack, Achim Rittmeyer, Michael Thomas, Juergen Alt, Justyna Rawluk, Claas Wesseler, Wilfried Eberhardt, Frank Griesinger; **Hong Kong:** Tony Mok; **Hungary:** Gyula Ostoros, Andrea Fülöp, Rita Vízhányó, Eszter Csánky, György Losonczy, Gabriella Gálffy; **Japan:** Shintaro Kanda, Tatsuya Yoshida, Makoto Nishio, Hidetoshi Hayashi, Koichi Goto, Hirotsugu Kenmotsu, Kazuo Kasahara, Masahiro Shinoda, Yu Hara, Satoshi Oizumi, Naoyuki Nogami, Toshiyuki Kozuki, Katsuyuki Hotta, Keisuke Aoe, Shoichi Kuyama, Akihiro Bessho, Haruhiro Saito, Isamu Okamoto, Koichi Azuma, Kaoru Kubota, Ken Masuda, Masashi Kondo; **Mexico:** Coonie Deneken Hernández, Froylan López-López, Oscar Arrieta Rodriguez, Osvaldo Hernández Flores, Francisco Medina Soto, Juan Vazquez Limón, Jorge Alatorre-Alexander, Abraham Ruíz García, Víctor Oyervides Juárez, José Escobar Penagos; **Peru:** Alejandro Figueroa, Carlos Farfan, Manuel Leiva, Natalia Valdiviezo, Renzo Alvarez, Luis Riva Gonzalez; **Poland:** Dariusz Kowalski, Andrzej Każarnowicz, Jan Cieślicki, Ewa Chmielowska; **Russia:** Konstantin Laktionov, Aleksandr Vasiliev, Alexander Luft, Galina Statsenko, Alexey Smolin, Vladimir Moiseyenko, Alexey Severtsev, Mikhail Dvorkin; **South Africa:** Paul Ruff, Conrad Jacobs, Bernardo Rapoport, Daniel Rens, Gregory Landers, Lydia Dreosti, Jean-Marc Maurel; **South Korea:** Ki Hyeong Lee, Jong Seok Lee, Sang-We Kim, Jin Seok Ahn, Byoung Chul Cho, Sung Sook Lee, Kyung Hee Lee, Eun Kyung Cho, Jin-Hyoung Kang, Young Joo Min; **Taiwan:** Chao-Hua Chiu, Yu-Feng Wei, Wu-Chou Su, Kang-Yun Lee, Chien-Te Li, Bin-Chuan Ji, Chih-Hsin Yang, Gee-Chen Chang, Tsung-Ying Yang, Cheng-Ta Yang, Te-Chun Hsia, Chin-Chou Wang; **Thailand:** Virote Sriuranpong, Sarayut Lucien Geater, Busyamas Chewaskulyong, Naiyarat Prasongsook, Teerapat Ungtrakul, Kunlatida Maneenil; **Ukraine:** Nataliia Voitko, Ihor Vynnychenko, Yaroslav Shparyk, Serhii Shevnia, Anna Kryzhanivska, Igor Bondarenko, Oleksii Kolesnik, Olexandr Goloborodko, Grygorii Ursol, Dmytro Trukhin, Yuriy Ostapenko; **United Kingdom:** Olivia Hatcher, Conrad Lewanski, Siow Ming Lee, Farah Louise Lim, Francisca Elena Marti, Samreen Ahmed; **United States:** Melissa L. Johnson, Helen Ross, Panayiotis Savvides, Anirudha Dasgupta, John Hamm, Sherman Baker, Edward B. Garon, Davey Daniel, Maen Hussein, Ivor Percent, Neal Rothschild, Ray Page, Joseph Stilwill, Ravindranath Patel, Ali Amjad, Yanyan Lou, Raza Khan; **Vietnam:** Ngoc Tran, Khiem Dang, Anh Pham.