Brief Report

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# A Brief Report of Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: Outcomes by Tumor PD-L1 Expression in the Phase 3 POSEIDON Study

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## Clinical Practice Points

- In the phase 3 POSEIDON study, patients with *EGFR*/*ALK* wild-type metastatic NSCLC (mNSCLC) were randomized (1:1:1) to first-line tremelimumab plus durvalumab and platinum-based chemotherapy (T + D + CT), durvalumab plus chemotherapy (D + CT), or chemotherapy alone (CT), with stratification by programmed cell death ligand-1 (PD-L1) tumor cell (TC) expression level (≥ 50% vs. < 50%), disease stage, and histology.
- In alpha-controlled analyses in the ITT population, T + D + CT significantly improved overall survival (OS) and progression-free survival (PFS) versus CT, leading to approval for this regimen. PFS was also significantly improved with D + CT versus CT; a trend for improved OS did not reach statistical significance.
- Patients with PD-L1-low or -negative tumors may show primary resistance to anti-PD-(L)1 therapy, with real-world data suggesting that treatment benefits observed in trials do not always translate into optimal outcomes in clinical practice.
- Here we report outcomes from POSEIDON from post-hoc exploratory analyses in subgroups with PD-L1 TC ≥ 1% versus < 1%.
- Among 1012/1013 randomized patients with known PD-L1 status, 644 (63.6%) versus 368 (36.4%) had PD-L1 TC ≥ 1% versus < 1%.
- Both T + D + CT and D + CT appeared to show OS/PFS benefit versus CT in patients with PD-L1 TC ≥ 1%.
- Consistent with the role of cytotoxic T-lymphocyte-associated antigen 4 and PD-L1 in the immune response, the addition of tremelimumab to first-line durvalumab and chemotherapy also conferred clinical benefit to patients with PD-L1 TC < 1% mNSCLC.
- This exploratory subgroup analysis of POSEIDON supports T + D + CT as a first-line treatment option for patients with mNSCLC irrespective of PD-L1 expression, including the harder-to-treat subgroup with PD-L1 TC < 1%.

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## Introduction

Immunotherapies targeting programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) have revolutionized the first-line treatment landscape for metastatic non-small-cell lung cancer (mNSCLC).[1] However, those patients with PD-L1-low or -negative tumors may show primary resistance to anti-PD-(L)1 therapy,[2,3] with real-world data suggesting that treatment benefits observed in trials do not always translate into optimal outcomes in clinical practice.[4] Novel immunotherapy-based combination regimens are therefore required.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibition is thought to be particularly important for PD-L1-negative NSCLC (defined here as PD-L1 expression on < 1% of tumor cells [TC]), which is more likely to lack activated antitumor T cells.[5] The addition of tremelimumab (anti-CTLA-4) to durvalumab (anti-PD-L1) and chemotherapy may enhance clinical benefit in this population.[6,7] Chemotherapy supports initial tumor control and can prime an antitumor immune response, PD-(L)1 inhibition overcomes T-cell suppression at the tumor site, and CTLA-4 inhibition promotes T-cell expansion, diversification and activation.[8-10]

In the phase 3 POSEIDON study, first-line tremelimumab plus durvalumab and chemotherapy (T + D + CT) significantly improved both progression-free survival (PFS; hazard ratio [HR] 0.72 [95% confidence interval {CI} 0.60-0.86]; $P = .0003$) and overall survival (OS; HR 0.77 [95% CI 0.65-0.92]; $P = .0030$) versus chemotherapy alone (CT) in patients with mNSCLC,[11] leading to approval for this regimen. PFS was also significantly improved with durvalumab plus chemotherapy (D + CT) versus CT, with a trend for improved OS that did not reach statistical significance.[11]

Here we report outcomes from POSEIDON in subgroups based on a PD-L1 expression cut-off of TC 1% (and limited analyses by a TC 50% cut-off [a stratification factor]).

## Methods

### *Study Design and Patients*

POSEIDON (NCT03164616) is a phase 3, global, randomized, open-label study; details of the study design (Supplemental Figure 1) were previously reported.[11] Eligible patients had *EGFR*/*ALK* wild-type stage IV NSCLC, were treatment-naïve for metastatic disease, and had PD-L1 TC status centrally assessed before randomization (immunohistochemistry assay with SP263 clone and OptiView DAB detection kit) (full eligibility criteria in Supplemental Table 1). Patients were randomized (1:1:1) with stratification by PD-L1 expression (TC ≥ 50% vs. < 50%), disease stage (IVA vs. IVB),[12] and histology (squamous versus non-squamous) to tremelimumab 75 mg plus durvalumab 1500 mg and chemotherapy every 3 weeks (q3w) for up to 4 cycles, followed by durvalumab 1500 mg every 4 weeks (q4w), with a fifth dose of tremelimumab post chemotherapy; durvalumab 1500 mg plus chemotherapy q3w for up to 4 cycles followed by durvalumab 1500 mg q4w; or chemotherapy q3w for 4-6 cycles. Chemotherapy comprised carboplatin or cisplatin plus gemcitabine (squamous), carboplatin or cisplatin plus pemetrexed followed by optional pemetrexed maintenance if eligible (non-squamous), or carboplatin plus nab-paclitaxel (any histology). Patients continued treatment until disease progression, unacceptable toxicity, or consent withdrawal.

### *Statistical Analysis*

The primary endpoints, PFS by blinded independent central review per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and OS for D + CT versus CT, and key alpha-controlled secondary endpoints of PFS and OS for T + D + CT versus CT, were analyzed in the intent-to-treat (ITT) population using a stratified log-rank test. Prespecified subgroup analyses for these endpoints included patients with PD-L1 TC ≥ 1, < 1%, ≥ 50%, and < 50%. Data cut-offs at the final analyses of superiority were July 24, 2019 for PFS (median follow-up in censored patients 10.3 [0.0-23.1] months) and other RECIST-related endpoints and March 12, 2021 for OS, safety, and all other data (median follow-up in censored patients 34.9 [0.0-44.5] months). In comprehensive post-hoc exploratory analyses, OS, PFS, objective response rate (ORR), duration of response (DoR), and safety were assessed in subgroups with PD-L1 TC ≥ 1% versus < 1% (and across further histological subdivisions). OS was also analyzed in subgroups with PD-L1 TC ≥ 50% versus < 50%. Long-term follow-up exploratory analyses of OS were prespecified; as only serious adverse events (AEs), including AEs leading to death, were collected during long-term follow-up, updated safety data are not presented here. For the PFS and OS subgroup analyses, unstratified Cox proportional hazards models were used to calculate HRs and 95% CIs. ORR was analyzed using an unstratified logistic regression model to calculate odds ratios (ORs) with 95% CIs.

## Results

### *Patients*

Overall, 1012/1013 randomized patients had known PD-L1 status (prospectively assessed: TC ≥ 1%, 644/1012 [63.6%]; TC < 1%, 368/1012 [36.4%]). Baseline characteristics were generally balanced across the arms and between PD-L1 subgroups (Supplemental Table 2). Among those with known histology in the as-treated population, most with non-squamous NSCLC received pemetrexed-platinum (598/626 [95.5%]) and most with squamous received gemcitabine-platinum (326/369 [88.3%]).[11]

### *Efficacy*

At the primary analysis of OS, T + D + CT numerically improved OS versus CT in both the PD-L1 TC ≥ 1% subgroup (HR 0.76 [95% CI 0.61-0.95]) and the TC < 1% subgroup (HR 0.77 [95% CI 0.58-1.00]) (Figure 1), consistent with the results from the ITT population (which met statistical significance). In both subgroups, median OS (95% CI) was longer with T + D + CT versus CT (TC ≥ 1%, 15.6 [11.6-18.1] vs. 12.5 [10.4-15.2] months; TC < 1%, 12.7 [9.9-15.5] vs. 11.0 [8.7-12.7] months). D + CT showed a numerical OS improvement versus CT in the TC ≥ 1% subgroup (HR 0.79 [95% CI 0.64-0.98]; median OS 14.4 [95% CI 11.8-17.5] months) but not in the TC < 1% subgroup (HR 0.99 [95% CI 0.76-1.30]; median OS 10.9 [95% CI 8.1-13.5] months) (Figure 1). In an updated follow-up exploratory analysis, after a median follow-up in censored patients of

**Figure 1** Overall survival in patients with (A) PD-L1 TC ≥ 1%, (B) PD-L1 TC < 1%, (C) PD-L1 TC ≥50%, and (D) PD-L1 TC < 50%, and progression-free survival in patients with (E) PD-L1 TC ≥ 1% and (F) PD-L1 TC < 1%. HRs were calculated using an unstratified Cox proportional hazards model, with data cut-off March 12, 2021 for OS analyses and July 24, 2019 for PFS analyses. Abbreviations: CI = confidence interval; CT = chemotherapy; D = durvalumab; HR = hazard ratio; OS = overall survival; PD-L1 = programmed cell death ligand-1; PFS = progression-free survival; T = tremelimumab; TC = tumor cell.

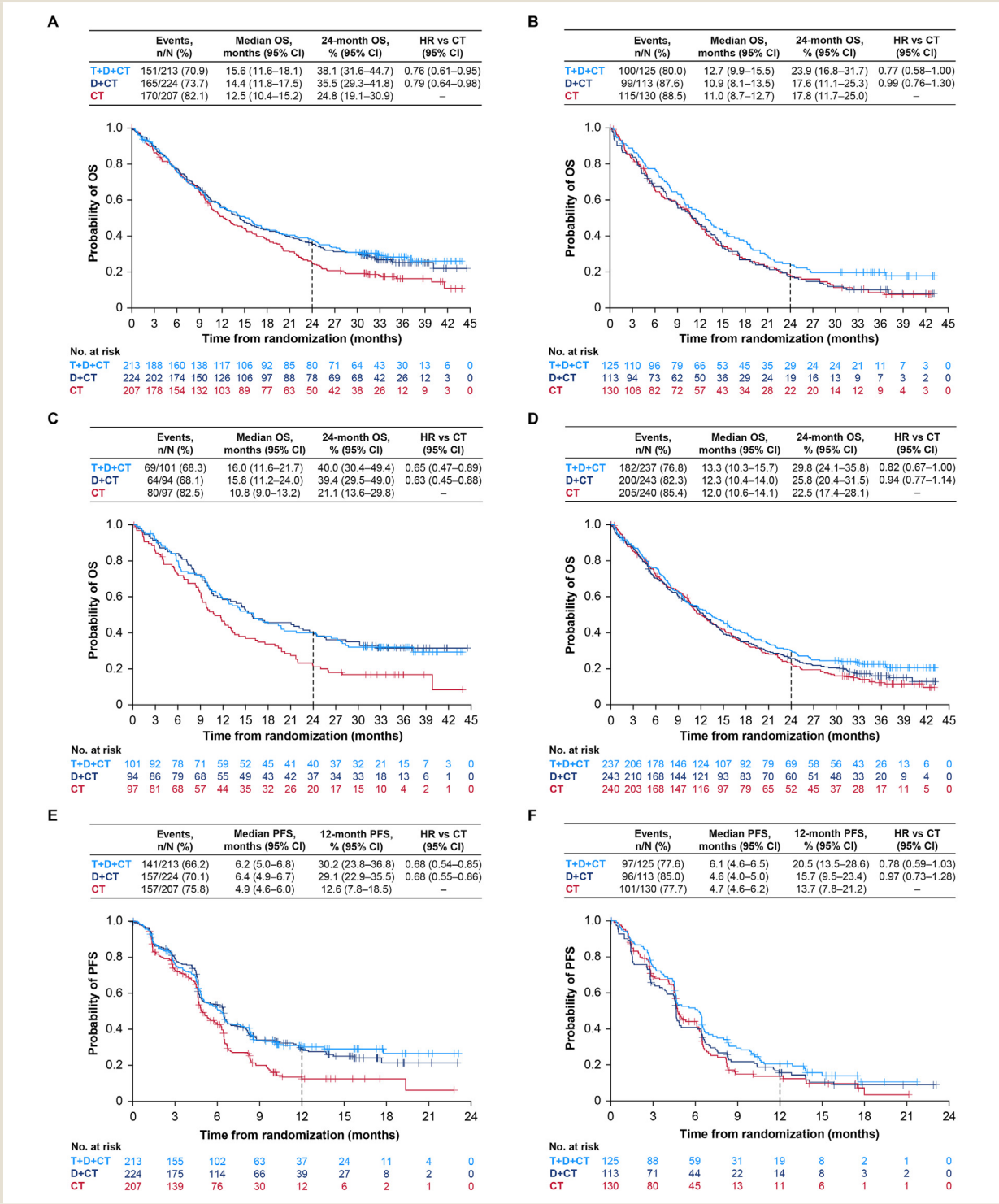


**Table 1** Confirmed Objective Response Rate and Duration of Response by PD-L1 Expression

| Confirmed Objective Response[a] | PD-L1 TC ≥ 1% | | | PD-L1 TC < 1% | | |
|---|---|---|---|---|---|---|
| | T + D + CT (*n* = 210) | D + CT (*n* = 218) | CT (*n* = 203) | T + D + CT (*n* = 125) | D + CT (*n* = 111) | CT (*n* = 129) |
| Responders, *n* (%) | 84 (40.0) | 107 (49.1) | 56 (27.6) | 46 (36.8) | 30 (27.0) | 25 (19.4) |
| Odds ratio vs. CT (95% CI)[b] | 1.75 (1.16-2.65) | 2.53 (1.69-3.82) | – | 2.42 (1.38-4.32) | 1.54 (0.84-2.84) | – |
| Median DoR, months (95% CI)[c] | 16.4 (7.2-NE) | 7.2 (5.6-12.7) | 5.1 (4.2-5.4) | 7.8 (5.1-12.5) | 6.7 (3.8-9.0) | 5.5 (3.7-12.7) |
| Remaining in response at 12 months, % (95% CI)[c] | 56.5 (44.8-66.6) | 42.2 (31.9-52.1) | 16.9 (8.1- 28.4) | 37.3 (22.4-52.3) | 28.4 (13.5-45.4) | 32.9 (14.0-53.3) |

Abbreviations: CI = confidence interval; CT = chemotherapy; D = durvalumab; DoR = duration of response; PD-L1 = programmed cell death ligand-1; T = tremelimumab; TC = tumor cell.
[a] Assessed by blinded independent central review among patients with measurable disease at baseline; confirmation was not required per protocol (post-hoc analysis); data cut-off July 24, 2019.
[b] Calculated using an unstratified logistic regression model.
[c] Calculated using the Kaplan-Meier method.

46.5 months (data cut-off March 11, 2022), numerical OS improvements with T + D + CT versus CT were maintained in both the PD-L1 TC ≥ 1% subgroup (HR 0.70 [95% CI 0.57-0.87]) and the TC < 1% subgroup (HR 0.80 [95% CI 0.62-1.04]) (Supplemental Figure 2; data presented across a range of PD-L1 TC subgroups). Updated OS results with D + CT versus CT were similar to those observed at the earlier data cut-off (TC ≥ 1%: HR 0.75 [95% CI 0.61-0.93]; TC < 1%: HR 0.98 [95% CI 0.75-1.28]).

Numerical OS improvement with T + D + CT versus CT was more evident in the TC ≥ 50% subgroup compared with the TC < 50% subgroup (HR [95% CI] 0.65 [0.47-0.89] and 0.82 [0.67-1.00]) (Figure 1); this trend was similar, but more pronounced, with D + CT versus CT (HR [95% CI] 0.63 [0.45-0.88] and 0.94 [0.77-1.14]). In the TC < 50% subgroup, long-term separation of the Kaplan-Meier curves was observed for T + D + CT (but not D + CT) versus CT.

As with OS, PFS benefit numerically favored T + D + CT versus CT in both the PD-L1 TC ≥ 1% (HR 0.68 [95% CI 0.54-0.85]) and TC < 1% (HR 0.78 [95% CI 0.59-1.03]) subgroups (Figure 1). For D + CT versus CT, numerical PFS improvement was notable in the TC ≥ 1% subgroup (HR 0.68 [95% CI 0.55-0.86]) but not the TC < 1% subgroup (HR 0.97 [95% CI 0.73-1.28]).

The benefit in confirmed ORR with T + D + CT versus CT was numerically greater in the PD-L1 TC < 1% subgroup (36.8% vs. 19.4%) than the TC ≥ 1% subgroup (40.0% vs. 27.6%; Table 1); the opposite pattern was observed for D + CT versus CT (27.0% vs. 19.4% and 49.1% vs. 27.6%). DoR was longest with T + D + CT in both PD-L1 subgroups (Table 1; more pronounced in those with TC ≥ 1%).

In patients with PD-L1 TC < 1%, there was a numerical trend for improved OS with T + D + CT versus CT irrespective of histology; in the TC ≥ 1% subgroup, this was only seen for non-squamous histology (Figure 2). For D + CT versus CT, numerical improvements in OS were only seen in the TC ≥ 1% subgroup, regardless of histology.

### *Safety*

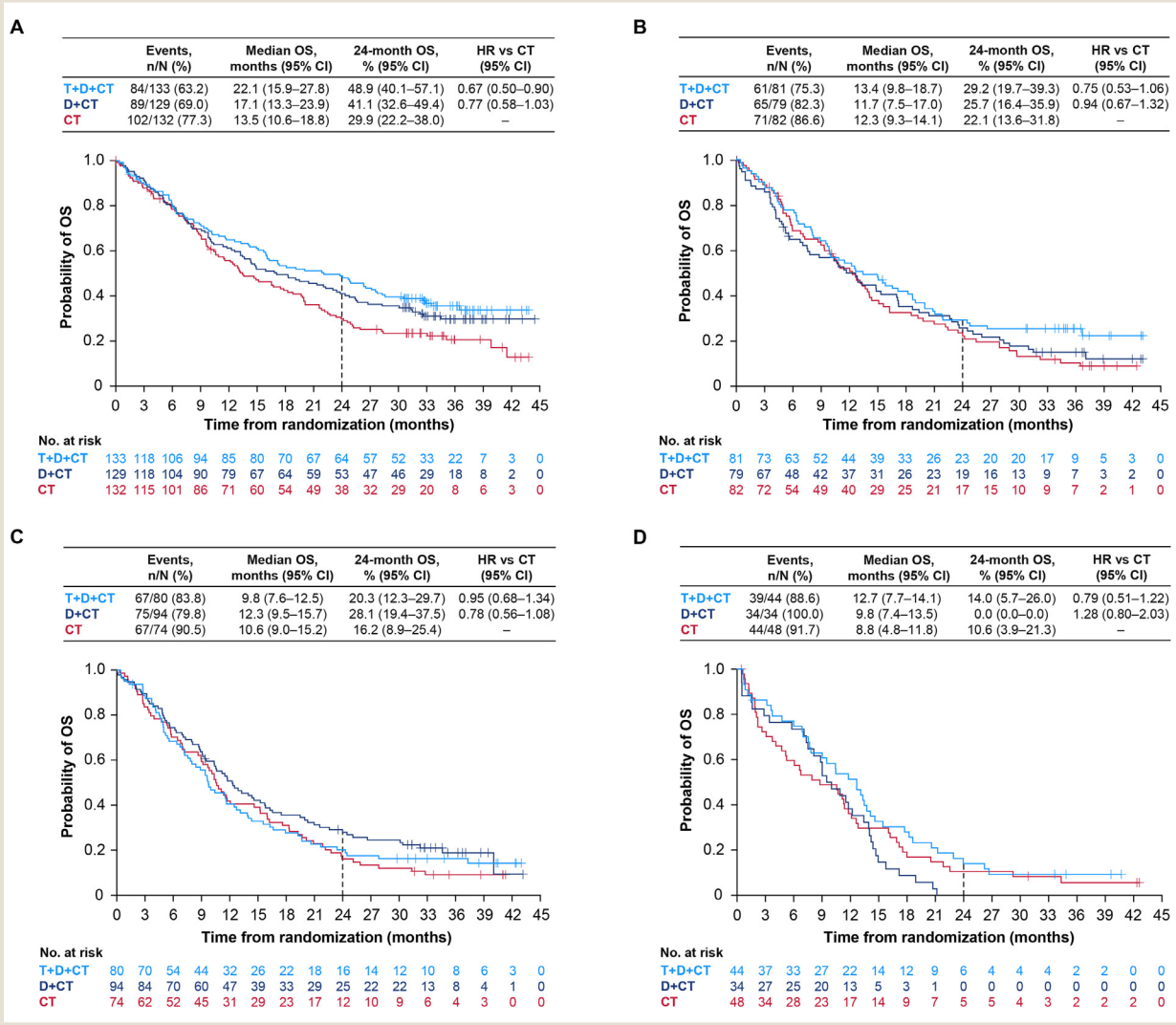
The safety profile in both PD-L1 subgroups (Supplemental Table 3) was generally consistent with the primary safety analysis.[11] The incidence of grade 3/4 treatment-related AEs with T + D + CT was numerically higher (TC ≥ 1%, 53.8%; TC < 1%, 48.3%) than with either D + CT (TC ≥ 1%, 46.0%; TC < 1%, 41.8%) or CT (TC ≥ 1%, 42.9%; TC < 1%, 46.9%). Similar patterns were seen for serious AEs and AEs leading to treatment discontinuation.

## Discussion

A numerical survival benefit was observed with T + D + CT versus CT irrespective of PD-L1 expression level based on a cut-off of PD-L1 TC 1%, consistent with results in the ITT population from POSEIDON (which met statistical significance).[11] It is of particular clinical relevance that the addition of tremelimumab to durvalumab and chemotherapy numerically reduced the risk of death compared with CT in the PD-L1 TC < 1% subgroup, while the risk of death appeared similar with D + CT versus CT. At the primary analysis of OS, this survival benefit was comparable in magnitude to that seen in the PD-L1 TC ≥ 1% subgroup with either T + D + CT or D + CT. Treatment effect with T + D + CT and (particularly) D + CT versus CT was numerically greater in those with PD-L1 TC ≥ 50% versus TC < 50%. In the ITT population, OS and PFS benefit with T + D + CT versus CT appeared more prominent among patients with non-squamous (than squamous) histology; this observation might have been associated with the chemotherapy employed in patients with squamous histology in the POSEIDON trial (gemcitabine-platinum 88.3%; others received nab-paclitaxel-carboplatin).[11] This was not seen in the PD-L1 TC < 1% subgroup (although numbers in histological subdivisions of PD-L1 subgroups were small, meaning results should be interpreted with caution). Safety was similar regardless of PD-L1 expression and consistent with the overall population.[11]

Notwithstanding the limited utility of cross-trial comparisons, results for the D + CT arm in the PD-L1 TC < 1% subgroup differed from those seen in some previous studies of anti-PD-(L)1 + CT.[13-16] In the ITT population of POSEIDON, D + CT significantly improved PFS versus CT in patients with mNSCLC, with a positive trend for OS improvement that did not reach statistical significance.[11] This limits the degree to which subgroup analyses of OS can be interpreted in this arm. There are also a number of more general factors related to cross-trial comparisons which could have contributed to this, including differences in study design (eg, PD-L1 TC expression cut-offs used for strati-

**Figure 2** Overall survival in patients with non-squamous histology and (A) PD-L1 TC ≥ 1% and (B) PD-L1 TC < 1%, and in patients with squamous histology and (C) PD-L1 TC ≥ 1% and (D) PD-L1 TC < 1%. HRs were calculated using an unstratified Cox proportional hazards model, with data cut-off March 12, 2021. One patient each in the D + CT and CT arms had "other" or "missing" histology. Abbreviations: CI = confidence interval; CT = chemotherapy; D = durvalumab; HR = hazard ratio; OS = overall survival; PD-L1 = programmed cell death ligand-1; T = tremelimumab; TC = tumor cell.




fication during randomization), population (eg, tumor histology), geographic footprint of the studies, and timing with respect to changes in the therapeutic landscape.

Among patients with advanced NSCLC lacking actionable mutations, approximately one third to one half have PD-L1 negative tumors (TC < 1%).[3,5,11,17] In an era defined by broad approvals for PD-(L)1 inhibitors,[1] the optimal first-line treatment strategy for this subgroup has remained unclear. Outcomes in clinical practice do not always reflect treatment benefits observed in trials.[4] Generally, in a real-world setting those with PD-L1-negative stage III–IV NSCLC appear to derive reduced benefit from anti-PD-(L)1 agents (alone or in combination with chemotherapy) compared to those with tumors expressing higher levels of PD-L1,[4] suggesting that new approaches are required for this important subgroup. Our results from the primary analysis of OS in POSEIDON (which was unique in its three-arm design, featuring anti-PD-L1 + CT both with and without anti-CTLA-4) showed that T + D + CT (but not D + CT) appeared to confer an equivalent level of numerical OS benefit to those with PD-L1 TC < 1% as was seen in those with TC ≥ 1%, with HRs in both subgroups being close to that seen in the ITT population.[11] These findings, alongside data from the CheckMate 9LA study of ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1) and chemotherapy, [18]are in line with expectations based on mechanism of action and validate the rationale for combining anti-

CTLA-4 with anti-PD-(L)1 and chemotherapy in patients with PD-L1-negative mNSCLC.

In conclusion, this exploratory subgroup analysis of POSEIDON supports the use of T + D + CT as a first-line treatment option for patients with mNSCLC irrespective of PD-L1 expression, including the harder-to-treat subgroup with PD-L1 TC < 1%. The results showed that the addition of tremelimumab to durvalumab and chemotherapy conferred clinical benefit to patients with PD-L1-negative disease, consistent with the role of CTLA-4 and PD-(L)1 checkpoint pathways in the immune response.

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## 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/.

## CRediT authorship contribution statement

**Edward B. Garon:** Investigation, Writing – review & editing. **Byoung Chul Cho:** Conceptualization, Data curation, Formal

analysis, Investigation, Methodology, Resources, Writing – review & editing. **Alexander Luft:** Formal analysis, Investigation, Writing – review & editing. **Jorge Alatorre-Alexander:** Investigation, Writing – review & editing. **Sarayut Lucien Geater:** Investigation, Writing – review & editing. **Dmytro Trukhin:** Investigation, Writing – review & editing. **Sang-We Kim:** Investigation, Writing – review & editing. **Grygorii 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 Henrique Araujo:** Investigation, Writing – review & editing. **Haruhiro Saito:** Investigation, Writing – review & editing. **Niels Reinmuth:** Investigation, Writing – review & editing. **Milena Kohlmann:** Writing – review & editing. **Caitlin Lowery:** Formal analysis, Supervision, Writing – review & editing. **Helen Mann:** Investigation, Writing – review & editing. **Solange Peters:** Conceptualization, Formal analysis, Investigation, Validation, Writing – review & editing. **Tony S. Mok:** Investigation, Writing – review & editing. **Melissa L. Johnson:** Investigation, Writing – review & editing.

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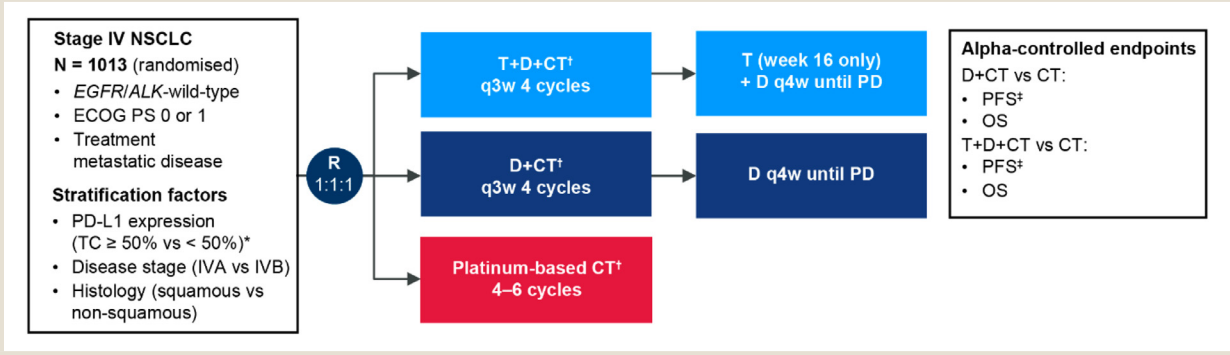
## Supplemental Methods

The study was done in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, Declaration of Helsinki, and applicable local regulations with approval from independent ethics committees. The protocol and amendments were approved by relevant ethics committees and regulatory authorities.

**Supplemental Figure 1** POSEIDON study design. *An IHC assay with the SP263 clone and OptiView DAB detection kit was used to measure PD-L1 expression on the TC membrane. †CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/ cisplatin (non-squamous) or nab-paclitaxel + carboplatin (either histology). Pemetrexed maintenance was permitted in eligible patients with non-squamous histology who initially received pemetrexed-platinum. ‡By BICR (RECIST 1.1). Abbreviations: BICR, blinded independent central review; CT = chemotherapy; D = durvalumab; ECOG = Eastern Cooperative Oncology Group; IHC, immunohistochemistry; NSCLC = non-small-cell lung cancer; OS = overall survival; PD, progressive disease; PD-L1 = programmed cell death ligand-1; PFS = progression-free survival; PS = performance status; q3w = every 3 weeks; q4w = every 4 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; T = tremelimumab; TC = tumor cell.




**Supplemental Table 1** Eligibility Criteria

| Inclusion Criteria |
|---|
| Age ≥ 18 years at the time of screening. In Japan, patients must be ≥ 20 years at the time of screening. |
| Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and in the protocol. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations. For patients aged < 20 years and enrolling in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative. |
| Histologically or cytologically documented stage IV NSCLC not amenable to curative surgery or radiation (according to version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology 2016).[12] |
| Patients must have tumors that lack activating *EGFR* mutations (eg, exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) and *ALK* fusions. If a patient has squamous histology or is known to have a tumor with a *KRAS* mutation, then *EGFR* and *ALK* testing is not required. |
| No prior chemotherapy or any other systemic therapy for metastatic NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for advanced disease are eligible, provided that progression has occurred > 12 months from end of last therapy. |
| Tumor PD-L1 status, confirmed by a reference laboratory using an IHC assay with the SP263 clone and OptiView DAB detection kit, must be known prior to randomization. As such, all patients must be able to undergo a fresh tumor biopsy during screening or to provide an available tumor sample taken < 3 months prior to enrollment. Tumor lesions used for newly acquired biopsies during screening should not be the same lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy; and in this instance only core needle (not excisional/incisional) biopsy is allowed. For patients with a single target lesion, if biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired. Samples with limited tumor content and fine needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component. The tumor specimen submitted to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC, TMB, and other exploratory biomarker analyses and is preferred in formalin-fixed paraffin embedded blocks. |

(*continued on next page*)

**Supplemental Table 1** (*continued*)

| Inclusion Criteria |
|---|
| ECOG performance status of 0 or 1 at enrollment and randomization. |
| Life expectancy $\geq$ 12 weeks at randomization (Day 1). |
| Body weight $>$ 30 kg. |
| At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as $\geq$ 10 mm in the longest diameter (except lymph nodes which must have a short axis $\geq$ 15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines. |
| No prior exposure to immune-mediated therapy including, but not limited to, other anti-cytotoxic T lymphocyte antigen-4, anti-programmed cell death-1, anti-PD-L1, and anti-programmed cell death ligand-2 antibodies, excluding therapeutic anticancer vaccines. |
| Adequate organ and marrow function as defined below:<br>• Hemoglobin $\geq$ 9.0 g/dL without transfusion 4 weeks prior to screening and randomization<br>• Absolute neutrophil count $\geq 1.5 \times 10^9$/L<br>• Platelet count $\geq 100 \times 10^9$/L<br>• Serum bilirubin $\leq$ 1.5 $\times$ ULN. This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician<br>• ALT and AST $\leq$ 2.5 $\times$ ULN; for patients with hepatic metastases, ALT and AST $\leq$ 5 $\times$ ULN<br>• Calculated creatinine clearance $\geq$ 40 mL/min as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine collection<br>• For patients receiving cisplatin, calculated creatinine clearance $\geq$ 50 mL/min as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine collection<br>*Males*:<br>$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$<br>*Females*:<br>$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$ |
| Evidence of post-menopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:<br>• Women $<$ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy)<br>• Women $\geq$ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced oophorectomy with last menses $>$ 1 year ago, had chemotherapy-induced menopause with last menses $>$ 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy) |

| Exclusion Criteria |
|---|
| Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). |
| Previous investigational product assignment in the present study. |
| Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study. |
| Participation in another clinical study with an investigational product during the last 12 months. |
| Mixed small-cell lung cancer and NSCLC histology, sarcomatoid variant. |
| Any concurrent chemotherapy, investigational product, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable. |
| No radiation therapy is allowed, unless it is 1) definitive radiation that had been administered at least 12 months prior, 2) palliative radiation to brain, with associated criteria for stability or lack of symptoms, or 3) palliative radiation to painful bony lesions (this must comprise $<$ 30% of the bone marrow). |
| Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of investigational product. Local surgery of isolated lesions for palliative intent is acceptable. |
| History of allogeneic organ transplantation. |
| Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.). The following are exceptions to this criterion:<br>• Patients with vitiligo or alopecia<br>• Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment<br>• Any chronic skin condition that does not require systemic therapy<br>• Patients without active disease in the last 5 years may be included but only after consultation with the study physician<br>• Patients with celiac disease controlled by diet alone |
| Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, that substantially increase risk of incurring adverse events or compromise the ability of the patient to give written informed consent. |
| Medical contraindication to platinum-based doublet chemotherapy. |

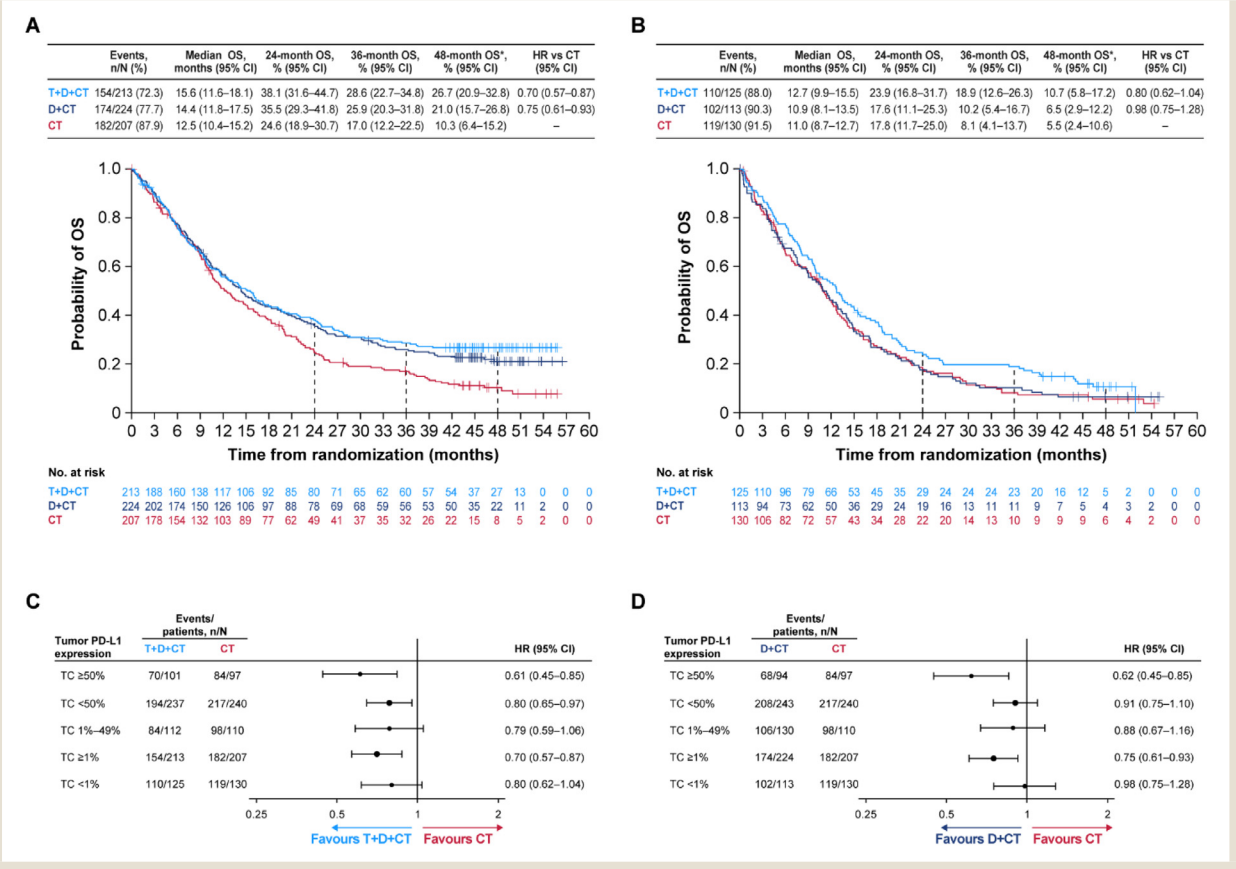
(*continued on next page*)

**Supplemental Table 1** (*continued*)

| Exclusion Criteria |
|---|
| History of another primary malignancy except for:<br>• Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of the investigational product and of low potential risk for recurrence<br>• Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease<br>• Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ) |
| History of leptomeningeal carcinomatosis. |
| Spinal cord compression. |
| Brain metastases. Patients with suspected brain metastases at screening should have intravenous contrast-enhanced MRI (preferred) or intravenous contrast-enhanced CT of the brain prior to study entry. If brain metastases are detected patients must be treated before randomization. Randomization is only permitted if patients with brain metastases have:<br>• Confirmed stable condition 4 weeks after the intervention using imaging<br>• Returned neurologically to baseline<br>• Completed associated steroids at least 5 days prior to randomization<br>Brain metastases will not be recorded as RECIST target lesions at baseline. |
| History of active primary immunodeficiency. |
| Active infection, including tuberculosis (clinical evaluation), HBV (positive HBV surface antigen result), HCV, or HIV (positive HIV 1 or 2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of HBV core antibody and absence of HBV surface antigen) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid. |
| Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:<br>• Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)<br>• Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent<br>• Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication, cytotoxic chemotherapy premedication) |
| Receipt of live, attenuated vaccine within 30 days prior to the first dose of investigational product. Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of investigational product. |
| Female patients who are pregnant or breast-feeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of tremelimumab plus durvalumab combination therapy. |
| Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients. |
| Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment. |
| Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions, and requirements. |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IHC = immunohistochemistry; MRI = magnetic resonance imaging; NSCLC = non-small-cell lung cancer; PD-L1 = programmed cell death ligand-1; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TMB = tumor mutational burden; ULN = upper limit of normal.

**Supplemental Figure 2** Updated follow-up exploratory analysis of overall survival, after median follow-up of 46.5 months, in patients with (A) PD-L1 TC ≥ 1% and (B) PD-L1 TC < 1% and (C-D) across a range of PD-L1 TC cut-offs. HRs were calculated using an unstratified Cox proportional hazards model, with data cut-off March 11, 2022. *Landmark values from later time-points are subject to greater uncertainty due to censoring in the tail of the end of the curves. Abbreviations: CI = confidence interval; CT = chemotherapy; D = durvalumab; HR = hazard ratio; OS = overall survival; PD-L1 = programmed cell death ligand-1; T = tremelimumab; TC = tumor cell.



**Supplemental Table 2** Baseline Patient Demographics and Disease Characteristics

| Characteristic | PD-L1 TC ≥ 1% | | | PD-L1 TC < 1% | | |
|---|---|---|---|---|---|---|
| | T + D + CT (*n* = 213) | D + CT (*n* = 224) | CT (*n* = 207) | T + D + CT (*n* = 125) | D + CT (*n* = 113) | CT (*n* = 130) |
| Median age (range), years | 63.0 (27-85) | 65.0 (40-81) | 64.0 (39-83) | 62.0 (39-87) | 62.0 (32-87) | 64.0 (32-84) |
| Sex | | | | | | |
| Male | 167 (78.4) | 170 (75.9) | 150 (72.5) | 102 (81.6) | 82 (72.6) | 98 (75.4) |
| Female | 46 (21.6) | 54 (24.1) | 57 (27.5) | 23 (18.4) | 31 (27.4) | 32 (24.6) |
| Race | | | | | | |
| White | 119 (55.9) | 115 (51.3) | 100 (48.3) | 86 (68.8) | 66 (58.4) | 79 (60.8) |
| Asian | 70 (32.9) | 88 (39.3) | 89 (43.0) | 29 (23.2) | 35 (31.0) | 39 (30.0) |
| Other | 24 (11.3) | 21 (9.4) | 18 (8.7) | 10 (8.0) | 12 (10.6) | 12 (9.2) |
| ECOG performance status[a] | | | | | | |
| 0 | 68 (31.9) | 81 (36.2) | 74 (35.7) | 42 (33.6) | 28 (24.8) | 45 (34.6) |
| 1 | 145 (68.1) | 143 (63.8) | 132 (63.8) | 83 (66.4) | 85 (75.2) | 85 (65.4) |
| Histology[a,b] | | | | | | |
| Squamous | 80 (37.6) | 94 (42.0) | 74 (35.7) | 44 (35.2) | 34 (30.1) | 48 (36.9) |
| Non-squamous | 133 (62.4) | 129 (57.6) | 132 (63.8) | 81 (64.8) | 79 (69.9) | 82 (63.1) |
| AJCC disease stage[c] | | | | | | |
| IVA | 111 (52.1) | 114 (50.9) | 103 (49.8) | 60 (48.0) | 55 (48.7) | 63 (48.5) |
| IVB | 101 (47.4) | 109 (48.7) | 103 (49.8) | 64 (51.2) | 58 (51.3) | 67 (51.5) |
| Smoking status[a] | | | | | | |
| Current/former | 175 (82.2) | 167 (74.6) | 159 (76.8) | 104 (83.2) | 86 (76.1) | 98 (75.4) |
| Never | 38 (17.8) | 57 (25.4) | 47 (22.7) | 21 (16.8) | 27 (23.9) | 32 (24.6) |
| CNS metastases | 20 (9.4) | 20 (8.9) | 26 (12.6) | 13 (10.4) | 8 (7.1) | 19 (14.6) |
| Liver metastases | 32 (15.0) | 39 (17.4) | 47 (22.7) | 37 (29.6) | 23 (20.4) | 33 (25.4) |

Data are n (%) except for age. Overall, 1012/1013 randomized patients had known PD-L1 status.
Abbreviations: AJCC = American Joint Committee on Cancer; CNS = central nervous system; CT = chemotherapy; D = durvalumab; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed cell death ligand-1; T = tremelimumab; TC = tumor cell.
[a] Data missing for one patient in the CT arm from the PD-L1 TC ≥ 1% subgroup.
[b] One patient in the D + CT arm from the PD-L1 TC ≥ 1% subgroup had other histology.
[c] Data missing for one patient each in the T + D + CT, D + CT, and CT arms from the PD-L1 TC ≥ 1% subgroup and for one patient in the T + D + CT arm from the PD-L1 TC < 1% subgroup.

**Supplemental Table 3** Safety Summary by PD-L1 Expression

| Treatment-Related AE[a] | PD-L1 TC ≥ 1% | | | PD-L1 TC < 1% | | |
|---|---|---|---|---|---|---|
| | T + D + CT (*n* = 210) | D + CT (*n* = 224) | CT (*n* = 203) | T + D + CT (*n* = 120) | D + CT (*n* = 110) | CT (*n* = 130) |
| Any | 194 (92.4) | 205 (91.5) | 181 (89.2) | 112 (93.3) | 91 (82.7) | 117 (90.0) |
| Maximum grade 3/4[b] | 113 (53.8) | 103 (46.0) | 87 (42.9) | 58 (48.3) | 46 (41.8) | 61 (46.9) |
| Serious | 63 (30.0) | 43 (19.2) | 37 (18.2) | 28 (23.3) | 22 (20.0) | 22 (16.9) |
| Led to treatment discontinuation[c] | 36 (17.1) | 36 (16.1) | 19 (9.4) | 15 (12.5) | 11 (10.0) | 14 (10.8) |
| Led to death | 7 (3.3) | 4 (1.8) | 4 (2.0) | 4 (3.3) | 3 (2.7) | 4 (3.1) |

Data are *n* (%).
Abbreviations: AE = adverse event; CT = chemotherapy; D = durvalumab; PD-L1 = programmed cell death ligand-1; T = tremelimumab; TC = tumor cell.
[a] Assessed among treated patients and includes AEs assessed by the investigator as possibly related to any study treatment; data cut-off March 12, 2021.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
[c] Includes patients who permanently discontinued at least one study drug.