Title:

Durvalumab ± tremelimumab + platinum-etoposide in extensive-stage small-cell lung cancer (CASPIAN): outcomes by PD-L1 expression and tissue tumor mutational burden

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Running title:

CASPIAN outcomes by PD-L1 expression and TMB

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Statement of Translational Relevance

Addition of durvalumab to first-line platinum-etoposide (EP) prolongs overall survival (OS) in patients with extensive-stage small-cell lung cancer (ES-SCLC). Some reports suggest programmed cell death ligand-1 (PD-L1) expression and tissue tumor mutational burden (tTMB) are predictive biomarkers of outcomes with PD-(L)1 inhibitors in other tumor types, but no evidence clearly supports their validity in SCLC. Exploratory analyses from the phase 3 CASPIAN trial showed low prevalence of PD-L1 expression, particularly on tumor cells. OS benefit with durvalumab plus EP versus EP was not linked to PD-L1 expression or tTMB, suggesting neither is useful in selecting patients or predicting outcomes with durvalumab plus EP in ES-SCLC. With durvalumab plus tremelimumab and EP, OS benefit versus EP appeared greater in subgroups with PD-L1 expression on ≥1% tumor or immune cells, suggesting PD-L1 may be a useful biomarker for treatment with anti-PD-(L)1 and anti-CTLA-4; however, confirmation from a prospective dataset is required.

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Abstract

Purpose: In the CASPIAN trial, first-line durvalumab plus platinum-etoposide (EP) significantly improved overall survival (OS) versus EP alone in extensive-stage small-cell lung cancer (ES-SCLC). We report exploratory analyses of CASPIAN outcomes by programmed cell death ligand-1 (PD-L1) expression and tissue tumor mutational burden (tTMB).

Experimental Design: Patients were randomized (1:1:1) to durvalumab (1500 mg) plus EP, durvalumab plus tremelimumab (75 mg) plus EP, or EP alone. Treatment effects in PD-L1 and tTMB subgroups were estimated using an unstratified Cox proportional hazards model.

Results: The PD-L1 and tTMB biomarker-evaluable populations (BEPs) comprised 54.4% (438/805) and 35.2% (283/805) of the intention-to-treat (ITT) population, respectively. PD-L1 prevalence was low: 5.7%, 25.8%, and 28.3% had PD-L1 expression on ≥1% tumor cells (TCs), ≥1% immune cells (ICs), and ≥1% TCs or ICs, respectively. OS benefit with durvalumab plus EP versus EP was similar across PD-L1 subgroups, with hazard ratios (HRs) all falling within the 95% CI for the PD-L1 BEP (0.47–0.79). OS benefit with durvalumab plus tremelimumab plus EP versus EP was greater in PD-L1 ≥1% versus <1% subgroups, although CIs overlapped. There was no evidence of an interaction between tTMB and treatment effect on OS (durvalumab plus EP versus EP, p=0.916; durvalumab plus tremelimumab plus EP versus EP, p=0.672).

Conclusions: OS benefit with first-line durvalumab plus EP in patients with ES-SCLC was observed regardless of PD-L1 or tTMB status. PD-L1 expression may prove to be a useful biomarker for combined treatment with PD-(L)1 and CTLA-4 inhibition, although this requires confirmation with an independent dataset.

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Introduction

After many years with little improvement in outcomes for extensive-stage small-cell lung cancer (ES-SCLC), the phase 3 CASPIAN and IMpower133 studies showed that the addition of immune checkpoint inhibitors targeting programmed cell death ligand-1 (PD-L1) to first-line platinum doublet chemotherapy prolonged overall survival (OS) in patients with this aggressive and rapidly fatal tumor (1-5).

Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that targets PD-L1, blocking its binding to programmed cell death-1 (PD-1) and CD80 (6). The phase 3 CASPIAN study investigated the efficacy and safety of first-line durvalumab, with or without the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitor tremelimumab, in combination with etoposide plus either carboplatin or cisplatin (EP), compared with EP alone in patients with treatment naïve ES-SCLC (2). At a planned interim analysis (data cut-off: March 11, 2019), durvalumab plus EP significantly improved OS compared with EP alone, with a hazard ratio (HR) of 0.73 (95% confidence interval [CI] 0.59–0.91; p=0.0047): median OS was 13.0 months and 10.3 months in the durvalumab plus EP and EP arms, respectively (2). This survival benefit was sustained at updated analyses after approximately 2 and 3 years of follow-up, establishing durvalumab plus EP as a global standard of care in this setting (3,5). However, durvalumab plus tremelimumab plus EP did not significantly improve OS versus EP (HR 0.82; 95% CI 0.68–1.00; p=0.0451) (3).

Although PD-L1 inhibition combined with chemotherapy represents a meaningful advance in the management of ES-SCLC, only a proportion of patients derive long-term benefit. The majority of patients progress or relapse after treatment, highlighting the need to identify those most likely to benefit from this therapeutic strategy. In other tumor types and in non-small-cell lung cancer (NSCLC) in particular, benefit from PD-1 and PD-L1 inhibitors has in some cases been associated with increased PD-L1 expression on tumor cells (TC) and on immune cells (IC) (7). Additionally, it has been reported that tumor mutational burden (TMB), measured either from circulating tumor DNA in blood or in tumor tissue samples, may be a predictive biomarker of efficacy outcomes in advanced solid tumors (8-12). To date, however, there is no clear, consistent evidence supporting the validity of any biomarkers for predicting outcomes with immunotherapy in combination with chemotherapy in SCLC.

The prevalence of tumor PD-L1 expression is substantially lower in SCLC compared with NSCLC, and data about the relevance of PD-L1 expression in this setting are conflicting (13,14). Among solid tumors, SCLC tumors have one of the highest burdens of somatic non-synonymous mutations, probably related to exposure to tobacco smoke (15-17). High TMB is hypothesized to be associated with the presence of neoantigens that are able to trigger a tumor-specific T-cell response, such as may be promoted by treatment with immune checkpoint inhibitors (13,18,19). Current data exploring the relationship between TMB and efficacy outcomes with immune checkpoint inhibitors in SCLC are inconsistent (4,20,21).

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Here, we report the results of exploratory analyses of PD-L1 expression and tTMB, and the relationship of these biomarkers with outcomes, in patients with treatment naïve ES-SCLC in the CASPIAN study. A plain language summary of this article can be found in the supplement.

Patients and Methods

Study design and patients

CASPIAN (NCT03043872) is an open-label, sponsor-blind, multicenter, randomized, international phase 3 study, for which the primary analyses have been previously published (2,3). In brief, eligible patients were aged ≥18 years and had treatment-naïve, histologically or cytologically documented ES-SCLC; World Health Organization (WHO) performance status score of 0 or 1; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (22); and a life expectancy of at least 12 weeks. Patients with asymptomatic or treated and stable brain metastases were permitted. All patients provided signed informed consent for participation in the study. The study protocol and all amendments were approved by the relevant ethics committees and regulatory authorities, and the study was run in accordance with the International Conference on Harmonisation good clinical practice guidelines, the Declaration of Helsinki, and applicable local regulations.

Treatment

Patients were randomized (1:1:1) to receive durvalumab plus EP, durvalumab plus tremelimumab plus EP, or EP; randomization was stratified according to planned platinum agent (carboplatin or cisplatin). In all arms, chemotherapy comprised etoposide 80–100 mg/m^2, administered on days 1 to 3 of each 21-day cycle, and investigator's choice of either carboplatin area under the curve (AUC) 5–6 mg/mL/min or cisplatin 75–80 mg/m^2, given on day 1 of each cycle. In the immunotherapy arms, patients received four cycles of EP plus durvalumab 1500 mg with or without tremelimumab 75 mg every 3 weeks, followed by maintenance durvalumab 1500 mg every 4 weeks; patients in the durvalumab plus tremelimumab plus EP arms also received one further dose of tremelimumab 75 mg after EP. In the EP arm, patients could receive an additional two cycles of EP (up to six cycles maximum) and prophylactic cranial irradiation administered at the investigator's discretion after chemotherapy. Treatment continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Study treatment beyond disease progression was allowed if there was evidence of clinical benefit.

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Endpoints and assessments

The two primary endpoints were OS for durvalumab plus EP versus EP and for durvalumab plus tremelimumab plus EP versus EP. Secondary endpoints included progression-free survival (PFS) and objective response rate (ORR; including unconfirmed responses) based on investigator assessment according to RECIST v1.1, as well as safety and tolerability graded per National Cancer Institute common terminology criteria for adverse events, version 4.03. Confirmed ORR was analyzed post hoc. Assessment of efficacy based on biomarkers, including PD-L1 expression on TCs and ICs, and tissue TMB (tTMB), was an exploratory endpoint. Provision of an archival (<3 years old) tumor tissue block (or ≥15 newly cut unstained slides) was mandatory for inclusion in the study, if such samples were available. Since there were no established prognostic or predictive biomarkers in SCLC at the time of designing the study, neither measurement of PD-L1 expression nor TMB was required during patient screening.

PD-L1 testing

PD-L1 expression on TCs and ICs was assessed using the VENTANA SP263 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ) (23).
The percentage of tumor-associated ICs with PD-L1 staining intensity above background determined the PD-L1 IC expression status (IC ≥1%), and the percentage of TCs with any membrane staining above background determined the PD-L1 TC expression status (TC ≥1%). Cut-offs for PD-L1 expression at ≥1% of ICs, ≥1% of TCs, and ≥1% of ICs or TCs were explored. Testing was done in a central laboratory by pathologists trained and qualified by Ventana to score the samples at specific cut-offs.

TMB assessment

TMB was assessed using the FoundationOne® CDx assay (Foundation Medicine, Cambridge, MA) in tissue biopsy samples remaining after PD-L1 testing; the algorithm has been described previously (24). Since this was an exploratory analysis, no cut-off points were predefined; instead, a range of cut-offs were selected based on the distribution of tTMB scores. A cut-off of 10 mutations per megabase (mut/Mb) was selected for more detailed analysis, as this threshold was shown to be predictive of PFS and response to nivolumab + ipilimumab in NSCLC (9,10). In addition, tTMB ≥10 mut/Mb was associated with higher ORR in patients with advanced solid tumors (including SCLC) treated with pembrolizumab, which led to the FDA approval of the FoundationOne® CDx assay as a companion diagnostic for pembrolizumab in the treatment of solid tumors with tTMB ≥10 mut/Mb (12,25).

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Statistical analysis

The biomarker analyses reported here were based on data from the updated analysis of CASPIAN with a median follow-up of 25.1 months (data cut-off: January 27, 2020). The PD-L1 and tTMB biomarker-evaluable populations (BEPs) included all randomized patients who had a tumor sample available for PD-L1 and tTMB testing, respectively, and an evaluable result. Within each subset, safety was assessed in all patients who received at least one dose of treatment.

For both the overall PD-L1 BEP and the overall tTMB BEP, OS and PFS were analyzed as for the intention-to-treat (ITT) population using a stratified log-rank test adjusted for planned platinum therapy at cycle 1, with HRs and 95% CI estimated using a Cox proportional hazards model. OS and PFS were estimated using the Kaplan-Meier method. PD-L1 and tTMB subgroup analyses (based on different cut-off thresholds) used an unstratified Cox proportional hazards model with treatment as the only covariate. The ORR was analyzed using a logistic regression model stratified for planned platinum at cycle 1 for the overall PD-L1 and tTMB BEPs, and an unstratified model for subgroup analyses, to calculate the odds ratios and associated 95% CIs comparing the response rate between treatment arms. An unstratified Cox proportional hazards or logistic regression model (for ORR) was used to test for any evidence of an interaction between treatment effect and tTMB; the model in each case included covariates for treatment effect, tTMB score (as a continuous variable), and a treatment by tTMB score interaction. A Chi-squared statistic from each model with and without the interaction term was used to calculate the p-value. Because the analyses of PD-L1 expression and TMB were exploratory, no adjustments were made for multiple comparisons. All analyses used SAS (version 9.4).

Data availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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Results

PD-L1 and tTMB BEPs

A total of 805 patients were randomized in the CASPIAN study (ITT population) and were assigned to durvalumab plus EP (*n* = 268), durvalumab plus tremelimumab plus EP (*n* = 268), or EP alone (*n* = 269) (2). Tumor samples were available for assessment of PD-L1 expression from 497 patients, although results could not be obtained for 59 patients (mainly due to insufficient number of slides or insufficient viable tumor for testing). The PD-L1 BEP therefore comprised 438 patients (54.4% of ITT; **Supplementary Figure S1**): 152 (56.7%), 157 (58.6%), and 129 (48.0%) in the durvalumab plus EP, durvalumab plus tremelimumab plus EP, and EP arms, respectively. All patients in the two immunotherapy arms of the PD-L1 BEP received treatment, but two patients in the EP arm did not receive any treatment (one patient died before being treated and another withdrew from the study) and were excluded from the PD-L1 safety population. Tumor samples for tTMB assessment were available from 355 patients; testing was not performed on samples from 72 patients (mainly due to sample QC failure). The tTMB BEP therefore comprised samples from 283 patients (35.2% of ITT; **Supplementary Figure S1**) that were evaluable for TMB status: 107 (39.9%) in the durvalumab plus EP arm, 105 (39.2%) in the durvalumab plus tremelimumab plus EP arm, and 71 (26.4%) in the EP arm. All patients received treatment and were included in both efficacy and safety analyses. Patient demographics and baseline disease characteristics were largely balanced across treatment arms within each BEP, and generally consistent with the ITT population (**Supplementary Table S1**). Representativeness of study participants is described in **Supplementary Table S2**.

In the PD-L1 BEP, the OS benefit appeared greater than that in the ITT population for both treatment comparisons (**Supplementary Figure S2**), with similar trends seen for PFS and ORR (**Supplementary Figure S3 and Figure S4**). For durvalumab plus EP versus EP, the HR for OS in the PD-L1 BEP was 0.61 (95% CI 0.47–0.79), compared with 0.75 (95% CI 0.62–0.91) in the ITT population. For durvalumab plus tremelimumab plus EP versus EP, the HRs for OS were 0.73 (95% CI 0.57–0.95) in the PD-L1 BEP and 0.82 (95% CI 0.68–1.00) in the ITT population.

In the tTMB BEP, OS benefit was comparable to the ITT population for both treatment comparisons (**Supplementary Figure S5**). For durvalumab plus EP versus EP, the HR for OS in the tTMB BEP was 0.71 (95% CI 0.51–0.99), while for durvalumab plus tremelimumab plus EP versus EP, the HR for OS was 0.83 (95% CI 0.60–1.16) in the tTMB BEP. Clinical benefit for PFS and confirmed ORR in the tTMB BEP were also generally similar to the ITT population (**Supplementary Figure S6; Supplementary Figure S7**).

Prevalence of PD-L1 expression

The prevalence of PD-L1 expression on TCs and ICs was low; 5.7% of patients had PD-L1 expression on ≥1% of TCs, 25.8% had PD-L1 expression on ≥1% of ICs, and 28.3% had PD-L1

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expression on ≥1% of TCs or ICs (**Supplementary Figure S8; Supplementary Table S1**). Because of the low levels of PD-L1 expression, a 1% cut-off in ICs and separately in TCs was chosen for exploratory analysis of PD-L1 positivity, as well as one combining TC and IC expression (*either* TC *or* IC ≥1% versus TC *and* IC <1%). Although randomization was not stratified by PD-L1 status, the proportion of patients with PD-L1 expression above and below the 1% cut-off was generally well balanced on TCs across treatment arms; however, the proportion of patients with IC ≥1% was higher in the durvalumab plus tremelimumab plus EP arm compared with the other two arms (**Supplementary Table S1**).

Relationship between PD-L1 expression and efficacy outcomes

For durvalumab plus EP versus EP, the OS benefit was broadly similar regardless of PD-L1 expression on either TCs or ICs, with HRs of 0.75, 0.59, and 0.61, respectively, for the PD-L1 ≥1% subgroups based on TC, IC, and TC or IC expression, and 0.62, 0.64, and 0.63, respectively, for the PD-L1 <1% subgroups based on TC, IC, or TC and IC expression (**Figure 1A**). For durvalumab plus tremelimumab plus EP versus EP, OS HRs appeared improved in the PD-L1 ≥1% subgroups based on TC, IC, and TC or IC expression (HRs 0.42, 0.53, and 0.50, respectively) compared with the PD-L1 <1% subgroups (HRs 0.76, 0.88, and 0.91, respectively), suggesting that PD-L1 expression based on a 1% cut-off may predict OS benefit (**Figure 1B**). In particular, the treatment effect on OS was more favorable in the subgroup of patients with TC or IC ≥1% (HR 0.50; 95% CI 0.31–0.83) than in the subgroup with TC and IC <1% (HR 0.91; 95% CI 0.68–1.23) (**Figure 2 A** and **B**).

Forest plots of HRs for PFS and odds ratios for confirmed ORR in the PD-L1 subgroups are shown in **Supplementary Figure S3** and **Supplementary Figure S4**. PFS benefit was improved in the PD-L1 TC or IC ≥1% subgroup compared with the PD-L1 TC and IC <1% subgroup, both for durvalumab plus EP versus EP (HR 0.55; 95% CI 0.33–0.93 vs HR 0.75; 95% CI 0.56–1.00) and for durvalumab plus tremelimumab plus EP versus EP (HR 0.62; 95% CI 0.38–1.01 vs HR 0.83; 95% CI 0.61–1.11). Odds ratios for confirmed ORR were largely similar across PD-L1 subgroups.

To further investigate the apparent association of PD-L1 expression with OS benefit for durvalumab plus tremelimumab plus EP versus EP, we examined baseline disease characteristics in the PD-L1 subgroups (**Table 1**). This revealed some imbalances between the treatment arms in key factors. In the TC or IC ≥1% subgroup, 24.1% of patients in the durvalumab plus tremelimumab plus EP arm had a WHO performance status score of 0 versus 37.5% of patients in the EP arm; 29.6% versus 37.5% of patients, respectively, had baseline liver metastases; and 18.5% versus 12.5%, respectively, had baseline brain metastases. A post-hoc exploratory analysis adjusted to account for the imbalances in these characteristics within this subgroup produced an HR of 0.53 (95% CI 0.31–0.90) for OS benefit with durvalumab plus tremelimumab plus EP versus EP, which was similar to the OS benefit observed in the unadjusted analysis (HR 0.50; 95% CI 0.31–0.83). Calculation of HRs between the PD-L1 subgroups within each treatment arm indicated longer OS in the TC or IC

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≥1% subgroup compared with the TC and IC <1% subgroup in the durvalumab plus tremelimumab plus EP arm (HR 0.50; 95% CI 0.33–0.75); the difference between PD-L1 subgroups was less pronounced in the durvalumab plus EP arm (HR 0.87; 95% CI 0.56–1.30) and the EP arm (HR 0.78; 95% CI 0.50–1.18) (**Figure 3A**, **B** and **C**).

tTMB score distribution

The overall distribution of tTMB scores was broadly similar across treatment arms within the tTMB BEP (**Supplementary Figure S9**). Based on the observed tTMB scores, cut-off points ranging from 6 mut/Mb to 14 mut/Mb were chosen for exploratory analysis; for each selected cut-off point, one or more of the treatment arms had at least 25% of the tTMB BEP in the smallest category of the cut-off.

Relationship between tTMB and efficacy outcomes

Exploratory analysis of OS at tTMB cut-offs ranging from 6–14 mut/Mb showed that HRs for durvalumab plus EP versus EP, and for durvalumab plus tremelimumab plus EP versus EP, all fell within the confidence interval associated with the HR in the tTMB BEP and favored the immunotherapy regimen across the tTMB subgroups, suggesting that tTMB did not predict treatment benefit (**Figure 4A** and **B**). When considering tTMB score on a continuous scale, there was no evidence of an interaction between treatment effect and tTMB for OS (durvalumab plus EP versus EP, $P = 0.916$; durvalumab plus tremelimumab plus EP versus EP, $P = 0.672$). Kaplan-Meier curves for OS in subgroups using a tTMB cut-off of 10 mut/Mb (selected based on previously published data with other immunotherapies; see Methods) are shown in **Supplementary Figure S10**. For durvalumab plus EP versus EP, the HR for OS was 0.77 (95% CI 0.50–1.20) in the tTMB <10 mut/Mb subgroup and 0.68 (95% CI 0.42–1.14) in the tTMB ≥10 mut/Mb subgroup. For durvalumab plus tremelimumab plus EP versus EP, the HR for OS was 0.83 (95% CI 0.54–1.29) in the tTMB <10 mut/Mb subgroup and 0.77 (95% CI 0.46–1.30) in the tTMB ≥10 mut/Mb subgroup.

Forest plots of HRs for PFS and odds ratios for confirmed ORR at tTMB cut-offs ranging from 6–14 mut/Mb are shown in **Supplementary Figure S6** and **Supplementary Figure S7**. For PFS, there was no evidence of an interaction between treatment and tTMB as a continuous variable when comparing durvalumab plus EP versus EP (p=0.613); however, a significant interaction was observed for durvalumab plus tremelimumab plus EP versus EP (p=0.044), with greater PFS improvements in the lower tTMB subgroups. There was no evidence of an interaction between treatment and tTMB on the continuous scale for confirmed ORR with either treatment comparison (durvalumab plus EP versus EP, $P = 0.115$; durvalumab plus tremelimumab plus EP versus EP, $P = 0.114$). For durvalumab plus tremelimumab plus EP versus EP, a notable difference in odds ratios

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between tTMB-high versus low subgroups was observed at cut-offs of 10 mut/Mb and higher, where odds ratios favored EP in the tTMB-high subgroups and favored durvalumab plus tremelimumab plus EP in the tTMB-low subgroups.

Relationship between PD-L1 expression and tTMB

A post-hoc analysis revealed no difference in tTMB score according to PD-L1 expression (P = 0.959). The overlap of patients with tTMB ≥10 mut/Mb and PD-L1 TC or IC ≥1% was limited (11.6% of patients who had both a PD-L1 and a tTMB result), suggesting that presence of these biomarkers is not correlated (**Supplementary Figure S11**).

Safety and treatment exposure

Safety in the PD-L1 and tTMB safety populations was similar to the overall safety population, although the rate of adverse events leading to treatment discontinuation in the EP arm was numerically higher in the PD-L1 and tTMB (versus the overall) safety populations (**Supplementary Table S3**). Analysis of exposure by PD-L1 subgroup showed that, in both immunotherapy arms, exposure to durvalumab was higher in the TC or IC ≥1% subgroups than in the TC and IC <1% subgroups, with the highest median number of durvalumab doses and longest median duration of durvalumab treatment among patients with TC or IC ≥1% in the durvalumab plus EP arm **Supplementary Table S4**. Safety was generally balanced between the TC and IC <1% subgroup and TC or IC ≥1% subgroup within each treatment arm, taking into account the small patient numbers of the subgroups (**Supplementary Table S5**).

Discussion

In this exploratory biomarker analysis from the CASPIAN study, tumor samples were collected from 64% of patients in the ITT population; PD-L1 and tTMB were evaluable in 54% and 35% of the ITT population, respectively. Based on the low prevalence of PD-L1 expression in the CASPIAN population, we explored thresholds of 1% expression on TCs, ICs, or TCs and ICs combined. We observed a similar benefit in OS with durvalumab plus EP versus EP regardless of PD-L1 expression. However, OS benefit with durvalumab plus tremelimumab plus EP versus EP appeared greater in the PD-L1 ≥1% subgroups, driven particularly by benefit in the IC ≥1% subgroup, suggesting potential predictive value of PD-L1 for this combination regimen. Since the predictive value of TMB has not been established in SCLC, there was no predefined tTMB cut-off in this study. However, analysis using a range of tTMB cut-offs that gave a meaningful sample size indicated that tTMB was not predictive of OS benefit with either durvalumab plus EP or with durvalumab plus tremelimumab plus EP, versus EP.

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Consistent with previously published data in SCLC (4,26-28), the overall prevalence of PD-L1 expression in CASPIAN was low, particularly on TCs. The PD-L1 BEP had better efficacy outcomes than the ITT population for both treatment comparisons; this increased clinical benefit appeared to be driven by a relatively poor performance in the EP arm, as indicated by a higher proportion of deaths and progression events, and lower confirmed ORR in patients from this treatment arm in the BEP when compared with the ITT population. While there were no obvious differences in baseline characteristics of the EP arm in each BEP, the higher rate of adverse events leading to treatment discontinuation in the EP arm of the PD-L1 safety population compared with the EP arm of the overall safety population may have contributed to the comparatively poor survival outcomes in the EP arm in the PD-L1 BEP.

The OS benefit was greater with durvalumab plus tremelimumab plus EP versus EP in the TC or IC ≥1% subgroup than in the TC and IC <1% subgroup. Randomization was not stratified by PD-L1 expression and there were some imbalances in baseline characteristics between treatment arms within the TC or IC ≥1% subgroup that could have influenced prognosis. However, the OS benefit remained after adjustment for these imbalances in a post-hoc analysis. Although total exposure to durvalumab was greater in the durvalumab plus EP arm than in the durvalumab plus tremelimumab plus EP arm in the TC or IC ≥1% population, treatment with durvalumab plus tremelimumab plus EP had a more pronounced effect on OS. These results suggest that CTLA-4 inhibition may better complement the effect of PD-L1 inhibition to maintain antitumor activity in patients with PD-L1 expression, but this finding would require prospective validation.

The lack of association between PD-L1 expression and efficacy outcomes with anti-PD-(L)1 in the absence of co-inhibition of CTLA-4 in CASPIAN is consistent with findings from the phase 3 IMpower133 study of first-line atezolizumab plus chemotherapy and the phase 3 KEYNOTE-604 study of first-line pembrolizumab plus chemotherapy, both in patients with ES-SCLC (4,28). Whether or not the relationship between PD-L1 expression and treatment effect might be influenced by the presence of chemotherapy is currently unclear. Conflicting results were reported from earlier phase studies of PD-1/PD-L1 inhibitors as monotherapy in pretreated SCLC without an active comparator arm (26,29,30). However, comparison of results across earlier phase studies is complicated by the use of different assays and scoring systems to evaluate PD-L1, as well as the exploratory nature of these analyses, and the potential confounding prognostic effects in single-arm studies.

For the CASPIAN tTMB BEP, baseline characteristics as well as efficacy and safety outcomes were generally consistent with the ITT population, suggesting that these patients are likely to be a representative sample. tTMB did not seem to predict OS with either immunotherapy regimen, when

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assessed either based on binary cut-offs or as a continuous variable. Overall, the value of TMB as a predictive biomarker of outcomes in SCLC is currently unclear, with inconsistent results across different studies. In the phase 3 IMpower133 study, treatment benefit with first-line atezolizumab plus chemotherapy in ES-SCLC was not associated with TMB measured in blood (bTMB) using a cut-off of either 10 or 16 mut/Mb (1,4). Consistent with both CASPIAN and IMpower133, results from the phase 3 KEYNOTE-604 study showed that tTMB was not positively associated with OS or PFS in patients treated with first-line pembrolizumab plus EP (31). However, analyses of the phase 1/2 CheckMate 032 study, in patients with SCLC previously treated with chemotherapy, have suggested an association of higher tTMB levels with improved outcomes to treatment with nivolumab monotherapy or nivolumab plus ipilimumab (20,32), and a small retrospective analysis has also suggested the possible value of tTMB as a biomarker in SCLC treated with immune checkpoint inhibitors (21). Indications that TMB is predictive of response to immunotherapy, but not of response to the combination of immunotherapy with chemotherapy, have also been observed in NSCLC: tTMB was associated with OS, PFS and ORR with first-line pembrolizumab monotherapy in the KEYNOTE-010 and KEYNOTE-042 studies (33,34), while tTMB was not significantly associated with efficacy of first-line pembrolizumab plus platinum-based chemotherapy in the KEYNOTE-021, 189, and 407 studies (35,36). Ultimately, comparison of findings across studies is complicated by significant variability in TMB measurement techniques, and there is a need for standardization of TMB assessment methodology across different assays, platforms, and centers to improve insights from future research (37).

The impact of tTMB on PFS and ORR in CASPIAN was less clear-cut: for durvalumab plus tremelimumab plus EP versus EP, the HRs for PFS and odds ratios for ORR appeared more favorable in the lower tTMB subgroups, with a significant interaction observed for PFS with tTMB as a continuous variable. However, it should be noted that these results were associated with wide confidence intervals, and PFS and ORR were secondary endpoints in CASPIAN. Since the trend was weak and inconsistent with the OS findings, and is also contrary to current knowledge indicating that tTMB ≥10 mut/Mb predicts better outcomes with immunotherapy in NSCLC (9,10,12), we believe this could be a chance finding. Similar results were reported in KEYNOTE-604, with lower TMB predicting higher PFS and OS benefit with pembrolizumab plus EP versus placebo plus EP. However, this finding is likely to have been impacted by the statistically significant positive association of TMB with OS in the placebo plus EP arm and given the exploratory nature of the analyses, should be interpreted with caution (31).

PD-L1 and TMB have been shown to identify different, but overlapping populations in SCLC (4) and NSCLC (8,11), and to be independent biomarkers in an analysis of nearly 10,000 clinical samples across a broad range of cancer types (27). In CASPIAN, there was no clear association between tTMB score and PD-L1 expression on either TC or IC, and it is conceivable that a combination of

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these two biomarkers may have greater predictive power for response to checkpoint inhibitors than either biomarker alone in SCLC. However, other biomarkers, such as SCLC molecular subtypes (38-40) or HLA genotype (41,42), may have a more important role than PD-L1 or tTMB in this setting, given the differences in immune biology compared with NSCLC. Exploration of such emerging biomarkers using genomic and transcriptomic profiling in the CASPIAN dataset is ongoing (43,44). Liquid biopsies can provide a rapid, non-invasive alternative to tumor biopsies to assess the molecular profile of a disease and to monitor its on-treatment clonal evolution. Previous studies in various tumor types have demonstrated that reduction in circulating tumor DNA (ctDNA) during immunotherapy treatment may be associated with patient outcomes, possibly indicating a decrease in disease burden in response to treatment (45,46), including in several studies in SCLC (47). In future, it is possible that ctDNA dynamics could be a useful tool to enable early clinical decision-making by identifying patients who are responding to or resistant to treatment for SCLC.

Limitations of this analysis primarily relate to its exploratory nature; CASPIAN was not designed to evaluate outcomes based on PD-L1 expression or tTMB, and although provision of archival tissue (if such samples were available) was mandatory, only half of patients were evaluable for PD-L1 and one-third for tTMB. This led to relatively small sample sizes in some of the biomarker-defined subgroups as indicated by the wide CIs. Furthermore, there was an imbalance in sample availability, with a smaller proportion of patients being evaluable for PD-L1 and tTMB in the EP arm compared with the durvalumab plus EP and durvalumab plus tremelimumab plus EP arms. Although the CASPIAN study was open label, the pre-treatment withdrawal rate was low. Thus, there appears to be no obvious reason that fewer patients should have known biomarker status in the EP arm, and we assume the data were missing at random. In addition, the PD-L1 BEP appeared to have better treatment outcomes compared with the ITT population, which could have confounded the analysis. However, both treatment comparisons displayed this difference in efficacy, suggesting that it was unlikely to explain the differential effect observed for durvalumab plus tremelimumab plus EP based on PD-L1 expression. It should also be noted that that no samples were collected in CASPIAN for analysis of bTMB, so no comparison with tTMB data in the same patients could be performed. It is possible that assessment of bTMB in ES-SCLC could provide a more accurate representation of the overall disease than tTMB, since it captures total tumor TMB, including both primary and metastatic sites.

In conclusion, these results support treatment benefit with first-line durvalumab plus EP in patients with ES-SCLC irrespective of biomarker status; there was no evidence that either PD-L1 expression or tTMB can be used to select patients or predict outcomes with durvalumab plus EP in this disease setting. However, our observations in the durvalumab plus tremelimumab plus EP arm suggest that PD-L1 expression may yet prove to be a useful biomarker for combined treatment with PD-(L)1 and CTLA-4 inhibition, although this requires confirmation with a prospective and independent dataset.

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FIGURE LEGENDS AND TABLES

Figure 1. Subgroup analysis of OS by PD-L1 TC and IC expression for (A) durvalumab plus tremelimumab plus EP versus EP and (B) durvalumab plus EP versus EP. In each panel, the shaded band shows the confidence interval for the ITT population; circle sizes are proportional to the number of events. CI, confidence interval; D, durvalumab; EP, platinum-etoposide; HR, hazard ratio; IC, immune cell; ITT, intention-to-treat; OS, overall survival; PD-L1, programmed cell death ligand-1; T, tremelimumab; TC, tumor cell.

Figure 2. Kaplan-Meier analysis of OS for (A) the PD-L1 TC or IC ≥1% subgroup and (B) the PD-L1 TC and IC <1% subgroup. CI, confidence interval; D, durvalumab; EP, platinum-etoposide; HR, hazard ratio; IC, immune cell; OS, overall survival; PD-L1, programmed cell death ligand-1; T, tremelimumab; TC, tumor cell.

Figure 3. Kaplan-Meier analysis of OS by PD-L1 subgroup in (A) durvalumab plus tremelimumab plus EP arm; (B) durvalumab plus EP arm; and (C) EP arm. CI, confidence interval; EP, platinum-etoposide; HR, hazard ratio; IC, immune cell; OS, overall survival; PD-L1, programmed cell death ligand-1; TC, tumor cell.

Figure 4. Subgroup analysis of OS by tTMB for (A) durvalumab plus tremelimumab plus EP versus EP and (B) durvalumab plus EP versus EP. In each panel, the shaded band shows the confidence interval for the ITT population; circle sizes are proportional to the number of events. BEP, biomarker evaluable population; CI, confidence interval; D, durvalumab; EP, platinum-etoposide; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; mut/Mb, mutations per megabase; T, tremelimumab; tTMB, tissue tumor mutational burden.

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Table 1. Baseline patient demographics and disease characteristics by PD-L1 subgroup

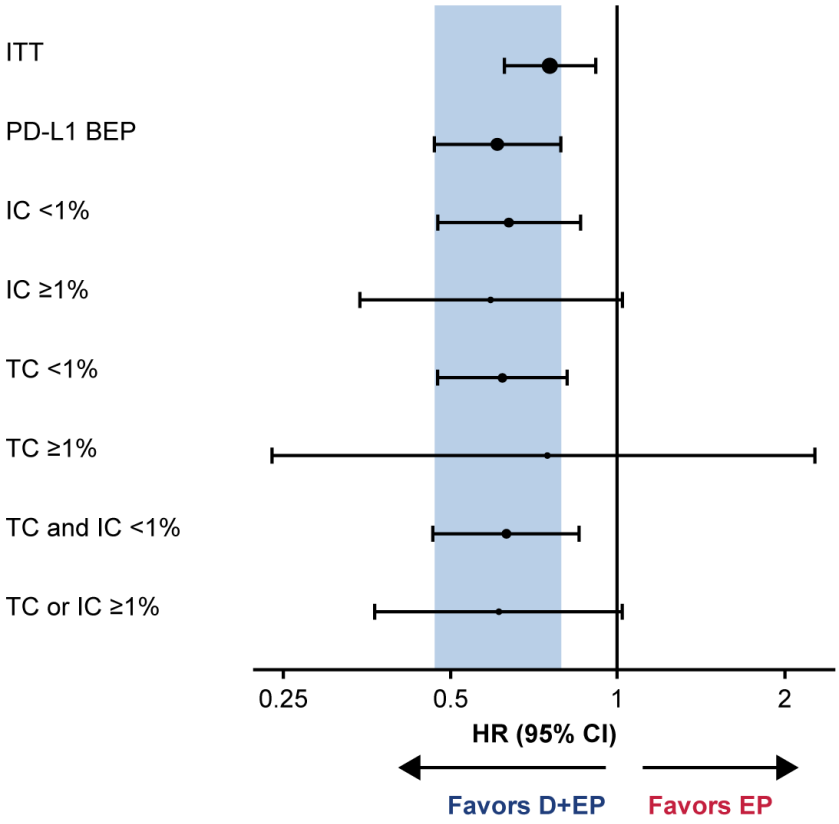
	Durvalumab + EP (*n* = 152)		Durvalumab + tremelimumab + EP (*n* = 157)		EP (*n* = 129)	
	TC and IC <1% (*n* = 114)	TC or IC ≥1% (*n* = 38)	TC and IC <1% (*n* = 103)	TC or IC ≥1% (*n* = 54)	TC and IC <1% (*n* = 97)	TC or IC ≥1% (*n* = 32)
Median age (range), years	62.5 (46–81)	66.0 (40–78)	63.0 (43–84)	60.5 (36–83)	63.0 (38–78)	61.5 (42–80)
Age group, n (%)						
<65	72 (63.2)	17 (44.7)	61 (59.2)	34 (63.0)	56 (57.7)	21 (65.6)
≥65	42 (36.8)	21 (55.3)	42 (40.8)	20 (37.0)	41 (42.3)	11 (34.4)
Sex, n (%)						
Men	83 (72.8)	28 (73.7)	75 (72.8)	38 (70.4)	68 (70.1)	21 (65.6)
Women	31 (27.2)	10 (26.3)	28 (27.2)	16 (29.6)	29 (29.9)	11 (34.4)
Race, n (%)						
White	97 (85.1)	36 (94.7)	87 (84.5)	46 (85.2)	79 (81.4)	27 (84.4)
Asian	14 (12.3)	2 (5.3)	15 (14.6)	8 (14.8)	14 (14.4)	5 (15.6)
Black	2 (1.8)	0	0	0	2 (2.1)	0
Other or missing data	1 (0.9)	0	1 (1.0)	0	2 (2.1)	0
Disease stage, n (%)						
III	13 (11.4)	5 (13.2)	5 (4.9)	4 (7.4)	8 (8.2)	2 (6.3)
IV	101 (88.6)	33 (86.8)	98 (95.1)	50 (92.6)	89 (91.8)	30 (93.8)
WHO PS, n (%)						
0	36 (31.6)	13 (34.2)	42 (40.8)	13 (24.1)	29 (29.9)	12 (37.5)
1	78 (68.4)	25 (65.8)	61 (59.2)	41 (75.9)	68 (70.1)	20 (62.5)
Smoking history, n (%)						
Never smoker	10 (8.8)	4 (10.5)	5 (4.9)	6 (11.1)	5 (5.2)	2 (6.3)
Former smoker	55 (48.2)	15 (39.5)	54 (52.4)	28 (51.9)	41 (42.3)	12 (37.5)
Current smoker	49 (43.0)	19 (50.0)	44 (42.7)	20 (37.0)	51 (52.6)	18 (56.3)
Brain or CNS metastases, n (%)	8 (7.0)	4 (10.5)	15 (14.6)	10 (18.5)	8 (8.2)	4 (12.5)
Liver metastases, n (%)	46 (40.4)	9 (23.7)	57 (55.3)	16 (29.6)	40 (41.2)	12 (37.5)

CNS, central nervous system; EP, platinum-etoposide; IC, immune cell; PD-L1, programmed cell death ligand-1; PS, performance status; TC, tumor cell; WHO, World Health Organization.

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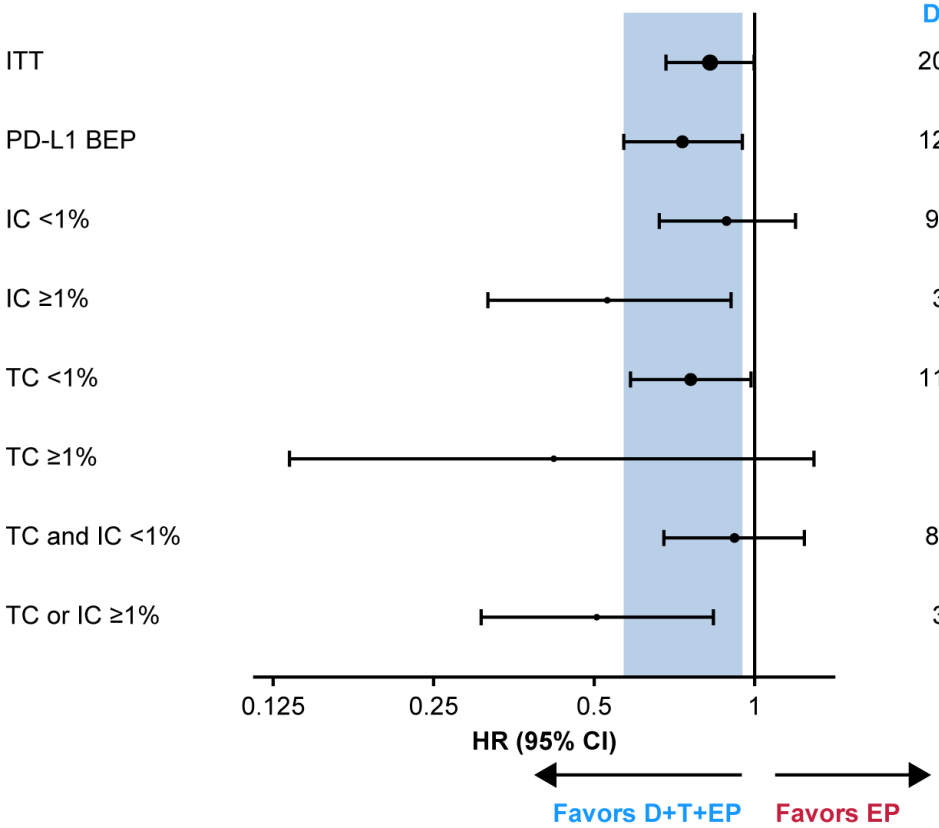
Figure 1

A



	Number of patients with event		
	D+EP	EP	HR (95% CI)
ITT	210 / 268	231 / 269	0.75 (0.62–0.91)
PD-L1 BEP	117 / 152	117 / 129	0.61 (0.47–0.79)
IC <1%	90 / 117	91 / 101	0.64 (0.47–0.85)
IC ≥1%	27 / 35	26 / 28	0.59 (0.34–1.02)
TC <1%	111 / 145	110 / 121	0.62 (0.47–0.81)
TC ≥1%	6 / 7	7 / 8	0.75 (0.24–2.27)
TC and IC <1%	87 / 114	87 / 97	0.63 (0.47–0.85)
TC or IC ≥1%	30 / 38	30 / 32	0.61 (0.37–1.02)

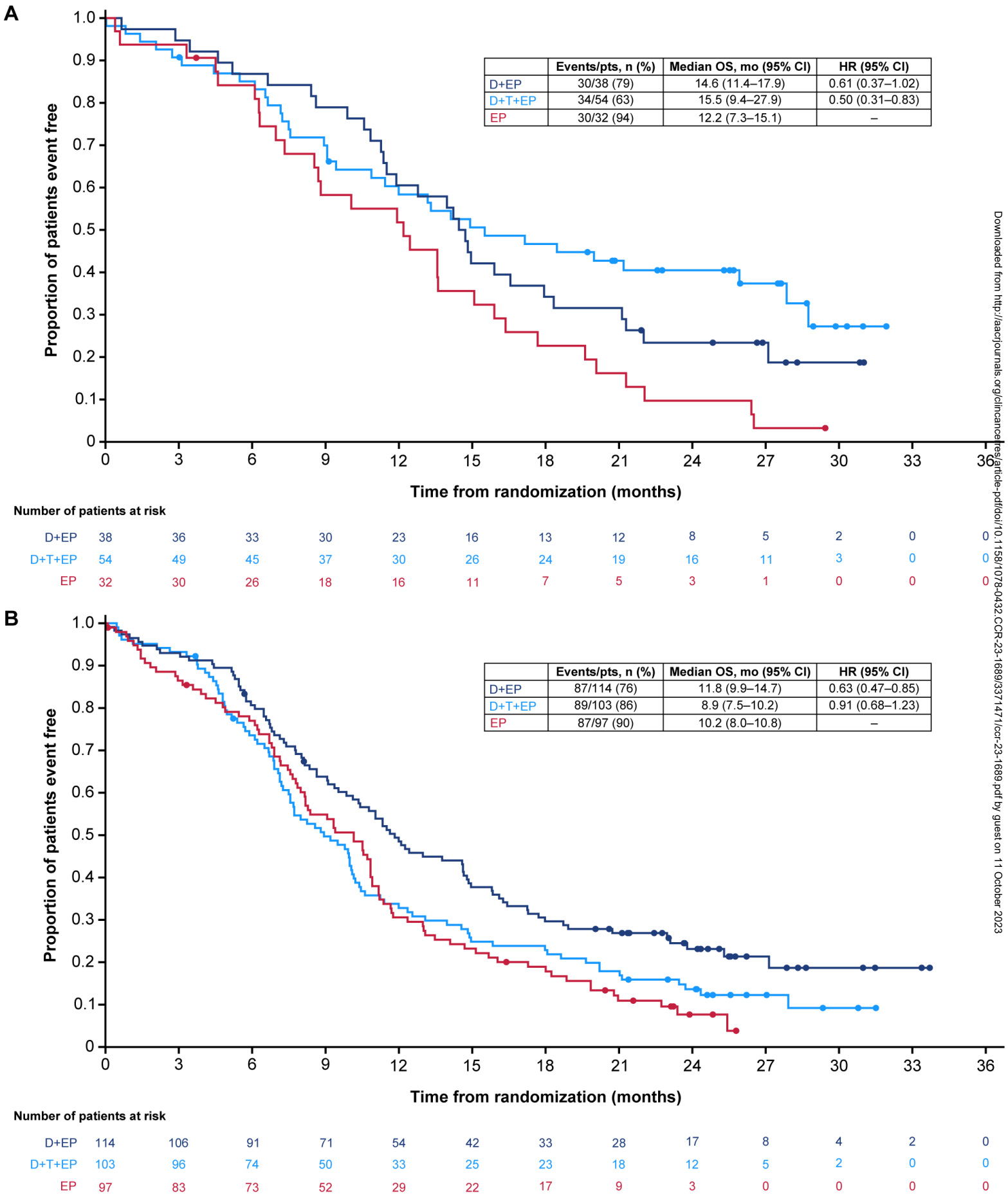
B



	Number of patients with event		
	D+T+EP	EP	HR (95% CI)
ITT	207 / 268	231 / 269	0.82 (0.68–1.00)
PD-L1 BEP	123 / 157	117 / 129	0.73 (0.57–0.95)
IC <1%	91 / 107	91 / 101	0.88 (0.66–1.19)
IC ≥1%	32 / 50	26 / 28	0.53 (0.31–0.90)
TC <1%	117 / 147	110 / 121	0.76 (0.58–0.99)
TC ≥1%	6 / 10	7 / 8	0.42 (0.13–1.29)
TC and IC <1%	89 / 103	87 / 97	0.91 (0.68–1.23)
TC or IC ≥1%	34 / 54	30 / 32	0.50 (0.31–0.83)

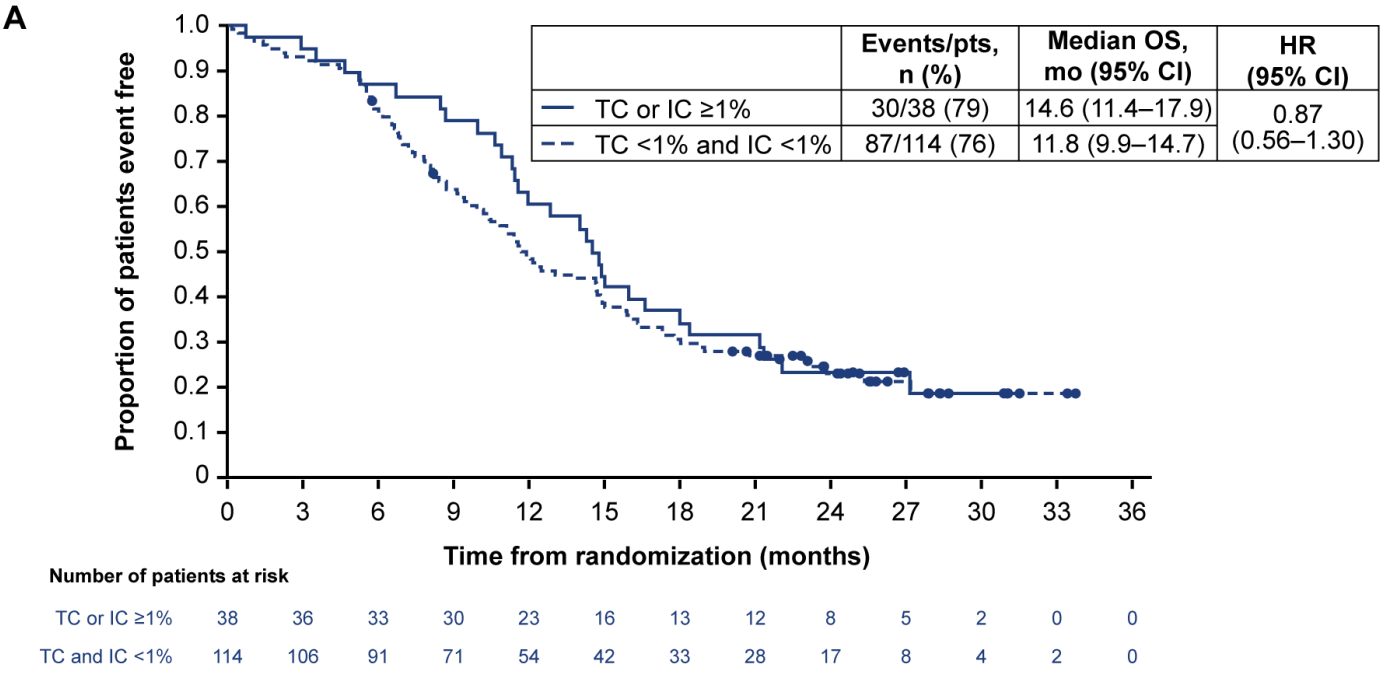
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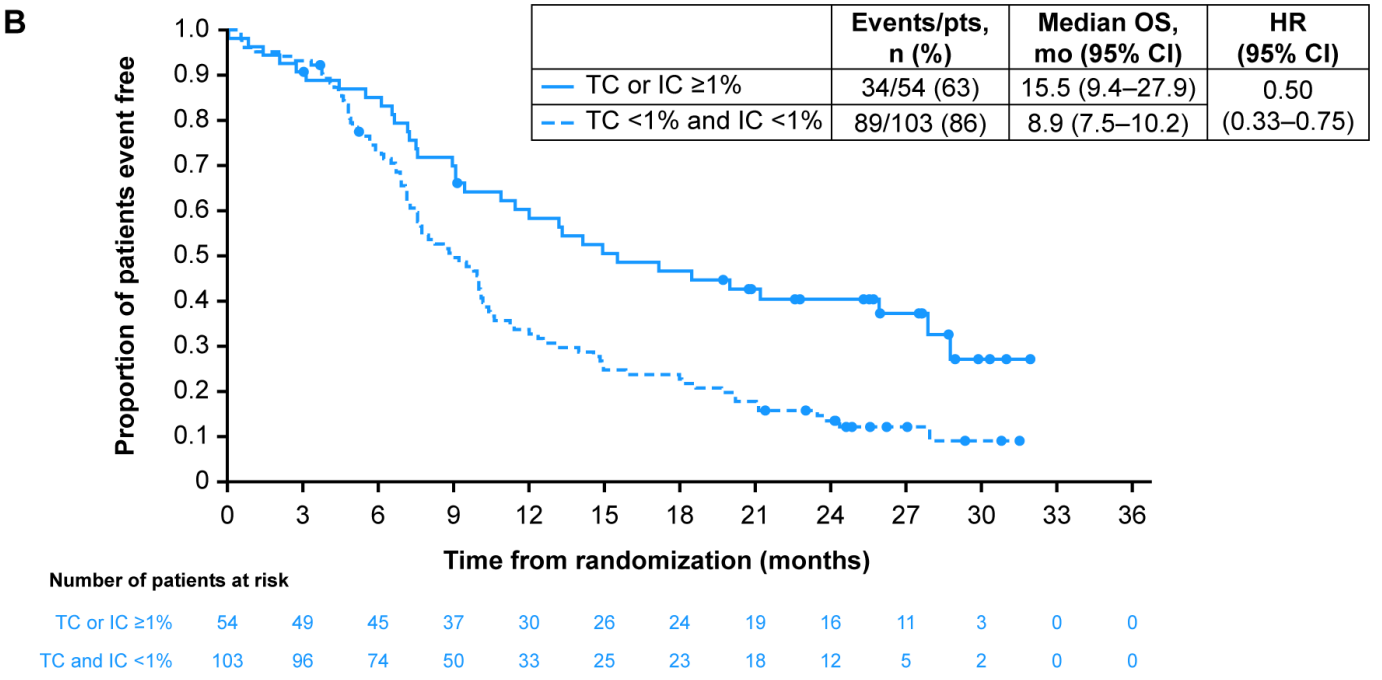
Figure 2

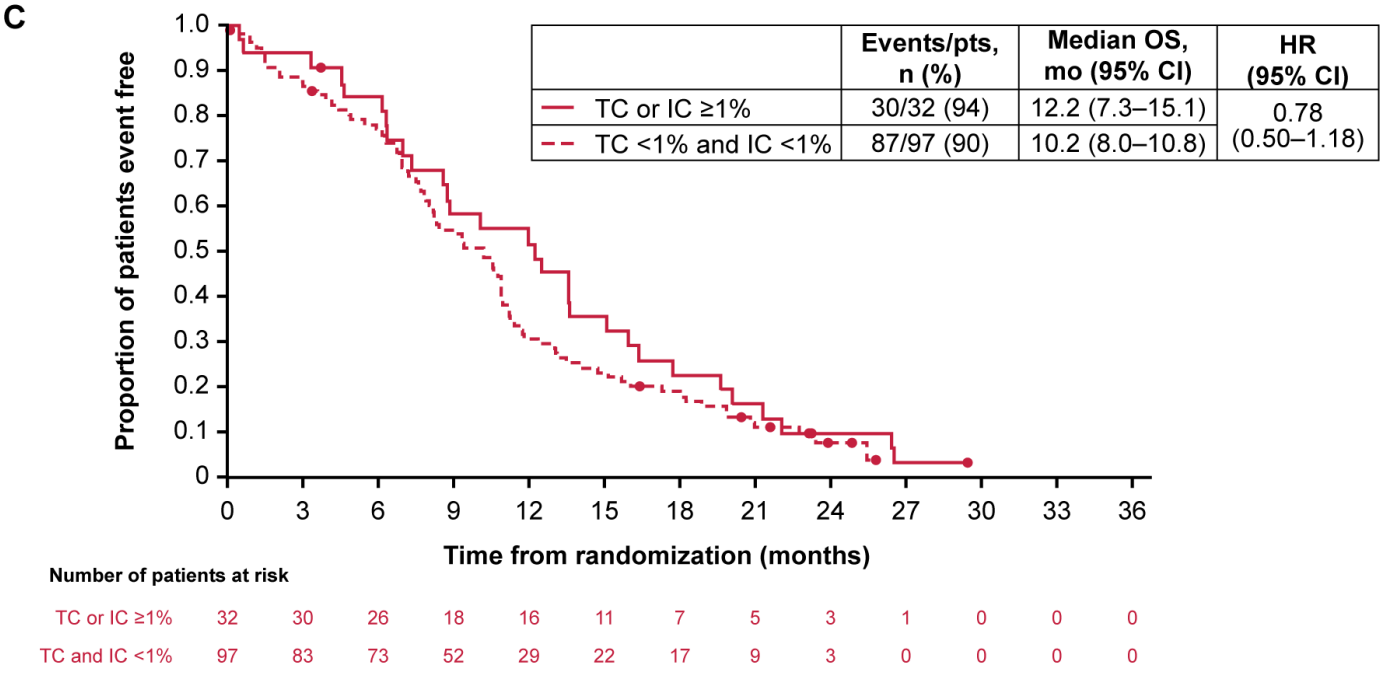


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Figure 3

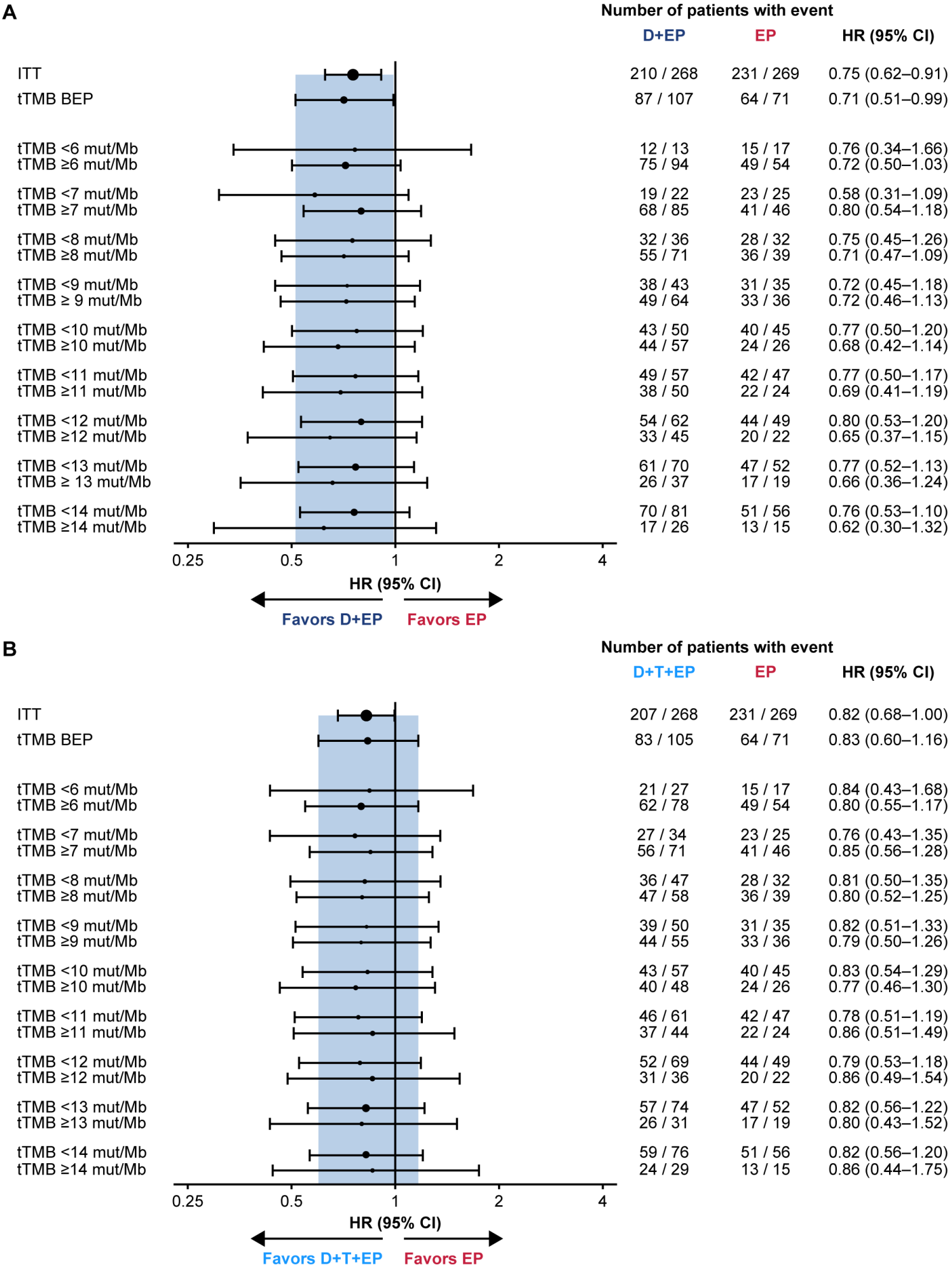






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Figure 4



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