Supplementary Online Content

Rizvi NA, Cho BC, Reinmuth N, et al; MYSTIC Investigators. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non–small cell lung cancer: the MYSTIC phase 3 randomized clinical trial. Published online April 9, 2020. *JAMA Oncol*. doi:10.1001/jamaoncol.2020.0237

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Study Oversight

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

Randomization and Dosing

Patients were randomly assigned (1:1:1) using an interactive voice or web response system to receive durvalumab 20 mg/kg every 4 weeks until disease progression, durvalumab 20 mg/kg every 4 weeks until disease progression plus tremelimumab 1 mg/kg every 4 weeks for up to four doses, or 4-6 cycles of investigator's choice of platinum-based doublet chemotherapy. Treatment was allocated in blocks of six in each stratum via a schedule generated by Perceptive Informatics (Nottingham, UK) who used a computerized randomized list generator. The study was open-label and allocation was unmasked. The dosing schedule for durvalumab (20 mg/kg every 4 weeks) was chosen to align with the every-4-week dosing of tremelimumab in the combination therapy; the doses and dosing schedules were based on acceptable pharmacokinetic/pharmacodynamics, safety, and efficacy profiles in preclinical and clinical studies.[1] The chemotherapy options included agents that were commonly used in the treatment of advanced or metastatic NSCLC at the time of the trial to allow sufficient flexibility for investigators and patients to select the agents that reflect their clinical practice and national guidelines.

Assessments

Tumor response was assessed by blinded independent central review using RECIST v1.1, with imaging performed every 6 weeks for the first 48 weeks, then every 8 weeks, until confirmed disease progression. Patients were followed for survival. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

PD-L1 expression was evaluated at multiple cut-offs (**eTable 2**) at a central laboratory using the VENTANA PD-L1 (SP263) immunohistochemistry (IHC) assay (Ventana Medical Systems, Tucson, AZ, USA).[2] Tumor samples obtained within 3 months prior to screening were permitted. Strong analytical agreement has been demonstrated across the dynamic range between the Dako PD-L1 IHC 22C3 pharmDx and VENTANA PD-L1 (SP263) IHC assays.[3,4]

TMB was evaluated from plasma samples using the GuardantOMNI next-generation sequencing platform (Guardant Health, Redwood City, CA, USA) comprising 500 genes (2.145 Mb). The OMNI TMB algorithm incorporates somatic synonymous and non-synonymous single nucleotide variants (SNVs) and short insertions/deletions (indels) at all variant allele fractions across 1.0 Mb of genomic coding sequence and is optimized to calculate TMB on plasma samples with low cell-free circulating tumor DNA content.[5,6] Alterations associated with clonal hematopoiesis, germline and oncogenic driver or drug resistance mechanisms were excluded from the TMB calculation. Samples with low tumor shedding (eg, maximum somatic allele fraction <0.3%) or low unique molecule coverage were considered bTMB-unevaluable. Tissue TMB was evaluated using the FoundationOne tissue next-generation sequencing platform (Foundation Medicine, Cambridge, MA, USA). The algorithm has been described previously.[7]

Statistical Analysis

The study was sized to characterize the OS benefit for durvalumab plus tremelimumab versus chemotherapy and durvalumab versus chemotherapy and PFS benefit for durvalumab plus tremelimumab versus chemotherapy in patients with PD-L1 TC ≥25%. Originally, the primary endpoints were to be evaluated in an all-comer population; however, the protocol was modified in December 2016 (after the trial completed accrual but before any planned analyses) to restrict the primary analysis population to patients with PD-L1 TC ≥25% based on prior studies and the evolving treatment landscape.[8-11] Approximately 1092 patients, including 480 patients with PD-L1 TC ≥25%, were needed to obtain 231 events for the primary PFS analysis across the durvalumab plus

tremelimumab and chemotherapy groups (72% maturity) and 225 OS events for the primary OS analysis across each treatment group comparison (70% maturity) (**eTable 3**). Two interim analyses of OS were planned: the first at the time of the primary PFS analysis and the second when 80% of the target 225 OS events had occurred. To control the overall type I error at 5% (two-sided), a hierarchical multiple testing procedure with gatekeeping strategy was used across endpoints, analysis populations, and treatment regimens (**eFigure 2**). For the PFS analysis, based on an assumed PFS HR of 0.59, the trial was estimated to have 88% power to demonstrate statistical significance with an overall two-sided significance level of 0.5% for the comparison of durvalumab plus tremelimumab versus chemotherapy. For the OS analysis, with an assumed OS HR of 0.62, the trial was estimated to have 90% power to demonstrate statistical significance with an overall two-sided significance level of 3% for the comparison of durvalumab versus chemotherapy and 86% power to demonstrate statistical significance with an overall two-sided significance level of 1.5% for the comparison of durvalumab plus tremelimumab versus chemotherapy (**eTable 3**). The assumed OS HRs were based on results from previous clinical studies with the therapies that were the standard of care at the time of designing the MYSTIC study,[12-14] as well as emerging data from early-phase durvalumab studies[1,11] and other trials of anti-PD-(L)1.[15-17]

The primary PFS analysis was performed using a stratified log-rank test adjusting for histology (stratification factor at randomization), with HR and 99.5% CI estimated using a Cox proportional hazards model; for statistical significance of durvalumab plus tremelimumab versus chemotherapy, $P<0.005$ was required.

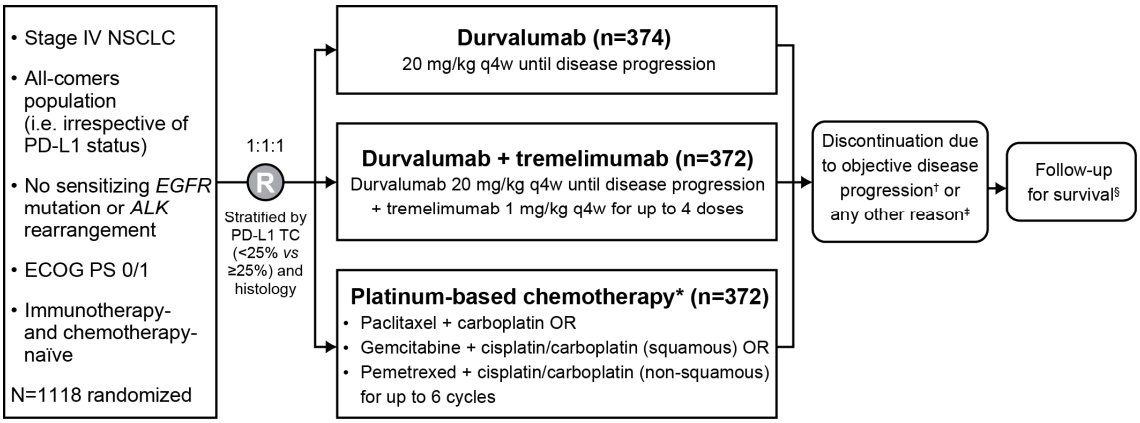
The primary OS analysis was performed using similar methodology, adjusted for two interim analyses, with HRs estimated with two-sided 97.54% and 98.77% CIs for comparisons of durvalumab and durvalumab plus tremelimumab, respectively, with chemotherapy; for statistical significance at final analysis, $P<0.0246$ for durvalumab versus chemotherapy and $P<0.0123$ for durvalumab plus tremelimumab versus chemotherapy were required (Lan-DeMets spending function

approximating O'Brien-Fleming boundary). Survival curves were generated using the Kaplan-Meier method. As a supportive analysis for OS in the PD-L1 TC ≥25% population, restricted mean survival time (RMST) was evaluated by calculating area under the curve for the OS Kaplan-Meier curve for each treatment arm. The difference in RMST (95% CI) for the immunotherapy versus chemotherapy arms based on the minimum of maximum event method is reported (truncation time is based on the minimum of maximum event time in months); a difference >0 favors the immunotherapy arm.

For secondary analyses performed on the PD-L1 TC ≥1% and ITT populations, the stratification was additionally adjusted for PD-L1 expression status (TC ≥25% vs TC <25%). Odds ratios and 95% CI for comparing ORR between treatment groups were calculated using a logistic regression model, adjusted for the same factors as PFS and OS. Prespecified exploratory TMB analysis was performed using an unstratified log-rank test, with HRs and 95% CIs estimated using a Cox proportional hazards model.

Efficacy was analyzed on an ITT basis, including all randomized patients or subsets of this population based on PD-L1 expression or TMB levels. Safety analyses included all patients who received at least one dose of study treatment (as-treated population).

eFigure 1. MYSTIC Study Design

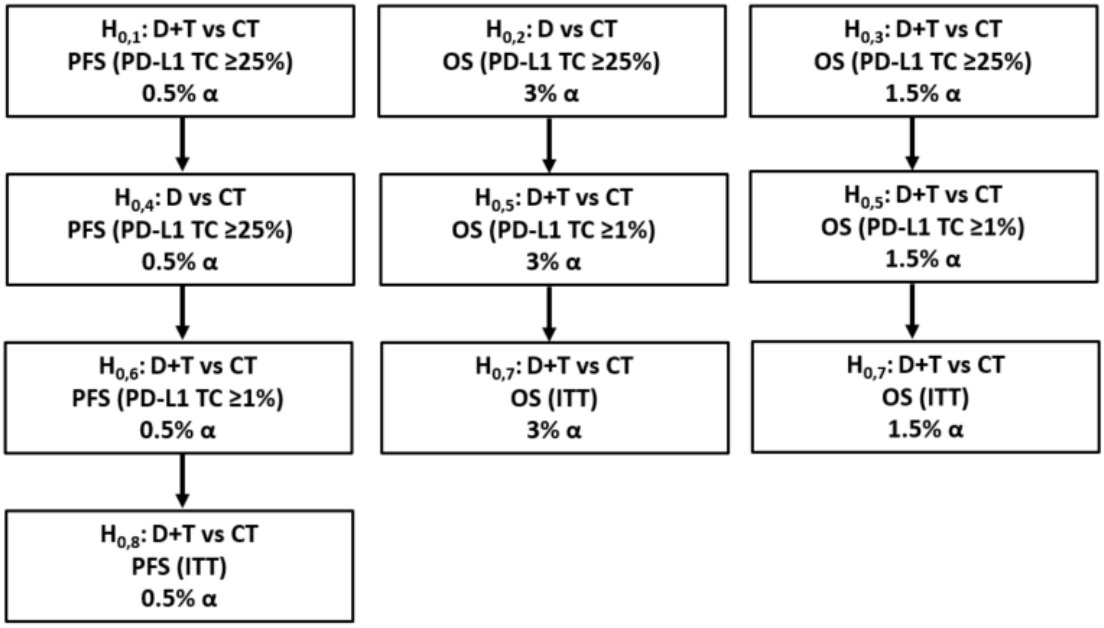


*Standard of care platinum-based doublet chemotherapy with any of the following regimens: (1) paclitaxel + carboplatin: paclitaxel 200 mg/m^2 and carboplatin area under the curve (AUC) 5 or 6 via i.v. infusion on day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD; (2) gemcitabine + cisplatin (squamous patients only): gemcitabine 1000 or 1250 mg/m^2 via i.v. infusion on days 1 and 8 of each 21-day cycle + cisplatin 75 or 80 mg/m^2 via i.v. infusion on day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD; (3) gemcitabine + carboplatin (squamous patients only): gemcitabine 1000 or 1250 mg/m^2 via i.v. infusion on days 1 and 8 of each 21-day cycle + carboplatin AUC 5 or 6 via i.v. infusion on day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD; (4) pemetrexed + cisplatin (nonsquamous patients only): pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 via i.v. infusion on day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD (patients who have not progressed after 4 cycles are eligible for pemetrexed maintenance therapy); (5) pemetrexed + carboplatin (nonsquamous patients only): pemetrexed 500 mg/m^2 and carboplatin AUC 5 or 6 via i.v. infusion on day 1 of each 21-day cycle, for 4 to 6 cycles or until documented PD (patients who have not progressed after 4 cycles are eligible for pemetrexed maintenance therapy).

†Confirmed progression according to RECIST v1.1, with a confirmatory scan required no earlier than 4 weeks after the previous assessment of PD. Patients allocated to initial durvalumab plus tremelimumab combination therapy were permitted to restart combination treatment if PD

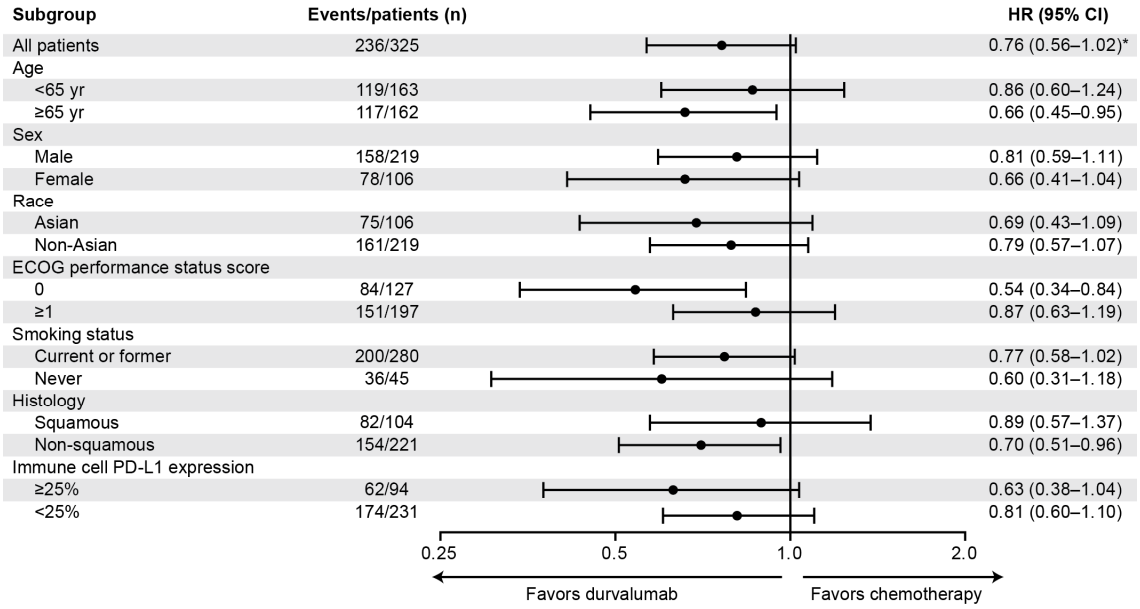
occurred after completion of the combination treatment phase, provided eligibility criteria were met. Patients in both immunotherapy groups were permitted to receive treatment through progression at the investigator's discretion provided they were considered to continue to receive benefit, unless progression occurred in a target lesion previously showing confirmed complete or partial response. Investigators were required to ensure that patients being considered for treatment in the setting of PD still met all of the inclusion criteria and none of the exclusion criteria, and that patients: i) provided written informed consent for retreatment; ii) had an absence of clinical symptoms or signs indicating clinically significant disease progression; iii) had no decline in ECOG performance status to >1; and iv) had absence of rapid disease progression or threat to vital organs or critical anatomical sites requiring urgent alternative medical intervention. [‡]Other reasons for discontinuing treatment included development of an adverse event necessitating treatment discontinuation, withdrawal of consent, pregnancy or intent to become pregnant, non-compliance with the study protocol or initiation of alternative anticancer therapy including another investigational agent. [§]Anticancer therapy utilized after discontinuation of study treatment was recorded as part of the follow-up schedule. CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; i.v., intravenous; NSCLC, non-small-cell lung cancer; PD, progressive disease; PD-L1, programmed cell death ligand-1; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell.

eFigure 2. Hierarchical Multiple Testing Procedure



A hierarchical MTP with a gatekeeping strategy was used to control family-wise type I error at a two-sided 5% significance level. With this approach, the hypotheses were to be tested in a predefined order, as outlined in the figure, with an alpha-exhaustive recycling strategy. A 3%, 1.5%, and 0.5% alpha was allocated to the primary endpoints of OS for D vs CT, and OS and PFS for D+T vs CT, respectively. Within a column, testing proceeds only if the previous level hypothesis is rejected. Testing starts at the top row. If a hypothesis in the top row is rejected, the next hypothesis in the subsequent row of the same column is tested. If that hypothesis is rejected, testing continues to the next subsequent row, and so on. The alpha values for each interim analysis and final analysis were adjusted using the Lan-DeMets spending function approximating O'Brien-Fleming boundary approach, where the alpha level applied at the interim depends upon the proportion of information available. D, durvalumab; ITT, intention-to-treat; MTP, multiple testing procedure; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; T, tremelimumab; TC, tumor cell.

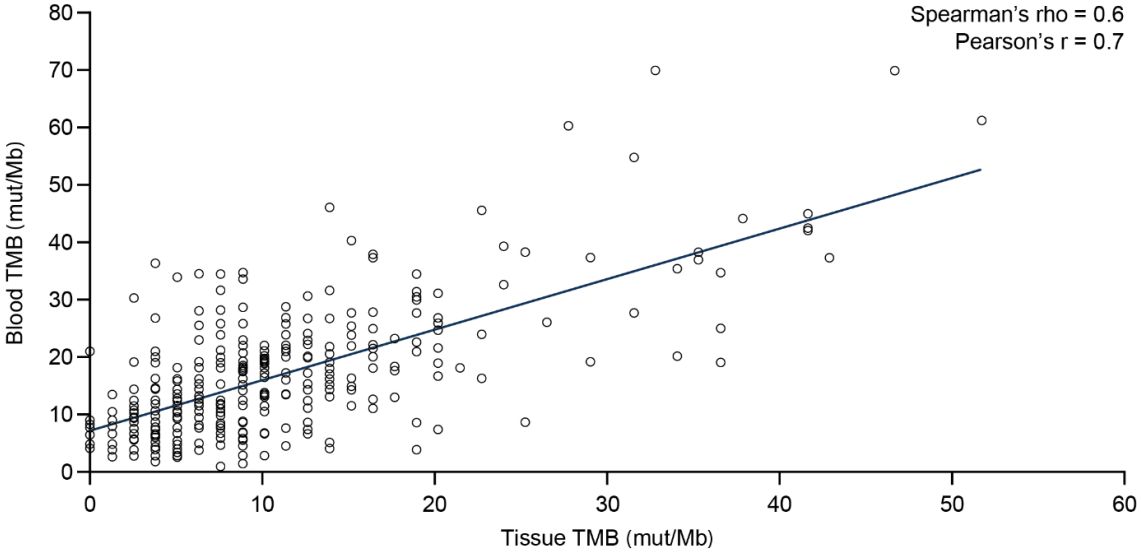
eFigure 3. Subgroup Analysis of Overall Survival for Durvalumab Monotherapy Versus Chemotherapy Among Patients With PD-L1 TC ≥25%



Primary analysis population. Analysis performed using a Cox proportional hazards model with a term for treatment and the subgroup covariate of interest. Subgroups according to sex, age, immune cell PD-L1 expression, histology, smoking history, and race were prespecified in the protocol. The analysis of subgroups according to performance status was post hoc. *97.54% CI is shown. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand-1; TC, tumor cell.

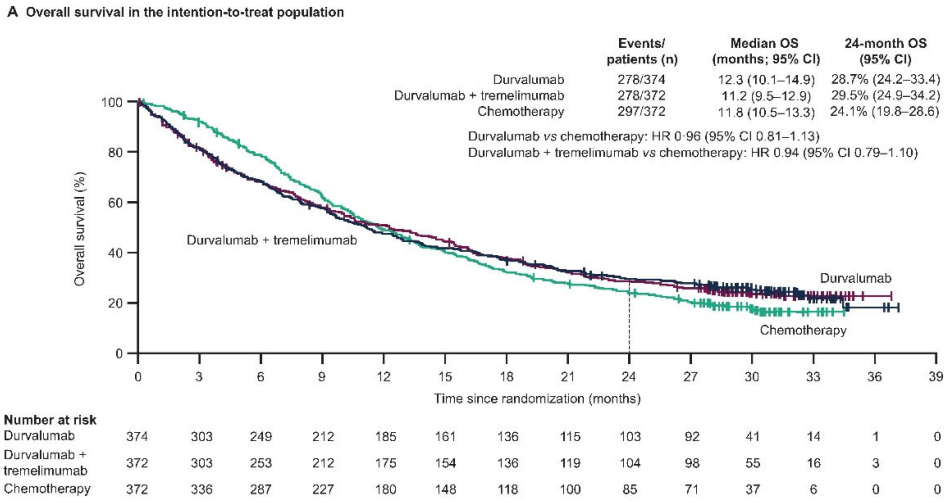
eFigure 4. TMB Dataset and Blood TMB Correlation With Tissue TMB

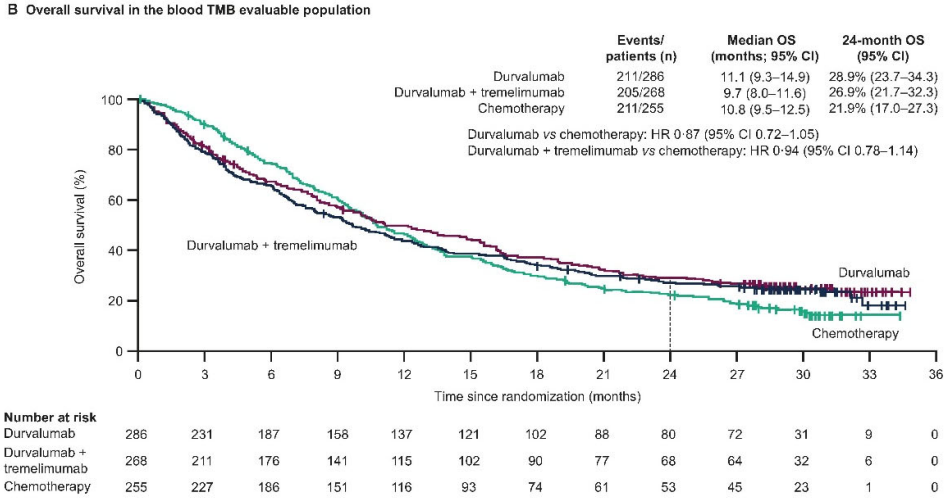
	Durvalumab Monotherapy (n = 374)	Durvalumab + Tremelimumab (n = 372)	Chemotherapy (n = 372)	Total (n = 1118)
Tissue samples available, n (%)	242 (64.7)	253 (68.0)	240 (64.5)	735 (65.7)
Tissue TMB evaluable, n (%)	145 (38.8)	164 (44.1)	151 (40.6)	460 (41.1)
Plasma samples available, n (%)	338 (90.4)	338 (90.9)	327 (87.9)	1003 (89.7)
Blood TMB evaluable, n (%)	286 (76.5)	268 (72.0)	255 (68.5)	809 (72.4)

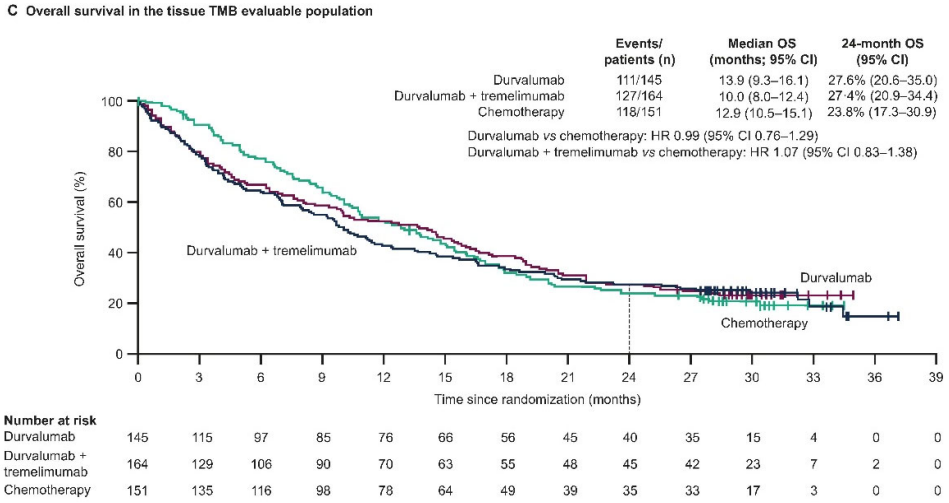


Data cut-off: October 4, 2018. The correlation plot is based on 352 patients with matched blood and tissue TMB data. The reference line is estimated using linear regression. Mb, megabase; mut, mutations; TMB, tumor mutational burden.

eFigure 5. Overall Survival in the ITT, Blood and Tissue TMB Evaluable Populations

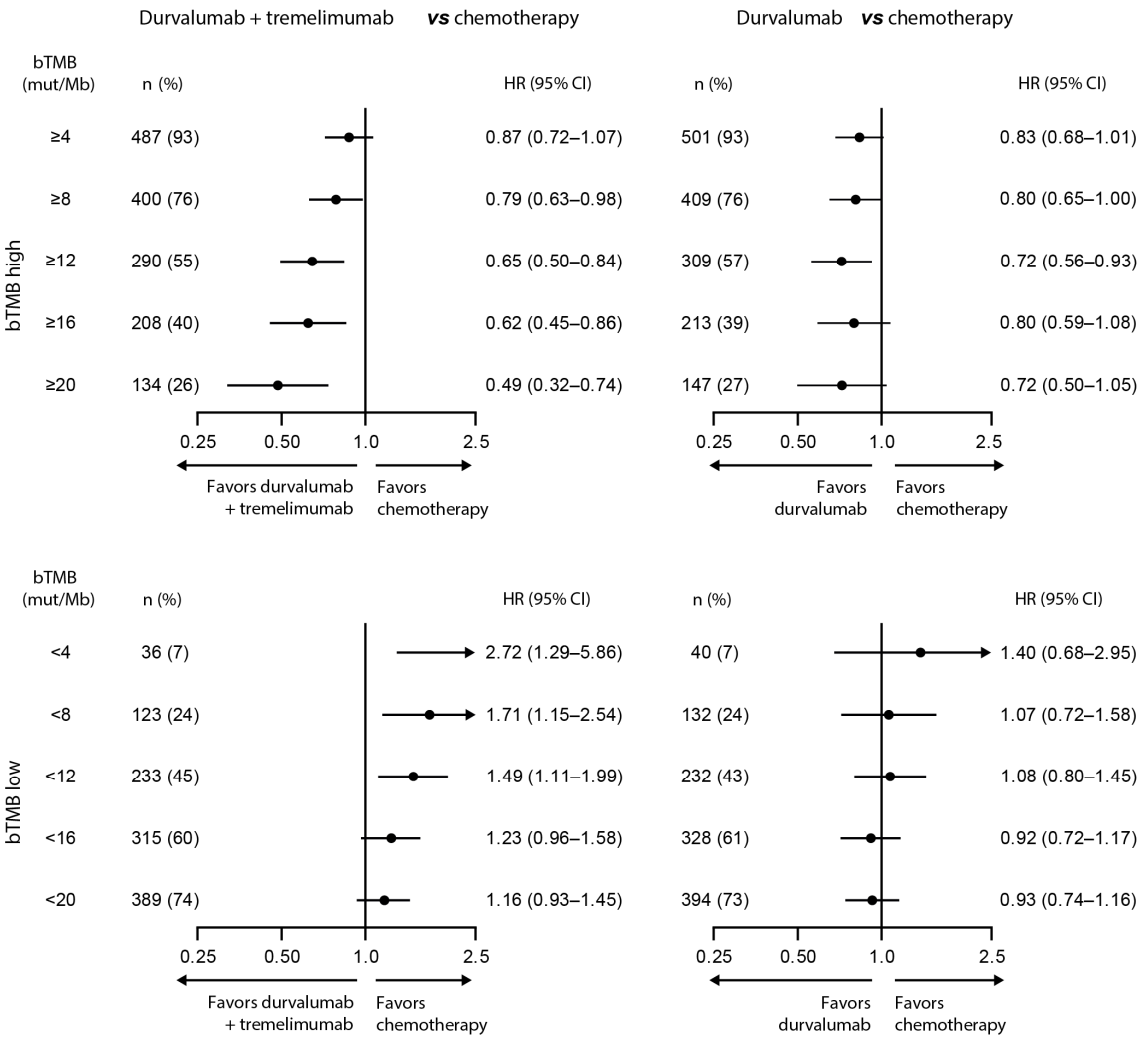






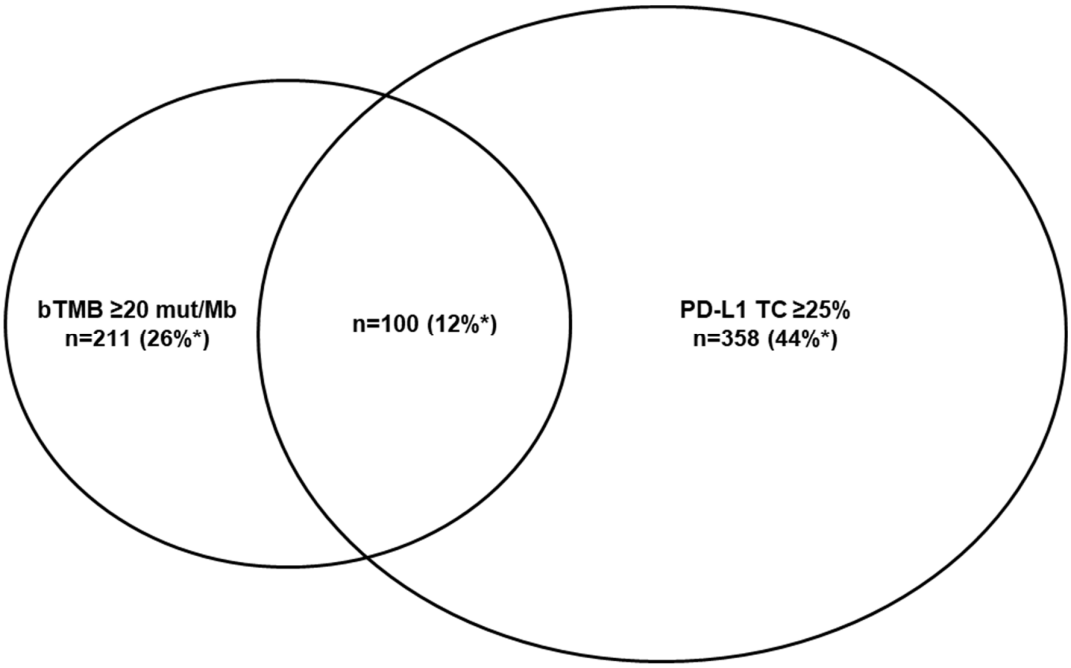
Data cut-off: October 4, 2018. CI, confidence interval; OS, overall survival; TMB, tumor mutational burden.

eFigure 6. Exploratory Analysis of Overall Survival Across Blood TMB Cut-offs



Data cut-off: October 4, 2018. CI, confidence interval; Mb, megabase; mut, mutations; PD-L1, programmed cell death ligand-1; TC, tumor cell; TMB, tumor mutational burden.

eFigure 7. Venn Diagram Showing Overlap of Patient Subgroups Based on Blood TMB and PD-L1



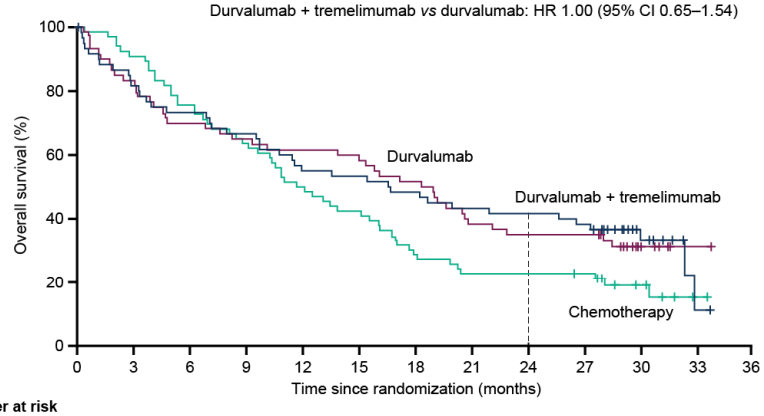
*Percentages are calculated from the bTMB evaluable population (n = 809). bTMB, blood tumor mutational burden; Mb, megabase; mut, mutations; PD-L1, programmed cell death ligand-1; TC, tumor cell.

eFigure 8. Exploratory Analysis of Overall Survival According to Tissue TMB

A **Overall survival in the tissue TMB ≥10 mut/Mb population**

	Events/ patients (n)	Median OS (months; 95% CI)	24-month OS (95% CI)
Durvalumab	41/60	18.6 (9.3–22·0)	35.0% (23.3–47.0)
Durvalumab + tremelimumab	41/60	16.6 (9.7–27.3)	41.7% (29.2–53.7)
Chemotherapy	54/67	11.9 (9.1–16·0)	22.7% (13.5–33.4)

Durvalumab *vs* chemotherapy: HR 0.70 (95% CI 0.47–1.06)
Durvalumab + tremelimumab *vs* chemotherapy: HR 0.72 (95% CI 0.48–1.09)
Durvalumab + tremelimumab *vs* durvalumab: HR 1.00 (95% CI 0.65–1.54)



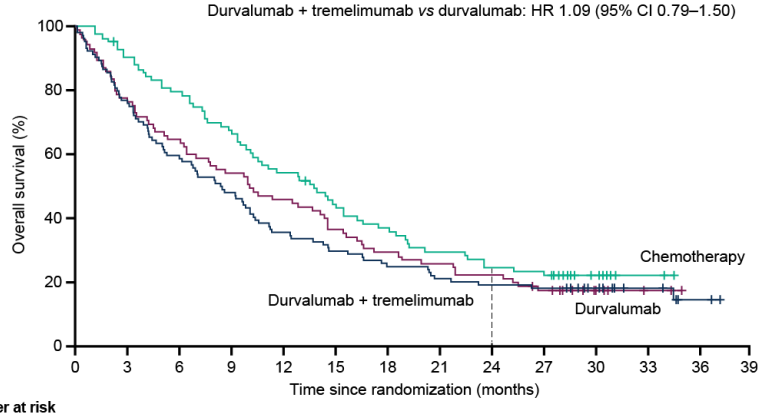
Number at risk

Durvalumab	60	50	42	39	37	35	31	23	21	21	9	2	0
Durvalumab + tremelimumab	60	49	44	40	33	32	29	26	25	23	10	1	0
Chemotherapy	67	60	50	42	33	28	19	15	15	14	7	1	0

B **Overall survival in the tissue TMB <10 mut/Mb population**

	Events/ patients (n)	Median OS (months; 95% CI)	24-month OS (95% CI)
Durvalumab	70/85	10.1 (6.4–14.6)	22.4% (14.2–31.7)
Durvalumab + tremelimumab	86/104	8.4 (5.3–10.3)	19.2% (12.3–27.3)
Chemotherapy	64/84	3.8 (10.1–16.3)	24.7% (16.0–34.4)

Durvalumab *vs* chemotherapy: HR 1.26 (95% CI 0.90–1.77)
Durvalumab + tremelimumab *vs* chemotherapy: HR 1.39 (95% CI 1.00–1.92)
Durvalumab + tremelimumab *vs* durvalumab: HR 1.09 (95% CI 0.79–1.50)



Number at risk

Durvalumab	85	65	55	46	39	31	25	22	19	14	6	2	0	0
Durvalumab + tremelimumab	104	80	62	50	37	31	26	22	20	19	13	6	2	0
Chemotherapy	84	75	66	56	45	36	30	24	20	19	10	2	0	0

Data cut-off: October 4, 2018. CI, confidence interval; Mb, megabase; OS, overall survival; mut, mutations; TMB, tumor mutational burden.

eTable 1. Inclusion and Exclusion Criteria

Inclusion Criteria
Age ≥18 years at the time of screening
Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the USA, 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 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology)[8]
Patients must have tumors that lack sensitizing *EGFR* mutation (eg, exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X or exon 20 S768I mutation) and *ALK* rearrangement. 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 advanced or metastatic NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant or definitive chemoradiation for advanced disease are eligible, provided that progression has occurred >6 months from last therapy
Tumor PD-L1 status, with the VENTANA PD-L1 (SP263) IHC assay confirmed by a reference laboratory, 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 fresh biopsies should not be target lesions, unless there are no other lesions suitable for biopsy. 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 and other exploratory biomarker analyses and is preferred in formalin-fixed paraffin embedded blocks
ECOG performance status of 0 or 1 at enrollment
At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per Response Evaluation Criteria in Solid Tumors version 1.1 guidelines
No prior exposure to immune-mediated therapy including, but not limited to, other anti-cytotoxic T-lymphocyte-associated 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: • Hemoglobin ≥9.0 g/dL • Absolute neutrophil count ≥1.5 × 10^9/L • Platelet count ≥100 × 10^9/L • Serum bilirubin ≤1.5 × ULN. This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician • ALT and AST ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN • Calculated creatinine clearance ≥50 mL/min as determined by Cockcroft–Gault (using actual body weight) or 24-hour urine collection: *Males:* Creatinine clearance (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$ *Females:* 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: • 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) • Women ≥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 >1-year interval since last menses or underwent surgical sterilization (bilateral oophorectomy 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)
Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study
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

Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable
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, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhea), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc., within the past 3 years prior to the start of treatment. The following are exceptions to this criterion: • Patients with vitiligo or alopecia • Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment
Any condition that, in the opinion of the investigator, would interfere with the evaluation of investigational product or interpretation of patient safety or study results, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring adverse events from durvalumab or tremelimumab, or compromise the ability of the patient to give written informed consent
Medical contraindication to platinum (cisplatin or carboplatin)-based doublet chemotherapy
History of another primary malignancy except for:

• Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease • Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)
History of leptomeningeal carcinomatosis
Brain metastases or spinal cord compression unless the patient is stable (asymptomatic, no evidence of new or emerging brain metastases) and off steroids for at least 14 days prior to start of study treatment. Following radiotherapy and/or surgery, patients with brain metastases must wait 4 weeks following the intervention and must confirm stability with imaging before randomization. Patients with suspected brain metastases at screening should have a CT/MRI of the brain prior to study entry
Mean QT interval corrected for heart rate using Fridericia's formula ≥470 ms
History of active primary immunodeficiency
Active infection, including tuberculosis (clinical evaluation), hepatitis B, hepatitis C or HIV (positive HIV 1 or 2 antibodies). Active HBV is defined by a known positive HBV surface antigen result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B 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: • Intranasal, inhaled, topical steroids or local steroid injections (eg, intra-articular injection) • Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent • Steroids as premedication for hypersensitivity reactions (eg, CT scan 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 180 days after the last dose of durvalumab plus tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy
Known allergy or hypersensitivity to investigational product or any excipient or to other humanized monoclonal antibodies

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; ULN, upper limit of normal.

eTable 2. Summary of Efficacy Endpoints Reported in this Publication

	Durvalumab vs Chemotherapy	**Durvalumab + Tremelimumab vs Chemotherapy**
Primary endpoints	• OS in PD-L1 TC ≥25%	• OS in PD-L1 TC ≥25% • PFS by BICR in PD-L1 TC ≥25%
Secondary endpoints	• PFS by BICR in PD-L1 TC ≥25% • ORR, DOR, and APF12 by BICR in PD-L1 TC ≥25%	• OS in PD-L1 TC ≥1% and ITT • ORR, DOR, and APF12 by BICR in PD-L1 TC ≥25%
Prespecified subgroup analyses	• OS in PD-L1 TC ≥50%, ≥1%, and <1% • OS in PD-L1 TC ≥25% by sex, age, immune cell PD-L1 expression, histology, smoking history, and race	• OS in PD-L1 TC ≥50% and <1%
Post-hoc subgroup analyses	• OS in PD-L1 TC 25–49% • OS in PD-L1 TC ≥25% by ECOG performance status	• OS in PD-L1 TC 25–49%
Exploratory analyses	• OS in blood TMB <20 and ≥20 mut/Mb • PFS by BICR in blood TMB <20 and ≥20 mut/Mb • ORR, DOR, and APF12 by BICR in blood TMB <20 and ≥20 mut/Mb • OS in tissue TMB <10 and ≥10 mut/Mb	

APF12, proportion of patients alive and progression-free at 12 months from randomization; BICR, blinded independent central review (per RECIST v1.1); DOR, duration of response; ITT, intention-to-treat; Mb, megabase; mut, mutations; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TC, tumor cell; TMB, tumor mutational burden.

eTable 3. Sample Size Assumptions in the PD-L1 ≥TC 25% Primary Analysis Population

Primary Endpoint	**Power (%)**	**HR**	**Events**	**Overall 2-sided Significance Level (%)**
PFS (durvalumab + tremelimumab vs chemotherapy)	88	0.59	231	0.5
OS (durvalumab vs chemotherapy)	90	0.62	225	3*
OS (durvalumab + tremelimumab vs chemotherapy)	86	0.62	225	1.5*

*Adjusting for two planned interim analyses and final analysis of OS, using the Lan-DeMets spending function that approximates an O'Brien-Fleming approach to account for multiple comparisons.[9] The first interim analysis was planned at the time of the primary PFS analysis, and the second when 80% of target OS events had occurred. HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TC, tumor cell.

eTable 4. Baseline Demographics and Disease Characteristics in the Intention-to-treat Population*

		Durvalumab Monotherapy (n = 374)	**Durvalumab + Tremelimumab (n = 372)**	**Chemotherapy (n = 372)**
Median age (range), years		65.0 (28–84)	66.0 (28–87)	64.0 (30–85)
Sex, n (%)	Male	256 (68.4)	266 (71.5)	250 (67.2)
	Female	118 (31.6)	106 (28.5)	122 (32.8)
Race, n (%)	White	243 (65.0)	249 (66.9)	243 (65.3)
	Asian	125 (33.4)	118 (31.7)	120 (32.3)
	Black/African American	3 (0.8)	3 (0.8)	4 (1.1)
ECOG performance status, n (%)	0	140 (37.4)	156 (41.9)	161 (43.3)
	1	232 (62.0)	216 (58.1)	209 (56.2)
	2	1 (0.3)	0	0
Histology, n (%)	Squamous	107 (28.6)	107 (28.8)	106 (28.5)
	Nonsquamous	267 (71.4)	265 (71.2)	266 (71.5)
Smoking history, n (%)	Never smoker	57 (15.2)	56 (15.1)	52 (14.0)
	Former smoker	211 (56.4)	233 (62.6)	227 (61.0)
	Current smoker	106 (28.3)	83 (22.3)	93 (25.0)
PD-L1 expression status, n (%)	TC ≥1%	279 (74.6)	296 (79.6)	289 (77.7)
	TC ≥25%	163 (43.6)	163 (43.8)	162 (43.5)
	TC ≥50%	118 (31.6)	108 (29.0)	107 (28.8)

Data cut-off: October 4, 2018. *All randomized patients. ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand-1; TC, tumor cell.

eTable 5. Subsequent Anticancer Therapy in Patients with PD-L1 TC ≥25%

	Durvalumab Monotherapy (n = 163)	Durvalumab + Tremelimumab (n = 163)	Chemotherapy (n = 162)
Patients who received study treatment, n (%)	161 (98.8)	163 (100)	153 (94.4)
Patients who discontinued study treatment	136 (83.4)	145 (89.0)	152 (93.8)
Patients remaining on study treatment	25 (15.3)	18 (11.0)	1 (0.6)
Patients receiving any subsequent therapy, n (%)	73 (44.8)	61 (37.4)	95 (58.6)
Re-treatment*	NA	10 (6.1)	NA
Immunotherapy	10 (6.1)	5 (3.1)	64 (39.5)
Cytotoxic chemotherapy	70 (42.9)	52 (31.9)	58 (35.8)
Other systemic therapies[†]	18 (11.0)	9 (5.5)	18 (11.1)

Primary analysis population. Data cut-off: October 4, 2018. *Re-treatment with durvalumab plus tremelimumab. Patients in the durvalumab plus tremelimumab group could restart treatment with the combination therapy if they completed 4 dosing cycles with durvalumab plus tremelimumab (with clinical benefit per investigator's judgment), but subsequently had disease progression during treatment with durvalumab alone and if they met eligibility criteria for retreatment. [†]Excluding immunotherapy and cytotoxic chemotherapy. NA, not applicable; PD-L1, programmed cell death ligand-1; TC, tumor cell.

eTable 6. Overall Survival in the ITT Population and by PD-L1 Expression Subgroup

		Durvalumab Monotherapy	Durvalumab + Tremelimumab	Chemotherapy
ITT population*	Number of events/patients	278/374	278/372	297/372
	Median overall survival, months (95% CI)	12.3 (10.1–14.9)	11.2 (9.5–12.9)	11.8 (10.5–13.3)
	Hazard ratio (95% CI)[†]	0.96 (0.81–1.13)	0.94 (0.79–1.10)[‡]	–
PD-L1 TC ≥1%	Number of patients	194/279	221/296	226/289
	Median overall survival, months (95% CI)	14.6 (10.5–17.7)	10.9 (9.1–13.5)	12.3 (10.6–14.6)
	Hazard ratio (95% CI)[†]	0.88 (0.73–1.07)[§]	1.01 (0.83–1.21)[‡]	–
PD-L1 TC 25–49%	Number of patients	33/45	45/55	46/55
	Median overall survival, months (95% CI)	11.1 (6.2–22.5)	10.5 (5.3–16.7)	13.3 (8.4–16.3)
	Hazard ratio (95% CI)[†]	0.78 (0.49–1.23)	0.95 (0.62–1.45)	–
PD-L1 TC ≥50%	Number of patients	75/118	68/108	82/107
	Median overall survival, months (95% CI)	18.3 (13.6–22.8)	15.2 (8.0–26.5)	12.7 (10.3–15.1)
	Hazard ratio (95% CI)[†]	0.76 (0.55–1.04)[§]	0.77 (0.56–1.07)[§]	–
PD-L1 TC <1%	Number of patients	84/95	57/76	71/83
	Median overall survival, months (95% CI)	10.1 (6.7–12.2)	11.9 (9.3–18.6)	10.3 (7.9–12.9)
	Hazard ratio (95% CI)[†]	1.18 (0.86–1.62)[§]	0.73 (0.51–1.04)[§]	–

Data cut-off: October 4, 2018. *The ITT population includes all randomized patients. [†]Hazard ratio compared with chemotherapy. [‡]Secondary endpoint.

[§]Prespecified subgroup analysis. CI, confidence interval; ITT, intention-to-treat; PD-L1, programmed cell death ligand-1; TC, tumor cell.

eTable 7. Summary of Tumor Response Amongst Patients With PD-L1 TC ≥25%

	Durvalumab Monotherapy (n = 163)	Durvalumab Plus Tremelimumab (n = 163)	Chemotherapy (n = 162)
ORR[*,†], n (%)	58 (35.6)	56 (34.4)	61 (37.7)
Estimated odds ratio vs chemotherapy (95% CI)[‡]	0.91 (0.58–1.44)	0.87 (0.55–1.36)	–
Risk ratio vs chemotherapy (95% CI)	0.94 (0.71–1.26)	0.91 (0.68–1.22)	
Best objective response, n (%)			
Complete response[†]	1 (0.6)	0	0
Partial response[†]	57 (35.0)	56 (34.4)	61 (37.7)
Stable disease ≥6 weeks	50 (30.7)	45 (27.6)	66 (40.7)
Progressive disease	53 (32.5)	59 (36.2)	25 (15.4)
Not evaluable	2 (1.2)	3 (1.8)	10 (6.2)
Median DOR[§], months (95% CI)	NR (9.7–NR)	NR (6.7–NR)	4.4 (3.5–5.5)
Remaining in response (%) at:			
6 months	66.9	67.6	32.4
12 months	61.3	54.9	18.0

Primary analysis population. *ORR by blinded independent central review per RECIST v1.1 is defined as the number (%) of patients with at least 1 visit response of complete response or partial response. The data cut-off for ORR occurred on June 1, 2017 (the same time as the primary PFS analysis for superiority). [†]Responses included unconfirmed responses. [‡]Analysis was performed using logistic regression adjusting for the stratification factor (at the time of randomization) of histology (squamous vs all other), with 95% CI calculated by profile likelihood. An odds ratio >1 favors immunotherapy. [§]DOR was calculated using the Kaplan-Meier technique and was defined as the time from the first documentation of complete response/partial response until the date of progression, death or the last evaluable RECIST assessment for patients that do not progress or for patients who progress or die after two or more missed visits. CI, confidence interval; DOR, duration of response; NR, not reached; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TC, tumor cell.

eTable 8. Baseline Demographics and Disease Characteristics (Patients with Blood TMB ≥20 and <20 mut/Mb)

		Blood TMB ≥20 mut/Mb			Blood TMB <20 mut/Mb		
		Durvalumab Monotherapy (n = 77)	**Durvalumab + Tremelimumab (n = 64)**	**Chemotherapy (n = 70)**	**Durvalumab Monotherapy (n = 209)**	**Durvalumab + Tremelimumab (n = 204)**	**Chemotherapy (n = 185)**
Median age (range), years		67.0 (43–83)	66.0 (42–81)	63.0 (42–81)	64.0 (28–84)	65.0 (34–83)	64.0 (30–85)
Sex, n (%)	Male	58 (75.3)	47 (73.4)	50 (71.4)	144 (68.9)	142 (69.6)	125 (67.6)
	Female	19 (24.7)	17 (26.6)	20 (28.6)	65 (31.1)	62 (30.4)	60 (32.4)
Race, n (%)	White	62 (80.5)	48 (75.0)	53 (75.7)	135 (64.6)	150 (73.5)	129 (69.7)
	Asian	15 (19.5)	16 (25.0)	14 (20.0)	70 (33.5)	51 (25.0)	52 (28.1)
	Black/African American	0	0	0	3 (1.4)	2 (1.0)	3 (1.6)
ECOG performance status, n (%)	0	24 (31.2)	28 (43.8)	30 (42.9)	84 (40.2)	86 (42.2)	78 (42.2)
	1	52 (67.5)	36 (56.3)	40 (57.1)	125 (59.8)	118 (57.8)	107 (57.8)
	2	1 (1.3)	0	0	0	0	0
Histology, n (%)	Squamous	29 (37.7)	25 (39.1)	29 (41.4)	59 (28.2)	57 (27.9)	47 (25.4)
	Nonsquamous	48 (62.3)	39 (60.9)	41 (58.6)	150 (71.8)	147 (72.1)	138 (74.6)
Smoking history, n (%)	Never smoker	3 (3.9)	3 (4.7)	4 (5.7)	33 (15.8)	33 (16.2)	19 (10.3)
	Former smoker	43 (55.8)	45 (70.3)	44 (62.9)	121 (57.9)	124 (60.8)	120 (64.9)
	Current smoker	31 (40.3)	16 (25.0)	22 (31.4)	55 (26.3)	47 (23.0)	46 (24.9)
PD-L1 expression status, n (%)	TC ≥25%	40 (51.9)	32 (50.0)	28 (40.0)	91 (43.5)	81 (39.7)	86 (46.5)

ECOG, Eastern Cooperative Oncology Group; Mb, megabase; mut, mutations; PD-L1, programmed cell death ligand-1; TC, tumor cell; TMB, tumor mutational burden.

eTable9. Baseline Demographics and Disease Characteristics (Patients with Tissue TMB ≥10 and <10 mut/Mb)

		Tissue TMB ≥10 mut/Mb			Tissue TMB <10 mut/Mb		
		Durvalumab Monotherapy (n = 60)	**Durvalumab + Tremelimumab (n = 60)**	**Chemotherapy (n = 67)**	**Durvalumab Monotherapy (n = 85)**	**Durvalumab + Tremelimumab (n = 104)**	**Chemotherapy (n = 84)**
Median age (range), years		64.0 (43–82)	67.0 (42–81)	63.0 (42–83)	65.0 (32–77)	67.5 (34–83)	63.5 (36–85)
Sex, n (%)	Male	49 (81.7)	41 (68.3)	47 (70.1)	59 (69.4)	72 (69.2)	55 (65.5)
	Female	11 (18.3)	19 (31.7)	20 (29.9)	26 (30.6)	32 (30.8)	29 (34.5)
Race, n (%)	White	46 (76.7)	49 (81.7)	44 (65.7)	59 (69.4)	73 (70.2)	61 (72.6)
	Asian	14 (23.3)	11 (18.3)	20 (29.9)	25 (29.4)	30 (28.8)	23 (27.4)
	Black/African American	0	0	2 (3.0)	1 (1.2)	0	0
ECOG performance status, n (%)	0	23 (38.3)	24 (40.0)	31 (46.3)	34 (40.0)	38 (36.5)	41 (48.8)
	1	36 (60.0)	36 (60.0)	36 (53.7)	51 (60.0)	66 (63.5)	43 (51.2)
	2	1 (1.7)	0	0	0	0	0
Histology, n (%)	Squamous	20 (33.3)	25 (41.7)	30 (44.8)	30 (35.3)	30 (28.8)	25 (29.8)
	Nonsquamous	40 (66.7)	35 (58.3)	37 (55.2)	55 (64.7)	74 (71.2)	59 (70.2)
Smoking history, n (%)	Never smoker	0	1 (1.7)	1 (1.5)	10 (11.8)	19 (18.3)	10 (11.9)
	Former smoker	37 (61.7)	40 (66.7)	42 (62.7)	47 (55.3)	67 (64.4)	49 (58.3)
	Current smoker	23 (38.3)	19 (31.7)	24 (35.8)	28 (32.9)	18 (17.3)	25 (29.8)

PD-L1 expression status, n (%)	TC ≥25%	30 (50.0)	24 (40.0)	34 (50.7)	39 (45.9)	38 (36.5)	32 (38.1)

ECOG, Eastern Cooperative Oncology Group; Mb, megabase; mut, mutations; PD-L1, programmed cell death ligand-1; TC, tumor cell; TMB, tumor mutational burden.

eTable 10. Exploratory Analysis of Tumor Response Among Patients With Blood TMB ≥20 mut/Mb and <20 mut/Mb

	Blood TMB ≥20 mut/Mb			Blood TMB <20 mut/Mb		
	Durvalumab Monotherapy (n = 77)	**Durvalumab + Tremelimumab (n = 64)**	**Chemotherapy (n = 70)**	**Durvalumab Monotherapy (n = 209)**	**Durvalumab + Tremelimumab (n = 204)**	**Chemotherapy (n = 185)**
ORR*, n (%)	23 (29.9)	31 (48.4)	15 (21.4)	43 (20.6)	34 (16.7)	58 (31.4)
Estimated odds ratio immunotherapy vs chemotherapy (95% CI)[†]	1.56 (0.74–3.36)	3.44 (1.65–7.46)		0.57 (0.36–0.89)	0.44 (0.27–0.71)	
Estimated odds ratio combination therapy vs durvalumab (95% CI)[†]		2.21 (1.11–4.45)			0.77 (0.47–1.27)	
Median DOR[‡], months (95% CI)	NR (NR–NR)	NR (NR–NR)	4.1 (3.0–4.3)	NR (5.9–NR)	11.1 (5.6–NR)	4.1 (2.8–5.6)
Remaining in response (%) at:						
6 months	86.5	85.6	14.4	64.0	66.6	33.3
12 months	80.3	81.7	7.2	59.1	48.2	14.3

Data cut-off: June 1, 2017. *ORR by blinded independent central review per RECIST v1.1 is defined as the number (%) of patients with at least 1 visit response of complete response or partial response. Responses included unconfirmed responses. [†]Analysis was performed using logistic regression, with 95% CI calculated by profile likelihood. An odds ratio >1 favors the first comparator listed. [‡]DOR was calculated using the Kaplan-Meier technique and was defined as the time from the first documentation of complete response/partial response until the date of progression, death or the last evaluable RECIST assessment for patients that do not progress or for patients who progress or die after two or more missed visits. CI, confidence interval; DOR, duration of

response; Mb, megabase; mut, mutations; NR, not reached; ORR, objective response rate; PD-L1, programmed cell death ligand-1; TC, tumor cell; TMB, tumor mutational burden.

eTable 11. Safety Summary in Patients with PD-L1 TC ≥25%*

	Durvalumab Monotherapy (n = 161)	Durvalumab + Tremelimumab (n = 163)	Chemotherapy (n = 153)
All-cause adverse events, n (%)			
Any grade	149 (92.5)	151 (92.6)	148 (96.7)
Grade 3/4	75 (46.6)	74 (45.4)	75 (49.0)
Leading to death	4 (2.5)	17 (10.4)	5 (3.3)
Serious	61 (37.9)	80 (49.1)	51 (33.3)
Leading to discontinuation†	18 (11.2)	35 (21.5)	22 (14.4)
Treatment-related adverse events‡, n (%)			
Any grade	99 (61.5)	91 (55.8)	135 (88.2)
Grade 3/4	30 (18.6)	30 (18.4)	59 (38.6)
Leading to death	1 (0.6)	1 (0.6)	1 (0.7)
Serious	12 (7.5)	30 (18.4)	27 (17.6)
Leading to discontinuation†	10 (6.2)	21 (12.9)	19 (12.4)

Data cut-off: October 4, 2018. *As-treated population (all patients with PD-L1 TC ≥25% who received at least one dose of study treatment). The table includes all adverse events that occurred during the treatment period and up to 90 days after the last dose of immunotherapy (30 days after the last dose of chemotherapy) or up to the start of any subsequent therapy (whichever occurred first). †This category includes patients who discontinued any study drug, even if (in combination arms) other components of study treatment were continued. ‡Adverse events assessed by the investigator as possibly related to study treatment. PD-L1, programmed cell death ligand-1; TC, tumor cell.

eTable 12. Safety Summary in Patients with Blood TMB ≥20 mut/Mb*

	Durvalumab Monotherapy (n = 77)	**Durvalumab + Tremelimumab (n = 64)**	**Chemotherapy (n = 70)**
All-cause adverse events, n (%)			
Any grade	74 (96.1)	62 (96.9)	67 (95.7)
Grade 3/4	38 (49.4)	30 (46.9)	30 (42.9)
Leading to death	4 (5.2)	7 (10.9)	4 (5.7)
Serious	28 (36.4)	32 (50.0)	19 (27.1)
Leading to discontinuation†	10 (13.0)	14 (21.9)	12 (17.1)
Treatment-related adverse events‡, n (%)			
Any grade	51 (66.2)	39 (60.9)	59 (84.3)
Grade 3/4	18 (23.4)	10 (15.6)	23 (32.9)
Leading to death	0	1 (1.6)	1 (1.4)
Serious	9 (11.7)	12 (18.8)	6 (8.6)
Leading to discontinuation†	3 (3.9)	8 (12.5)	8 (11.4)

Data cut-off date: October 4, 2018. *As-treated population (all patients with TMB ≥20 mut/Mb who received at least one dose of study treatment). The table includes all adverse events that occurred during the treatment period and up to 90 days after the last dose of immunotherapy (30 days after the last dose of chemotherapy) or up to the start of any subsequent therapy (whichever occurred first). †This category includes patients who discontinued any study drug, even if (in combination arms) other components of study treatment were continued. ‡Adverse events assessed by the investigator as possibly related to study treatment. Mb, megabase; mut, mutations; TMB, tumor mutational burden.

eTable 13. All-cause Adverse Events*

	Durvalumab Monotherapy (n = 369)		Durvalumab + Tremelimumab (n = 371)		Chemotherapy (n = 352)	
	Any Grade	**Grade 3, 4 or 5**	**Any Grade**	**Grade 3, 4 or 5**	**Any Grade**	**Grade 3, 4 or 5**
Any event, n (%)	343 (93.0)	153 (41.5)	341 (91.9)	194 (52.3)	337 (95.7)	166 (47.2)
Event leading to discontinuation†, n (%)	42 (11.4)	31 (8.4)	75 (20.2)	56 (15.1)	53 (15.1)	27 (7.7)
Event leading to death‡, n (%)	13 (3.5)	13 (3.5)	33 (8.9)	33 (8.9)	15 (4.3)	15 (4.3)
Event occurring in ≥10% in any group§, n (%)						
Nausea	46 (12.5)	1 (0.3)	79 (21.3)	4 (1.1)	145 (41.2)	6 (1.7)
Decreased appetite	74 (20.1)	6 (1.6)	89 (24.0)	6 (1.6)	78 (22.2)	4 (1.1)
Fatigue	65 (17.6)	10 (2.7)	86 (23.2)	11 (3.0)	80 (22.7)	8 (2.3)
Anemia	37 (10.0)	8 (2.2)	37 (10.0)	6 (1.6)	145 (41.2)	43 (12.2)
Constipation	64 (17.3)	1 (0.3)	61 (16.4)	2 (0.5)	83 (23.6)	1 (0.3)
Diarrhea	53 (14.4)	2 (0.5)	82 (22.1)	11 (3.0)	46 (13.1)	5 (1.4)
Asthenia	48 (13.0)	11 (3.0)	47 (12.7)	10 (2.7)	48 (13.6)	11 (3.1)
Vomiting	32 (8.7)	4 (1.1)	31 (8.4)	1 (0.3)	75 (21.3)	7 (2.0)
Rash	39 (10.6)	3 (0.8)	58 (15.6)	1 (0.3)	40 (11.4)	1 (0.3)
Pruritus	42 (11.4)	0	67 (18.1)	0	17 (4.8)	0
Back pain	40 (10.8)	1 (0.3)	38 (10.2)	2 (0.5)	32 (9.1)	3 (0.9)
Pyrexia	41 (11.1)	3 (0.8)	43 (11.6)	0	26 (7.4)	0
Dyspnea	40 (10.8)	10 (2.7)	35 (9.4)	7 (1.9)	33 (9.4)	6 (1.7)
Cough	40 (10.8)	1 (0.3)	38 (10.2)	0	26 (7.4)	0
Weight decreased	39 (10.6)	3 (0.8)	43 (11.6)	3 (0.8)	18 (5.1)	1 (0.3)
Insomnia	27 (7.3)	1 (0.3)	39 (10.5)	2 (0.5)	22 (6.3)	1 (0.3)
Neutropenia	6 (1.6)	3 (0.8)	2 (0.5)	0	65 (18.5)	36 (10.2)
Thrombocytopenia	3 (0.8)	1 (0.3)	8 (2.2)	0	46 (13.1)	18 (5.1)
Alopecia	3 (0.8)	0	8 (2.2)	0	42 (11.9)	0

Data cut-off: October 4, 2018. *As-treated population (all patients who received at least one dose of study treatment). Listed are all adverse events that occurred during the treatment period and up to 90 days after the last dose of immunotherapy (30 days after the last dose of chemotherapy) or up to the start of any subsequent therapy (whichever occurred first). [†]This category includes patients who discontinued any study drug, even if (in combination arms) other components of study treatment were continued. [‡]Adverse events leading to death in the durvalumab monotherapy group were pneumonia (n = 3); septic shock (n = 2); aspiration pneumonia, cardiac tamponade, cytomegalovirus pneumonia, death, pneumonitis, pulmonary edema, sudden death, and suicide (each n = 1). Adverse events leading to death in the durvalumab plus tremelimumab combination group were interstitial lung disease, pneumonia, pulmonary embolism, respiratory failure, sepsis, and sudden death (each n = 2), and acute hepatic failure, acute myocardial infarction, acute pancreatitis, anaphylactic shock, aspiration pneumonia, cardiac failure, cerebral infarction, cerebral ischemia, chronic obstructive pulmonary disease and septic shock (in the same patient), death, euthanasia, hypercapnia, intestinal ischemia, ischemic stroke, *Pneumocystis jirovecii* pneumonia, pneumonitis, pneumothorax, pulmonary edema, small intestinal obstruction, small intestinal perforation, and thrombosis (each n = 1). Adverse events leading to death in the chemotherapy group were pneumonia (n = 4); pulmonary embolism (n = 3); alveolitis and renal failure (in the same patient), death, empyema, gastric perforation, peptic ulcer hemorrhage, respiratory tract infection, sepsis, and thrombocytopenia (each n = 1). [§]The events are listed in descending order of frequency across all three treatment groups.

eTable 14. Treatment-related Serious Adverse Events Occurring in ≥2 Patients in Any Treatment Group*

	Durvalumab Monotherapy (n = 369)		Durvalumab + Tremelimumab (n = 371)		Chemotherapy (n = 352)	
	Any Grade	**Grade 3, 4 or 5**	**Any Grade**	**Grade 3, 4 or 5**	**Any Grade**	**Grade 3, 4 or 5**
Serious adverse event[†], n (%)	32 (8.7)	21 (5.7)	76 (20.5)	56 (15.1)	51 (14.5)	39 (11.1)
Diarrhea	2 (0.5)	0	11 (3.0)	8 (2.2)	2 (0.6)	2 (0.6)
Pneumonitis	5 (1.4)	5 (1.4)	8 (2.2)	6 (1.6)	0	0
Anemia	0	0	0	0	11 (3.1)	9 (2.6)
Interstitial lung disease	1 (0.3)	1 (0.3)	7 (1.9)	4 (1.1)	0	0
Colitis	1 (0.3)	1 (0.3)	6 (1.6)	6 (1.6)	0	0
Pneumonia	3 (0.8)	2 (0.5)	3 (0.8)	3 (0.8)	1 (0.3)	1 (0.3)
Pancytopenia	0	0	0	0	6 (1.7)	4 (1.1)
Drug-induced liver injury	0	0	5 (1.3)	3 (0.8)	0	0
Fatigue	0	0	4 (1.1)	3 (0.8)	0	0
Adrenal insufficiency	1 (0.3)	1 (0.3)	2 (0.5)	1 (0.3)	0	0
Dyspnea	1 (0.3)	1 (0.3)	2 (0.5)	2 (0.5)	0	0
Hepatitis	1 (0.3)	1 (0.3)	2 (0.5)	2 (0.5)	0	0
Lipase increased	0	0	3 (0.8)	3 (0.8)	0	0
Nausea	0	0	0	0	3 (0.9)	1 (0.3)
Edema peripheral	0	0	0	0	2 (0.6)	0
Enterocolitis	0	0	2 (0.5)	0	0	0
Hypothyroidism	2 (0.5)	1 (0.3)	0	0	0	0
Febrile neutropenia	0	0	0	0	2 (0.6)	2 (0.6)
General physical health deterioration	0	0	0	0	2 (0.6)	0
Hypophagia	0	0	0	0	2 (0.6)	2 (0.6)
Hypophysitis	0	0	2 (0.5)	1 (0.3)	0	0
Neutrophil count decreased	0	0	0	0	2 (0.6)	2 (0.6)
Pyrexia	0	0	2 (0.5)	0	0	0

	Durvalumab Monotherapy (n = 369)		Durvalumab + Tremelimumab (n = 371)		Chemotherapy (n = 352)	
	Any Grade	**Grade 3, 4 or 5**	**Any Grade**	**Grade 3, 4 or 5**	**Any Grade**	**Grade 3, 4 or 5**
Secondary adrenocortical insufficiency	0	0	2 (0.5)	2 (0.5)	0	0
Thrombocytopenia	0	0	0	0	2 (0.6)	2 (0.6)
Vomiting	0	0	0	0	2 (0.6)	2 (0.6)

Data cut-off: October 4, 2018. *As-treated population (all patients who received at least one dose of study treatment). Listed are all serious adverse events assessed by the investigator as possibly related to study treatment that occurred during the treatment period and up to 90 days after the last dose of immunotherapy (30 days after the last dose of chemotherapy) or up to the start of any subsequent therapy (whichever occurred first). [†]The events are listed in descending order of frequency across all three treatment groups.

eTable 15. Treatment-related Adverse Events Leading to Treatment Discontinuation Occurring in ≥2 Patients in Any Treatment Group*

	Durvalumab Monotherapy (n = 369)		Durvalumab + Tremelimumab (n = 371)		Chemotherapy (n = 352)	
	Any Grade	**Grade 3, 4 or 5**	**Any Grade**	**Grade 3, 4 or 5**	**Any Grade**	**Grade 3, 4 or 5**
Event leading to discontinuation[†,‡], n (%)	20 (5.4)	16 (4.3)	49 (13.2)	35 (9.4)	33 (9.4)	12 (3.4)
Pneumonitis	3 (0.8)	3 (0.8)	7 (1.9)	5 (1.3)	1 (0.3)	0
Interstitial lung disease	2 (0.5)	1 (0.3)	5 (1.3)	4 (1.1)	1 (0.3)	0
Blood creatinine increased	0	0	1 (0.3)	0	4 (1.1)	0
Colitis	0	0	5 (1.3)	4 (1.1)	0	0
Diarrhea	0	0	4 (1.1)	3 (0.8)	1 (0.3)	1 (0.3)
Drug-induced liver injury	0	0	4 (1.1)	3 (0.8)	0	0
Neutropenia	0	0	0	0	4 (1.1)	1 (0.3)
Anemia	0	0	0	0	3 (0.9)	2 (0.6)
Fatigue	0	0	0	0	3 (0.9)	2 (0.6)
Thrombocytopenia	0	0	0	0	3 (0.9)	2 (0.6)
White blood cell count decreased	0	0	0	0	3 (0.9)	0
Asthenia	0	0	0	0	2 (0.6)	1 (0.3)
Chronic kidney disease	0	0	0	0	2 (0.6)	0
Hepatitis	0	0	2 (0.5)	2 (0.5)	0	0
Lipase increased	0	0	2 (0.5)	2 (0.5)	0	0
Pancytopenia	0	0	0	0	2 (0.6)	1 (0.3)
Renal failure	0	0	0	0	2 (0.6)	0

Data cut-off: October 4, 2018. *As-treated population (all patients who received at least one dose of study treatment). Listed are all adverse events leading to discontinuation assessed by the investigator as possibly related to study treatment that occurred during the treatment period and up to 90 days after the last dose of immunotherapy (30 days after the last dose of chemotherapy) or up to the start of any subsequent therapy (whichever occurred first). [†]Adverse

events are included if they led to discontinuation of any study treatment in a given treatment group, even if other components of study treatment were continued. [‡]The events are listed in descending order of frequency across all three treatment groups.

eTable 16. Immune-mediated Adverse Events (Grouped Terms) Occurring in ≥2 Patients in Any Treatment Group*

	Durvalumab Monotherapy (n = 369)			Durvalumab + Tremelimumab (n = 371)			Chemotherapy (n = 352)		
	Any Grade	**Grade 3/4**	**Grade 5**	**Any Grade**	**Grade 3/4**	**Grade 5**	**Any Grade**	**Grade 3/4**	**Grade 5**
Immune-mediated adverse event (grouped term)[†,‡], n (%)	50 (13.6)	15 (4.1)	1 (0.3)	105 (28.3)	40 (10.8)	4 (1.1)	12 (3.4)	2 (0.6)	1 (0.3)
Hypothyroidism	21 (5.7)	2 (0.5)	0	28 (7.5)	3 (0.8)	0	2 (0.6)	0	0
Pneumonitis	8 (2.2)	4 (1.1)	1 (0.3)	25 (6.7)	8 (2.2)	3 (0.8)	5 (1.4)	1 (0.3)	1 (0.3)
Diarrhea	7 (1.9)	1 (0.3)	0	17 (4.6)	8 (2.2)	0	1 (0.3)	1 (0.3)	0
Rash	5 (1.4)	4 (1.1)	0	16 (4.3)	2 (0.5)	0	2 (0.6)	0	0
Colitis	2 (0.5)	1 (0.3)	0	12 (3.2)	7 (1.9)	0	0	0	0
Adrenal insufficiency	1 (0.3)	1 (0.3)	0	10 (2.7)	3 (0.8)	0	1 (0.3)	0	0
Hyperthyroidism	4 (1.1)	0	0	7 (1.9)	1 (0.3)	0	1 (0.3)	0	0
Hepatitis	1 (0.3)	1 (0.3)	0	9 (2.4)	7 (1.9)	1 (0.3)	0	0	0
Pancreatic laboratory investigations reported as adverse events	2 (0.5)	1 (0.3)	0	6 (1.6)	6 (1.6)	0	0	0	0
Dermatitis	2 (0.5)	0	0	5 (1.3)	0	0	0	0	0
Hepatic laboratory parameters reported as adverse events	2 (0.5)	1 (0.3)	0	2 (0.5)	1 (0.3)	0	0	0	0
Hypophysitis	0	0	0	2 (0.5)	1 (0.3)	0	0	0	0
Nephritis	0	0	0	2 (0.5)	0	0	0	0	0
Thyroid laboratory parameters reported as adverse events (decreased thyroid activity)	2 (0.5)	0	0	0	0	0	0	0	0
Type 1 diabetes mellitus	0	0	0	2 (0.5)	1 (0.3)	0	0	0	0
Other rare/miscellaneous	2 (0.5)	1 (0.3)	0	0	0	0	0	0	0

Data cut-off: October 4, 2018. *As-treated population (all patients who received at least one dose of study treatment). Listed are all immune-mediated adverse events that occurred during the treatment period and up to 90 days after the last dose of immunotherapy (30 days after the last dose of chemotherapy) or up to the start of any subsequent therapy (whichever occurred first). †An adverse event of special interest requiring the use of systemic steroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy, consistent with an immune-mediated mechanism of action, and where there is no clear alternate etiology. ‡The events are listed in descending order of frequency across all three treatment groups.

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