

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

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IMPORTANCE Checkpoint inhibitors targeting programmed cell death 1 or its ligand (PD-L1) as monotherapies or in combination with anti-cytotoxic T-lymphocyte-associated antigen 4 have shown clinical activity in patients with metastatic non-small cell lung cancer.

OBJECTIVE To compare durvalumab, with or without tremelimumab, with chemotherapy as a first-line treatment for patients with metastatic non-small cell lung cancer.

DESIGN, SETTING, AND PARTICIPANTS This open-label, phase 3 randomized clinical trial (MYSTIC) was conducted at 203 cancer treatment centers in 17 countries. Patients with treatment-naïve, metastatic non-small cell lung cancer who had no sensitizing *EGFR* or *ALK* genetic alterations were randomized to receive treatment with durvalumab, durvalumab plus tremelimumab, or chemotherapy. Data were collected from July 21, 2015, to October 30, 2018.

INTERVENTIONS Patients were randomized (1:1:1) to receive treatment with durvalumab (20 mg/kg every 4 weeks), durvalumab (20 mg/kg every 4 weeks) plus tremelimumab (1 mg/kg every 4 weeks, up to 4 doses), or platinum-based doublet chemotherapy.

MAIN OUTCOMES AND MEASURES The primary end points, assessed in patients with $\geq 25\%$ of tumor cells expressing PD-L1, were overall survival (OS) for durvalumab vs chemotherapy, and OS and progression-free survival (PFS) for durvalumab plus tremelimumab vs chemotherapy. Analysis of blood tumor mutational burden (bTMB) was exploratory.

RESULTS Between July 21, 2015, and June 8, 2016, 1118 patients were randomized. Baseline demographic and disease characteristics were balanced between treatment groups. Among 488 patients with $\geq 25\%$ of tumor cells expressing PD-L1, median OS was 16.3 months (95% CI, 12.2-20.8) with durvalumab vs 12.9 months (95% CI, 10.5-15.0) with chemotherapy (hazard ratio [HR], 0.76; 97.54% CI, 0.56-1.02; $P = .04$ [nonsignificant]). Median OS was 11.9 months (95% CI, 9.0-17.7) with durvalumab plus tremelimumab (HR vs chemotherapy, 0.85; 98.77% CI, 0.61-1.17; $P = .20$). Median PFS was 3.9 months (95% CI, 2.8-5.0) with durvalumab plus tremelimumab vs 5.4 months (95% CI, 4.6-5.8) with chemotherapy (HR, 1.05; 99.5% CI, 0.72-1.53; $P = .71$). Among 809 patients with evaluable bTMB, those with a bTMB ≥ 20 mutations per megabase showed improved OS for durvalumab plus tremelimumab vs chemotherapy (median OS, 21.9 months [95% CI, 11.4-32.8] vs 10.0 months [95% CI, 8.1-11.7]; HR, 0.49; 95% CI, 0.32-0.74). Treatment-related adverse events of grade 3 or higher occurred in 55 (14.9%) of 369 patients who received treatment with durvalumab, 85 (22.9%) of 371 patients who received treatment with durvalumab plus tremelimumab, and 119 (33.8%) of 352 patients who received treatment with chemotherapy. These adverse events led to death in 2 (0.5%), 6 (1.6%), and 3 (0.9%) patients, respectively.

CONCLUSIONS AND RELEVANCE The phase 3 MYSTIC study did not meet its primary end points of improved OS with durvalumab vs chemotherapy or improved OS or PFS with durvalumab plus tremelimumab vs chemotherapy in patients with $\geq 25\%$ of tumor cells expressing PD-L1. Exploratory analyses identified a bTMB threshold of ≥ 20 mutations per megabase for optimal OS benefit with durvalumab plus tremelimumab.

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Immune checkpoint inhibitors targeting programmed cell death 1 (PD-1) or its ligand (PD-L1) have reshaped the first-line metastatic non-small cell lung cancer (mNSCLC) treatment landscape. Pembrolizumab is globally approved as a first-line monotherapy in patients with a PD-L1 tumor proportion score of 50% or more, with a recent extension to all patients with PD-L1-positive (tumor proportion score of 1% or more) tumors in the US and Japan, based on data from the KEYNOTE-042 study.¹ The combination of PD-1 and PD-L1 antibodies with chemotherapy has also improved outcomes in patients with unselected mNSCLC.²⁻⁷

Early studies have shown that genomic landscape, including tumor mutational burden (TMB), shapes responses to anti-PD-L1 therapy.^{8,9} Recently, TMB measured using tissue (tTMB) has emerged as a predictive biomarker of improved response and progression-free survival (PFS) with immunotherapy that is independent of PD-L1 expression.¹⁰⁻¹³ However, to our knowledge, a predictive effect of tTMB on overall survival (OS) benefit with immunotherapy vs chemotherapy has not been shown in NSCLC. More recently, measurement of TMB from blood (bTMB) has been demonstrated, obviating some of the logistic and technical challenges associated with tTMB measurement.¹⁴⁻¹⁷

Durvalumab is a selective, high-affinity human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80.¹⁸ Durvalumab is indicated for the treatment of patients with unresectable, stage III NSCLC whose disease has not progressed after platinum-based chemoradiotherapy, based on data from the PACIFIC study,^{19,20} and has demonstrated clinical activity in patients with pretreated advanced NSCLC in phase 2 and 3 trials.^{21,22} Tremelimumab, a monoclonal immunoglobulin G2 antibody targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), prevents normal downregulation of T cells and prolongs T-cell action, thereby enhancing immune function.²³ Combining anti-PD-1/PD-L1 with anti-CTLA-4 therapies may amplify antitumor T-cell responses through nonredundant immune checkpoint blockade and provide additive or synergistic activity. Durvalumab, in combination with tremelimumab, has shown clinical activity in patients with advanced NSCLC in a phase 1 and 2 investigation.²⁴

We report the final analyses of OS and PFS in patients with mNSCLC and PD-L1 expression on $\geq 25\%$ of tumor cells (PD-L1 TC $\geq 25\%$; primary efficacy analysis population) from the MYSTIC study, an open-label, phase 3 randomized clinical trial of first-line treatment with durvalumab, with or without tremelimumab, vs platinum-based chemotherapy. We also report the results of prespecified secondary and exploratory analyses to assess the effects of additional PD-L1 expression thresholds, as well as bTMB and tTMB, on outcomes.

Methods

Patients

The study was performed at 203 cancer treatment centers in 17 countries. Adults with stage IV NSCLC were eligible provided they had not previously received systemic therapy for

Key Points

Question Does first-line durvalumab treatment with or without tremelimumab improve survival outcomes vs chemotherapy in patients with metastatic non-small cell lung cancer?

Findings In this phase 3 randomized clinical trial including 1118 patients with non-small cell lung cancer, although the trial did not meet its primary end points, treatment with durvalumab resulted in a numerically reduced risk of death vs chemotherapy in patients with programmed cell death ligand 1 expression on at least 25% of tumor cells. In exploratory analyses, a blood tumor mutational burden threshold of at least 20 mutations per megabase was identified for optimal clinical benefit with durvalumab plus tremelimumab vs chemotherapy.

Meaning These findings highlight the need for further investigation and prospective validation of blood tumor mutational burden as a predictive biomarker for immunotherapy.

advanced or metastatic NSCLC, had an Eastern Cooperative Oncology Group performance status²⁵ of 0 to 1, demonstrated measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,²⁶ and had known tumor PD-L1 expression status prior to randomization. Patients with sensitizing *EGFR* or *ALK* genetic alterations and those with symptomatic, unstable brain metastases were excluded (eTable 1 in Supplement 1).

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 (Supplement 2) were approved by the institutional review boards or ethics committees of all participating centers and the relevant regulatory authorities. All patients provided written informed consent.

Study Design and Treatment

Patients were randomized (1:1:1) to receive 20 mg/kg of durvalumab every 4 weeks until disease progression, 20 mg/kg of durvalumab every 4 weeks until disease progression plus 1 mg/kg of tremelimumab every 4 weeks for up to 4 doses, or 4 to 6 cycles of platinum-based doublet chemotherapy of the investigator's choice (eFigure 1 in Supplement 1). Randomization was stratified by PD-L1 TC $\geq 25\%$ vs $< 25\%$ and histologic subtype (squamous or nonsquamous). See the eMethods in Supplement 1 for additional randomization and dosing details.

Maintenance pemetrexed therapy was allowed in patients with nonsquamous NSCLC whose disease had not progressed after 4 cycles of pemetrexed combined with a platinum agent. In-study crossover from chemotherapy to the immunotherapy arms was not allowed. Patients continued treatment until objective disease progression (RECIST version 1.1), development of an adverse event necessitating treatment discontinuation, or withdrawal of consent (eFigure 1 in Supplement 1).

End Points

The primary end points were OS (time from randomization to death due to any cause) for both immunotherapy arms vs

chemotherapy, and PFS (time from randomization to objective disease progression according to blinded independent central review, or death) for durvalumab plus tremelimumab vs chemotherapy, all in patients with PD-L1 TC $\geq 25\%$. Secondary end points included PFS for durvalumab vs chemotherapy, objective response rate and duration of response for both immunotherapy arms vs chemotherapy (all in patients with PD-L1 TC $\geq 25\%$), and safety and tolerability. Investigation of the relationship between biomarkers, including TMB, and clinical outcomes was a prespecified exploratory objective. See eTable 2 in Supplement 1 for additional end points and the eMethods in Supplement 1 for details of assessments.

Statistical Analysis

The study was sized to characterize the OS benefit for durvalumab plus tremelimumab vs chemotherapy and for durvalumab vs chemotherapy as well as the PFS benefit for durvalumab plus tremelimumab vs chemotherapy in patients with PD-L1 TC $\geq 25\%$. Originally, the primary end points were to be evaluated in all patients, irrespective of tumor PD-L1 expression; 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 $\geq 25\%$ based on prior studies and the evolving treatment landscape.^{21,24,27,28}

Approximately 1092 patients, including 480 patients with PD-L1 TC $\geq 25\%$, were needed to obtain 231 events for the primary PFS analysis across the durvalumab plus tremelimumab group and the chemotherapy group (72% maturity), as well as 225 OS events for the primary OS analysis across each treatment group comparison (70% maturity) (eTable 3 in Supplement 1). 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 for overall type I error at 5% (2-sided), a hierarchical multiple-testing procedure with gatekeeping strategy was used across end points, analysis populations, and treatment regimens (eFigure 2 in Supplement 1).

For the PFS analysis, which was based on an assumed PFS HR of 0.59, the trial was estimated to have 88% power to demonstrate statistical significance with an overall 2-sided significance level of 0.5% for the comparison of durvalumab plus tremelimumab vs 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 2-sided significance level of 3% for the comparison of durvalumab vs chemotherapy and 86% power to demonstrate statistical significance with an overall 2-sided significance level of 1.5% for the comparison of durvalumab plus tremelimumab vs chemotherapy (eTable 3 in Supplement 1). The assumed OS HRs were based on results from previous clinical studies with the therapies that were the standard of care when the MYSTIC study was designed,²⁹⁻³¹ as well as emerging data from early-phase durvalumab studies^{28,32} and other trials of anti-PD-1 or PD-L1.³³⁻³⁵

The primary PFS analysis was performed using a stratified log-rank test adjusting for histologic subtype (stratification factor at randomization), with HR and 99.5% CI esti-

mated using a Cox proportional hazards model. For statistical significance of durvalumab plus tremelimumab vs chemotherapy, $P < .005$ was required.

The primary OS analysis was performed using similar methods, adjusted for 2 interim analyses, with HRs estimated with 2-sided 97.54% and 98.77% CIs, respectively, for comparisons of durvalumab and durvalumab plus tremelimumab with chemotherapy. For statistical significance at final analysis, $P < .0246$ for durvalumab vs chemotherapy and $P < .0123$ for durvalumab plus tremelimumab vs chemotherapy were required (Lan-DeMets spending function approximating O'Brien-Fleming boundary³⁶). Survival curves were generated using the Kaplan-Meier method. As a supportive analysis for OS in the population with PD-L1 TC $\geq 25\%$, restricted mean survival time was evaluated by calculating area under the curve for the OS Kaplan-Meier curve for each treatment arm. The difference in restricted mean survival time (95% CI) for the immunotherapy vs 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 higher than 0 favors the immunotherapy arm.

For secondary analyses performed in the population with PD-L1 TC $\geq 1\%$ and the intention-to-treat (ITT) population, the stratification was additionally adjusted for PD-L1 expression status (TC $\geq 25\%$ vs $< 25\%$). Odds ratios and 95% CIs for comparing objective response rate 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.

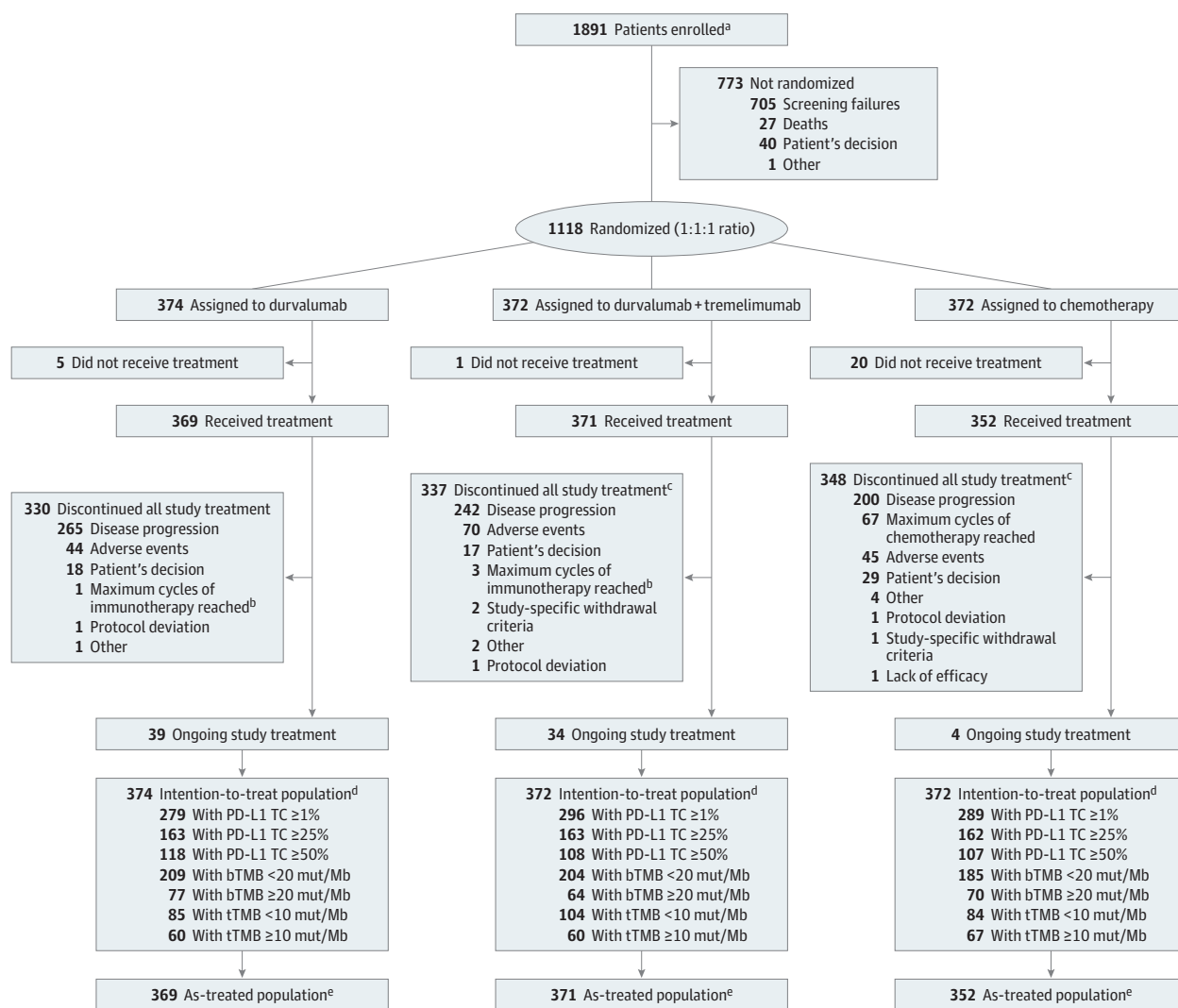
Efficacy was analyzed on an ITT basis, including all randomized patients or subsets of this population based on PD-L1 expression or TMB levels. Safety analyses included all patients who received at least 1 dose of study treatment (as-treated population).

Results

Patients and Treatment

Between July 21, 2015, and June 8, 2016, 1891 patients were enrolled. Of the 1118 randomized patients, 1092 (97.7%) received at least 1 dose of study treatment: 369 of 374 patients (98.7%) in the durvalumab group, 371 of 372 patients (99.7%) in the durvalumab plus tremelimumab group, and 352 of 372 patients (94.6%) in the chemotherapy group (Figure 1). In the chemotherapy group, the most common regimens for patients with nonsquamous and squamous histologic subtypes of tumor were pemetrexed plus carboplatin (138 of 253 patients [54.5%]) and gemcitabine plus carboplatin (49 of 99 patients [49.5%]), respectively. The primary analysis population (patients with PD-L1 TC $\geq 25\%$) comprised 488 of 1118 randomized patients (43.6%): 163 of 374 patients (43.6%) in the durvalumab group, 163 of 372 patients (43.8%) in the durvalumab plus tremelimumab group, and 162 of 372 patients (43.5%) in the chemotherapy group. The baseline demo-

Figure 1. CONSORT Diagram



Data cutoff date: October 4, 2018. bTMB indicates blood tumor mutational burden; mut/Mb, mutations per megabase; PD-L1, programmed cell death ligand 1; TC, tumor cell; tTMB, tissue tumor mutational burden.

^a Screening consent received for PD-L1 status.

^b Only applicable for patients completing study treatment before implementation of clinical study protocol amendment, which allowed patients to continue receiving immunotherapy until disease progression, whereas

previously a maximum of 12 months was allowed.

^c Reason for discontinuation applies to the latest component discontinued.

^d Intention-to-treat population includes all randomized patients.

^e As-treated population includes all patients who received at least 1 dose of study treatment.

graphic and disease characteristics of patients with PD-L1 TC $\geq 25\%$ were generally consistent with the ITT population and were balanced between treatment groups (Table 1; eTable 4 in Supplement 1).

At the data cutoff date for the final OS analysis (October 4, 2018), among patients with PD-L1 TC $\geq 25\%$, 25 of 163 patients (15.3%) in the durvalumab group, 18 of 163 patients (11.0%) in the durvalumab plus tremelimumab group, and 1 of 162 patients (0.6%) in the chemotherapy group were continuing to receive the study treatment. Of these, 5 patients in the durvalumab group and 1 patient in the durvalumab plus tremelimumab group were treated through

disease progression, and 5 patients in the durvalumab plus tremelimumab group who were continuing to receive treatment with durvalumab at the data cutoff date received retreatment with tremelimumab. In addition, 73 patients (44.8%) in the durvalumab group, 61 patients (37.4%) in the durvalumab plus tremelimumab group, and 95 patients (58.6%) in the chemotherapy group received subsequent systemic cancer therapy (eTable 5 in Supplement 1). Among these, immunotherapy was received by 10 of 73 patients (14%) in the durvalumab group, 5 of 61 patients (8%) in the durvalumab plus tremelimumab group, and 64 of 95 patients (67%) in the chemotherapy group.

Table 1. Baseline Demographic and Disease Characteristics in Patients with PD-L1 TC $\geq 25\%$ ^a

	Durvalumab monotherapy (n = 163)	Durvalumab plus tremelimumab (n = 163)	Chemotherapy (n = 162)
Age, median (range), y	64.0 (32-84)	65.0 (34-87)	64.5 (35-85)
<65 y	82 (50.3)	77 (47.2)	81 (50.0)
≥ 65 y	81 (49.7)	86 (52.8)	81 (50.0)
Sex, No. (%)			
Male	113 (69.3)	118 (72.4)	106 (65.4)
Female	50 (30.7)	45 (27.6)	56 (34.6)
Race, No. (%)			
White	101 (62.0)	111 (68.1)	113 (69.8)
Asian	59 (36.2)	50 (30.7)	47 (29.0)
Black	2 (1.2)	1 (0.6)	1 (0.6)
ECOG performance status, No. (%)			
0	57 (35.0)	65 (39.9)	70 (43.2)
1	105 (64.4)	98 (60.1)	91 (56.2)
2 ^b	1 (0.6)	0	0
Tumor histologic subtype, No. (%)			
Squamous	52 (31.9)	53 (32.5)	52 (32.1)
Nonsquamous	111 (68.1)	110 (67.5)	110 (67.9)
Smoking history, No. (%)			
Never smoker	24 (14.7)	25 (15.3)	21 (13.0)
Former smoker	92 (56.4)	96 (58.9)	102 (63.0)
Current smoker	47 (28.8)	42 (25.8)	39 (24.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; TC, tumor cell.

^a Primary analysis population. Data cutoff date: October 4, 2018.

^b Patients were required to have an ECOG performance status²⁵ score of 0 or 1 during screening, but at baseline the score had worsened to 2 in 1 patient.

Efficacy

Overall Survival

As of October 4, 2018, median (range) follow-up for OS was 30.2 (0.3-37.2) months. Durvalumab and durvalumab plus tremelimumab did not statistically significantly improve OS vs chemotherapy in patients with PD-L1 TC $\geq 25\%$.

The median OS was 16.3 months (95% CI, 12.2-20.8) with durvalumab vs 12.9 months (95% CI, 10.5-15.0) with chemotherapy (hazard ratio [HR], 0.76; 95% CI, 0.56-1.02; $P = .04$ (Figure 2A). The 24-month OS rate was 38.3% (95% CI, 30.7%-45.7%) with durvalumab and 22.7% (95% CI, 16.5%-29.5%) with chemotherapy. Most planned patient subgroups in the primary analysis population treated with durvalumab had numerical improvement in OS vs chemotherapy (eFigure 3 in Supplement 1).

The median OS was 11.9 months (95% CI, 9.0-17.7) and the 24-month OS rate was 35.4% (95% CI, 28.1%-42.8%) with durvalumab plus tremelimumab (HR vs chemotherapy, 0.85; 95% CI, 0.61-1.17; $P = .20$) (Figure 2B). The OS in the ITT population and in subgroups defined by different PD-L1 expression levels (TC <1%, $\geq 1\%$, 25%-49%, and $\geq 50\%$) is shown in eTable 6 in Supplement 1. In patients with PD-L1 TC $\geq 50\%$ and PD-L1 TC between 25% and 49%, OS HRs for durvalumab vs chemotherapy were 0.76 (95% CI, 0.55-1.04) and 0.78 (95% CI, 0.49-1.23), respectively (eTable 6 in Supplement 1). A supportive analysis for OS in patients with PD-L1 TC $\geq 25\%$ showed a restricted mean survival time difference of 1.99 months (95% CI, -0.37 to 4.35) for durvalumab vs chemotherapy and 0.76 months (95% CI, -1.62 to 3.14) for durvalumab plus tremelimumab vs chemotherapy.

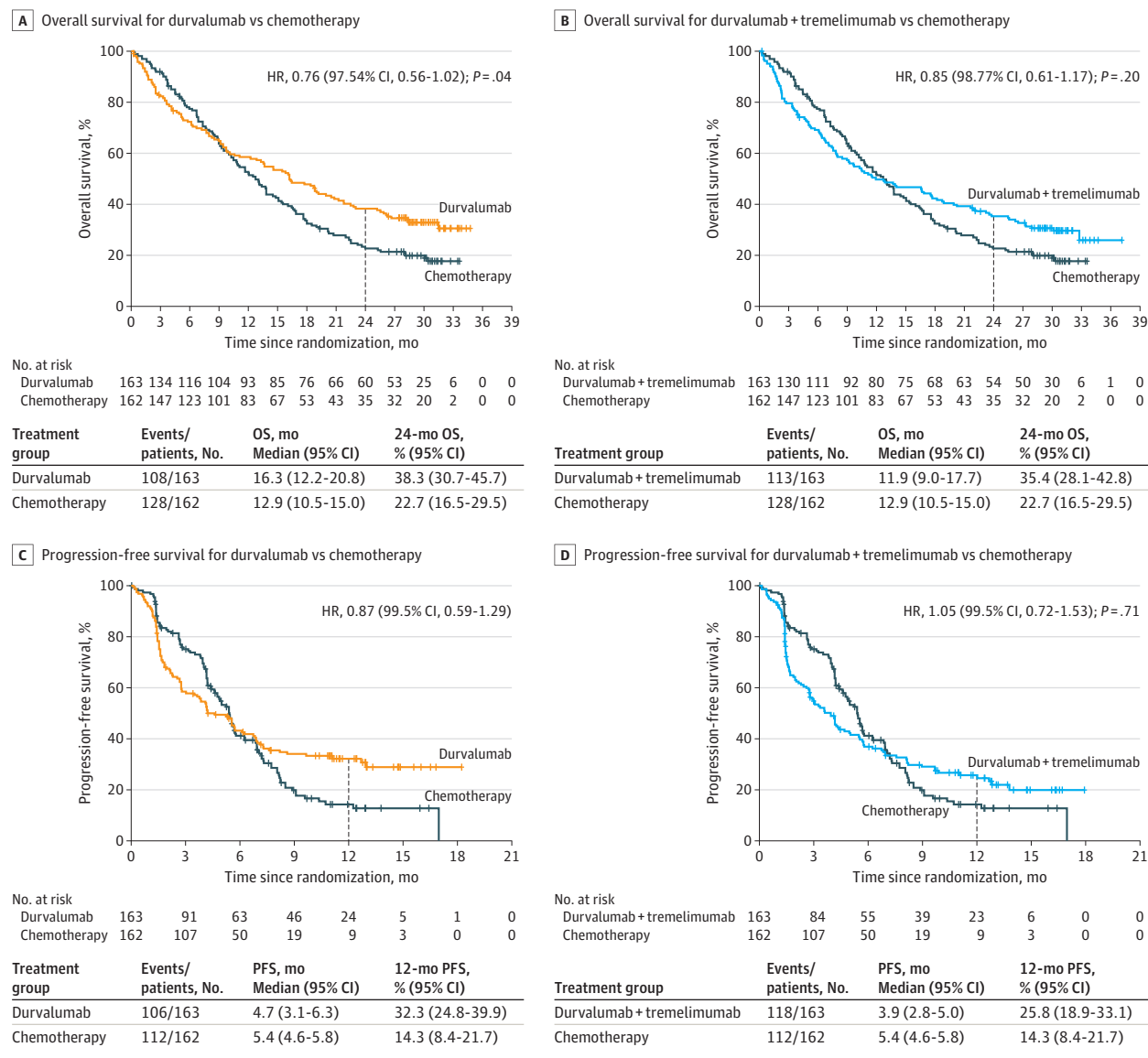
Progression-Free Survival

As of June 1, 2017 (data cutoff date for the primary PFS analysis), median (range) follow-up for PFS was 10.6 (0-18) months. There was no statistically significant difference in PFS between the durvalumab and chemotherapy groups (secondary end point) (Figure 2C) or between the durvalumab plus tremelimumab and chemotherapy groups (primary end point) (Figure 2D). Median PFS was 3.9 months (95% CI, 2.8-5.0) with durvalumab plus tremelimumab vs 5.4 months (95% CI, 4.6-5.8) with chemotherapy (HR, 1.05; 95% CI, 0.72-1.53; $P = .71$); the 12-month PFS rate was 25.8% (95% CI, 18.9%-33.1%) with durvalumab plus tremelimumab vs 14.3% (8.4%-21.7%) with chemotherapy. Median PFS in the ITT population was 2.9 months (95% CI, 2.6-3.4) with durvalumab plus tremelimumab vs 5.4 months (95% CI, 4.8-5.6) with chemotherapy (HR, 1.25; 95% CI, 1.05-1.49).

Tumor Response

As of June 1, 2017, the objective response rate among patients with PD-L1 TC $\geq 25\%$ was 35.6%, 34.4%, and 37.7% with durvalumab, durvalumab plus tremelimumab, and chemotherapy, respectively (eTable 7 in Supplement 1). The median duration of response was not reached in the immunotherapy arms and was 4.4 months with chemotherapy. More patients had an ongoing response at 12 months in the immunotherapy treatment groups (61.3%, 54.9%, and 18.0% in the durvalumab, durvalumab plus tremelimumab, and chemotherapy arms, respectively) (eTable 7 in Supplement 1).

Figure 2. Overall Survival and Progression-free Survival Among Patients With Programmed Cell Death Ligand 1 TC ≥25%



Primary analysis population. A and B, Data cutoff date: October 4, 2018. C and D, Data cutoff date: June 1, 2017. Progression-free survival was determined by blinded independent central review according to Response Evaluation in Solid

Tumors (RECIST) version 1.1.²⁶ Parts A, B, and D depict primary end points; part C, secondary end point. HR indicates hazard ratio; OS, overall survival; PFS, progression-free survival; TC, tumor cell.

Exploratory Analysis of bTMB and tTMB

Pretreatment plasma samples were available from 1001 patients (median plasma volume, 1.71 mL per patient [range, 0.2-3.5 mL]), of whom 809 patients (72.4% of those randomized) were evaluable for bTMB; 194 did not have valid bTMB results owing to low cell-free DNA input, low tumor DNA shedding, or other quality control failures. Pretreatment tissue samples were available from 735 patients, of whom 460 (41.1% of those randomized) were evaluable for tTMB; 275 samples did not produce a useable tTMB result owing to a variety of reasons, including insufficient tissue and/or tumor cells, insufficient DNA extracted, or a poor-quality next-generation sequencing library.

The TMB values did not correlate with PD-L1 expression levels (blood: Spearman $\rho = 0.05$; Pearson $r = 0.01$; tissue: Spearman $\rho = 0.09$; Pearson $r = 0.06$). Among 352 patients with matched samples (31.5% of randomized patients), bTMB and tTMB were correlated (Spearman $\rho = 0.6$; Pearson $r = 0.7$) (eFigure 4 in Supplement 1). Baseline characteristics in the populations with evaluable bTMB and tTMB were consistent with the ITT population (eTables 8 and 9 in Supplement 1). The OS in the populations with evaluable TMB was consistent with the ITT population in the 3 treatment arms (eFigure 5 in Supplement 1). For durvalumab plus tremelimumab vs chemotherapy, the HR for OS improved gradually as the bTMB threshold was increased (eFigure 6 in Supplement 1). The group with

bTMB ≥ 20 mutations per megabase (mut/Mb) was selected for further analysis because there was a clinically relevant effect size for durvalumab plus tremelimumab and the patient population that derived benefit. The group with tTMB ≥ 10 mut/Mb was studied based on a threshold shown to be predictive for PFS and response in previous trials of nivolumab plus ipilimumab in patients with NSCLC.^{11,12} Further exploratory analyses in groups with tTMB values ≥ 10 mut/Mb were limited by small sample sizes.

In groups with bTMB ≥ 20 mut/Mb or tTMB ≥ 10 mut/Mb, there were greater proportions of patients with a history of smoking and squamous histologic subtype of tumor compared with the corresponding lower-TMB subgroups (eTables 8 and 9 in Supplement 1). There was 12% overlap between the population with bTMB ≥ 20 mut/Mb and that with PD-L1 TC $\geq 25\%$ (eFigure 7 in Supplement 1).

A bTMB ≥ 20 mut/Mb was associated with improved OS for durvalumab plus tremelimumab vs chemotherapy (median, 21.9 months [95% CI, 11.4-32.8] vs 10.0 months [95% CI, 8.1-11.7]; unadjusted HR, 0.49; 95% CI, 0.32-0.74) (Figure 3A); 24-month OS rates were 48.1% (95% CI, 35.5%-59.7%) with durvalumab plus tremelimumab vs 19.4% (95% CI, 11.0%-29.5%) with chemotherapy. In contrast, there was no improvement in OS for durvalumab plus tremelimumab vs chemotherapy in patients with bTMB < 20 mut/Mb (median, 8.5 months [95% CI, 6.7-9.8] vs 11.6 months [95% CI, 9.6-13.1]; unadjusted HR, 1.16; 95% CI, 0.93-1.45) (Figure 3B). A bTMB ≥ 20 mut/Mb, but not < 20 mut/Mb, was also associated with improved PFS (Figure 3C and D) and objective response rate (eTable 10 in Supplement 1) for durvalumab plus tremelimumab vs chemotherapy.

For patients with bTMB ≥ 20 mut/Mb who received durvalumab alone, the median OS was 12.6 months (95% CI, 7.8-18.6) (unadjusted HR vs chemotherapy, 0.72; 95% CI, 0.50-1.05). The HR for durvalumab plus tremelimumab vs durvalumab alone was 0.74 (95% CI, 0.48-1.11) (Figure 3A), supporting an additional contribution of tremelimumab.

A tTMB ≥ 10 mut/Mb, but not < 10 mut/Mb, was associated with numerically longer OS in both immunotherapy groups vs chemotherapy. The median OS was 16.6 months (95% CI, 9.7-27.3) with durvalumab plus tremelimumab, 18.6 months (95% CI, 9.3-22.0) with durvalumab, and 11.9 months (95% CI, 9.1-16.0) with chemotherapy. The HR was 0.72 (95% CI, 0.48-1.09) for durvalumab plus tremelimumab vs chemotherapy and 0.70 (95% CI, 0.47-1.06) for durvalumab vs chemotherapy (eFigure 8 in Supplement 1).

Safety

As of October 4, 2018, the median (range) actual duration of treatment was 16.0 (0.4-148.6) weeks for durvalumab; 16.0 (0.6-161.3) and 12.0 (0.6-32.0) weeks for durvalumab and tremelimumab, respectively, in the combination arm; and 17.9 (1.1-137.4) weeks for chemotherapy. All-grade adverse events that were considered by the investigator to be treatment related (TRAEs) occurred in 54.2% (200/369), 60.1% (223/371), and 83.0% (292/352) of patients treated with durvalumab, durvalumab plus tremelimumab, and chemotherapy, respectively (Table 2). Rates of grade 3 or higher TRAEs were lower

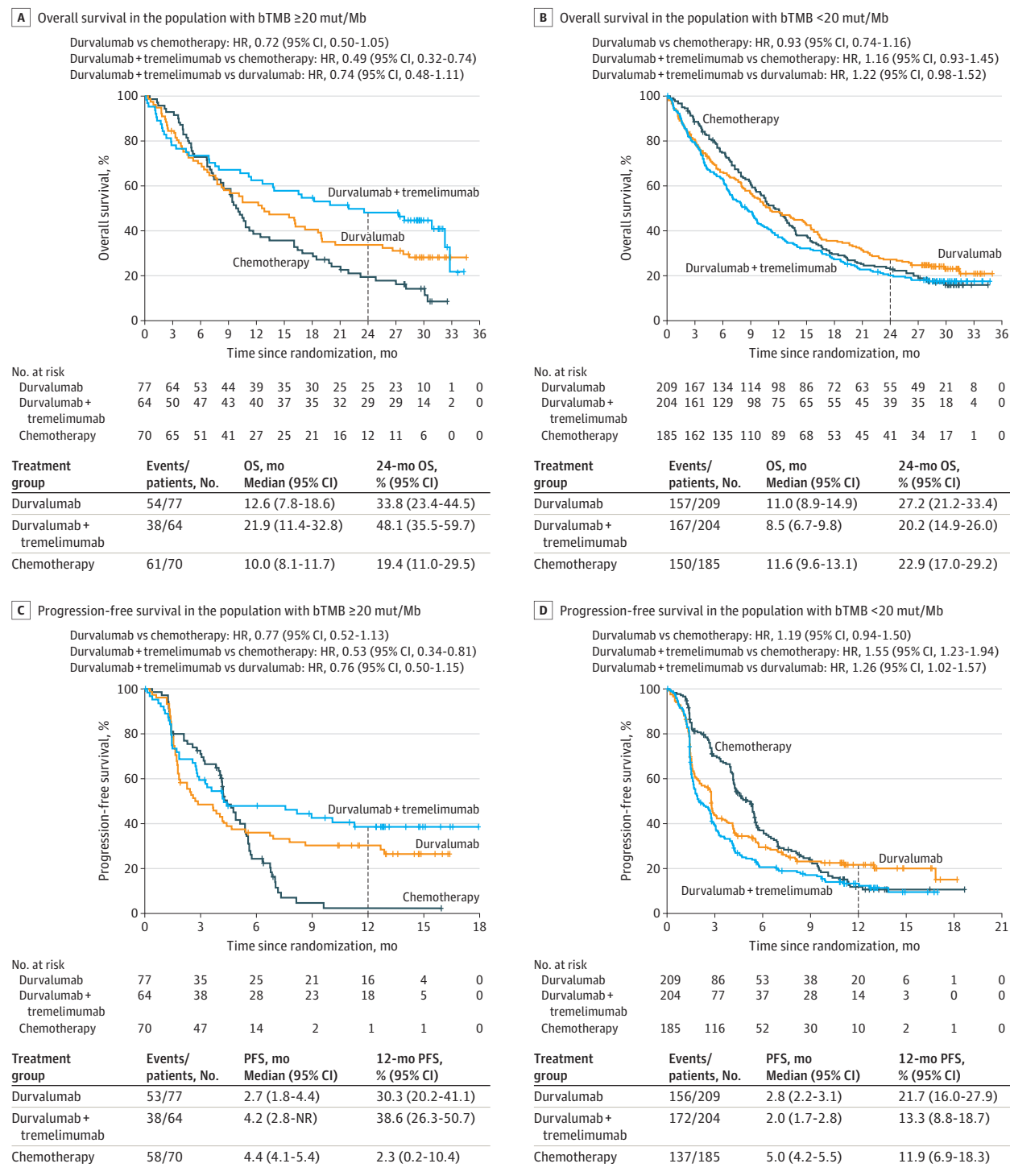
with durvalumab (55/369; 14.9%) and durvalumab plus tremelimumab (85/371; 22.9%) than with chemotherapy (119/352; 33.8%), and fewer patients had TRAEs leading to discontinuation in the durvalumab group (5.4% [20/369] vs 13.2% [49/371] and 9.4% [33/352], respectively). Treatment-related deaths occurred in 2 of 369 patients (0.5%) in the durvalumab group, 6 of 371 patients (1.6%) in the durvalumab plus tremelimumab group, and 3 of 352 patients (0.9%) in the chemotherapy group. Safety in the population with PD-L1 TC $\geq 25\%$ (primary analysis population) and the population with bTMB ≥ 20 mut/Mb was consistent with safety findings in the overall as-treated population (eTables 11 and 12 in Supplement 1). For additional safety details, see eTables 13 through 16 in Supplement 1.

Immune-mediated adverse events were reported in 13.6% (50/369), 28.3% (105/371), and 3.4% (12/352) of patients in the durvalumab, durvalumab plus tremelimumab, and chemotherapy groups, respectively (eTable 16 in Supplement 1). These events were grade 3 or 4 in 4.1% (15/369), 10.8% (40/371), and 0.6% (2/352) of patients, respectively.

Discussion

In patients with mNSCLC and PD-L1 TC $\geq 25\%$, first-line treatment with durvalumab did not statistically significantly improve OS vs chemotherapy. Durvalumab was associated with a numerically reduced risk of death (HR, 0.76; 97.54% CI, 0.56-1.02; $P = .04$), with a 24-month OS rate of 38.3%, indicating a longer-term treatment benefit compared with chemotherapy (24-month OS rate, 22.7%). Although patients with PD-L1 TC between 25% and 49% had a reduction in risk of death equivalent to patients with PD-L1 TC $\geq 50\%$, they had improved outcomes compared with patients with PD-L1 TC $< 25\%$, indicating that PD-L1 TC $\geq 25\%$ is an appropriate cutoff point for durvalumab monotherapy in patients with mNSCLC. The OS analyses across planned patient subgroups showed numerical improvement in HRs for durvalumab vs chemotherapy, consistent with the primary OS end point; these results should be interpreted with caution owing to the low numbers of patients across individual subgroups. Results from the MYSTIC study align with those of previously reported treatment-naive, PD-L1 biomarker-selected trials,^{1,10,37} including KEYNOTE-042,¹ in which the OS HR was 0.77 with pembrolizumab vs chemotherapy in patients with a PD-L1 tumor proportion score of 20% or more. Durvalumab vs chemotherapy is being evaluated further in the phase 3 PEARL study³⁸ in a larger population (approximately 325 patients per arm) of treatment-naive patients with mNSCLC and PD-L1 TC $\geq 25\%$. In this rapidly evolving treatment landscape, PD-1 and PD-L1 antibodies combined with chemotherapy have emerged as a standard of care for many patients with mNSCLC without *EGFR*, *ALK*, or *ROS1* genetic alterations. In combination with chemotherapy, pembrolizumab and atezolizumab are associated with OS HRs of 0.49 and 0.79, respectively.^{2,4} The phase 3 POSEIDON study³⁹ demonstrated improvement in PFS with durvalumab plus chemotherapy, as well as with durvalumab plus tremelimumab plus chemotherapy, vs chemotherapy alone in

Figure 3. Exploratory Analysis of Overall Survival and Progression-free Survival According to Blood Tumor Mutational Burden



A and B, Data cutoff date: October 4, 2018. C and D, Data cutoff date: June 17, 2017. Progression-free survival was determined by blinded independent central review according to Response Evaluation in Solid Tumors (RECIST) version 1.1.²⁶

bTMB indicates blood tumor mutational burden; HR, hazard ratio; mut/Mb, mutations per megabase; NR, not reached; OS, overall survival; PFS, progression-free survival.

patients with previously treated mNSCLC; the study continues to assess OS.

Durvalumab plus tremelimumab did not significantly improve OS or PFS vs chemotherapy in patients with PD-L1 TC

$\geq 25\%$. In contrast to single-agent anti-PD-1 or PD-L1 treatment, for which PD-L1 is an established patient selection biomarker, TMB may be a better biomarker for combination immunotherapy with anti-PD-1 or PD-L1 and anti-CTLA-4.

Table 2. Treatment-related Adverse Events^a

Adverse event	No. (%)					
	Durvalumab monotherapy (n = 369)		Durvalumab plus 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	200 (54.2)	55 (14.9)	223 (60.1)	85 (22.9)	292 (83.0)	119 (33.8)
Event leading to discontinuation ^b	20 (5.4)	16 (4.3)	49 (13.2)	35 (9.4)	33 (9.4)	12 (3.4)
Event leading to death ^c	2 (0.5)	2 (0.5)	6 (1.6)	6 (1.6)	3 (0.9)	3 (0.9)
Event occurring in ≥10% of patients in any group ^d						
Nausea	13 (3.5)	0	28 (7.5)	1 (0.3)	126 (35.8)	6 (1.7)
Fatigue	27 (7.3)	6 (1.6)	47 (12.7)	8 (2.2)	64 (18.2)	7 (2.0)
Anemia	8 (2.2)	0	5 (1.3)	0	110 (31.3)	36 (10.2)
Decreased appetite	19 (5.1)	1 (0.3)	32 (8.6)	4 (1.1)	58 (16.5)	4 (1.1)
Diarrhea	31 (8.4)	2 (0.5)	47 (12.7)	9 (2.4)	24 (6.8)	2 (0.6)
Rash	26 (7.0)	3 (0.8)	39 (10.5)	1 (0.3)	31 (8.8)	1 (0.3)
Pruritus	32 (8.7)	0	47 (12.7)	0	13 (3.7)	0
Asthenia	20 (5.4)	1 (0.3)	18 (4.9)	0	37 (10.5)	8 (2.3)
Vomiting	5 (1.4)	0	10 (2.7)	0	59 (16.8)	7 (2.0)
Neutropenia	2 (0.5)	1 (0.3)	1 (0.3)	0	64 (18.2)	35 (9.9)
Thrombocytopenia	1 (0.3)	0	3 (0.8)	0	43 (12.2)	18 (5.1)
Constipation	6 (1.6)	0	3 (0.8)	0	36 (10.2)	1 (0.3)
Alopecia	0	0	3 (0.8)	0	39 (11.1)	0

^a As-treated population (all patients who received at least 1 dose of study treatment). Listed are all 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). Data cutoff date: October 4, 2018.

^b Includes patients who discontinued any study drug, even if (in combination arms) other components of study treatment were continued.

^c Treatment-related adverse events leading to death in the durvalumab monotherapy group were cytomegalovirus pneumonia and pneumonitis in

1 patient each. Treatment-related adverse events leading to death in the durvalumab plus tremelimumab combination group were interstitial lung disease in 2 patients and acute hepatic failure, acute pancreatitis, small intestinal obstruction, and sudden death in 1 patient each. Treatment-related adverse events leading to death in the chemotherapy group were alveolitis, empyema, and thrombocytopenia in 1 patient each. A bacterial component was identified for each of the 3 pneumonitis or interstitial lung disease cases that occurred in the immunotherapy arms.

^d The events are listed in descending order of frequency across all 3 treatment groups.

A multivariate analysis across cancer types suggested improved OS with immunotherapy at high TMB levels; however, the actual threshold for high TMB varied markedly between cancer types.⁴⁰ Previous NSCLC trials have demonstrated improved PFS with PD-1/CTLA-4 combination blockade in tumors with a high tTMB independent of PD-L1 expression.^{11,12} However, OS was similar regardless of whether patients had a high or low TMB.⁴¹ Both turnaround time and tumor tissue availability have been areas of concern for implementation of tTMB as a biomarker for patient selection.^{14,16,17} In this study, TMB was evaluable from blood in 72.4% (809/1118) of patients (consistent with other studies¹⁶) and from tissue in 41.1% (460/1118). Matched bTMB and tTMB data were available in 31.5% (352/1118) of patients, with a modest correlation observed despite important technical differences between sample types and platforms, consistent with previously reported findings.¹⁶ Blood TMB proved to be an appropriate biomarker of immunotherapy benefit in this trial and may be more representative of clonal mutations,⁴² accounting for tumor heterogeneity in patients with advanced NSCLC,⁴³ but this needs to be validated in prospective studies.

A tTMB threshold of 10 mut/Mb for nivolumab plus ipilimumab in NSCLC was based on single-arm, phase 2 response

data and supported by phase 3 PFS data.^{11,12} However, to our knowledge, this study is the first analysis to date to optimize a TMB threshold based on a relevant OS improvement in NSCLC. This exploratory analysis in a large data set evaluated multiple bTMB thresholds and identified a threshold of ≥20 mut/Mb for durvalumab plus tremelimumab that was predictive of optimal OS benefit. Of 809 patients with evaluable bTMB, 211 (26.1%) had bTMB ≥20 mut/Mb, which was associated with a clear OS improvement in patients receiving durvalumab plus tremelimumab vs chemotherapy (HR, 0.49; 95% CI, 0.32-0.74), in addition to improvements in PFS and objective response rate. The benefit of combination immunotherapy was durable, with 48.1% of patients alive at 2 years vs 19.4% with chemotherapy. In contrast, in patients with bTMB <20 mut/Mb, durvalumab plus tremelimumab was not associated with any improvement in clinical outcomes (OS HR, 1.16; 95% CI, 0.93-1.45). A smaller clinical benefit was observed with durvalumab alone vs chemotherapy in the population with bTMB ≥20 mut/Mb. Accordingly, this cutoff point revealed a meaningful contribution of tremelimumab in the combination immunotherapy group vs durvalumab alone (OS HR, 0.74; 95% CI, 0.48-1.11).

The safety and tolerability profiles of durvalumab and durvalumab plus tremelimumab in this study were consistent with

data from previous trials.^{19-23,32,44} Both immunotherapy arms were associated with fewer grade 3 or higher TRAEs than chemotherapy. The durvalumab plus tremelimumab combination was associated with a higher rate of TRAEs leading to discontinuation than durvalumab or chemotherapy.

Limitations

One of the limitations of the study was that, in response to the evolving treatment landscape and the emergence of PD-L1 expression as a predictive biomarker for anti-PD-1/PD-L1 therapy during the conduct of the MYSTIC study, the primary analysis population for the study was amended to include only patients with PD-L1 TC $\geq 25\%$. As a result, the primary study end points were evaluated in 44% of the overall randomized population and therefore with reduced power. The open-label study design was another limitation, which may explain why 20 patients randomized to the chemotherapy arm did not receive their assigned treatment; these patients may have received first-line immunotherapy instead and potentially biased the OS results. In addition, imbalances in subsequent anticancer treatment that favored the control arm, in which substantially more patients received subsequent immunotherapy compared with the durvalumab arm or durvalumab plus tremelimumab arm, highlight the effect this may have on OS as an end point. Finally, scientific understanding of TMB as a potential biomarker for efficacy with immune

checkpoint inhibitors has evolved since the time of study initiation. The TMB analyses were exploratory, and there were limitations associated with the availability of plasma and tumor tissue samples as well as a lack of prespecified statistical adjustment or stratification based on TMB.

Conclusions

In conclusion, although statistical significance was not achieved, first-line durvalumab treatment was associated with an OS HR of 0.76 vs chemotherapy in patients with mNSCLC who had PD-L1 TC $\geq 25\%$, in line with OS outcomes observed with other anti-PD-1 and PD-L1 agents in similar populations. Whereas durvalumab plus tremelimumab did not statistically significantly improve OS or PFS vs chemotherapy in patients with PD-L1 TC $\geq 25\%$, the combination showed clinical activity in patients with bTMB ≥ 20 mut/Mb. This exploratory analysis, representing the largest from a phase 3 trial correlated with long-term outcomes in first-line treatment of mNSCLC, identified a bTMB threshold of 20 mut/Mb for durvalumab plus tremelimumab that was predictive of optimal benefit in OS in addition to improved PFS and objective response rate. Further investigation and prospective validation of bTMB as a predictive biomarker for benefit with immunotherapy are warranted.

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Invited Commentary

The Mystic Role of Tumor Mutational Burden in Selecting Patients With Lung Cancer for First-Line Immunotherapy

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Recent advances in our understanding of the biologic characteristics of tumors and the cancer immunity cycle have led to an important shift in the standard-of-care treatment for metastatic non-small cell lung cancer (NSCLC). First-line platinum-



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based doublet chemotherapy was established as the standard of care about 2 decades ago and has served as the yardstick for comparing incremental benefits afforded by emerging treatments. This dogma changed with the approval of first-line single-agent anti-programmed cell death 1 (PD-1) therapy, and subsequently anti-PD-1 therapy in combination with platinum-based doublet chemotherapy ushered in a new standard of care: immunotherapy with or without chemotherapy.^{1,2} Nivolumab in combination with ipilimumab was the first anti-PD-1 and anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) therapy to show a progression-free survival (PFS) advantage compared with platinum-based chemotherapy in patients with a high tumor mutational burden (TMB), with a 1-year PFS of 42.6% with nivolumab and ipilimumab vs 13.2% with chemotherapy, as shown in the CheckMate 227³ study. In addition, CheckMate 227 met its other coprimary end point of improved overall survival (OS) with nivolumab and ipilimumab (median OS, 17.1 months) compared with chemotherapy (14.9 months) in patients with programmed cell death ligand 1 (PD-L1) expression of 1% or greater.⁴

In the current study, Rizvi and colleagues⁵ report the results of the phase 3 MYSTIC study, in which 1118 patients with previously untreated metastatic NSCLC without *EGFR* or *ALK* genetic alterations were randomized (1:1:1) to receive platinum-based doublet chemotherapy, single-agent durvalumab (anti-PD-L1 antibody), or durvalumab with tremelimumab (anti-CTLA-4 monoclonal antibody) combination therapy. The primary end points of the study were assessed in the 488 patients with PD-L1 expression in 25% of tumor cells or more and included OS for durvalumab vs platinum-based doublet chemotherapy, and OS and PFS for the durvalumab and tremeli-

mumab combination vs chemotherapy. Exploratory end points included examining the association of biomarkers, including tissue and blood TMB, with clinical outcomes. The MYSTIC study did not meet its primary end points. The median OS in patients with PD-L1 expression in 25% of tumor cells or more was 16.3 months for patients treated with durvalumab, which was numerically superior to the 12.9 months with platinum-based doublet chemotherapy, although it did not meet statistical significance. Furthermore, the median OS for the durvalumab and tremelimumab combination was 11.9 months, which was lower than for both the durvalumab and the chemotherapy arms. Median PFS for durvalumab and tremelimumab was disappointing, at 3.9 months, whereas the PFS with chemotherapy was 5.4 months. Adverse events were consistent with the known safety profile of durvalumab and tremelimumab, with the frequency of grade 3 or higher adverse events being lower for both the durvalumab and durvalumab with tremelimumab groups compared with the chemotherapy group.

Pretreatment tissue samples were available from 735 patients, with TMB data available from 460 tumor samples. Tissue TMB of 10 or more mutations per megabase (mut/Mb) was associated with numerically longer median OS in the 2 immunotherapy groups (16.6 months with durvalumab and tremelimumab vs 18.6 months with durvalumab) compared with 11.9 months with platinum-based doublet chemotherapy, although this did not meet statistical significance. Small sample sizes limited further analyses using TMB cutoffs greater than 10 mut/Mb.

Overall, 809 patients were evaluable for blood TMB assessment, and the TMB cutoff chosen by the authors was 20 or more mut/Mb based on the greatest effect size using this cutoff. Patients with 20 or more mut/Mb had improved OS with the durvalumab and tremelimumab combination vs chemotherapy, at 21.9 months vs 10.0 months, in addition to improved PFS and overall response rate.

Why did MYSTIC fail to meet its primary end points, unlike the CheckMate 227³ study? The patient population