

# Safety of First-Line Nivolumab Plus Ipilimumab in Patients With Metastatic NSCLC: A Pooled Analysis of CheckMate 227, CheckMate 568, and CheckMate 817

Luis G. Paz-Ares, MD, PhD,<sup>a,\*</sup> Tudor-Eliade Ciuleanu, MD, PhD,<sup>b</sup> Adam Pluzanski, MD, PhD,<sup>c</sup> Jong-Seok Lee, MD, PhD,<sup>d</sup> Justin F. Gainor, MD,<sup>e</sup> Gregory A. Otterson, MD,<sup>f</sup> Clarisse Audigier-Valette, MD,<sup>g</sup> Neal Ready, MD, PhD,<sup>h</sup> Michael Schenker, MD,<sup>i</sup> Helena Linardou, MD, PhD,<sup>j</sup> Reyes Bernabe Caro, MD, PhD,<sup>k</sup> Mariano Provencio, MD,<sup>l</sup> Bogdan Zurawski, MD,<sup>m</sup> Ki Hyeong Lee, MD,<sup>n</sup> Sang-We Kim, MD,<sup>o</sup> Claudia Caserta, MD,<sup>p</sup> Suresh S. Ramalingam, MD,<sup>q</sup> David R. Spigel, MD,<sup>r</sup> Julie R. Brahmer, MD,<sup>s</sup> Martin Reck, MD, PhD,<sup>t</sup> Kenneth J. O'Byrne, MD, PhD,<sup>u</sup> Nicolas Girard, MD, PhD,<sup>v</sup> Sanjay Popat, PhD,<sup>w,x</sup> Solange Peters, MD, PhD,<sup>y</sup> Arteid Memaj, MSc,<sup>z</sup> Faith Nathan, MD,<sup>aa</sup> Nivedita Aanur, MD,<sup>aa</sup> Hossein Borghaei, DO, MS<sup>bb</sup>

<sup>a</sup>Medical Oncology Department, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain

<sup>b</sup>Department of Medical Oncology, Institutul Oncologic Prof. Dr. Ion Chiricuta and University of Medicine and Pharmacy Iulia Hatieganu, Cluj-Napoca, Romania

<sup>c</sup>Department of Lung Cancer and Chest Tumours, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

<sup>d</sup>Department of Hematology/Oncology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

\*Corresponding author.

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<sup>e</sup>Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

<sup>f</sup>The Ohio State University-James Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio

<sup>g</sup>Orientation Oncologique, Hôpital Sainte-Musse, Toulon, France

<sup>h</sup>Department of Medicine, Duke University School of Medicine, Durham, North Carolina

<sup>i</sup>Department of Medical Oncology, Sf Nectarie Oncology Center, Craiova, Romania

<sup>j</sup>Fourth Oncology Department and Comprehensive Clinical Trials Center, Metropolitan Hospital, Athens, Greece

<sup>k</sup>Medical Oncology Department, Hospital Universitario Virgen Del Rocio, Instituto de Biomedicina de Seville, Seville, Spain

<sup>l</sup>Medical Oncology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain

<sup>m</sup>Chemotherapy Department, Ambulatorium Chemioterapii, Bydgoszcz, Poland

<sup>n</sup>Medical Oncology, Chungbuk National University Hospital, Cheongju-si, Republic of Korea

<sup>o</sup>Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

<sup>p</sup>Medical Oncology Department, Santa Maria Hospital, Terni, Italy

<sup>q</sup>Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, Georgia

<sup>r</sup>Thoracic Medical Oncology, Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, Tennessee

<sup>s</sup>Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland

<sup>t</sup>Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, LungClinic, Grosshansdorf, Germany

<sup>u</sup>Princess Alexandra Hospital, Translational Research Institute and Queensland University of Technology, Brisbane, Queensland, Australia

<sup>v</sup>Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France

<sup>w</sup>Lung Unit, Royal Marsden Hospital, London, United Kingdom

<sup>x</sup>The Institute of Cancer Research, University of London, London, United Kingdom

<sup>y</sup>Oncology Department, Lausanne University Hospital, Lausanne, Switzerland

<sup>z</sup>Global Biometrics and Data Sciences, Bristol Myers Squibb, Princeton, New Jersey

<sup>aa</sup>OneClinical, Bristol Myers Squibb, Princeton, New Jersey

<sup>bb</sup>Hematology and Oncology Department, Fox Chase Cancer Center, Temple Health System, Philadelphia, Pennsylvania

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Address for correspondence: Luis G. Paz-Ares, MD, PhD, Medical Oncology Department, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Av. de Córdoba SN, 28041 Madrid, Spain. E-mail: [lpazares@seom.org](mailto:lpazares@seom.org)

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**ABSTRACT**

**Introduction:** We characterized the safety of first-line nivolumab plus ipilimumab (NIVO+IPI) in a large patient population with metastatic NSCLC and efficacy outcomes after NIVO+IPI discontinuation owing to treatment-related adverse events (TRAEs).

**Methods:** We pooled data from three first-line NIVO+IPI studies (NIVO, 3 mg/kg or 240 mg every 2 wk; IPI, 1 mg/kg every 6 wk) in metastatic NSCLC (CheckMate 227 part 1, CheckMate 817 cohort A, CheckMate 568 part 1). Safety end points included TRAEs and immune-mediated adverse events (IMAEs) in the pooled population and patients aged 75 years or older.

**Results:** In the pooled population (N = 1255), any-grade TRAEs occurred in 78% of the patients, grade 3 or 4 TRAEs in 34%, and discontinuation of any regimen component owing to TRAEs in 21%. The most frequent TRAE and IMAE were diarrhea (20%; grade 3 or 4, 2%) and rash (17%; grade 3 or 4, 3%), respectively. The most common grade 3 or 4 IMAEs were hepatitis (5%) and diarrhea/colitis and pneumonitis (4% each). Pneumonitis was the most common cause of treatment-related death (5 of 16). Safety in patients aged 75 years or older (n = 174) was generally similar to the overall population, but discontinuation of any regimen component owing to TRAEs was more common (29%). In patients discontinuing NIVO+IPI owing to TRAEs (n = 225), 3-year overall survival was 50% (95% confidence interval: 42.6–56.0), and 42% (31.2–52.4) of 130 responders remained in response 2 years after discontinuation.

**Conclusions:** First-line NIVO+IPI was well tolerated in this large population with metastatic NSCLC and in patients aged 75 years or older. Discontinuation owing to TRAEs did not reduce long-term survival.

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**Keywords:** NSCLC; Nivolumab; Ipilimumab; Immune-mediated adverse events; Safety

**Introduction**

Current first-line treatment options for metastatic NSCLC without genomic driver alterations include immunotherapy-based regimens either alone or in combination with platinum-doublet chemotherapy.<sup>1–7</sup> These regimens were found to have survival benefit compared with chemotherapy<sup>8–15</sup> and have become the standard of care for first-line treatment of metastatic NSCLC. Nevertheless, continued assessment of safety remains of key importance to clinicians as, together with clear clinical benefits, immunotherapies have a safety profile distinct from

chemotherapy and other anticancer therapies. This includes a spectrum of adverse events termed immune-mediated adverse events (IMAEs), which arise owing to the specific mechanisms of action of immunotherapies and require careful management.<sup>16–18</sup> Older patients with NSCLC, compared with their younger counterparts, may present with characteristics such as multiple comorbidities and decline in cognitive function, which require careful consideration during NSCLC treatment.<sup>19</sup> Despite the prevalence of lung cancer in older adults (36.3% of diagnoses are in patients aged  $\geq 75$  y), this patient population is generally underrepresented in cancer trials.<sup>20–22</sup> Therefore, understanding the safety of immunotherapy regimens in patients aged  $\geq 75$  years is of particular interest.<sup>23</sup>

Nivolumab, a fully human anti-programmed death protein 1 antibody, and ipilimumab, a fully human anti-cytotoxic T-lymphocyte antigen 4 antibody, are immune checkpoint inhibitors with distinct but complementary mechanisms of action.<sup>24–27</sup> Nivolumab plus ipilimumab was found to have durable overall survival (OS) benefit in multiple cancers, including NSCLC, renal cell carcinoma, melanoma, and malignant pleural mesothelioma.<sup>28–32</sup> Notably, in the phase 3 CheckMate 227 part 1 study (NCT02477826), nivolumab plus ipilimumab had significant OS benefit versus chemotherapy ( $p = 0.007$ ) as a first-line treatment in patients with metastatic NSCLC and tumor programmed death ligand 1 (PD-L1) expression greater than or equal to 1%; survival benefit was long-term, together with notably prolonged duration of response (DOR).<sup>8,30</sup> In a pre-specified descriptive analysis, similar benefit was found in patients with tumor PD-L1 expression less than 1%.<sup>8,30</sup> The safety profile of nivolumab plus ipilimumab was manageable. As a result of these findings, nivolumab plus ipilimumab was approved in the United States and other countries as a first-line treatment for adults with metastatic NSCLC and tumor PD-L1 expression greater than or equal to 1% with no *EGFR* or *ALK* genomic tumor aberrations<sup>5</sup> and in Argentina and Japan as first-line treatment for patients with PD-L1 expression greater than or equal to 1% or less than 1%.<sup>33,34</sup> Nivolumab plus ipilimumab is also recommended by the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology (NCCN Guidelines) and the European Society for Medical Oncology guidelines as a first-line treatment option for eligible patients with metastatic NSCLC with either tumor PD-L1 greater than or equal to 1% or less than 1% with no targetable driver alterations, regardless of histology.<sup>1,6</sup> Data with a 4-year minimum follow-up revealed that nivolumab plus ipilimumab continued to provide durable responses and clinical benefits versus chemotherapy; safety was



consistent with previous reports.<sup>8,30</sup> Survival and safety outcomes from cohort A of the single-arm phase 3b CheckMate 817 study (NCT02869789)<sup>35-37</sup> and the single-arm phase 2 CheckMate 568 part 1 study (NCT02659059)<sup>38</sup> further support use of first-line nivolumab plus ipilimumab in metastatic NSCLC.

Here, to better understand the safety profile of nivolumab plus ipilimumab, we report safety analyses of a large population pooled from three clinical studies investigating this combination as a first-line treatment of NSCLC, which are as follows: CheckMate 227 part 1,<sup>8</sup> CheckMate 817 cohort A,<sup>35-37</sup> and CheckMate 568 part 1.<sup>38</sup> Furthermore, we report safety in patients aged 75 years or older, a population of clinical interest with small patient numbers enrolled in individual clinical studies.<sup>23</sup> Finally, we evaluate the effect of discontinuation of nivolumab plus ipilimumab owing to treatment-related adverse events (TRAEs) on efficacy.

## Materials and Methods

### Study Designs and Patients

To further characterize the safety profile of nivolumab plus ipilimumab, data were pooled from three open-label clinical studies of first-line treatment with nivolumab plus ipilimumab for patients with metastatic NSCLC, which are as follows: phase 3 CheckMate 227 part 1, phase 3b CheckMate 817 cohort A, and phase 2 CheckMate 568 part 1. The study design, eligibility, and primary outcomes for these three studies have been previously reported (Supplementary Table 1).<sup>8,35-39</sup> All three studies included adult patients with squamous or nonsquamous stage IV or recurrent NSCLC (per Seventh International Association for the Study of Lung Cancer classification) and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. No patient in the pooled population had received previous systemic anticancer therapy for advanced or metastatic disease. Patients were required to have tumor samples available for evaluation of PD-L1 expression.<sup>8,37,38</sup> In the randomized CheckMate 227 part 1 study, patients were assigned to part 1a or 1b and treated with nivolumab-based regimens or chemotherapy dependent on tumor PD-L1 expression level ( $\geq 1\%$  or  $< 1\%$ ). In both parts 1a and 1b, patients received nivolumab 3 mg/kg every 2 weeks (Q2W) plus ipilimumab 1 mg/kg every 6 weeks (Q6W) or platinum-doublet chemotherapy (every 3 weeks [Q3W] for up to four cycles) and optional pemetrexed maintenance (500 mg/m<sup>2</sup>) in patients with nonsquamous NSCLC.<sup>8,39</sup> Part 1a also included a group receiving nivolumab monotherapy 240 mg Q2W, and part 1b included a group receiving nivolumab 360 mg Q3W plus platinum-doublet chemotherapy. In the single-arm studies, patients received nivolumab 240 mg Q2W plus

ipilimumab 1 mg/kg Q6W (CheckMate 817 cohort A)<sup>37</sup> or nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W (CheckMate 568 part 1).<sup>38</sup> In all studies, treatment with nivolumab plus ipilimumab continued until disease progression, until unacceptable toxicity, or for a maximum of 2 years.

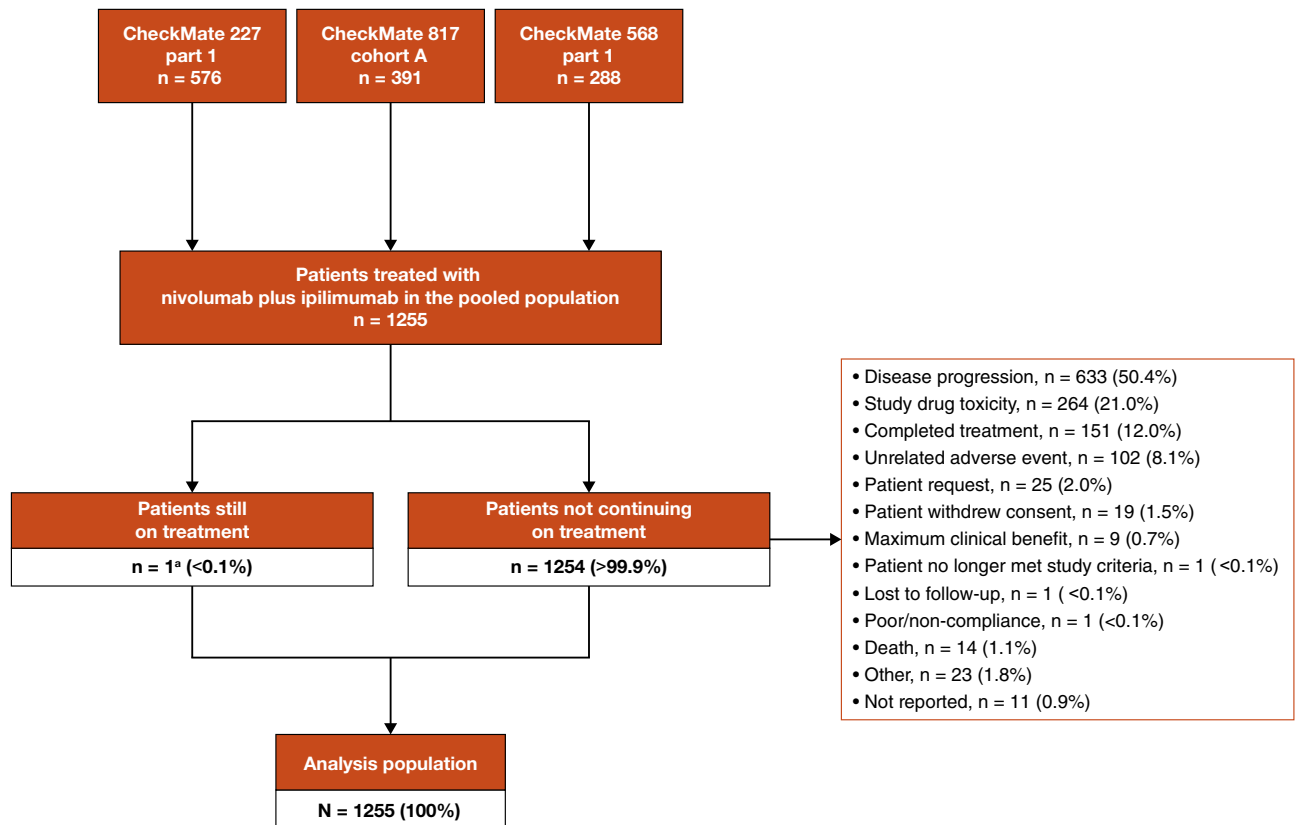
The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. Independent ethics committees or institutional review boards at participating study centers approved the protocols and all amendments. All patients provided written informed consent. The Bristol Myers Squibb policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html>.

### Safety End Points and Assessments

All end points in the pooled population were considered exploratory, as all analyses were post hoc. These pooled safety analyses evaluated TRAEs (including serious events and those leading to discontinuation) reported between the first dose and 30 days after the last dose of the study treatment. Overall incidences of TRAEs and TRAEs leading to discontinuation in the chemotherapy arm of CheckMate 227 part 1 are also reported. In addition, IMAEs (including those leading to discontinuation) and time to onset and resolution of IMAEs were analyzed. IMAEs were defined as specific events (or groups of preferred terms describing specific events) that included pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine events (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by the investigator, regardless of causality, that occurred within 100 days of the last dose, with no clear alternate cause on the basis of investigator assessment, or with an immune-mediated component, that were treated with immune-modulating medication. Endocrine adverse events were considered IMAEs regardless of immune-modulating medication use because endocrine drug reactions are often managed without immune-modulating medication. Patients who experienced an IMAE without worsening from baseline grade were excluded from time-to-resolution analyses; events without an end date or with a stop date equal to the death date were considered unresolved.

### Assessment of Efficacy in Patients Who Discontinued Nivolumab Plus Ipilimumab Owing to TRAEs

Efficacy was analyzed in the population of patients who had a TRAE (reported between the first dose and 30 days



**Figure 1.** CONSORT flow diagram. <sup>a</sup>One patient in CheckMate 227 part 1 discontinued treatment but was captured as still on treatment by the statistical algorithm because an off-treatment date was not provided by the site.

after the last dose of the study treatment) that led to the discontinuation of all components of the study treatment. OS (from randomization) and treatment-free interval (TFI; defined as the time from the last dose of study therapy to the start of the first subsequent systemic therapy or death, whichever occurred first) were evaluated. TFI was set to zero for patients who received subsequent therapy before treatment discontinuation. Additional end points evaluated were progression-free survival, objective response rate (ORR), and DOR from the time of treatment discontinuation. Responses were assessed using Response Evaluation Criteria in Solid Tumors version 1.1 per the investigators.

### Statistical Analyses

All analyses were post hoc and carried out in all treated patients or subgroups of treated patients. OS, investigator-assessed progression-free survival, investigator-assessed DOR, TFI, and other time-to-event end points were estimated using Kaplan–Meier methodology. Exact two-sided 95% confidence intervals (CIs) for ORR were calculated using the Clopper–Pearson method. Descriptive statistics were used to summarize safety results, where applicable.

## Results

### Patient Demographics and Treatment Summary

A total of 1255 patients treated with nivolumab plus ipilimumab were pooled across the three studies (CheckMate 227, n = 576; CheckMate 817, n = 391; CheckMate 568, n = 288). Baseline demographics of the pooled population are reported in [Supplementary Table 2](#). Although baseline characteristics were generally similar across studies, CheckMate 227 part 1 had a higher proportion of patients with tumor PD-L1 expression greater than or equal to 1% compared with the other studies owing to the study design. Minimum follow-up (time between first dose and database lock) was 38.0 months (CheckMate 227), 30.6 months (CheckMate 817), and 37.7 months (CheckMate 568). In the pooled population, median age was 65 (range: 26–91) years and 174 (14%) patients were aged 75 years or older. Patients received a median of 9.0 doses of nivolumab and 3.0 doses of ipilimumab, with median duration of treatment of 4.1 months (range: 0–25.8) ([Supplementary Table 3](#)). At the time of analysis, all patients had discontinued treatment; main reasons for treatment discontinuation were disease progression

**Table 1.** Safety Summary in All Patients and Patients Aged 75 Years or Older Treated With Nivolumab Plus Ipilimumab in the Pooled Population and With Chemotherapy in CheckMate 227 Part 1

Patients with an event	Pooled Overall Population, n (%)		Patients Aged $\geq 75$ y, n (%)		CheckMate 227 Part 1, n (%)	
	Nivolumab Plus Ipilimumab (N = 1255)		Nivolumab Plus Ipilimumab (n = 174)		Chemotherapy (n = 570)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any TRAE	977 (77.8)	431 (34.3)	135 (77.6)	76 (43.7)	469 (82.3)	206 (36.1)
TRAEs in $\geq 10\%$ of patients						
Diarrhea	256 (20.4)	30 (2.4)	34 (19.5)	5 (2.9)	55 (9.6)	4 (0.7)
Fatigue	219 (17.5)	22 (1.8)	34 (19.5)	3 (1.7)	108 (18.9)	8 (1.4)
Pruritus	210 (16.7)	8 (0.6)	33 (19.0)	2 (1.1)	7 (1.2)	0
Rash	175 (13.9)	18 (1.4)	21 (12.1)	2 (1.1)	30 (5.3)	0
Hypothyroidism	149 (11.9)	5 (0.4)	21 (12.1)	1 (0.6)	0	0
Decreased appetite	135 (10.8)	5 (0.4)	21 (12.1)	0	112 (19.6)	7 (1.2)
Nausea	133 (10.6)	6 (0.5)	16 (9.2)	0	206 (36.1)	12 (2.1)
Asthenia	98 (7.8)	15 (1.2)	7 (4.0)	1 (0.6)	73 (12.8)	5 (0.9)
Rash maculopapular	98 (7.8)	17 (1.4)	21 (12.1)	4 (2.3)	8 (1.4)	0
Vomiting	63 (5.0)	6 (0.5)	6 (3.4)	1 (0.6)	77 (13.5)	13 (2.3)
Constipation	33 (2.6)	0	1 (0.6)	0	85 (14.9)	2 (0.4)
Anemia	16 (5.6)	1 (0.3)	8 (4.6)	2 (1.1)	191 (33.5)	66 (11.6)
Decreased neutrophil count	7 (0.6)	0	1 (0.6)	0	64 (11.2)	36 (6.3)
Neutropenia	2 (0.2)	1 (<0.1)	0	0	99 (17.4)	55 (9.6)
Any TRAE leading to discontinuation of a drug component	259 (20.6)	174 (13.9)	51 (29.3)	36 (20.7)	53 (9.3)	28 (4.9)
Serious TRAEs	291 (23.2)	226 (18.0)	50 (28.7)	42 (24.1)	79 (13.9)	61 (10.7)
Treatment-related deaths <sup>a</sup>		16 (1.3)		2 (1.1)		6 (1.1)

Note: Includes events reported between the first dose and 30 days after the last dose of study therapy.

<sup>a</sup>Treatment-related deaths in the pooled nivolumab plus ipilimumab arm included pneumonitis (n = 5), myocarditis (patient aged  $\geq 75$  y), acute tubular necrosis, shock, cardiac tamponade, heart failure owing to rhabdomyolysis, Guillain-Barré syndrome, autoimmune esophagitis (patient aged  $\geq 75$  y), autoimmune hepatitis, hypoxia, cardiomegaly, and pancreatitis and elevated bilirubin (n = 1 each). Treatment-related deaths in the CheckMate 227 part 1 chemotherapy arm included sepsis (n = 2), febrile neutropenia with sepsis, multiple brain infarctions, interstitial lung disease, and thrombocytopenia (n = 1 each).

TRAE, treatment-related adverse event.

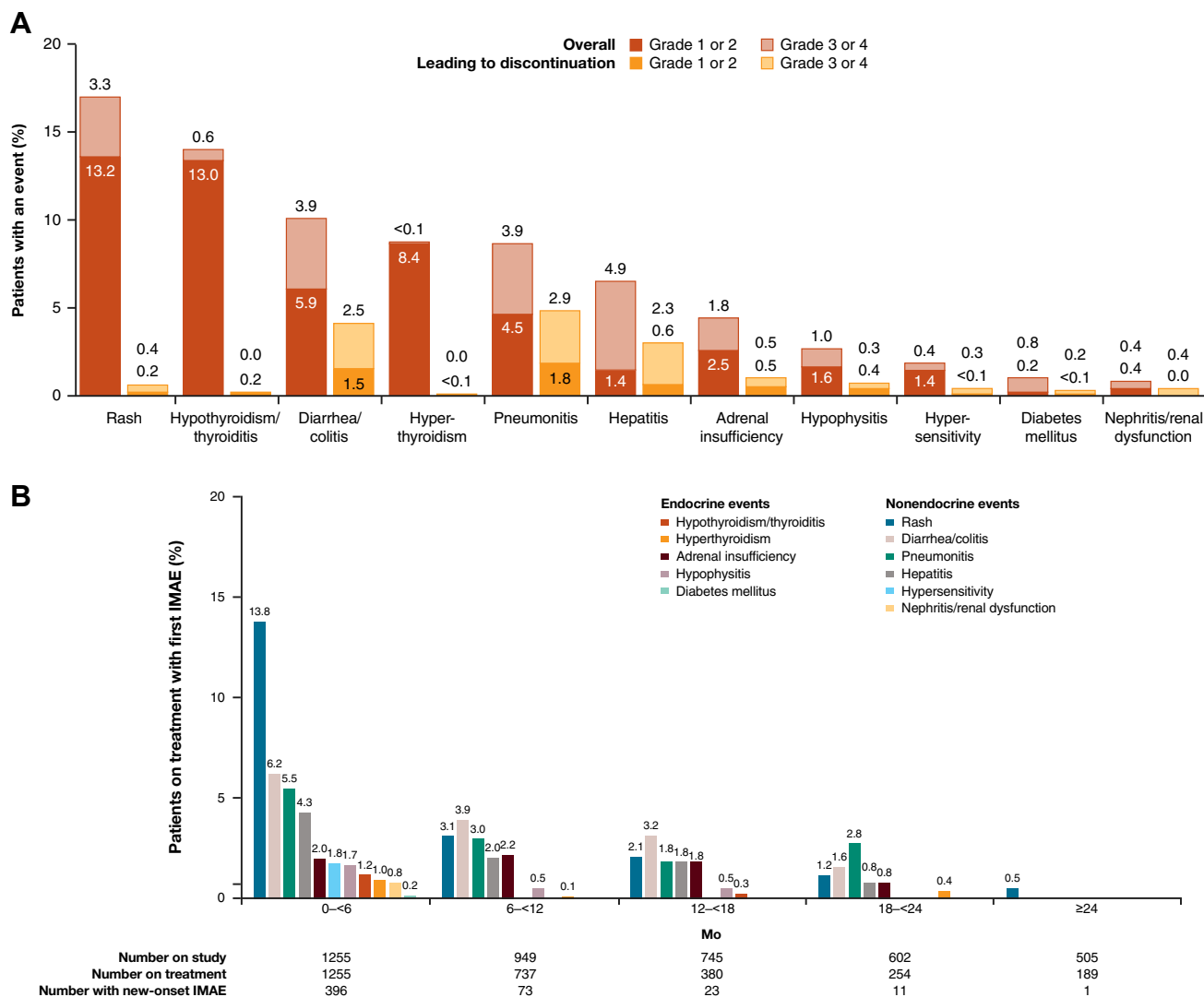
(50%), study drug toxicity (21%), and completed treatment (12%) (Fig. 1).

Baseline demographics of patients aged 75 years or older from the pooled population were broadly similar to the overall population; however, more of these patients had an ECOG PS of 1 (Supplementary Table 4). Patients aged 75 years or older received a median of 8.0 doses of nivolumab (range: 1–55) and 3.0 doses of ipilimumab (range: 1–19), with a median duration of treatment of 3.9 (range: 0–25.6) months (Supplementary Table 5). Similar to the overall pooled population, the main reasons for discontinuation were disease progression (38%), study drug toxicity (29%), and completed treatment (14%) (Supplementary Table 6).

### Safety Profile

In the pooled patient population treated with nivolumab plus ipilimumab, TRAEs of any grade occurred in 78% of patients; grade 3 or 4 TRAEs occurred in 34%. Diarrhea was the most common

TRAE of any grade (20%), followed by fatigue (18%) and pruritus (17%); the most common grade 3 or 4 TRAEs were increased lipase (6%), diarrhea (2%), and fatigue (2%) (Table 1). TRAEs leading to discontinuation of any component of the treatment regimen occurred in 21% of patients treated with nivolumab plus ipilimumab in the pooled population and 9% of patients treated with chemotherapy in CheckMate 227 part 1. In patients treated with nivolumab plus ipilimumab, the most common TRAEs of any grade leading to discontinuation of any drug component were pneumonitis (4%), diarrhea (3%), and colitis (2%) (Supplementary Table 7). TRAEs leading to discontinuation of all components of the treatment regimen occurred in 18% of patients treated with nivolumab plus ipilimumab in the pooled population and 8% of patients treated with chemotherapy in CheckMate 227 part 1. Serious TRAEs occurred in 23% of patients treated with nivolumab plus ipilimumab; the most common serious adverse events were pneumonitis (4%), diarrhea (2%), and colitis (2%). Treatment-



**Figure 2.** (A) Overall incidence of IMAEs and IMAEs leading to discontinuation and (B) time to first IMAE in all patients receiving nivolumab plus ipilimumab in the pooled population. IMAEs were defined as specific events (or groups of preferred terms describing specific events) that included pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine events (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events considered as potential immune-mediated events by the investigator, regardless of causality, that occurred within 100 days of the last dose, with no clear alternate etiology on the basis of investigator assessment or with an immune-mediated component, that were treated with immune-modulating medication. Endocrine adverse events were considered IMAEs regardless of immune-modulating medication use because endocrine drug reactions are often managed without immune-modulating medication. CTCAE version 4.0; MedDRA version 22.1. CTCAE, Common Terminology Criteria for Adverse Events; IMAE, immune-mediated adverse event.

related deaths occurred in 16 (1%) patients; pneumonitis was the most common cause of death (n = 5) in these patients (Table 1). Notably, the incidence of TRAEs with nivolumab plus ipilimumab was similar in patients with squamous or nonsquamous NSCLC (Supplementary Table 8). The overall incidence of TRAEs reported in the chemotherapy arm of Check-Mate 227 part 1 (82%) was similar to that observed with nivolumab plus ipilimumab in this pooled analysis (78%) (Table 1). Nevertheless, the incidence of TRAEs (any grade) leading to discontinuation was

lower with chemotherapy (9%) than with nivolumab plus ipilimumab (21%). The most common TRAEs leading to discontinuation in patients treated with chemotherapy were fatigue and anemia (both 1%) (Supplementary Table 7).

The most common IMAE reported in the pooled nivolumab plus ipilimumab population was rash, with 17% of patients experiencing an event of any grade and 3% experiencing a grade 3 or 4 event; overall, most IMAEs were grade 1 or 2. The most common grade 3 or 4 IMAE was hepatitis, reported in 5% of the patients

**Table 2.** Time to Onset and Resolution of IMAEs<sup>a</sup> and Use of Systemic Corticosteroids ( $\geq 40$  mg) in All Patients Treated With Nivolumab Plus Ipilimumab in the Pooled Population

	Any-Grade Events, n (%)	Time to Onset, Median (IQR), mo	Time to Resolution, Median (95% CI), mo <sup>b</sup>	Any-Grade Events That Resolved, n (%) <sup>c</sup>	Corticosteroid $\geq 40$ mg, n (%)	Duration of Corticosteroid $\geq 40$ mg, Median, wk
<b>Endocrine</b>						
Adrenal insufficiency	54 (4.3)	6.0 (3.8-8.4)	NR (NR-NR)	17 (31.5)	14 (25.9)	3.0
Hypothyroidism/thyroiditis	171 (13.6)	3.2 (2.2-5.6)	NR (NR-NR)	52 (30.6)	6 (3.5)	4.0
Diabetes mellitus	13 (1.0)	4.6 (1.8-6.4)	NR (1.22-NR)	3 (23.1)	1 (7.7)	0.1 <sup>d</sup>
Hyperthyroidism	106 (8.4)	1.4 (1.4-2.8)	1.9 (1.4-2.3)	82 (77.4)	8 (7.5)	1.2
Hypophysitis	33 (2.6)	4.4 (2.5-6.2)	NR (1.4-NR)	13 (39.4)	12 (36.4)	0.6
<b>Nonendocrine</b>						
Pneumonitis	105 (8.4)	4.2 (1.6-7.3)	1.4 (1.0-2.0)	81 (77.1)	95 (90.5)	3.0
Diarrhea/colitis	123 (9.8)	4.0 (2.1-8.7)	0.7 (0.5-1.0)	114 (92.7)	99 (80.5)	2.0
Hepatitis	78 (6.2)	3.2 (1.4-7.3)	1.4 (1.2-2.1)	70 (89.7)	68 (87.2)	2.8
Nephritis/renal dysfunction	10 (0.8)	1.4 (0.5-2.8)	0.3 (0.1-2.3)	8 (80.0)	9 (90.0)	1.4
Rash	208 (16.6)	1.5 (0.4-4.4)	1.5 (1.3-2.2)	168 (81.2)	51 (24.5)	1.6
Hypersensitivity	22 (1.8)	0.5 (0.5-1.6)	<0.1 (<0.1-0.4)	20 (90.9)	10 (45.5)	0.1 <sup>d</sup>

<sup>a</sup>IMAEs were defined as specific events (or groups of preferred terms describing specific events) that included pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine events (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events considered as potential immune-mediated events by the investigator, regardless of causality, that occurred within 100 days of the last dose, with no clear alternate cause based on investigator assessment, or with an immune-mediated component, that were treated with immune-modulating medication. Endocrine adverse events were considered IMAEs regardless of immune-modulating medication use because endocrine drug reactions are often managed without immune-modulating medication. CTCAE version 4.0; MedDRA version 22.1.

<sup>b</sup>Per Kaplan-Meier estimates.

<sup>c</sup>Denominator based on number of any-grade events for each event category.

<sup>d</sup>Equivalent to 1 d.

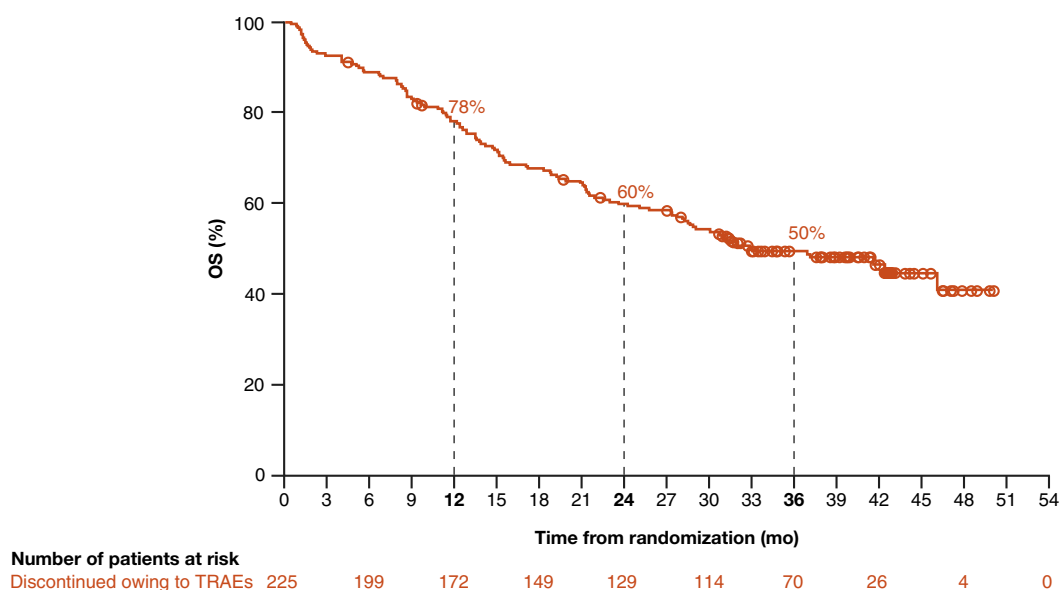
CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; IMAE, immune-mediated adverse event; IQR, interquartile range; NR, not reached.

(Fig. 2A). IMAEs were generally similar regardless of tumor histology (Supplementary Fig. 1). IMAEs of any grade leading to discontinuation in more than 1% of patients were pneumonitis (5%), diarrhea/colitis (4%), and hepatitis (3%) (Fig. 2A). IMAEs tended to occur within the first 6 months of treatment, with events generally trending down in each successive 6-month period (Fig. 2B). The IMAE with shortest median time to onset was hypersensitivity (0.5 mo), approximately corresponding to one 2-week dosing interval; hyperthyroidism, nephritis/renal dysfunction, and rash all tended to occur within the first 2 months of treatment (Table 2 and Supplementary Fig. 2A). Nonendocrine IMAEs tended to resolve within the study period (77%–93% resolved; median time to resolution  $\leq 1.5$  mo), whereas hyperthyroidism was the only endocrine IMAE with the majority of events resolved (77%) (Table 2 and Supplementary Fig. 2B).

In patients aged 75 years or older, the proportion of those with TRAEs of any grade was similar to the overall pooled population (78% for both). Grade 3 or 4 TRAEs were reported in a somewhat higher proportion of patients aged 75 years or older than in the overall

population (44% versus 34%, respectively), and TRAEs leading to discontinuation were numerically more frequent among patients aged 75 years or older (29% versus 21%, respectively) (Supplementary Table 9). Serious TRAEs were also numerically more frequent among older adult patients (29% versus 23%; grade 3 or 4, 24% versus 18%) (Table 1). Treatment-related deaths occurred in two (1%) patients aged 75 years or older (myocarditis and autoimmune esophagitis;  $n = 1$  each), which was consistent with the overall population (Table 1). The incidence of IMAEs of any grade in patients aged 75 years or older was also comparable with the overall population and with patients younger than 75 years (Supplementary Fig. 3). As with the overall population, IMAEs in patients aged 75 years or older tended to occur within the first 6 months of treatment (Supplementary Table 10), with the exception of diabetes mellitus, which had a median time to onset of 9.4 (range: 0.7–18.2) months; this occurred in only two patients, making the data difficult to interpret. Similar to the pooled population, the IMAE with the shortest median time to onset was hypersensitivity (0.5 mo); hyperthyroidism, nephritis/renal dysfunction, and rash all





**Figure 3.** OS in patients who discontinued nivolumab plus ipilimumab owing to TRAEs. Minimum follow-up, 29.1 months; 1-year survival rate 95% CI: 72.1-83.0; 2-year survival rate 95% CI: 53.1-66.0; 3-year survival rate 95% CI: 42.6-56.0. CI, confidence interval; OS, overall survival; TRAE, treatment-related adverse event.

tended to occur within the first 2 months of treatment (Supplementary Table 10). As with the overall population, most nonendocrine IMAEs resolved ( $\geq 76\%$ ) during the study period, whereas adrenal insufficiency and hyperthyroidism were the only endocrine IMAEs with most events resolved (75% and 57%, respectively) (Supplementary Table 10).

### Management of IMAEs

In the pooled patient population, across categories, most nonendocrine IMAEs were treated with

corticosteroids at doses of 40 mg or greater prednisone or equivalent (Table 2); use of corticosteroids tended to be higher for nonendocrine than for endocrine events, as expected, because endocrine IMAEs are often managed with hormone-replacement medication. Corticosteroid use ranged from 4% in patients with hypothyroidism/thyroiditis to 90% in patients with pneumonitis or nephritis/renal dysfunction (Table 2). Median duration of corticosteroid use ranged from 0.1 weeks (1 d) for diabetes mellitus and hypersensitivity to 4.0 weeks for hypothyroidism/thyroiditis. Median duration of corticosteroid use for pneumonitis and diarrhea/colitis was 3.0

**Table 3.** Outcomes in Patients Who Discontinued All Components of the Nivolumab Plus Ipilimumab Regimen owing to TRAEs

	Patients Who Discontinued owing to TRAEs (n = 225)
Progression free after discontinuation	
$\geq 1$ y after discontinuation, % (95% CI)	47.2 (39.2-54.9)
$\geq 2$ y after discontinuation, % (95% CI)	31.1 (23.2-39.3)
ORR, <sup>a</sup> n (%)	130 (57.8)
95% CI	51.0-64.3
DOR after discontinuation, <sup>a</sup> % (95% CI)	
Ongoing response $\geq 1$ y after discontinuation	61.0 (51.0-69.7)
Ongoing response $\geq 2$ y after discontinuation	42.0 (31.2-52.4)
Treatment-free interval, <sup>b</sup> % (95% CI)	
1 y	52.9 (46.2-59.2)
2 y	38.2 (31.5-44.8)

Note: Post hoc analysis; includes patients with TRAEs (reported between the first dose and 30 days after the last dose of study treatment) that were considered as leading to discontinuation of all components of study treatment.

<sup>a</sup>Per investigator.

<sup>b</sup>Treatment-free interval was defined as the time from the last dose of study therapy to the start of the first subsequent systemic therapy or death, whichever occurred first, and was set to zero for patients who received subsequent therapy before treatment discontinuation.

CI, confidence interval; DOR, duration of response; ORR, objective response rate; TRAE, treatment-related adverse event.

and 2.0 weeks, respectively. A similar pattern of IMAE management with corticosteroids at doses of 40 mg or greater prednisone or equivalent was found in patients aged 75 years or older (Supplementary Table 10) and in patients with IMAEs leading to treatment discontinuation (Supplementary Table 11).

Few patients received immunosuppressive treatment other than corticosteroids for management of IMAEs. Infliximab was received by four patients with pneumonitis and five patients with diarrhea/colitis, among whom the IMAE led to discontinuation of study treatment in three and four patients, respectively. Mycophenolic acid was received by seven patients with hepatitis, which led to treatment discontinuation in five of these patients, including one patient who also received azathioprine. Among patients aged 75 years or older, only one received immunosuppressive treatment other than corticosteroids; this patient was one of those treated with infliximab for diarrhea/colitis who discontinued study treatment.

### Outcomes in Patients With TRAEs Leading to Discontinuation of Nivolumab Plus Ipilimumab

A total of 225 patients were included in the analysis of efficacy outcomes in patients who discontinued nivolumab plus ipilimumab owing to TRAEs. In general, the baseline characteristics of this population were consistent with the overall pooled population (Supplementary Table 12). Patients received a median of 9.0 (range: 1–51) doses of nivolumab and 3.0 (1–17) doses of ipilimumab; median duration of treatment was 4.2 (range: 0–23.5) months. The 3-year OS rate (from time of randomization) was 50% (95% CI: 42.6–56.0) in patients who discontinued nivolumab plus ipilimumab owing to TRAEs (Fig. 3) and 35% (95% CI: 32.5–37.9) in the pooled population (Supplementary Fig. 4). Investigator-assessed ORR was 58% (95% CI: 51.0–64.3). Two years after treatment discontinuation owing to TRAEs, 31% (95% CI: 23.2–39.3) of 225 patients overall were progression free and 42% (95% CI: 31.2–52.4) of 130 responders remained in response to nivolumab plus ipilimumab; 38% (95% CI: 31.5–44.8) of patients did not receive subsequent systemic treatment for 2 years or longer (Table 3). OS in patients aged 75 years or older who discontinued nivolumab plus ipilimumab owing to TRAEs (Supplementary Fig. 5) was consistent with the overall population.

## Discussion

To our knowledge, this study of 1255 patients and a minimum follow-up of more than 2 years is the largest safety analysis to date from clinical trials of a first-line

immunotherapy regimen for metastatic NSCLC. Data from the pooled safety analyses were consistent with individual trial data<sup>30,37,38</sup> and revealed a manageable safety and tolerability profile with no new safety signals identified. The safety profile of nivolumab plus ipilimumab was consistent across patients with squamous or nonsquamous NSCLC. Notably, onset of new IMAEs tended to occur within the first 6 months of treatment, suggesting those patients who received long-term treatment with nivolumab plus ipilimumab did not experience an increased burden of toxicity. Most IMAEs were grade 1 or 2 and resolved with corticosteroid treatment; other immunomodulatory drugs were rarely used to manage IMAEs. Pneumonitis was the most common IMAE leading to treatment discontinuation, in 5% of patients; 77% of pneumonitis cases resolved.

Discontinuing nivolumab plus ipilimumab owing to TRAEs did not negatively affect the long-term survival benefit observed in the overall pooled population, consistent with previous reports in patients who discontinued nivolumab-based regimens.<sup>30,40</sup> Patients who discontinued nivolumab plus ipilimumab owing to TRAEs experienced a notable DOR and treatment-free period after discontinuation of the regimen; approximately 40% of patients remained in response, and a similar proportion were treatment free 2 years after discontinuation. Although any assessment of the impact of one treatment outcome (discontinuation owing to TRAEs) on another (OS and other efficacy end points) is subject to time bias, this analysis addresses an important clinical question.

This large, pooled population also provided an opportunity for robust analyses of the subgroup of patients aged 75 years or older, which has not been feasible in individual studies owing to small sample sizes. Of note, a numerically higher proportion of patients aged 75 years or older had an ECOG PS of 1 (72%) compared with the overall pooled population (61%). Nevertheless, rates of TRAEs and IMAEs with nivolumab plus ipilimumab in these patients were similar to the overall patient population. Although the incidences of grade 3 or 4 TRAEs, serious TRAEs, and discontinuation owing to TRAEs were somewhat higher among patients aged 75 years or older, the results indicate a generally consistent and manageable safety profile for this treatment regimen across age groups. As with the overall population, most nonendocrine IMAEs resolved, suggesting these events are manageable in this patient population. Patients aged 75 years or older who discontinued nivolumab plus ipilimumab treatment owing to TRAEs also had OS benefits similar to the overall pooled population.

As reported previously,<sup>8</sup> CheckMate 227 part 1 not only assessed nivolumab plus ipilimumab but also

provided the opportunity to compare different nivolumab-based regimens within one study. Other regimens assessed were nivolumab monotherapy and nivolumab plus chemotherapy, with safety data from a 4-year follow-up recently reported.<sup>30</sup> In the pooled nivolumab plus ipilimumab population, modest relative increases in IMAEs were observed compared with the nivolumab monotherapy or nivolumab plus chemotherapy arms of CheckMate 227. For example, the most common grade 3 or 4 IMAEs in the pooled analysis were hepatitis (5%), diarrhea/colitis (4%), and pneumonitis (4%); the equivalent incidences with nivolumab monotherapy were 4%, 1%, and 2%, respectively, and for nivolumab plus chemotherapy were 2%, 1%, and 3%, respectively.<sup>30</sup> Nevertheless, most IMAEs with nivolumab plus ipilimumab were low grade and resolved (except endocrine events), similar to the patterns observed across the immunotherapy-containing arms of CheckMate 227. IMAE management with nivolumab plus ipilimumab in this pooled analysis was similar to previously reported findings with nivolumab monotherapy or nivolumab plus chemotherapy in CheckMate 227; across immunotherapy-containing regimens, very few patients required immunomodulating agents beyond systemic corticosteroids and the duration of corticosteroid use was relatively short (median <5 wk).<sup>30</sup> Slightly higher incidences of any-grade and grade 3 or 4 TRAEs were observed in patients treated with nivolumab plus ipilimumab in this pooled analysis (78% and 34%, respectively) compared with the nivolumab monotherapy arm of CheckMate 227 (66% and 20%); notably, TRAEs with nivolumab plus ipilimumab in our pooled analysis were less frequent than with nivolumab plus chemotherapy (92% and 56%).<sup>30</sup>

Identifying patient risk factors for specific adverse events is an important clinical question to improve benefit-risk assessments for individual patients. Despite the large sample size in this pooled analysis, the number of patients experiencing any individual adverse event (preferred term) of clinical interest remained small, limiting a detailed analysis of risk factors. This remains an area for future research in prospective studies and real-world data sets.

Since the first approval of nivolumab plus ipilimumab for metastatic melanoma, the optimization of the dosing regimen for various tumor types has been important for clinical management of TRAEs. Across the three studies in this pooled safety analysis, ipilimumab was consistently dosed at 1 mg/kg Q6W. This dosing regimen was first found to be tolerable in combination with nivolumab for treating patients with NSCLC in a phase 1 study that investigated several dosing regimens of nivolumab plus ipilimumab.<sup>41</sup> A limitation of our study is that different nivolumab dosing regimens were used across the individual studies in this pooled population (flat dose

versus weight based), where pharmacokinetic modeling has revealed that exposure, safety, and efficacy of flat-dose nivolumab are similar to weight-based dosing.<sup>42</sup> In addition, as the pooled analyses included patients from single-arm studies (CheckMate 817 and CheckMate 568), there was no pooled comparator arm available to directly evaluate alongside nivolumab plus ipilimumab combination therapy; TRAEs from the chemotherapy arm of CheckMate 227 have been included for additional context. Finally, this pooled analysis was performed retrospectively and was not statistically powered. Of note, our post hoc analysis had a median duration of therapy of 4.1 months, and per protocol, safety follow-up after treatment discontinuation was 100 days. As such, robust conclusions regarding longer-term safety of nivolumab plus ipilimumab are beyond the scope of this analysis.

In conclusion, this large, pooled safety analysis of nivolumab plus ipilimumab reveals that this combination immunotherapy regimen provides a manageable safety and tolerability profile in patients with metastatic NSCLC, consistent with the individual studies. Safety was generally consistent regardless of age or tumor histology, and treatment discontinuation owing to TRAEs had no negative effect on survival outcomes.

## CRediT Authorship Contribution Statement

**Luis G. Paz-Ares:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Tudor-Eliade Ciuleanu:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Adam Pluzanski:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Jong-Seok Lee:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Justin F. Gainor:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Gregory A. Otterson:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Clarisse Audigier-Valette:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Neal Ready:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Michael Schenker:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Helena Linardou:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Reyes Bernabe Caro:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Mariano Provencio:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Bogdan Zurawski:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Ki Hyeong Lee:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Sang-We Kim:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Claudia Caserta:** Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Suresh S. Ramalingam:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**David R. Spiegel:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Julie R. Brahmer:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Martin Reck:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Kenneth J. O'Byrne:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

**Nicolas Girard:** Conceptualization, Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Sanjay Popat:** Conceptualization, Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Solange Peters:** Conceptualization, Validation, Investigation, Resources, Data curation, Writing—review and editing.

**Arteid Memaj:** Software, Formal Analysis, Data curation, Writing—review and editing, Visualization.

**Faith Nathan:** Conceptualization, Methodology, Validation, Data curation, Writing—review and editing, Visualization, Supervision, Project administration, Funding acquisition.

**Nivedita Aanur:** Validation, Data curation, Writing—review and editing, Visualization, Supervision, Project administration, Funding acquisition.

**Hossein Borghaei:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing, Supervision.

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## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at [www.jto.org](http://www.jto.org) and at <https://doi.org/10.1016/j.jtho.2022.08.014>.

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