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ORIGINAL ARTICLE

Long-term survival with first-line nivolumab plus ipilimumab in patients with advanced non-small-cell lung cancer: a pooled analysis

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Background: First-line nivolumab plus ipilimumab prolongs survival versus chemotherapy in advanced non-small-cell lung cancer (NSCLC). We further characterized clinical benefit with this regimen in a large pooled patient population and assessed the effect of response on survival.

Patients and methods: Data were pooled from four studies of first-line nivolumab plus ipilimumab in advanced NSCLC (CheckMate 227 Part 1, 817 cohort A, 568 Part 1, and 012). Overall survival (OS), progression-free survival (PFS), objective response rate, duration of response, and safety were assessed. Landmark analyses of OS by response status at 6 months and by tumor burden reduction in responders to nivolumab plus ipilimumab were also assessed.

Results: In the pooled population ($N = 1332$) with a minimum follow-up of 29.1-58.9 months, median OS was 18.6 months, with a 3-year OS rate of 35%; median PFS was 5.4 months (3-year PFS rate, 17%). Objective response rate was 36%; median duration of response was 23.7 months, with 38% of responders having an ongoing response at 3 years. In patients with tumor programmed death-ligand 1 (PD-L1) $<1\%$, $\geq 1\%$, 1%-49%, or $\geq 50\%$, 3-year OS rates were 30%, 38%, 30%, and 48%. Three-year OS rates were 30% and 38% in patients with squamous or non-squamous histology. Efficacy outcomes in patients aged ≥ 75 years were similar to the overall pooled population (median OS, 20.1 months; 3-year OS rate, 34%). In the pooled population, responders to nivolumab plus ipilimumab at 6 months had longer post-landmark OS than those with stable or progressive disease; 3-year OS rates were 66%, 22%, and 14%, respectively. Greater depth of response was associated with prolonged survival; in patients with tumor burden reduction $\geq 80\%$, 50% to $<80\%$, or 30% to $<50\%$, 3-year OS rates were 85%, 72%, and 44%, respectively. No new safety signals were identified in the pooled population.

Conclusion: Long-term survival benefit and durable response with nivolumab plus ipilimumab in this large patient population further support this first-line treatment option for advanced NSCLC.

Key words: NSCLC, dual immunotherapy, nivolumab, ipilimumab

INTRODUCTION

First-line immunotherapy with programmed death (ligand) 1 [PD-(L)1]-blocking antibodies as single agents or in combination with other treatment modalities has improved overall survival (OS) for patients with advanced non-small-cell lung cancer (NSCLC) with no targetable genomic driver

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alterations.[1-8] Notably, dual immunotherapy with nivolumab, a fully human anti-programmed cell death protein 1 (anti-PD-1) antibody, and ipilimumab, a fully human anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibody, has shown durable survival benefit with a manageable safety profile across several tumor types, including NSCLC.[9-12]

The randomized phase III CheckMate 227 Part 1 study (NCT02477826) demonstrated significant OS benefit with nivolumab plus ipilimumab versus chemotherapy in patients with advanced NSCLC and tumor programmed death-ligand 1 (PD-L1) expression level ≥1% (primary endpoint); progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) also favored nivolumab plus ipilimumab.[11] Similar clinical benefit with nivolumab plus ipilimumab was also observed in patients with tumor PD-L1 expression level <1% (prespecified descriptive analysis).[11] These findings led to approval of nivolumab plus ipilimumab in the United States and other countries as first-line treatment for adult patients with metastatic NSCLC expressing tumor PD-L1 ≥1% with no *EGFR* or *ALK* genomic tumor aberrations, and in some countries as first-line treatment regardless of tumor PD-L1 expression level.[13-15] Nivolumab plus ipilimumab is also recommended by National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology (NCCN Guidelines®) and European Society for Medical Oncology guidelines as a first-line treatment option for eligible patients with metastatic NSCLC with either PD-L1 ≥1% or <1%.[16-18] Recent 5-year results of CheckMate 227 Part 1, representing the longest survival follow-up reported to date among randomized phase III trials assessing first-line immunotherapy combinations in advanced NSCLC, have shown that nivolumab plus ipilimumab provides durable and long-term clinical benefit versus chemotherapy.[19] Furthermore, single-arm studies, including the phase IIIb CheckMate 817 study cohort A (NCT02869789), phase II CheckMate 568 Part 1 study (NCT02659059), and phase I CheckMate 012 study (NCT01454102), have also demonstrated the efficacy of first-line nivolumab plus ipilimumab in advanced NSCLC.[20-23]

Here, we report the efficacy of first-line nivolumab plus ipilimumab treatment in a large, pooled population of patients with advanced NSCLC from CheckMate 227 Part 1, CheckMate 817 (cohort A), CheckMate 568 Part 1, and CheckMate 012 (arms P and Q). We also evaluated efficacy in patients aged ≥75 years, a patient population of high clinical interest. The impact of response status and depth of response on OS in this pooled population was also evaluated.

PATIENTS AND METHODS

Study design and data collection

Study designs, eligibility criteria, and primary outcomes from CheckMate 227 Part 1, 817 cohort A, 568 Part 1, and 012 have been previously reported and are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.11.006.[11,23-25] To analyze long-term efficacy outcomes in patients with advanced NSCLC, data from those treated with first-line nivolumab plus ipilimumab in the four studies were pooled.

All four studies included adult patients with no prior systemic therapy for advanced disease, squamous or non-squamous stage IV or recurrent NSCLC (per 7th International Association for the Study of Lung Cancer classification), an Eastern Cooperative Oncology Group performance status of 0 or 1, and tumor samples available for PD-L1 evaluation (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.11.006). In the CheckMate 227 Part 1 study, patients with tumor PD-L1 expression level ≥1% were randomized 1:1:1 to nivolumab [3 mg/kg every 2 weeks (Q2W)] plus ipilimumab [1 mg/kg every 6 weeks (Q6W)], nivolumab monotherapy (240 mg Q2W), or chemotherapy [every 3 weeks (Q3W) for ≤4 cycles]; patients with tumor PD-L1 expression level <1% were randomized 1:1:1 to nivolumab (3 mg/kg Q2W) plus ipilimumab (1 mg/kg Q6W), nivolumab (360 mg Q3W) plus chemotherapy (Q3W for ≤4 cycles), or chemotherapy alone.[11] In the single-arm studies, patients received nivolumab (240 mg Q2W) plus ipilimumab (1 mg/kg Q6W) in cohort A of the phase IIIb CheckMate 817 study,[24] nivolumab (3 mg/kg Q2W) plus ipilimumab (1 mg/kg Q6W) in the phase II CheckMate 568 Part 1 study,[23] and nivolumab (3 mg/kg Q2W) plus ipilimumab [1 mg/kg Q6W or every 12 weeks (Q12W)] in cohorts P and Q of the phase I CheckMate 012 study.[25] Treatment with nivolumab plus ipilimumab continued until disease progression, unacceptable toxicity, or for up to 2 years, except in CheckMate 012, in which treatment was not limited to 2 years.

The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. The independent ethics committee or institutional review board of each participating study center 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.

Endpoints and assessments

All endpoints in this *post hoc* analysis were exploratory; assessments were made in all treated patients in the pooled population. OS was assessed in the pooled population overall, by tumor PD-L1 expression level, and by histology. PFS, ORR, best overall response (BOR), and DOR were assessed using RECIST v1.1 per investigator assessment in the pooled population.

To assess the effect of response status on subsequent long-term OS with nivolumab plus ipilimumab, we conducted OS analysis from a 6-month landmark in patients categorized by response status [complete/partial response (CR/PR), stable disease (SD), progressive disease (PD)] at the 6-month time point, as has been previously described for a pooled analysis with nivolumab monotherapy in patients with previously treated advanced NSCLC.[26] Landmark analyses aim to reduce the immortal time bias that can lead to overestimation of the effect of response on survival. Patients without a radiographic tumor assessment at

6 months due to death or loss to follow-up were not included in the analyses. In the landmark analyses, response categories were based on information at 6 months only, in contrast to BOR, which was based on all data from study follow-up. The 6-month time point was chosen because most of the responses in each treatment arm occurred within that period and were ongoing at 6 months; few responses occurred after this time point.

In a separate analysis of OS by BOR (best response was recorded from the start of the study treatment throughout the entire duration of study follow-up) and depth of response, patients were categorized as responders (CR/PR; response-evaluable patients were those with baseline and at least one on-treatment tumor assessment) or non-responders (SD or PD). Responders were further grouped by depth of response, defined as best change from baseline in tumor burden (30% to <50%, 50% to <80%, or ≥80% reduction in the sum of the diameters of target lesions), as per a similar analysis conducted earlier with the CheckMate 227 study.[27] Best reduction was based on evaluable target lesion measurements up to progression or start of subsequent anticancer therapy.

Treatment-related adverse events (TRAEs) were assessed in the pooled population and included all events reported from the time of the first dose to 30 days after the last dose of study drug. Immune-mediated adverse events (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 (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events considered to be potential immune-mediated events by the investigator, regardless of causality, that occurred within 100 days of the last dose, with no clear alternative etiology 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 since endocrine drug reactions are often managed without these medications.

Statistical analysis

Analysis methods for survival curves, rates for time-to-event endpoints, hazard ratios (HRs), and objective response have been previously described.[11,26,28] Survival curves and rates for time-to-event endpoints (OS, PFS, and DOR) were estimated using Kaplan—Meier methodology. Exact two-sided 95% confidence intervals (CIs) for ORRs were calculated using the Clopper—Pearson method. The methodology for analyzing the effect of response status on OS for nivolumab plus ipilimumab in the pooled population was previously described.[26] HRs and CIs for OS in responders versus non-responders (in the analysis of OS by BOR and depth of response) were estimated using a Cox proportional hazards model with the time to tumor reduction category as a time-dependent covariate to account for the difference in time taken to reach a given response.

RESULTS

Patients and treatment

A total of 1332 patients were treated with first-line nivolumab plus ipilimumab across the four studies included in the analysis [CheckMate 227 Part 1, CheckMate 817 cohort A, CheckMate 568 Part 1, and CheckMate 012 (arms P and Q)]. Baseline characteristics of the pooled population are shown in Table 1 and were largely similar between individual studies (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.11.006).

Median duration of nivolumab plus ipilimumab treatment was 4.2 months (range, 0-56.1 months) in the pooled population (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.11.006). Minimum follow-up for OS was 36.6, 29.1, 36.0, and 58.9 months, respectively, in CheckMate 227 Part 1, CheckMate 817 cohort A, CheckMate 568 Part 1, and CheckMate 012. Subsequent therapy received in the pooled population is shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.11.006.

Efficacy of nivolumab plus ipilimumab

Median OS in all patients treated with nivolumab plus ipilimumab in the pooled population was 18.6 months

Table 1. Demographics and baseline characteristics of patients treated with nivolumab plus ipilimumab (pooled patient population)

	Pooled patient population (*N* = 1332)
Age, median (range), years	65 (26-91)
Age ≥75 years	186 (14.0)
Female	524 (39.3)
ECOG PS	
0	507 (38.1)
1	817 (61.3)
≥2	8 (0.6)
Smoking status[a]	
Current/former smoker	1173 (88.1)
Never smoker	147 (11.0)
Tumor histology[b]	
Non-squamous	971 (72.9)
Squamous	360 (27.0)
Tumor PD-L1 expression level[c]	
<1%	505 (40.2)
≥1%	752 (59.8)
1%-49%	401 (31.9)
≥50%	351 (27.9)
Metastasis	
Brain[d]	130 (9.8)
Liver[d]	159 (11.9)
Bone[d]	106 (8.0)
LIPI score	
Poor	104 (7.8)
Intermediate	363 (27.3)
Good	460 (34.5)
Not reported	405 (30.4)

Data presented as *n* (%) unless otherwise indicated.
ECOG PS, Eastern Cooperative Oncology Group performance status; LIPI, Lung Immune Prognostic Index; PD-L1, programmed death-ligand 1.
[a]Unknown smoking status (*n* = 11); unreported smoking status (*n* = 1).
[b]Histology not reported for one patient.
[c]Calculated as a percentage of quantifiable patients (*n* = 1257).
[d]Per blinded independent central review.

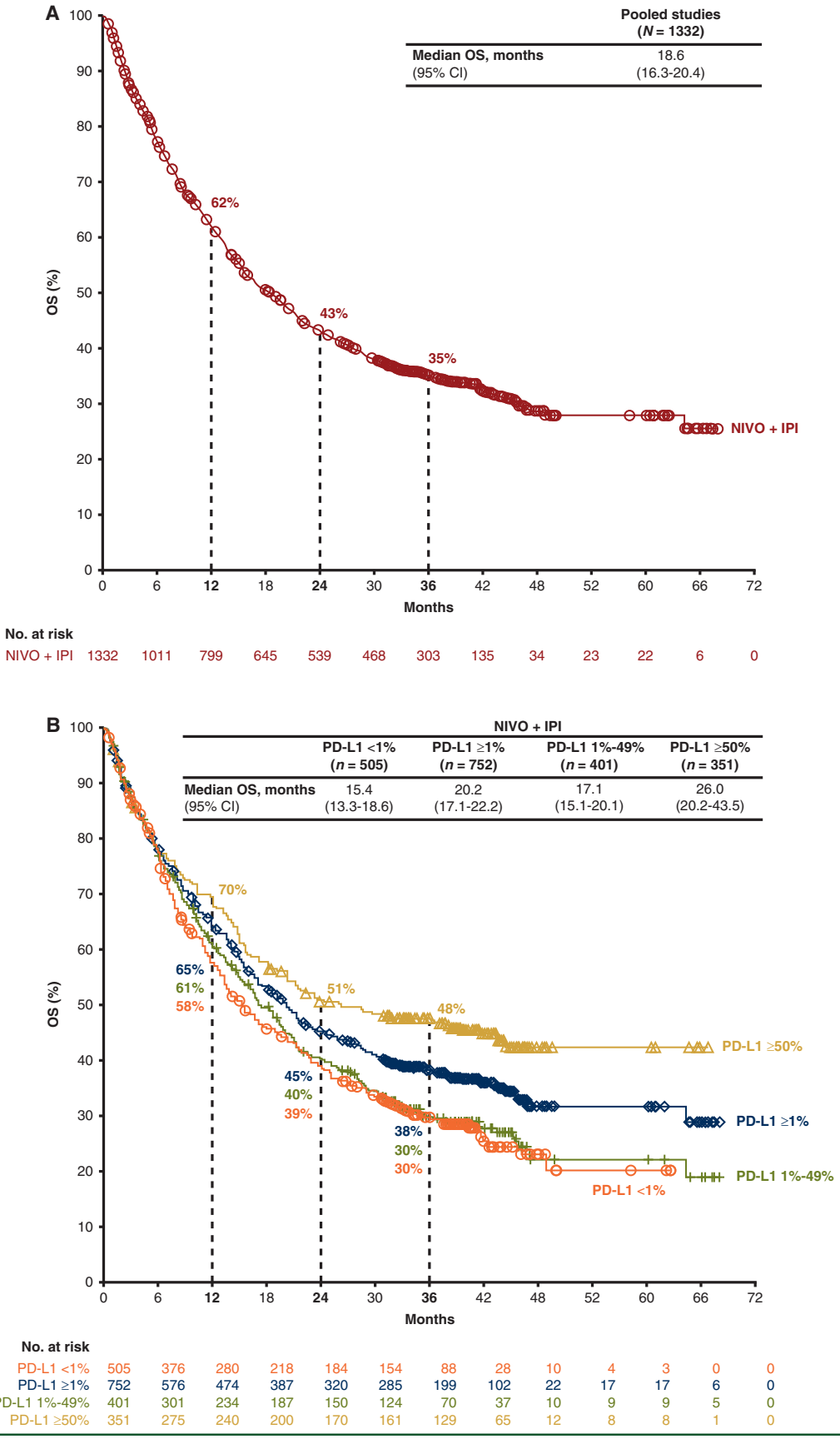

Figure 1. OS in the pooled patient population treated with nivolumab plus ipilimumab. Kaplan—Meier estimates of OS in (A) all patients, (B) all patients by tumor PD-L1 expression level, and (C) all patients by tumor histology.
CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival, PD-L1, programmed death-ligand 1.

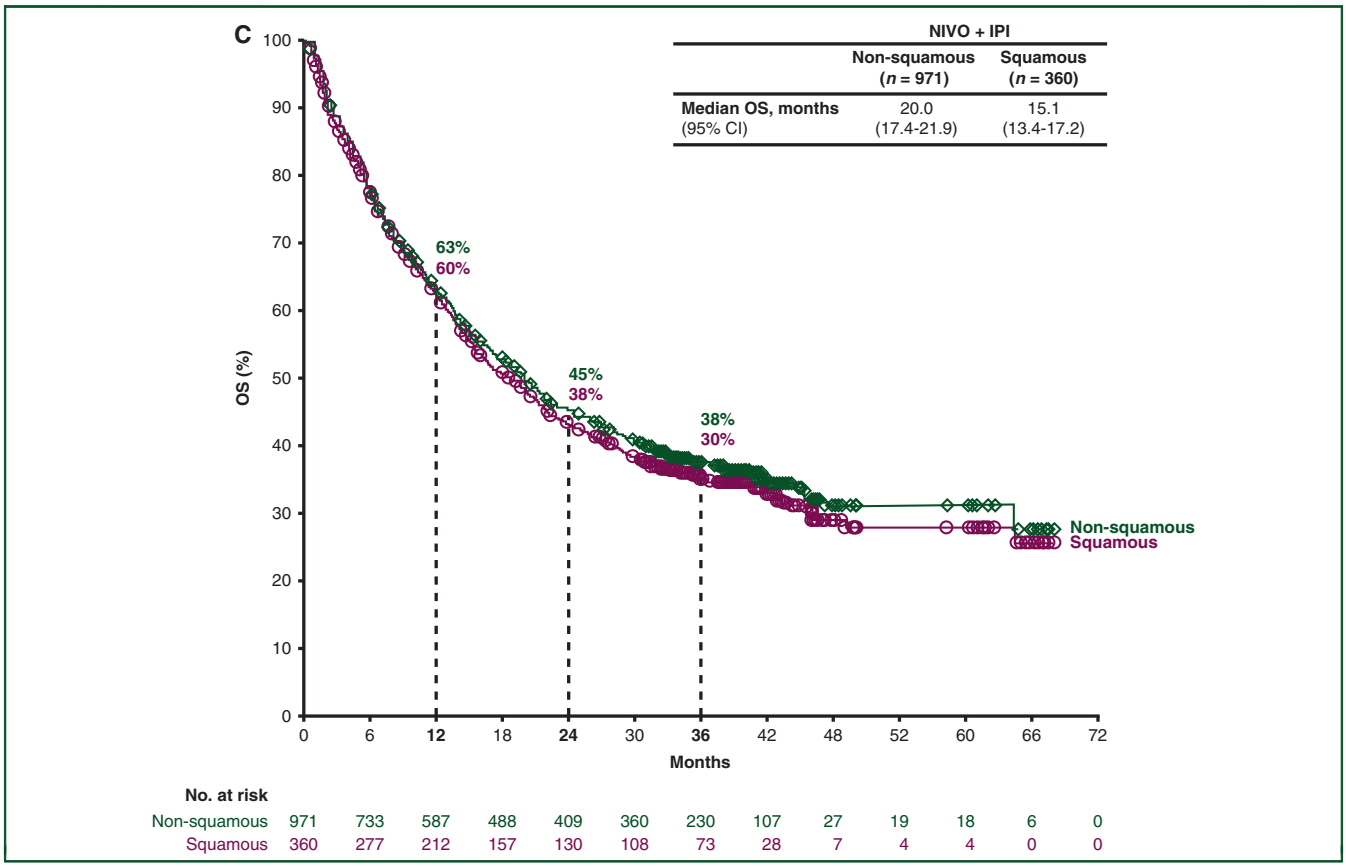

Figure 1. Continued

(95% CI 16.3-20.4 months), with a 3-year OS rate of 35% (95% CI 33% to 38%) (Figure 1A). OS with nivolumab plus ipilimumab in the pooled patient population was consistent with OS reported in the individual studies in this analysis (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.11.006). Notably, in CheckMate 012, which had the longest survival follow-up, the 5-year OS rate was 34%. In the pooled population, median OS was 15.4, 20.2, 17.1, and 26.0 months in patients with tumor PD-L1 expression level <1%, ≥1%, 1%-49%, and ≥50%, respectively; 3-year OS rates were 30%, 38%, 30%, and 48% (Figure 1B). Median OS was 15.1 and 20.0 months in patients with squamous and non-squamous histology, respectively, with 3-year OS rates of 30% and 38% (Figure 1C).

Median PFS in the pooled study population was 5.4 months (95% CI 4.9-5.7 months), with a 3-year PFS rate of 17% (95% CI 15% to 20%) (Figure 2A). The ORR was 36%, and median DOR was 23.7 months (95% CI 18.7-28.1 months); among responders, 38% (95% CI 33% to 43%) had an ongoing response at 3 years (Figure 2B). PFS, ORR, BOR, and DOR across tumor histologies and tumor PD-L1 expression levels are shown in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.11.006.

Efficacy in patients aged ≥75 years

Efficacy outcomes in patients aged ≥75 years ($n = 186$) were similar to those in the overall pooled population. Median OS in these patients was 20.1 months (95% CI 14.7-26.9 months), with a 3-year OS rate of 34% (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.11.006). Median PFS was 6.9 months (95% CI 5.2-9.8 months), and the 3-year PFS rate was 15% (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.11.006). The ORR was 37%; among responders, median DOR was 18.7 months (95% CI 12.5-24.1 months) and 30% had an ongoing response at 3 years.

Characterization of patients with clinical benefit

To identify characteristics that may be predictive of long-term clinical benefit, baseline characteristics were compared in patients who were either alive or free of progression at ≥2 or <2 years after the first dose, or responders (in response ≥2 years or <2 years) and non-responders. Characteristics were found to be generally consistent across these groups and the overall population (Supplementary Tables S7-S9, available at https://doi.org/10.1016/j.annonc.2022.11.006).

Impact of response on survival in patients treated with nivolumab plus ipilimumab

In the landmark analysis of OS based on response status at 6 months, 1002 (75%) of 1332 pooled patients treated with nivolumab plus ipilimumab were included; 467 (47%) patients had CR/PR, 362 (36%) had SD, and 173 (17%) had PD.

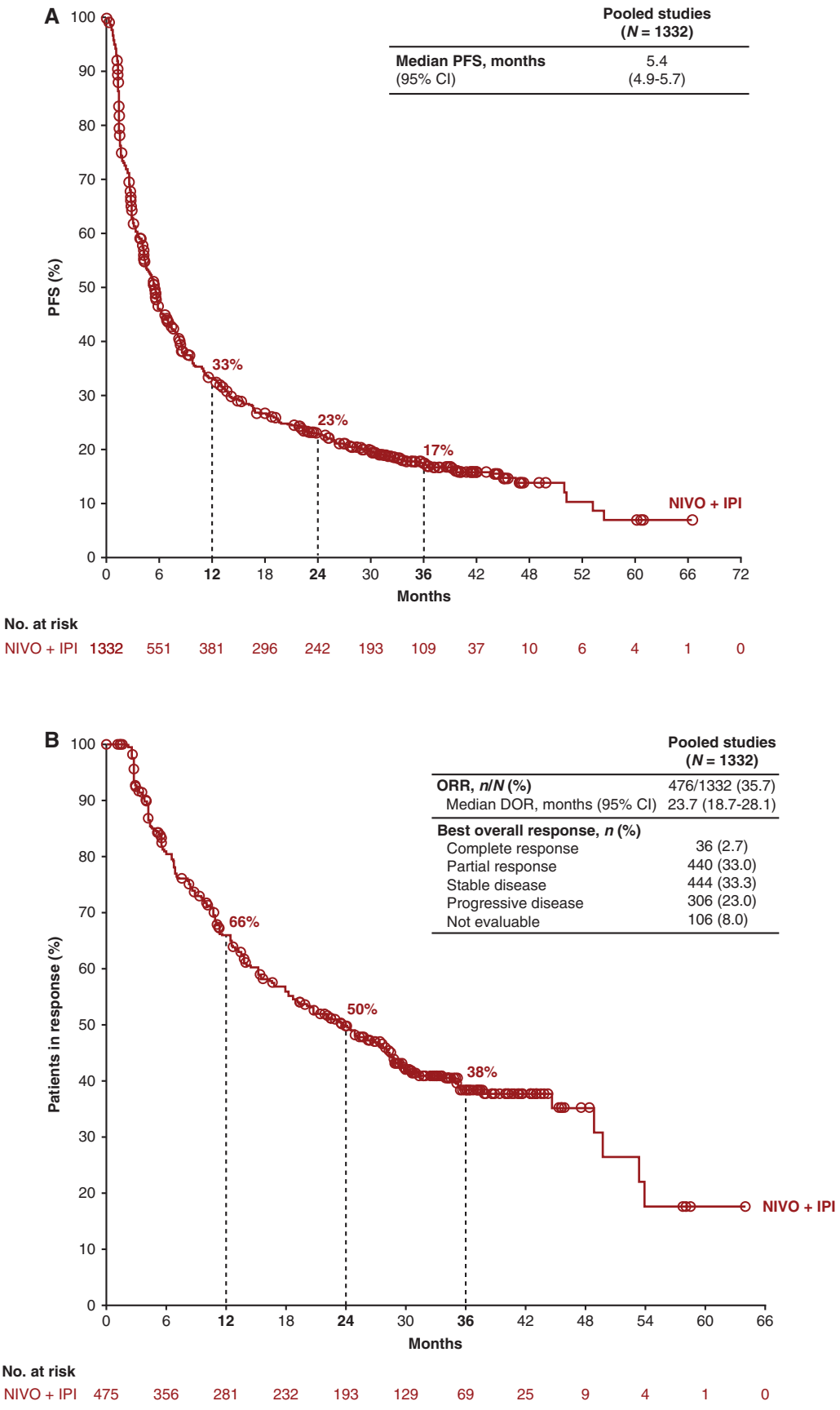

Figure 2. PFS, ORR, and DOR. Kaplan–Meier estimates of (A) PFS and (B) DOR in the pooled patient population (per investigator assessment) treated with nivolumab plus ipilimumab. Kaplan–Meier estimates of DOR and associated numbers of patients at risk represent patients with no missing response dates. ORR per investigator assessment in all patients in the pooled population is also shown.

CI, confidence interval; DOR, duration of response; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PFS, progression-free survival.

Of the 330 patients not included in the analysis, most were non-evaluable or had died before 6 months (Figure 3). Patients who were responders (CR/PR) at 6 months had longer subsequent OS than non-responders (SD/PD). Median OS was not reached, and the 3-year post-landmark OS rate (42 months after the first dose) was 66% in patients with CR/PR. In patients with SD and PD, median OS was 13.4 and 8.1 months, respectively; 3-year OS rates post-landmark were 22% and 14% (Figure 3A). OS was improved in responders versus those with SD/PD at 6 months regardless of tumor PD-L1 expression level (Figure 3B and C).

Analysis of OS by BOR (assessed throughout the entire follow-up duration of the study) and depth of response in the pooled patient population showed that responders (CR/PR) had improved survival with nivolumab plus ipilimumab compared with non-responders (SD/PD); additionally, responders with greater tumor burden reduction based on RECIST v1.1 had better OS (Figure 4A). Among all response-evaluable patients ($N = 1162$) in the pooled patient population, 119 (10%), 236 (20%), and 121 (10%) patients (responders) had $\geq$80%, 50% to <80%, and 30% to <50% reductions in tumor burden, respectively (Figure 4A). Median OS was not reached in responders with $\geq$80% or 50% to <80% reduction in tumor burden, and was 30.4 months in responders with 30% to <50% reduction; OS rates at 3 years were 85%, 72%, and 44%, respectively. HRs for OS in responders (in the three depth-of-response categories) compared with non-responders (SD/PD) were 0.16, 0.21, and 0.44, respectively. This trend was observed regardless of tumor PD-L1 expression level (Figure 4B and C).

Safety

Safety data with nivolumab plus ipilimumab in the pooled population was consistent with previously reported results in individual studies, with no new safety signals (Table 2). Overall, grade 3 or 4 TRAEs occurred in 459 (34%) patients, serious TRAEs (any grade) occurred in 315 (24%) patients, and TRAEs (any grade) leading to discontinuation occurred in 277 (21%) patients (Table 2). Treatment-related deaths were reported in 17 (1%) patients in the pooled population. The most common IMAEs (any grade) were rash and hypothyroidism/thyroiditis, reported in 248 (19%) and 191 (14%) patients, respectively (Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2022.11.006). Treatment exposure was 969.1 person-years with nivolumab plus ipilimumab in the pooled patient population. The overall incidence rate of TRAEs per 100 person-years was 580.3 (Supplementary Table S11, available at https://doi.org/10.1016/j.annonc.2022.11.006).

DISCUSSION

To our knowledge, this is the largest survival analysis of any first-line anti-PD-(L)1 immunotherapy combination in advanced NSCLC published to date, with a pooled population of 1332 patients and a minimum follow-up of 29.1-58.9 months across studies. The efficacy analysis in this pooled population highlights the durable long-term survival with nivolumab plus ipilimumab, with more than one-third of the patients alive at 3 years and a median DOR of almost 2 years. Similar to the overall pooled population, OS benefit with nivolumab plus ipilimumab was also observed in patients aged $\geq$75 years, a patient population of high clinical interest. The safety profile in the pooled population was consistent with previous reports, with no new safety signals.[11,23-25] Additionally, a detailed analysis of safety in a patient population ($N = 1225$) pooled from three of the studies utilized in the current report (CheckMate 227 Part 1, CheckMate 817 cohort A, and CheckMate 568 Part 1) showed that first-line nivolumab plus ipilimumab was well tolerated in the large overall population as well as in patients aged $\geq$75 years.[29]

The results of the pooled analyses were consistent with those of the individual studies, in particular, the randomized, controlled, phase III CheckMate 227 study, which allows for comparison of treatment outcomes with nivolumab plus ipilimumab versus chemotherapy and other nivolumab-based regimens. In CheckMate 227 as recently reported, after a minimum follow-up of 5 years, nivolumab plus ipilimumab continues to demonstrate clinically meaningful and sustained efficacy improvements over chemotherapy, regardless of tumor PD-L1 expression level or histology.[19]

Long-term OS benefit observed with nivolumab plus ipilimumab in previously untreated patients with advanced NSCLC in this pooled analysis is consistent with long-term survival observed with dual immunotherapy regimens across other tumor types, including untreated advanced melanoma (minimum follow-up, 7.5 years) and advanced renal cell carcinoma (minimum follow-up, 5 years).[30,31] This durable benefit may reflect the biological effect of ipilimumab in induction of *de novo* antitumor T-cell responses and memory T cells.[32,33] A notable example of this was the impressive 5-year OS rate of 34% with nivolumab plus ipilimumab observed in CheckMate 012 in the current analysis regardless of PD-L1 expression level, which was similar to that reported with pembrolizumab monotherapy in a PD-L1-enriched population (PD-L1 $\geq$50%), although cross-trial comparisons are limited by various factors and caution should be used around interpretation.[34] Although in the current pooled analysis, patients with tumor PD-L1 expression level $\geq$1% and $\geq$50% seemed to have a numerically longer median OS and higher 3-year OS rates than those with tumor PD-L1 expression level <1%, it is important to note that clinical benefit with nivolumab plus ipilimumab versus chemotherapy has been observed regardless of PD-L1 expression level in the randomized, controlled, phase III CheckMate 227 study (median OS with nivolumab plus ipilimumab, 17.1 and 17.4 months in the PD-L1 $\geq$1% and <1% groups, respectively).[19] Moreover, results reported in the overall population in CheckMate 227 Part 1 at 5 years support the long-term and durable benefit of nivolumab plus ipilimumab, as illustrated by the prolonged DOR versus chemotherapy; despite similar ORRs (33% versus 28%), median DOR was notably longer

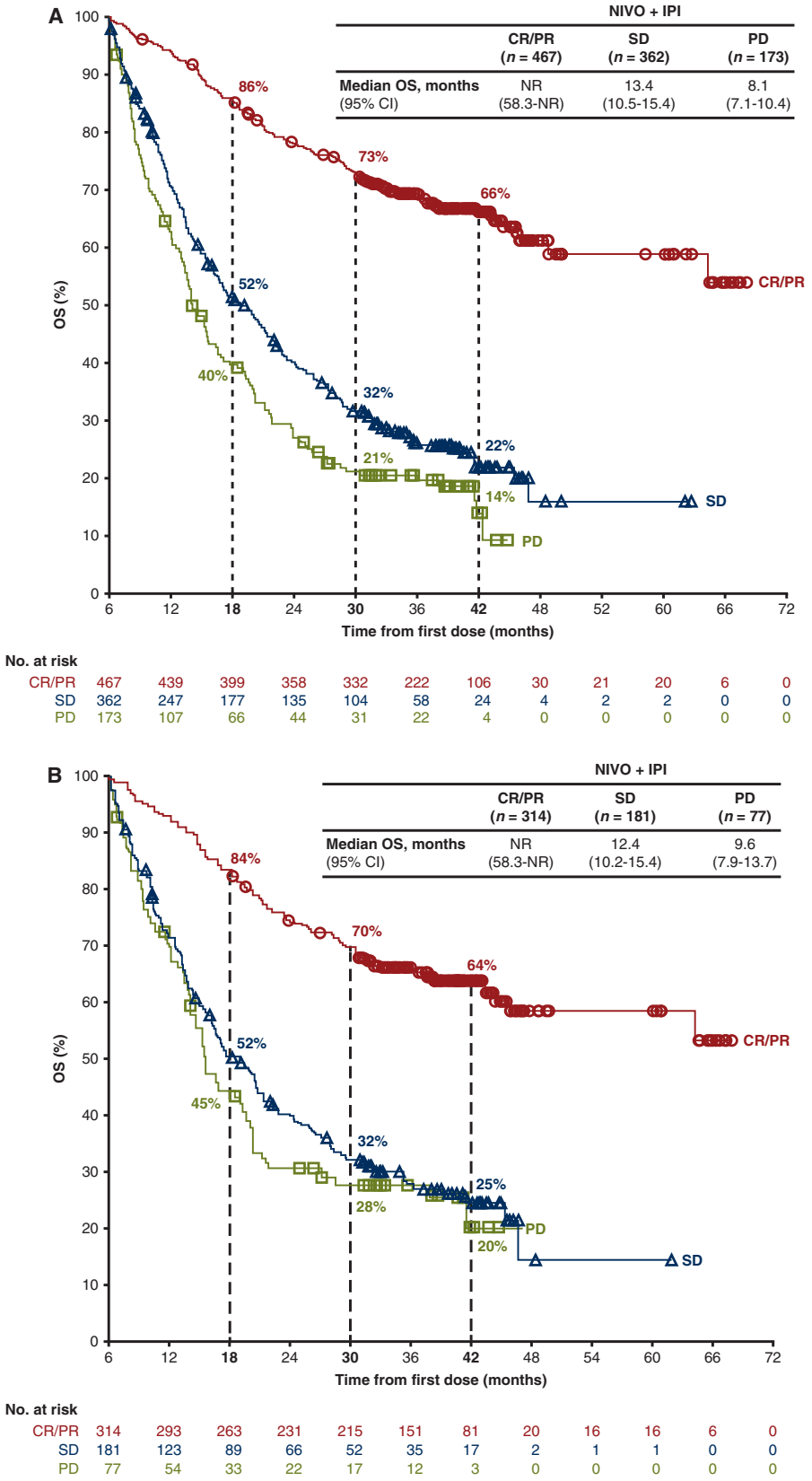

Figure 3. OS landmark analysis by BOR at 6 months (per investigator assessment) in (A) all patients in the pooled population[a] and in patients with tumor PD-L1 expression level (B) ≥1% or (C) <1%. Kaplan—Meier estimates of OS are shown from the time of the landmark response at 6 months.

BOR, best overall response; CI, confidence interval; CR, complete response; IPI, ipilimumab; NIVO, nivolumab; NR, not reached; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

[a]Of the 330 patients treated with nivolumab plus ipilimumab in the pooled population who were excluded from this analysis, 106 patients were not assessable, 194 had died before 6 months, 18 withdrew consent, 9 were lost to follow-up, and 3 were excluded for other reasons.

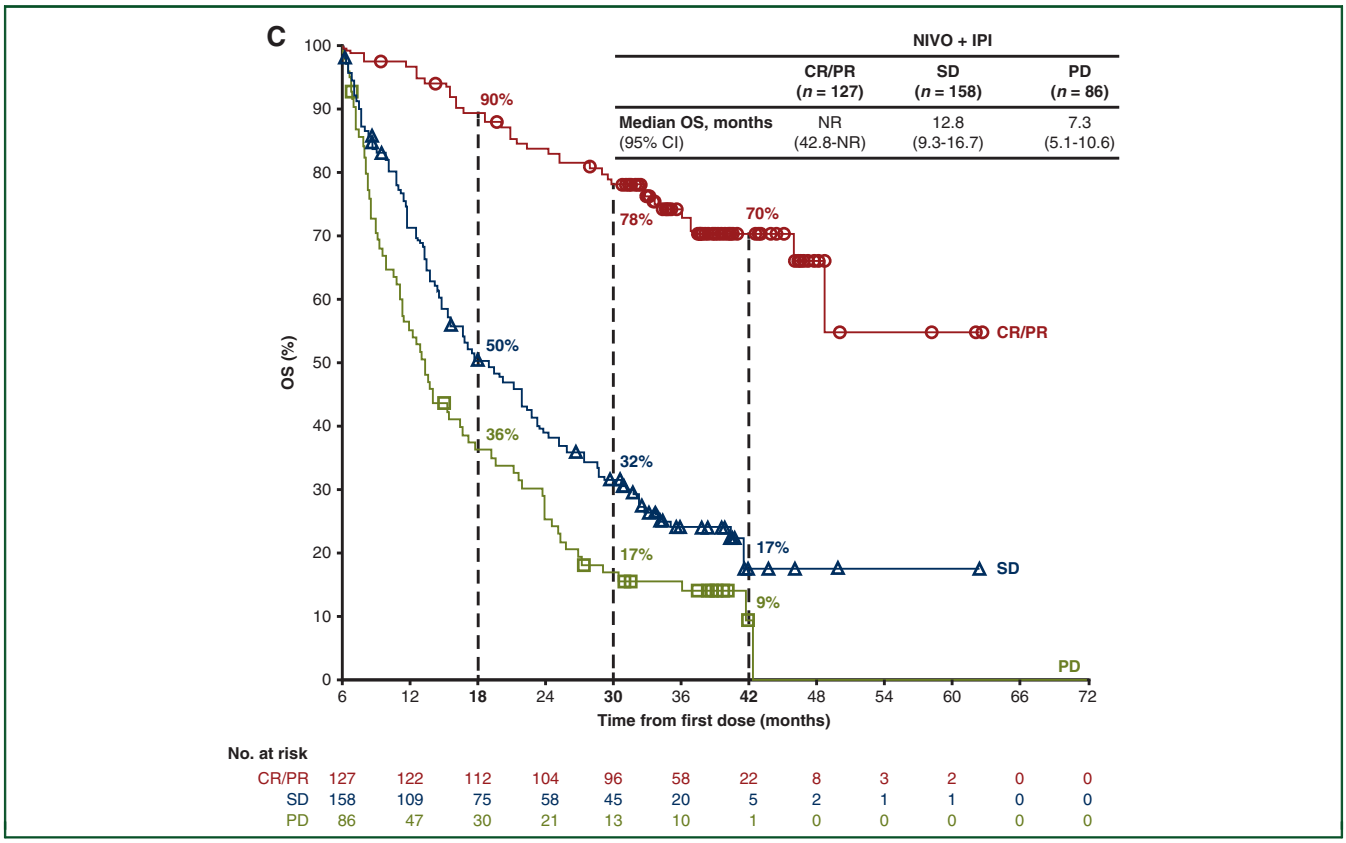

Figure 3. **Continued**

(21.7 months versus 5.8 months), with more patients having an ongoing response at 5 years (27% versus 3%). Whereas recent data from a randomized phase III study in NSCLC showed no incremental clinical benefit with the addition of ipilimumab to pembrolizumab as first-line therapy (in patients with PD-L1 expression level ≥50%),[35] OS data in this study were limited by the relatively short follow-up (minimum follow-up, 12.4 months), and additional follow-up may be needed to determine the long-term clinical benefit of combining CTLA-4 inhibitors with PD-1 inhibitors.

This pooled efficacy analysis provided an opportunity to investigate the association between response and subsequent OS in a large patient population with advanced NSCLC treated with first-line nivolumab plus ipilimumab. When assessing the impact of one future outcome (response) on another (OS), immortal time bias must be considered. Therefore, two analyses using different methods to minimize this bias were carried out. The OS landmark analysis carried out in patients who were alive at a 6-month time point showed that patients with CR/PR to nivolumab plus ipilimumab at 6 months after the first dose had improved subsequent OS versus those with SD/PD. Complementing the OS landmark analysis were the analyses of OS by BOR, which also showed that responders to nivolumab plus ipilimumab had better OS than non-responders. Furthermore, responders with higher tumor burden reduction from baseline derived prolonged OS benefit. These results were consistent with earlier findings from CheckMate 227, in which achievement of CR/PR at a 6-month landmark was associated with improved subsequent OS and responders with higher tumor burden reduction from baseline had greater long-term OS benefit in all treatment arms.[27,36] However, these associations observed in CheckMate 227 were more pronounced with nivolumab plus ipilimumab compared with chemotherapy, which suggested a long-term survival advantage associated with greater DOR in this dual immunotherapy regimen compared with chemotherapy.

The current standard of care in previously untreated patients with advanced NSCLC without targetable mutations is immunotherapy with or without chemotherapy, with treatment selection in clinical practice largely based on tumor PD-L1 expression level and histology. Patients with squamous or non-squamous histology and tumor PD-L1 ≥50% are frequently treated with anti-PD-(L)1 monotherapy, whereas patients with high disease burden or lower levels of tumor PD-L1 expression usually receive immunotherapy plus chemotherapy.[1-4,7,16,18,37] Although immunotherapy plus chemotherapy is an approved regimen in patients with tumor PD-L1 expression levels ≥1% and <1%, long-term outcomes are lower in patients with tumor PD-L1 <1%.[2,3,6,16,18,38] Data from this large pooled analysis support the clinically meaningful efficacy improvements, such as the durable survival benefit observed previously with nivolumab plus ipilimumab across tumor PD-L1 expression levels and histologies,[11,19] including in patients

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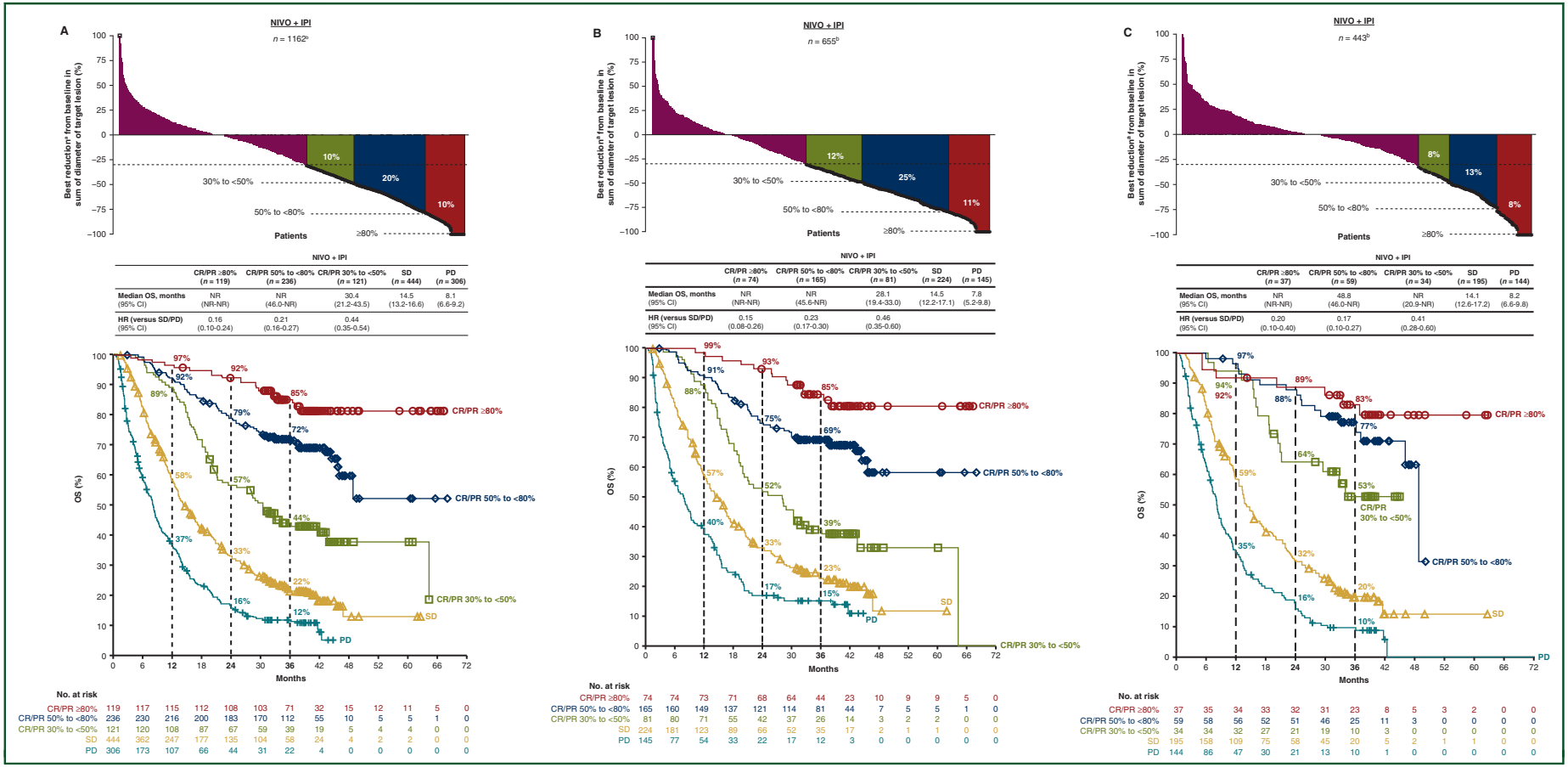

Figure 4. Tumor burden reduction and OS by depth of response (per investigator assessment) in (A) all patients in the pooled population and in patients with tumor PD-L1 expression level (B) ≥1% or (C) <1%. BOR was considered first when categorizing by BOR and best tumor burden reduction.

BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; NR, not reached; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

[a]Based on evaluable target lesion measurements up to progression or start of subsequent anticancer therapy.

[b]Includes patients with baseline and at least one on-treatment tumor assessment per BICR.

*Responders per RECIST v1.1.

Table 2. Treatment-related adverse events in patients treated with nivolumab plus ipilimumab (pooled patient population)

	Pooled patient population ($N = 1332$)	
	Any grade	Grade 3 or 4
Any	1039 (78)	459 (34)
Occurred in ≥10% of patients in any study		
Diarrhea	275 (21)	32 (2)
Fatigue	237 (18)	23 (2)
Pruritus	225 (17)	8 (1)
Rash	189 (14)	20 (2)
Hypothyroidism	157 (12)	5 (<1)
Nausea	146 (11)	7 (<1)
Decreased appetite	146 (11)	5 (<1)
Serious events[a]	315 (24)	246 (18)
Leading to discontinuation[a]	277 (21)	182 (14)
Treatment-related deaths	17 (1)	

Data presented as *n* patients with an event (%).
[a]Includes events reported between first dose and 30 days after last dose of study therapy.

with tumor PD-L1 <1% and those with squamous tumor histology (patient populations with typically higher unmet need for durable responses). Further building on the durable efficacy observed with dual immunotherapy is the nivolumab plus ipilimumab combination with a limited course of chemotherapy, which has also shown clinical benefit across tumor PD-L1 expression levels and histologies.[39] It is important to both continue to assess longer-term clinical data and carry out additional research to better understand the biological differences that may contribute to long-term clinical benefit of nivolumab plus ipilimumab and other immunotherapy-based treatments. Ultimately, a randomized trial is the only possible way to address the choice of immunotherapy plus chemotherapy versus dual immunotherapy in patients with unmet need (such as patients with tumor PD-L1 expression level <1%).

Limitations of the current analyses, inherent to pooled analyses, included interstudy differences in treatment regimen, dose, and patient population. CheckMate 817 utilized a flat dosing regimen for nivolumab rather than the weight-based dosing used in the other three studies, and one arm in CheckMate 012 ($n = 39$) had a different ipilimumab dosing schedule (1 mg/kg Q12W versus 1 mg/kg Q6W in the remainder of patients). There were also minor differences in the patient populations, such as a lower proportion of patients with quantifiable tumor PD-L1 in CheckMate 817. Despite these differences, the efficacy results in the pooled population were generally consistent with those of the individual studies.

In summary, durable long-term benefit with first-line nivolumab plus ipilimumab reported in this large pooled patient population overall and in patients aged ≥75 years further support the use of this regimen in advanced NSCLC. Efficacy outcomes with nivolumab plus ipilimumab were observed regardless of histology or tumor PD-L1 expression level. Response status (complete or partial) at 6 months and greater reduction in tumor burden were associated with higher magnitude of survival benefit.

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