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Long-term outcomes among patients who respond within the first year to nivolumab plus ipilimumab or nivolumab monotherapy: A pooled analysis in 935 patients

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ABSTRACT

Purpose: To investigate the predictive value of RECIST response within 3, 6, or 12 months on long-term survival, and explore differences between nivolumab+ipilimumab and nivolumab monotherapy, we analyzed pooled 5-year data of 935 responder and non-responder patients at various time points after treatment initiation in CheckMate 069, 066, and 067 studies.

Patients and methods: Treatment-naive advanced melanoma patients received nivolumab+ipilimumab or nivolumab monotherapy. To decrease immortal time bias, 3-, 6-, or 12-month overall survival (OS) and progression-free survival (PFS) landmark analyses were performed. Association between characteristics and response was evaluated by univariate and multivariate analyses.

Results: Response rates at any time were 58 % (239/409) for nivolumab+ipilimumab and 44 % (230/526) for nivolumab monotherapy. In 12-month landmark analyses, 5-year OS rates for responders versus non-responders were 82 % versus 40 % with nivolumab+ipilimumab (HR=0.23 [95 % CI, 0.15–0.35]) and 76 % versus 32 % with nivolumab monotherapy (HR=0.22 [95 % CI, 0.16–0.31]). PFS rates were 83 % versus 32 % and 69 % versus 46 %, respectively. Similar strong associations between response at 3 and 6 months and 5-year OS and PFS were also observed with more than 70 % of the responses observed in the first 3 months. Response rates correlated with baseline LDH and PD-L1 status by multivariate analysis but the association between response and

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long-term survival was maintained in landmark analyses even among patients with high LDH and low PD-L1 expression.
Conclusion: Clinical response evaluated in the first months of therapy is a strong predictor of long-term survival, even in patients with poor prognostic biomarkers.

1. Introduction

Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) such as nivolumab and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), ipilimumab, have significantly improved long-term outcomes for patients with melanoma. Nivolumab is approved as monotherapy or in combination with ipilimumab globally for the treatment of advanced melanoma [1–7].

Currently, no established robust baseline biomarkers predict the long-term survival of patients treated with ICIs, although complete response (CR), partial response (PR) and complete metabolic response (both RECIST CR or PR) were shown to be associated with survival benefit [8–10]. When assessing the predictive value of an event such as response, which occurs after inclusion in a study, it is crucial to address the inherent immortality bias and utilize an appropriate statistical methodology. As such, using landmark analyses and pooled 5-year data from the CheckMate 066, 069, and 067 studies (N = 935), we investigated survival data based on RECIST v1.1 response within 3–12 months of treatment with ICI monotherapy or combination to help clinicians with both treatment decisions and discussions of expected prognosis with patients after treatment initiation.

2. Materials and methods

2.1. Individual study designs and patients

For this post hoc analysis, data were pooled for patients with previously untreated, advanced melanoma treated with nivolumab+ipilimumab or nivolumab alone in CheckMate 066 (NCT01721772; refs. [1,11], CheckMate 069 (NCT01927419; refs. [2,3]), and CheckMate 067 (NCT01844505; refs. [4,6]). Eligibility criteria, study designs, and safety assessments, along with trial compliance information, have all been described previously [1,2,4].

2.2. Pooled analysis assessments

Efficacy and safety data were pooled for the three studies, comparing responders and non-responders. Responders were patients with investigator-assessed unconfirmed CR or PR per RECIST v1.1. Landmark survival analyses investigated responders in time periods of 3, 6, and 12 months. Analyses based on response at any time were also performed on the total ITT patient population (Fig 1).

Outcomes for overall and progression-free survival (OS and PFS) were conducted using 3-, 6-, or 12-month landmark analyses (Fig 1**)** to reduce the time guarantee bias associated with the analysis of time-to-event endpoints by on-treatment factors [12]; melanoma-specific survival was not analyzed at this time. The time points served a dual purpose in these landmark analyses. First, patients who discontinued the study or had an event within 3, 6, or 12 months of treatment were excluded in that respective analysis population. For OS, patients who died in the landmark interval were excluded, and for PFS, patients who progressed or died were excluded. Secondly, patients in the resulting landmark population were separated into those who either did or did not demonstrate a response in the respective landmark timeframe (i.e., 3, 6, or 12 months) and were then followed for survival to investigate the relationship between response and long-term OS and PFS rates. Therefore, for each analysis, the population was unique for that landmark timeframe and survival endpoint.

Naive analyses were those in which the total population without any landmark division was divided into responder and non-responder (patients with stable disease [SD], a PR, or not evaluable [NE]) groups. These analyses included overall objective response, baseline characteristics, subsequent therapy use, patient disposition, and univariate and multivariate analyses (Fig 1).

2.3. Statistical analysis

For the survival analyses, Kaplan-Meier estimates of OS and PFS with

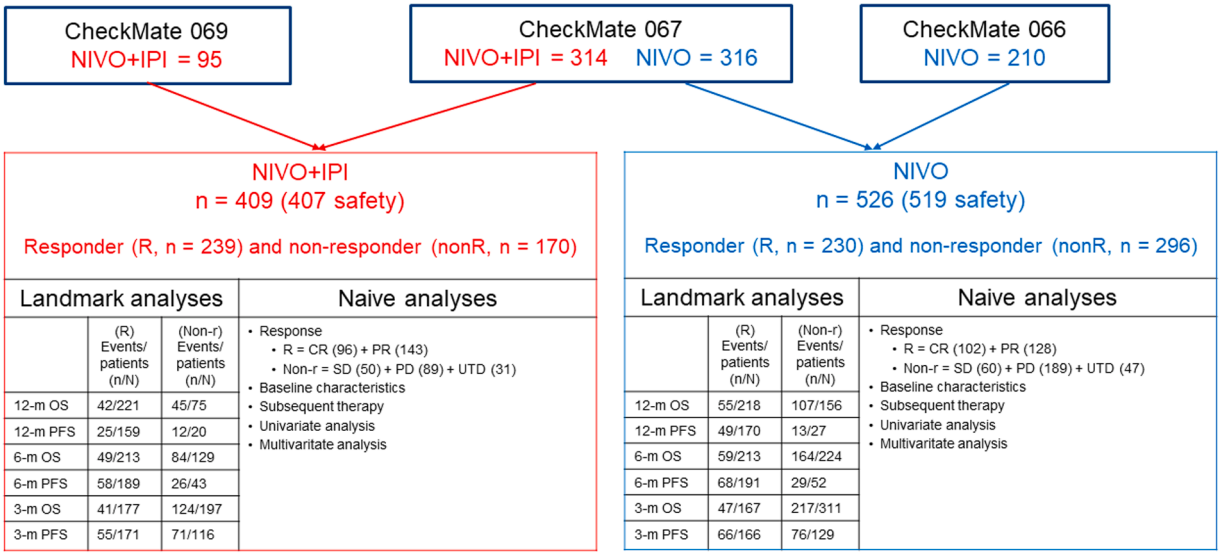

Fig. 1. Disposition of patients with a response treated with nivolumab+ipilimumab or nivolumab alone included in the pooled analysis. CR, complete response; NIVO, nivolumab; NIVO+IPI, nivolumab+ipilimumab; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; UTD, unable to determine.

two-sided 95 % confidence intervals (CIs) were calculated using the Brookmeyer and Crowley method. Descriptive hazard ratios (HRs) and CIs comparing responders to non-responders were estimated using an unstratified Cox proportional hazards model.

The calculation of 95 % CIs for objective response rates (ORRs) was based on the Clopper and Pearson method. Baseline characteristics of responders and non-responders were compared using the chi-square test for categorical variables and two-sample t-test for continuous variables. The association of clinically relevant baseline characteristics with response was assessed using univariate and multivariate analyses per treatment group. Baseline characteristics included age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), region, disease characteristics (e.g., metastasis [M]-stage and history, lesion sites and size), programmed death ligand 1 [PD-L1] expression, *BRAF* mutation status, and lactate dehydrogenase [LDH] level). Factors associated with response in the univariate analysis ($P \leq 0.1$) were subsequently included in a Cox proportional hazards multivariate analysis. All analyses were conducted using SAS software (v9.3 or higher; SAS Institute, Cary, NC).

2.4. Data availability

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.

3. Results

3.1. Patients

A total of 409 patients randomized to nivolumab+ipilimumab (239 responders and 170 non-responders) and 526 patients to nivolumab alone (230 responders and 296 non-responders) were included in this analysis (Fig 1). Minimum follow-up was 60 months in each study. Pooled median follow-up for patients treated with nivolumab+ipilimumab or nivolumab alone was 62.8 and 63.0 months, respectively, for responders, and 10.5 and 12.8 months for non-responders.

3.2. Overall response assessments

In the response assessment at any time in the total population, the ORR was 58 % for nivolumab+ipilimumab and 44 % for nivolumab alone (Supplementary Table S1). In the nivolumab+ipilimumab group, 96 patients (23 %) had a CR among all patients throughout the study and 79 patients (40 %) had a CR among patients alive at 5 years, meaning 79/96 (82 %) of all patients with a CR at any time were alive at 5 years. Similarly, in the nivolumab group, 102 patients (19 %) had a CR among all patients throughout the study and 91 patients (44 %) had a CR among patients alive at 5 years, meaning 91/102 (89 %) of all patients with a CR at any time were alive at 5 years. Proportions of patients alive at 5 years in categories of PR, SD, and PD are shown in Supplementary Table S1. Median duration of response was not reached for either treatment group.

In the total population, subsequent systemic therapy was received by 57/239 (24 %) of responders and 81/170 (48 %) of non-responders treated with nivolumab+ipilimumab, and by 59/230 (26 %) of responders and 193/296 (65 %) of non-responders treated with nivolumab alone (Supplementary Table S2). Among responders versus non-responders, 67 % versus 12 % treated with nivolumab+ipilimumab and 64 % versus 10 % treated with nivolumab alone had not received any subsequent systemic therapy at 5 years, excluding patients who died and never received subsequent therapy.

3.3. Survival analyses

The 12-month landmark OS analysis included 296/409 (72 %) of nivolumab+ipilimumab-treated patients and 374/526 (71 %) nivolumab-treated patients (i.e., patients who had not died in the first 12 months). This population was divided into patients with a response within 12 months (responders) and all other patients (non-responders). For the nivolumab+ipilimumab group, 221/296 (75 %) patients were responders, representing 92 % of responses at any time for this arm of treatment, and 75/296 (25 %) were non-responders; for the nivolumab group, 218/374 (58 %) patients were responders (95 % of responses at any time) and 156/374 (42 %) were non-responders (Fig 1). Five-year OS rates with nivolumab+ipilimumab were 82 % for responders and 40 % for non-responders (HR = 0.23 [95 % CI, 0.15–0.35]); with nivolumab alone, rates were 76 % and 32 %, respectively (HR = 0.22 [95 % CI, 0.16–0.31]) (Fig 2A and B).

There were 179/409 (44 %) nivolumab+ipilimumab-treated patients and 197/526 (37 %) nivolumab-treated patients available for the 12-month landmark PFS analysis (i.e., patients who had not progressed or died in the first 12 months; Fig 1). Of this patient population, 159/179 (89 %) of nivolumab+ipilimumab-treated patients had a response in the first 12 months and 20/179 (11 %) were non-responders; for the nivolumab group, it was 170/197 (86 %) for responders and 27/197 (14 %) for non-responders. Five-year PFS rates with nivolumab+ipilimumab were 83 % in responders and 32 % in non-responders (HR = 0.18 [95 % CI, 0.09–0.35]); with nivolumab monotherapy, rates were 69 % and 46 %, respectively (HR = 0.37 [95 % CI, 0.20–0.69]) (Fig 2C and D).

Landmark survival analyses were repeated with 3- and 6-month time points for both OS and PFS (Fig 3). HR values show a strong survival benefit for responders versus non-responders for both the 6-month OS landmark (nivolumab+ipilimumab HR = 0.24 [95 % CI, 0.17–0.35] and nivolumab monotherapy HR = 0.22 [95 % CI, 0.16–0.30]) and the 3-month OS landmark (nivolumab+ipilimumab HR = 0.26 [95 % CI, 0.18–0.37] and nivolumab monotherapy HR = 0.25 [95 % CI, 0.18–0.34]) (Fig 3A–D). Responses in the OS analysis achieved within 6 months represented 89 % of responses at any time for the combination arm and 93 % for monotherapy; responses achieved within the 3-month landmark represented respectively 74 % and 73 % of responses at any time, respectively. Similar to OS, responder versus non-responder 6-month PFS landmark HRs were 0.38 (95 % CI, 0.24–0.61) for nivolumab+ipilimumab and 0.44 (95 % CI, 0.29–0.69) for nivolumab alone; 3-month PFS landmark HRs were 0.36 (95 % CI, 0.25–0.51) and 0.49 (95 % CI, 0.35–0.69), respectively (Fig 3E–H).

Similar survival analyses with all three landmark times (3, 6, and 12 months) were conducted for patients according to RECIST v1.1 response category (patients categorized as NE were not included; patient numbers are shown in Supplementary Table S3). Of patients available for the OS analyses in the 12-month time period, 18 % had a CR and 58 % had a PR within the first 12 months in the nivolumab+ipilimumab arm, and 13 % had a CR and 46 % had a PR in the nivolumab arm (Supplementary Table S3). Five-year OS rates for patients with a CR in the first 12 months were 85 % with nivolumab+ipilimumab and 86 % with nivolumab alone. Five-year OS rates for those with a PR in the first 12 months were 81 % and 74 %, respectively (Fig 4A and B). Among the nivolumab+ipilimumab and nivolumab groups, respectively, with PR in the first 12 months, 40/168 (24 %) and 51/169 (30 %) demonstrated a CR afterward. In patients available for the PFS analysis (Supplementary Table S3), the 5-year PFS rate for patients with a CR in the first 12 months was 84 % with nivolumab+ipilimumab and 82 % with nivolumab alone. The 5-year PFS rate for those with a PR in the first 12 months was 82 % and 64 %, respectively (Fig 4C and D). Results in patients at the 3- and 6-month landmarks (Supplementary Table S3) showed similar survival results for both OS (Supplementary Fig. S1A-D) and PFS (Supplementary Fig. S1E-H). Among patients treated with nivolumab+ipilimumab who were alive and had SD at 3 months, 33/87 (38 %) went on to have a PR and 13/87 (15 %) went on to have a CR; for

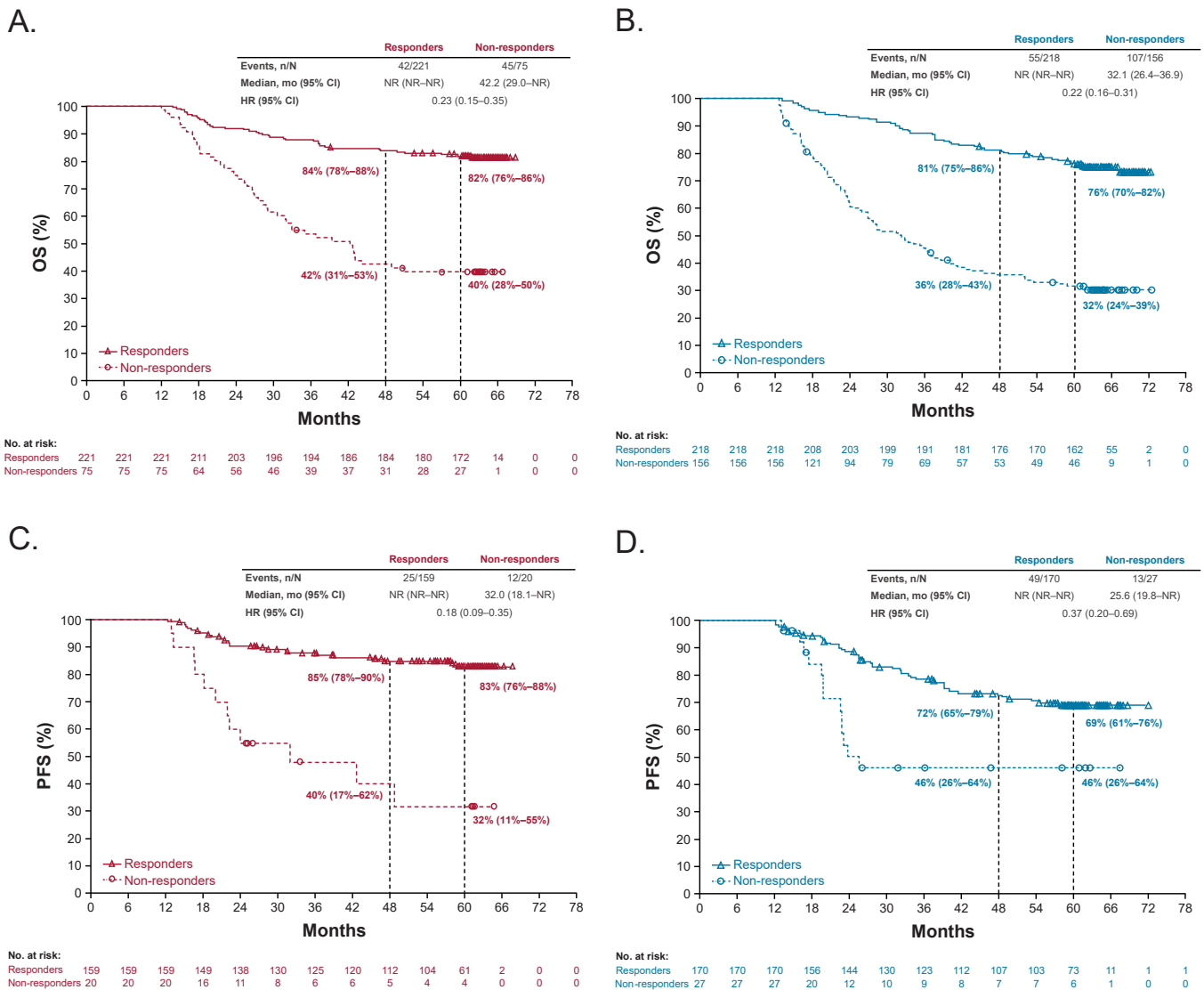

Fig. 2. Kaplan-Meier 12-month landmark plots of (**A** and **B**) OS and (**C** and **D**) PFS in pooled patients treated with nivolumab+ipilimumab or nivolumab alone who either did or did not demonstrate a response in the first 12 months of treatment. Survival rates at 4 and 5 years with respective 95 % CIs are shown, along with HRs for responder versus non-responder. A. Nivolumab+ipilimumab OS 12 months. B. Nivolumab OS 12 months. C. Nivolumab+ipilimumab PFS 12 months. D. Nivolumab PFS 12 months. CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

nivolumab treatment, it was 30/90 (33 %) and 16/90 (18 %), respectively. Patient number analyses for patients with an SD at 3 or 6 months and either alive at 3 or 6 months or alive and not progressed at 3 or 6 can be found in Supplementary Table S4.

3.4. Responder characteristics

Baseline characteristics of responders and non-responders in the total population were similar between the two treatment groups, with the exception that patients with a *BRAF* mutation had a higher likelihood of response when treated with the combination (34 %) versus nivolumab only (16 %; Table 1).

By univariate analysis in the total population, normal LDH level, M0/M1A/M1B stage, PD-L1 status ($\geq$ 1 % and 5 %), and smaller tumor burden (i.e., sum of target lesion reference diameter) were significantly associated with higher response rates in both treatment groups (Supplementary Table S5). For PD-L1 association, the difference based on response rate ($\geq$ 5 % vs. $<$ 5 %) was greater in the nivolumab-only group than in the combination group. ECOG PS 0 and male gender were significantly associated with a higher response rate only for the nivolumab-only group, while a smaller number of lesion sites was significantly associated with a higher response rate only for the nivolumab+ipilimumab group. No significant association with response rate were observed within subgroups based on age, history of brain metastases, or *BRAF* status in either treatment group.

Results from the univariate analysis were used to perform a multivariate analysis for each treatment separately in the total population. According to this analysis, baseline normal LDH expression and PD-L1 expression $>$ 1 % were associated with response in both treatment groups; male gender was specific for the nivolumab group (Table 2).

We explored the relationship of baseline LDH and PD-L1 expression levels, response, and survival using 6-month OS and PFS landmark analyses as described above. HR analysis of responder versus non-responder for each treatment shows that regardless of LDH expression, patients have better survival if they have a response within 6 months (Supplementary Fig. S2 [OS] and Supplementary Fig. S3 [PFS]), although for PFS, there was no response benefit for either treatment at LDH expression levels $>$ upper limit of normal (ULN). In addition, patients with a response within 6 months had better survival (OS and PFS), regardless of PD-L1 expression levels (Supplementary Fig. S4 and

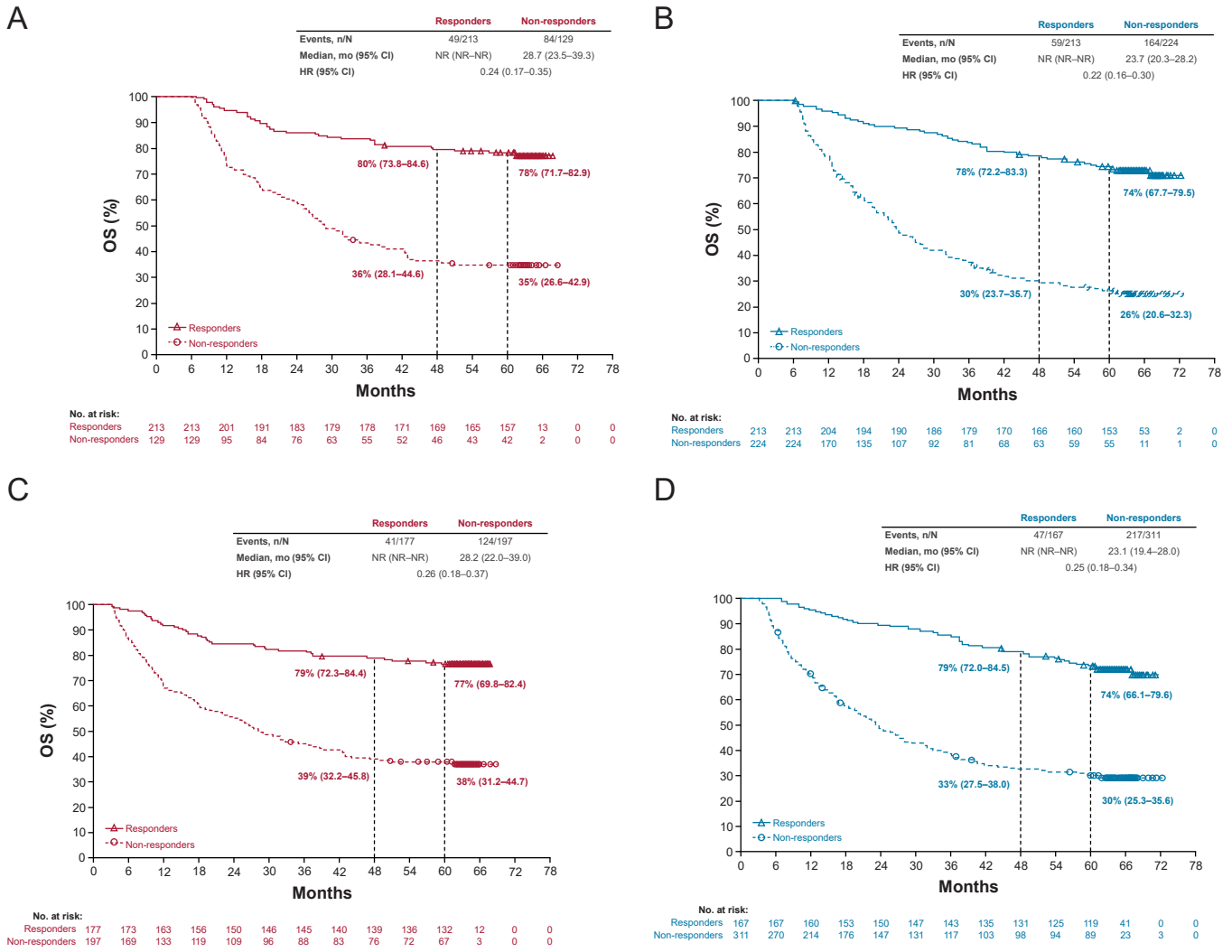

Fig. 3. A–D, Kaplan-Meier 6-month (**A-B**) and 3-month (**C-D**) landmark OS plots in pooled patients treated with nivolumab+ipilimumab (**A** and **C**) or nivolumab alone (**B** and **D**) who either did or did not demonstrate a response in the landmark period. **E–H,** Kaplan-Meier 6-month (**E-F**) and 3-month (**G-H**) landmark PFS plots in pooled patients treated with nivolumab+ipilimumab (**E** and **G**) or nivolumab alone (**F** and **H**) who either did or did not demonstrate a response in the landmark period. Survival rates at 4 and 5 years with respective 95 % CIs are shown, along with HRs for responder versus non-responder. CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

Supplementary Fig. S5).

4. Discussion

Our results show that responses achieved within the first year of treatment with nivolumab+ipilimumab or nivolumab alone are strongly associated with long-term survival even in patients with poor baseline prognostic characteristics. These long-term survival data provide information for the practicing clinician to counsel patients about the expected prognosis after a response is observed early during the treatment course. This is relevant for most patients who respond to immunotherapy because more than 70 % and 89 % of responses were observed during the first 3 and 6 months, respectively, for both treatment arms. For this study, we used landmark analyses to decrease the immortal time bias generated when an analysis that is timed from enrollment or randomization is compared across groups defined by an event that occurs during follow-up [12] and, simultaneously, evaluated responders at the same time points used for the landmark analyses.

In the landmark analyses, patients with a CR within 12 months of treatment with nivolumab+ipilimumab or nivolumab alone had high, and similar, 5-year OS rates (85 % and 86 %, respectively) and PFS rates (84 % and 82 %, respectively). Patients with a PR within 12 months of nivolumab+ipilimumab treatment appeared to have better 5-year outcomes than those who received nivolumab alone for both OS (81 % vs. 74 %) and PFS (82 % vs. 64 %). The apparent benefit of combination therapy versus nivolumab monotherapy appears to continue with a response within 3 or 6 months, specifically in terms of PFS. This suggests that the overall numeric improvement in PFS and OS with nivolumab+ipilimumab over nivolumab monotherapy is mostly due to patients with PR. Anti-CTLA-4 has been indicated to have a role in T-cell memory and as an indirect modulator of tumor immunogenicity [13–15]. One possibility is that some patients treated with nivolumab+ipilimumab with a PR may in fact have a CR with persisting tumor-free radiographic lesions due to fibrotic reactions and remnant immune cells. Such a scenario might be more frequent with the combination than with nivolumab monotherapy and explain why patients with a PR and a CR have similar long-term outcomes with combination therapy, but not with nivolumab monotherapy. One possible limitation for this portion of the study is the lack of melanoma-specific survival data. However, recently published 10-year follow-up data from

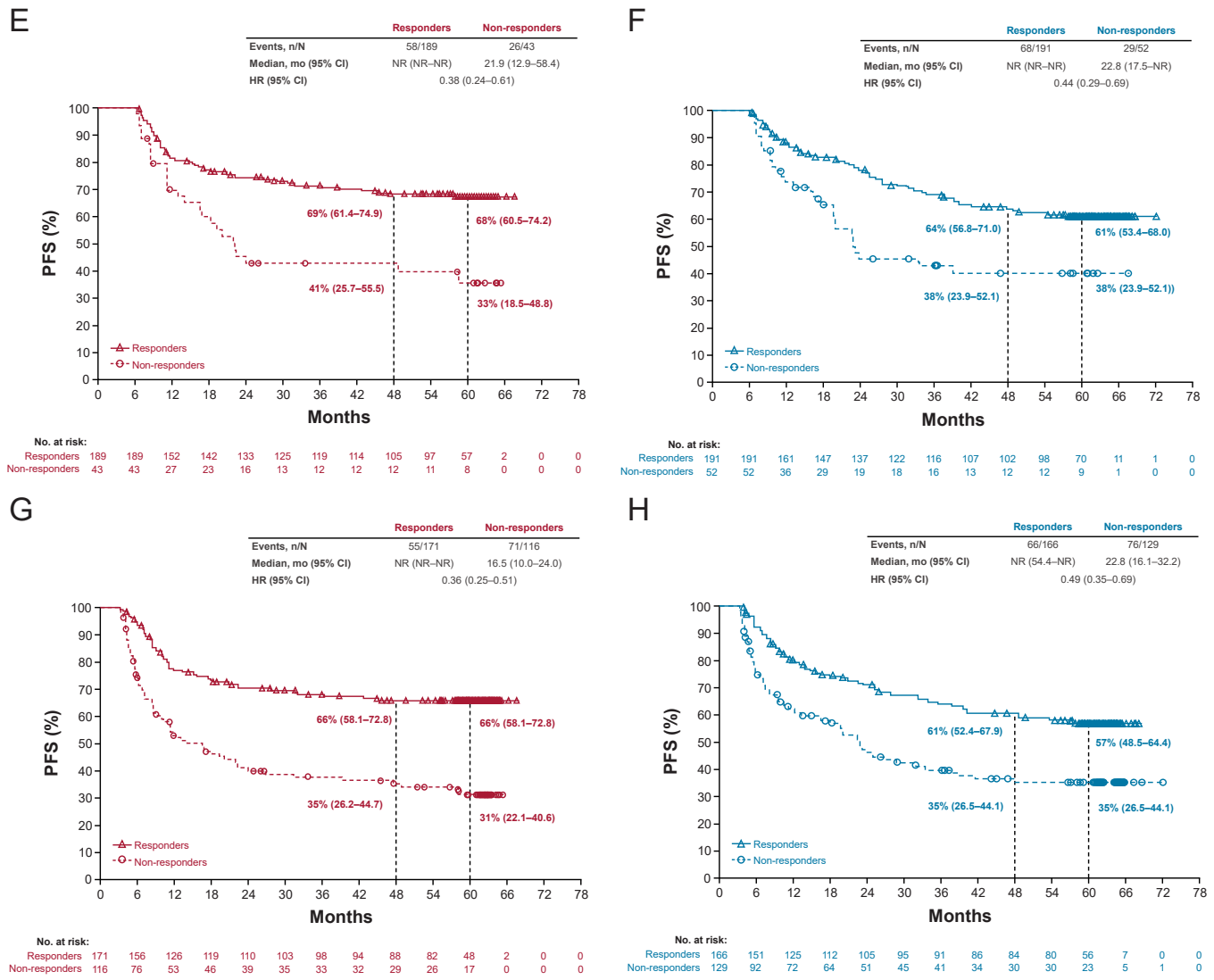

Fig. 3. (*continued*).

CheckMate 067, the trial in which most of the patients in this study were enrolled, includes melanoma-specific survival analyses [16].

Characteristics associated with response in our multivariate analysis for nivolumab+ipilimumab-treated patients were baseline LDH status and PD-L1 expression and for nivolumab-treated patients were gender (male), baseline LDH status, and PD-L1 expression. Our analysis adds to a recent study identifying baseline clinical parameters that could guide patient discussions about prognosis, and possibly help treatment selection between anti-PD-1 plus ipilimumab versus anti-PD-1 monotherapy [17]. Importantly, follow-up survival analyses from the current analysis show that patients with a response within the first year and as early as 3 or 6 months after treatment initiation (i.e., at the first and the second evaluation, respectively), show high survival despite poor prognostic baseline characteristics (OS HR for response at 3 and 6 months are approximately 0.25 for both treatment regimens). Indeed, baseline characteristics may be linked to treatment response, but their predictive accuracy is often insufficient to confidently guide therapeutic decision-making. We show here that response predicts survival and that achieving an objective response to treatment may override poor prognostic factors at baseline, changing baseline prognostic expectations for certain patients. These results could be a foundation on which future investigations of tissue- and blood-based markers could add additional information for increased prediction value. However, tumor PD-L1 expression and blood LDH were available for the current analysis.

5. Conclusion

In summary, results from this pooled analysis show that objective response to ICI treatment achieved in the first year is associated with long-term survival, including in patients with poor baseline prognostic markers for survival. Differences were observed between nivolumab+ipilimumab and nivolumab monotherapy treatment: while CR has the same predictive value for each regimen, the association of PR with longer OS is stronger for nivolumab+ipilimumab than for nivolumab alone. This analysis provides information that will help clinicians counsel patients about long-term prognostic expectations based on response outcomes occurring within the first 3 to 12 months of treatment.

CRediT authorship contribution statement

C. Robert: Conceptualization, Methodology, Resources, Writing – review & editing. **G.V. Long:** Resources, Writing – review & editing. **J. Larkin:** Resources, Writing – review & editing. **J.D. Wolchok:** Resources, Writing – review & editing. **J.C. Hassel:** Resources, Writing – review & editing. **D. Schadendorf:** Resources, Writing – review &

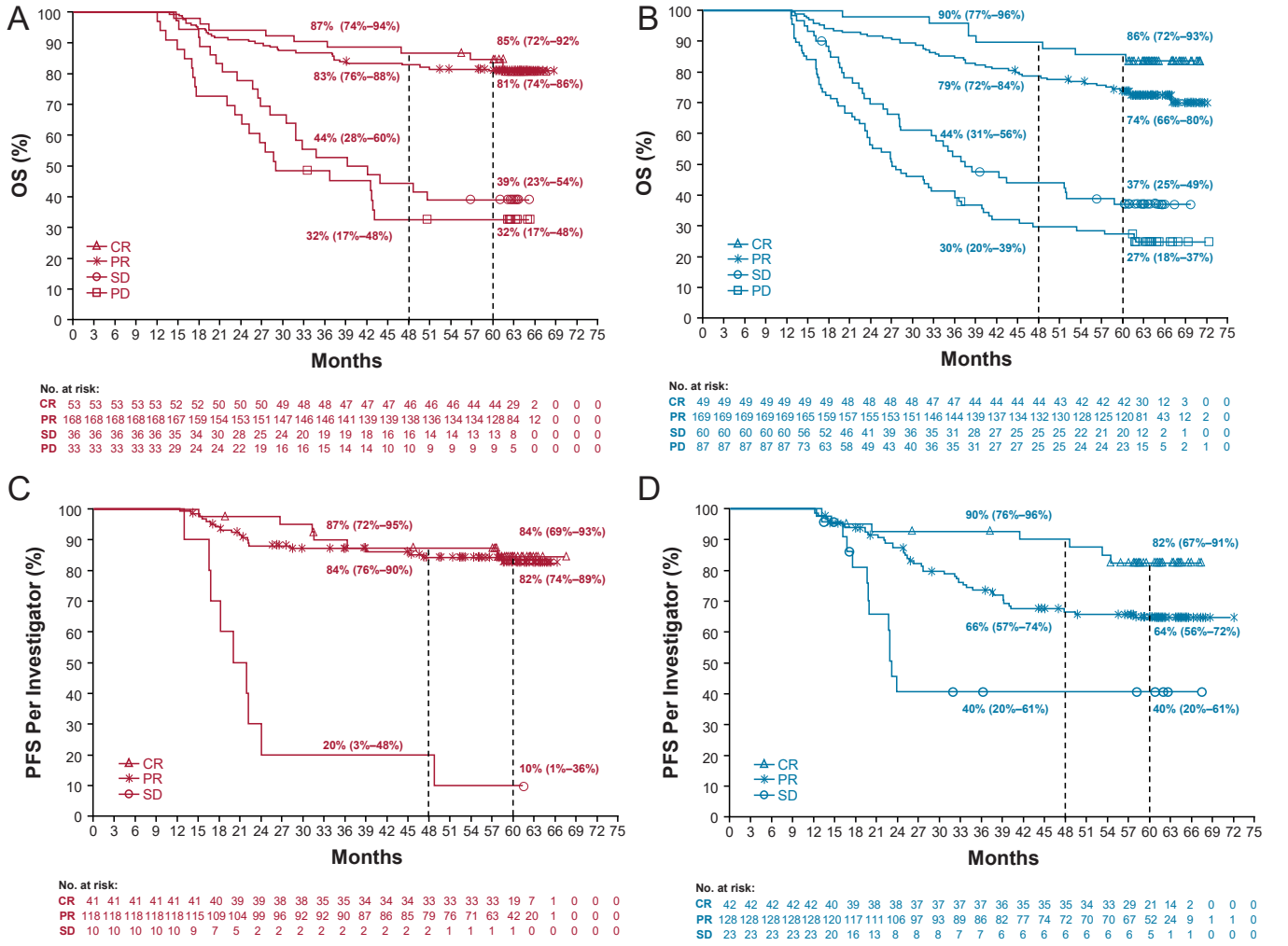

Fig. 4. Kaplan-Meier 12-month landmark plots of OS (**A–B**) or PFS (**C–D**) in pooled patients treated with nivolumab+ipilimumab (**A** and **C**) or nivolumab alone (**B** and **D**) by best overall response in the first 12 months of treatment. Survival rates at 4 and 5 years with respective 95 % CIs are shown. CI, confidence interval; CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

editing. **F.S. Hodi:** Resources, Writing – review & editing. **C. Lebbe:** Resources, Writing – review & editing. **J.-J. Grob:** Resources, Writing – review & editing. **J.R. Hyngstrom:** Resources, Writing – review & editing. **J. Wagstaff:** Resources, Writing – review & editing. **J. Chesney:** Resources, Writing – review & editing. **M.O. Butler:** Resources, Writing – review & editing. **O. Bechter:** Resources, Writing – review & editing. **I. Márquez-Rodas:** Resources, Writing – review & editing. **A.C. Pavlick:** Resources, Writing – review & editing. **P. Durani:** Formal analysis, resources, Writing – review & editing. **M. Pe Benito:** Formal analysis, resources, Writing – review & editing. **P. Wang:** Formal analysis, Writing – review & editing. **M.A. Postow:** Conceptualization, Methodology, Resources, Writing – review & editing. **P.A. Ascierto:** Conceptualization, Methodology, Resources, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. **C. Robert** disclosed medical writing support from Bristol Myers Squibb and received personal fees from Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, Pierre Fabre, Regeneron, Roche, and Sunpharma (consulting fees); Bristol Myers Squibb, Pierre Fabre, and Sanofi (honoraria); and Regeneron and Ultimovacs (safety monitoring or advisor board). **G.V. Long** received consulting fees from Agenus Inc, Amgen Inc, Array Biopharma, Boehringer Ingelheim International GmbH, Bristol Myers Squibb, Evaxion Biotech A/S, Hexal AG (Sandoz Company), Highlight Therapeutics S.L., Innovent Biologics USA Inc, Merck Sharp & Dohme (Australia) Pty Limited, Novartis Pharma AG, OncoSec Medical Australia, Pierre Fabre, Provectus Australia, Qbiotics Group Limited, and Regeneron Pharmaceuticals and received honoraria from Bristol Myers Squibb and Pierre Fabre. **J. Larkin** received consulting fees from Apple Tree, Bristol Myers Squibb, Debipharm, Eisai, Incyte, iOnctura, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Philogen, and Telix; grants or contracts to his institution from Achilles, AVEO, Bristol Myers Squibb, Immunocore, Merck Sharp & Dohme, Nektar, Pfizer, Pharmacyclics, and Roche; honoraria from Agence Unik, Bristol Myers Squibb, Eisai, GCO, Immatics, Incyte, Insighter, Merck, Novartis, Pfizer, Royal College of Physicians, TouchEXPERTS, TouchIME, and VJOncology; and discloses participation in a data safety monitoring or advisory board for IKCC. **J.D. Wolchok** disclosed support for the current manuscript to self as well as grant support to his institution from Bristol Myers Squibb; disclosed leadership or fiduciary role with AACR, SITC, and Ludwig Institute for Cancer Research; disclosed stock or stock options with Apricity, Ascentage Pharma, ArsenalIO/CellCarta, Georgiamune, Imvaq, Maverick, Psioxus, Tizona, and Xenimmune; received royalties and/or licenses for Xenogenic DNA Vaccines, Newcastle Disease viruses for Cancer Therapy, Myeloid-derived suppressor cell assay, Prediction of Responsiveness to treatment with immunomodulatory, anti-PD1 antibody, Anti-CTLA4 antibody, and anti-GITR antibodies and methods thereof; received

Table 1
Baseline characteristics of responders[a] and non-responders treated with nivolumab+ipilimumab or nivolumab alone. Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology; LDH, lactate dehydrogenase; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease; ULN, upper limit of normal. [a]Assessed per investigator using RECIST v1.1 criteria. Responders' category consists of patients with a CR or PR. Non-responders' category consists of patients with SD, PD, or a nonevaluable response [b]Patients with unknown baseline characteristics were excluded from *P* value calculations. [c]Defined as the sum of the longest dimension of all measurable target lesions.

	Nivolumab+ipilimumab ($N = 409$)			Nivolumab ($N = 526$)		
	Responders ($n = 239$)	Non-responders ($n = 170$)	*P* value	Responders ($n = 230$)	Non-responders ($n = 296$)	*P* value
Median age, years (range)	62.0 (18 −87)	63.0 (23 −88)	0.743	62.5 (25 −89)	61.0 (18 −90)	0.269
Male, No. (%)	166 (69)	103 (61)	0.062	158 (69)	165 (56)	0.002
ECOG performance status, No. (%)			0.349			0.014
0	185 (77)	124 (73)		181 (79)	204 (69)	
≥ 1	54 (23)	45 (26)		49 (21)	91 (31)	
Unknown[b]	0	1 (1)		0	1 (< 1)	
Baseline LDH level, No. (%)			< 0.0001			< 0.0001
≤ ULN	176 (74)	93 (55)		163 (71)	154 (52)	
> ULN to < 2 × ULN	48 (20)	47 (28)		51 (22)	82 (28)	
≥ 2 × ULN	14 (6)	29 (17)		10 (4)	48 (16)	
Unknown[b]	1 (< 1)	1 (1)		6 (3)	12 (4)	
M stage, No. (%)			0.008			0.020
M0/M1A/M1B	118 (49)	61 (36)		107 (47)	108 (36)	
M1C	121 (51)	108 (64)		123 (53)	188 (64)	
Unknown[b]	0	1 (1)		0	0	
M stage, No. (%)			0.015			0.107
M0	10 (4)	9 (5)		18 (8)	17 (6)	
M1A	46 (19)	16 (9)		32 (14)	38 (13)	
M1B	62 (26)	36 (21)		57 (25)	53 (18)	
M1C	121 (51)	108 (64)		123 (53)	188 (64)	
Unknown[b]	0	1 (1)		0	0	
History of brain metastasis, No. (%)			0.237			0.947
Yes	11 (5)	4 (2)		6 (3)	8 (3)	
No	228 (95)	165 (97)		224 (97)	288 (97)	
Unknown[b]	0	1 (1)		0	0	
BRAF status, No. (%)			0.083			0.183
Mutant	81 (34)	44 (26)		37 (16)	61 (21)	
Wild-type	158 (66)	126 (74)		191 (83)	232 (78)	
Unknown[b]	0	0		2 (1)	3 (1)	
PD-L1 status, n/n (%)			0.031			0.0004
Known value	211/239 (88)	147/170 (86)		217/230 (94)	257/296 (87)	
≥ 5 %	63/211 (30)	29/147 (20)		81/217 (37)	58/257 (23)	
< 5 %	148/211 (70)	118/147 (80)		136/217 (63)	199/257 (77)	
Unknown value	28/239 (12)	23/170 (14)		13/230 (6)	39/296 (13)	
Number of lesion sites, No. (%)			0.019			0.261
1	86 (36)	42 (25)		65 (28)	65 (22)	
2 −3	120 (50)	91 (54)		128 (56)	175 (59)	
> 3	33 (14)	37 (22)		37 (16)	54 (18)	
Unknown[b]	0	0		0	2 (1)	
Median target lesion sum[c] of reference diameter, cm (range)	4.6 (1.0 −37.2)	7.2 (1.0 −25.7)	< 0.0001	4.6 (1.0 −37.3)	6.1 (1.0 −38.4)	0.004

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Table 2
Multivariate analysis[a].

	Odds ratio (95% CI)	*P* value
Nivolumab+ipilimumab (*n* = 409)		
Baseline LDH status		0.023
> ULN - < 2× ULN vs. ≤ ULN	0.64 (0.38–1.08)	
≥ 2× ULN vs. ≤ ULN	0.37 (0.17–0.81)	
M stage at study entry		0.082
M1A vs. M0	2.93 (0.88–9.75)	
M1B vs. M0	1.47 (0.48–4.48)	
M1C vs. M0	1.18 (0.41–3.41)	
PD-L1 status		0.003
1%-5% vs. < 1%	1.23 (0.76–2.00)	
> 5% vs. < 1%	3.15 (1.61–6.16)	
Nivolumab (n = 526)		
Sex		0.010
Male vs. female	1.70 (1.13–2.56)	
Baseline LDH status		0.0002
> ULN – < 2× ULN vs. ≤ ULN	0.71 (0.45–1.11)	
≥ 2× ULN vs. ≤ULN	0.19 (0.08–0.42)	
PD-L1 status		0.0002
1%–5% vs. < 1%	1.59 (1.03–2.48)	
> 5% vs. < 1%	2.91 (1.74-4.86)	

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

[a] For each category, the last level specified is the reference category. *P* value and odds ratio are based on odds of response vs. no response.

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Appendix A. Supporting information

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