Title: Nivolumab alone or in combination with ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a prospective, open-label, phase 1/2 trial

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ABSTRACT *(Maximum 300; current count 380 words)*

BACKGROUND

Treatments for small-cell lung cancer (SCLC) after failure of platinum-based chemotherapy are limited. We assessed safety and activity of nivolumab and nivolumab plus ipilimumab in patients with SCLC who progressed after one or more prior regimens.

METHODS

The SCLC cohort of this phase 1/2 international multiarm open-label trial was conducted at 23 sites. Eligible patients were 18 years of age or older, had limited or extensive-stage SCLC, and had disease progression after at least one prior platinum-containing regimen. Patients received nivolumab (3 mg/kg) every 2 weeks, or nivolumab plus ipilimumab (1 mg/kg plus 1 mg/kg, 1 mg/kg plus 3 mg/kg, or 3 mg/kg plus 1 mg/kg, respectively) every 3 weeks for four cycles, followed by nivolumab 3 mg/kg every 2 weeks. Patients were either assigned to nivolumab monotherapy or assessed in a dose escalating safety phase for the nivolumab/ipilimumab combination beginning at nivolumab-1/ipilimumab-1. Depending on tolerability, patients were then assigned to nivolumab-1/ipilimumab-3 or nivolumab-3/ipilimumab-1. The primary endpoint was objective response rate (ORR). All analyses included patients who were enrolled at least 90 days prior to database lock. This trial is ongoing; an interim analysis is reported here. This study is registered with ClinicalTrials.gov, number NCT01928394.

FINDINGS

Between Nov 18, 2013 and July 28, 2015, 216 patients were enrolled and treated (n=98, nivolumab-3; n=3, nivolumab-1/ipilimumab-1; n=61, nivolumab-1/ipilimumab-3; n=54, nivolumab-3/ipilimumab-1). ORRs were 10% (10/98), 23% (14/61), and 19% (10/54) for patients receiving nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1, respectively. In the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, respectively, 13 (13%), 18 (30%), and 10 (19%) patients reported grade 3 or 4 treatment-related adverse events; across arms, the most commonly reported grade 3 or 4 treatment-related AEs were increased lipase (5 [2%]), diarrhea (4 [2%]), dyspnea (3 [1%]), and pneumonitis (3 [1%]), In the nivolumab-3, nivolumab-

1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, respectively, four (4%), seven (11%), and four (7%) patients discontinued due to treatment-related adverse events. One patient who received nivolumab-1/ipilimumab-3 died from treatment-related myaesthenia gravis.

INTERPRETATION

Nivolumab monotherapy and nivolumab plus ipilimumab showed antitumour activity with durable responses and manageable safety profiles in previously treated patients with SCLC. These data suggest a potential new treatment approach for a population of patients with limited treatment options and support the evaluation of nivolumab and nivolumab plus ipilimumab in phase 3 randomised controlled trials in SCLC.

FUNDING

Bristol-Myers Squibb

INTRODUCTION

Small-cell lung cancer (SCLC), which accounts for approximately 14% of all lung cancers, is strongly associated with tobacco use and has high mutation rates without known oncogenic drivers.[1,2] Most patients present with extensive-stage disease characterised by widespread metastases and poor survival.[2] Although 35% to 86% of patients respond to first-line chemotherapy, disease progresses rapidly, and outcomes with second-line treatment are poor.[3-6]

Standard first-line chemotherapy for SCLC is a platinum-etoposide doublet, with topotecan as second-line therapy in the United States (US) and European Union (EU)[1] and amrubicin as second-line therapy in Japan.[7] Though response rates with topotecan are 23% and 9% for platinum-sensitive and platinum-resistant/refractory patients, respectively, they are not durable.[8]

Nivolumab, a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody, significantly improved overall survival and had a favourable safety profile compared with docetaxel in two phase 3 studies of patients with non-SCLC (NSCLC) who progressed after first-line platinum-based doublet chemotherapy,[9,10] leading to its approval in the US for treatment of patients with metastatic NSCLC and in the EU for treatment of patients with locally advanced or metastatic squamous NSCLC.[11] Ipilimumab, a fully human IgG1 cytotoxic T-lymphocyte antigen 4 (CTLA-4) immune-checkpoint inhibitor, significantly improved overall survival in two phase 3 studies in patients with advanced melanoma, leading to approval in the US and the EU for this indication.[12,13]

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumour activity,[14] and the combination of nivolumab plus ipilimumab has demonstrated deep and durable responses in several tumour types.[15-17] The combination of nivolumab plus ipilimumab is approved in the US for treatment of advanced melanoma. Based on the efficacy of combination treatment in melanoma, CheckMate 032 was designed as a phase 1/2 trial to investigate the activity and safety of nivolumab as monotherapy or in combination with ipilimumab in several advanced or metastatic tumour types. The evaluation of nivolumab monotherapy and the combination of nivolumab and ipilimumab in patients with advanced or metastatic solid tumours for which no standard of care in advanced lines of treatment exists will potentially generate evidence of antitumour activity as a basis for further clinical development in these tumour types. Here, we report activity, safety, and biomarker analyses for the SCLC cohort.

METHODS

STUDY DESIGN AND PARTICIPANTS

This was an international phase 1/2, two-stage, open-label multiarm trial. Patients with SCLC were enrolled at 23 sites in six countries (Finland, Germany, Italy, Spain, UK, and US) (page 18, appendix). Eligible patients had histologically or cytologically-confirmed limited or extensive-stage SCLC, with progressive disease after at least one platinum-based chemotherapy regimen. Patients with platinum-sensitive or platinum-resistant disease (relapse ≥ or <90 days after, or during, chemotherapy, respectively) were eligible regardless of programmed death-ligand 1 (PD-L1) expression. Patients were ≥18 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (0 to 5 scale: 0, no symptoms; 1, mild; higher numbers, greater tumour-related disability) and had adequate organ function. Patients were required to have measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST), version 1·1,[18] and baseline tumour biopsy or archival tumour material available for biomarker analyses. Tumour material was acceptable from biopsies performed before the screening period if the biopsy was done up to 3 months prior to start of treatment and no other systemic cancer therapy was administered in that time. Baseline laboratory tests required to assess eligibility included white blood cell counts, neutrophils, platelets, haemoglobin, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, lipase, and amylase. Key exclusion criteria included active brain or leptomeningeal metastases, a history of autoimmune disease (except for vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger), the need for immunosuppressive doses of systemic corticosteroids (>10 mg per day prednisone equivalents) 2 weeks prior to study drug administration, and prior treatment with antibodies that modulate T-cell function or checkpoint pathways. Patients were also excluded if they tested positive for hepatitis B virus or human immunodeficiency virus, and had unresolved toxicities from prior anticancer therapies.

Patient selection was not based on estimated survival. Median survival for patients with relapsed SCLC has been reported as approximately 3·5–12 months.[4]

The study protocol was approved by an institutional review board or ethics committee at each participating centre. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonisation. Prior to performing any study-specific procedures, written informed consent was obtained from all patients.

PROCEDURES

Considerations for the dosing in the combination cohorts were as follows: the 1 mg/kg nivolumab plus 3 mg/kg ipilimumab regimen is the approved dose for the treatment of advanced melanoma;[11,19] the 3 mg/kg nivolumab plus 1 mg/kg ipilimumab regimen was chosen to maximize the nivolumab dose based on nivolumab exposure response data (1 mg/kg vs 3 mg/kg);[20] and to ensure that nivolumab plus ipilimumab is tolerable in patients with SCLC, an initial dose-escalating safety evaluation step was performed (starting with 1 mg/kg nivolumab plus 1 mg/kg ipilimumab). The safety of the 1 mg/kg nivolumab plus 3 mg/kg ipilimumab and the 3 mg/kg nivolumab plus 1 mg/kg ipilimumab regimens have been previously assessed in studies of other tumour types.[15-17,21,22]

Patients with SCLC were assigned to one of the following treatment cohorts, nivolumab as monotherapy at 3 mg per kilogram of body weight (nivolumab-3) administered intravenously every 2 weeks, orcombination treatment of nivolumab plus ipilimumab administered intravenously every 3 weeks for 4 cycles, at dose level 1 (nivolumab 1 mg/kg + ipilimumab 1 mg/kg [nivolumab-1/ipilimumab-1]), dose level 2 (nivolumab 1 mg/kg + ipilimumab 3 mg/kg [nivolumab-1/ipilimumab-3]), or dose level 2b (nivolumab 3 mg/kg + ipilimumab 1 mg/kg [nivolumab-3/ipilimumab-1]), followed by 3 mg/kg of nivolumab every 2 weeks. To ensure that the planned combination regimens would be tolerable in patients with SCLC, an initial dose-escalating safety evaluation for the combination arms was conducted. The first dose cohort was level 1. If this was deemed tolerable, then level 2 was initiated. If dose level 2 was deemed not tolerable, dose level 2b was investigated. Once the highest dose level for further investigation was confirmed in the dose-escalating safety evaluation phase, the combination arms continued enrolling patients. Patients on active treatment needed to be followed up for at least 6 weeks after the start of study treatment before tolerability of a dose level was determined based on prespecified tolerability assessment criteria. However, tolerability beyond 6 weeks was also taken into consideration. For combination treatment, nivolumab was administered first (60-minute infusion), followed by ipilimumab (90-minute infusion), as per previous studies evaluating nivolumab plus ipilimumab.[21,22] Patients received open-label treatment until disease progression or occurrence of unacceptable toxicity (figure 1). Treatment beyond RECIST, version 1·1-defined progression was permitted if the patient was tolerating and benefiting from treatment, based on investigator assessment. Using an interactive voice response system, patients were enrolled in one of the four cohorts in a sequential manner, or

assigned if more than one cohort was open for enrolment. Patients progressing on nivolumab-3 could cross over to combination cohorts.

No dose reductions or modifications were permitted for nivolumab or ipilimumab. Criteria for dose delays (which were required for protocol-defined reasons) and treatment discontinuation are detailed in the appendix.

Tumour assessments by radiographic imaging were done at baseline, every 6 weeks for the first 24 weeks, and every 12 weeks thereafter until disease progression (investigator-assessed per RECIST, version 1·1-defined progression) or treatment discontinuation. Survival was monitored continuously while patients were on treatment and every 3 months after treatment discontinuation. Safety was evaluated throughout the study (page 19, appendix), and adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4·0.

Tumour PD-L1 protein expression was assessed retrospectively in pretreatment (archival or fresh) tumour biopsy specimens with the use of a validated, automated immunohistochemical assay (Dako North America, Carpinteria, CA, USA) using a rabbit antihuman PD-L1 antibody (clone 28-8, Epitomics Inc, Burlingame, CA, USA).[23] Tumour PD-L1 expression was categorised as positive when staining of tumour-cell membranes (at any intensity) was observed at prespecified expression levels of ≥1% or ≥5% of tumour cells in a section that included ≥100 evaluable tumour cells. In the initial study protocol, analysis of the specimen was not required in advance of patient randomisation; the protocol was later revised and this was made a requirement via a study amendment on August 6, 2015.

OUTCOMES

The primary endpoint of this study was the proportion of patients with a confirmed objective response (defined as the number of patients with a best overall response of complete response or partial response [as per investigator-assessed RECIST, version 1·1 criteria] divided by the number of assigned patients). The objective response rate was the primary endpoint as the trial objective was to evaluate antitumour activity of nivolumab monotherapy or in combination with ipilimumab.

The secondary endpoints included overall survival, progression-free survival, duration of response, and the rate of treatment-related adverse events leading to treatment discontinuation. Overall survival was defined as the time

between the date of treatment assignment and the date of death due to any cause. Progression-free survival was defined as the time from treatment assignment to the date of the first documented tumour progression, as determined by the investigator (per RECIST, version 1·1), or death due to any cause, whichever occurred first. Duration of response was defined as the time from a best overall response of partial or complete response until the date progressive disease was documented (using RECIST version 1·1) or death due to any cause. The correlation between PD-L1 expression by tumour cells and antitumour activity was a prespecified exploratory endpoint.

All activity analyses were performed on the basis of the original treatment assignment, not by crossover status.

STATISTICAL ANALYSIS

In parallel to the safety evaluation phase for the combination arms (as described in Procedures), enrolment of patients followed a Simon two-stage design.[24] This design was used to test whether nivolumab and/or the combination of nivolumab and ipilimumab yields an objective response rate that is of clinical interest in each of the tumour types; it also limits the expected number of patients who receive treatment when the true response rate is not of clinical value. The two-stage test was conducted independently in each cohort.

For each cohort, the Simon design requires 18 treated patients for the first stage and calls for termination of a cohort at stage 1 if there is less than one responder among the 18 treated patients within the cohort. Otherwise, if two or more responders are identified in up to 18 patients in a cohort, additional patients will be assigned, to a total of 40 treated patients in that cohort. The treatment will be considered of clinical interest if, at the end of the second stage, there are eight or greater responders among 40 treated patients in any single cohort.

Only treatment arms that met an objective response rate threshold proceeded from stage 1 to stage 2. Enrolment in stage 2 in a given treatment arm could continue even if the other treatment arm was still in stage 1.

For stage 2, upon completion of enrolment for the initial 40 patients, additional patients were assigned into the nivolumab monotherapy arm and the combination arms up to a total of 100 patients (including those assigned in stage 1) in each treatment arm. When nivolumab monotherapy or nivolumab-1/ipilimumab-3 proceeded to stage 2, assessment of dose level 2b in stage 2 (nivolumab-3/ipilimumab-1) was initiated.

The date of the database lock for all activity and safety data was November 6, 2015. All analyses included treated patients who were enrolled at least 90 days prior to database lock.

Objective response rates were summarised by a binomial response rate and corresponding two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method. Progression-free survival and overall survival were summarised descriptively using Kaplan-Meier methodology; median values were estimated with two-sided 95% CIs, calculated using the Brookmeyer-Crowley method. Only treatment cohorts with more than six patients are represented in Kaplan-Meier plots. Patient with less than 12 weeks follow-up were excluded from Kaplan-Meier plots. Progression-free survival and overall survival rates were also estimated with two-sided 95% CIs, calculated using the Greenwood formula. Duration of response was summarised using the Kaplan-Meier product-limit method. For PD-L1 biomarker analysis, best overall response was summarised for each cohort by baseline PD-L1 expression and objective response rates, with exact 95% CIs computed using the Clopper-Pearson method. All statistical analyses were performed using SAS software (version 9.02).

This study is registered with ClinicalTrials.gov, number NCT01928394.

ROLE OF THE FUNDING SOURCE

The funder provided the study drug and worked with the investigators to design the study, and to collect, analyse, and interpret the data. All authors made the decision to submit the report for publication, and all drafts of the report were prepared by the corresponding author with input from coauthors and editorial assistance from professional medical writers, funded by the sponsor. Raw data were made accessible to the authors and professional medical writers.

RESULTS

PATIENTS AND TREATMENT

From November 18, 2013, through July 28, 2015, 216 patients with SCLC were enrolled and treated, including 98 patients in the nivolumab-3 cohort. While the nivolumab-1/ipilimumab-3 and nivolumab-3/ipilimumab-1 regimens were expected to be tolerable based on prior studies in other tumour types,[15,16,21,22] an initial safety evaluation of nivolumab-1/ipilimumab-1 was conducted. Patients in this first combination–dose-level cohort, nivolumab-1/ipilimumab-1 (n=3), tolerated the combination well, allowing for further escalation and expansion in the other two

combination cohorts: nivolumab-1/ipilimumab-3 (n=61) and nivolumab-3/ipilimumab-1 (n=54) (figure 1). Data on the three patients who remained in the nivolumab-1/ipilimumab-1 cohort are provided as supplementary materials (pages 20–22, appendix). At database lock, the median follow-up for patients continuing in the study was 198·5 days (interquartile range [IQR], 163·0–464·0), 361·0 days (IQR, 273·0–470·0), and 260·5 days (IQR, 248·0–288·0) in the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, respectively (page 23, appendix). In the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, 59%, 48%, and 57% of patients, respectively, had been treated with two or more previous regimens; 31%, 38%, and 39%, respectively, had platinum-resistant disease (table 1).

Patients received a median of 3.5 infusions of nivolumab (IQR, 2·0–6·0) in the nivolumab-3 cohort, three infusions each of nivolumab (IQR, 2·0–14·0) and ipilimumab (IQR, 2·0–4·0) in the nivolumab-1/ipilimumab-3 cohort, and two infusions each of nivolumab (IQR, 2·0–6·0) and ipilimumab (IQR, 2·0–4·0) in the nivolumab-3/ipilimumab-1 cohort (page 23, appendix). At the time of analysis, 79%, 69%, and 80% of patients in the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, respectively, had discontinued treatment; the most common cause was disease progression (page 23, appendix).

CLINICAL ACTIVITY

The rate of confirmed objective response was 10% (10/98, 95% CI, 5–18) with nivolumab-3, 23% (14/61, 95% CI, 13–36) with nivolumab-1/ipilimumab-3, and 19% (10/54, 95% CI, 9–31) with nivolumab-3/ipilimumab-1 (table 2; figures 2A, 2B, and 2C). The median duration of response was not reached (95% CI, 4·4–not reached) with nivolumab-3, 7·7 months (95% CI, 4·0–not reached) with nivolumab-1/ipilimumab-3, and 4·4 months (95% CI, 3·7–not reached) with nivolumab-3/ipilimumab-1. Median time to response was 2·0 months (IQR, 1·3–2·8), 2·1 months (IQR, 1·4–2·8), and 1·4 months (IQR, 1·3–2·7) in the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, respectively (table 2). At the time of database lock, eight of 10, seven of 14, and seven of 10 responses were ongoing in the nivolumab-3, nivolumab-1/ipilimumab-3 and nivolumab-3/ipilimumab-1 arms, respectively. Thirty, 15, and 6 patients in the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, respectively, continued treatment beyond progression.

In the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, median overall survival was 4·7 months (95% CI, 3·0–9·3), 7·7 months (95% CI, 3·6–not reached), and 7·2 months (95% CI, 3·7–not

reached), respectively, and median progression-free survival was 1·4 months (95% CI, 1·4–1·9), 2·6 months (95% CI, 1·4 –4·1), and 1·4 months (95% CI, 1·3 –2·2), respectively. At the time of analysis, 48/98 (49%), 30/61 (49%), and 25/54 (46%) patients had died, and 76/98 (78%), 44/61 (72%) and 42/54 (78%) experienced disease progression or death in the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, respectively. One-year overall survival rates were 31% (95% CI, 19–45) and 42% (95% CI, 28–56) for the nivolumab-3 and nivolumab-1/ipilimumab-3 cohorts, respectively (figure 3A), whereas 1-year progression-free survival rates were 11% and 19%, respectively (figure 3B). The nivolumab-3/ipilimumab-1 cohort had not met the 1-year milestone at the time of database lock.

SUBGROUP ANALYSES

Objective response rates were 10% (4/40), 28% (9/32), and 22% (5/23) for the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohort patients with one prior line of therapy, respectively, and 10% (6/58), 17% (5/29), and 16% (5/31), respectively, for patients with two or more prior therapies (page 24, appendix). Median overall survival and progression-free survival were not substantially different for patients with one versus two or more prior treatments, with the possible exception of longer progression-free survival in patients with one prior therapy receiving nivolumab-1/ipilimumab-3 (pages 4–9, appendix). Of nine patients who crossed over from the nivolumab monotherapy arm to the combination cohorts (one to nivolumab-1/ipilimumab-3 and eight to nivolumab-3/ipilimumab-1), eight patients experienced disease progression; one patient in the nivolumab-3/ipilimumab-1 arm withdrew consent, and response could not be determined.

In patients treated with a platinum agent in first line, objective response rates of 11% (6/55), 28% (7/25), and 19% (4/21) in patients with platinum-sensitive disease and of 10% (3/30), 17% (4/23), and 10% (2/21) in patients with platinum-resistant disease were reported for the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, respectively (pages 10–13 and page 24, appendix). Among patients with platinum-sensitive disease, 4% (2/55) and 8% (2/25) of patients in the nivolumab-3 and nivolumab-1/ipilimumab-3 arms, respectively, received subsequent platinum-based cancer therapy. No patients with platinum-sensitive disease in the nivolumab-3/ipilimumab-1 arm received subsequent platinum-based cancer therapy.

Overall, PD-L1 expression was evaluable in 146 patient samples (69%), of which 39 (27%) were provided as fresh biopsies and 107 (73%) were archived specimens. Of the evaluable samples, 24 (16%) had PD-L1 expression ≥1%,

and seven (5%) had PD-L1 expression ≥5% (table 1). Tumour responses occurred in patients with ≥1% and in patients with <1% tumour PD-L1 expression (pages 14–17, appendix).

Analysis of antitumour activity by levels of PD-L1 expression was a prespecified exploratory endpoint; all other subgroup analyses were performed post-hoc.

SAFETY

The rates of grade 3 or 4 treatment-related adverse events were 13% (13/98), 30% (18/61), and 19% (10/54), respectively, in the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts; four (4%), seven (11%), and four (7%) patients, respectively, discontinued study because of treatment-related adverse events (table 3 and page 23, appendix). One patient in the nivolumab-1/ipilimumab-3 cohort died from treatment-related myaesthenia gravis (page 3, appendix).[25]

Two patients had grade 2 limbic encephalitis: one in the nivolumab-3 cohort (reported as not treatment-related by investigator) and one in the nivolumab-1/ipilimumab-3 cohort (reported as treatment-related by investigator); both events resolved with immunosuppressive treatment. One patient in the nivolumab-3 cohort had grade 4 limbic encephalitis (reported as treatment-related by investigator) that did not resolve with intravenous immunoglobulin and corticosteroid treatment.

Pneumonitis occurred in nine patients (4%, three patients in each cohort), leading to treatment discontinuation in five patients; one patient in each cohort had grade 3 or 4 pneumonitis. Treatment-related grade 3 or 4 elevations in liver function tests resulted in treatment discontinuation for two patients in the nivolumab-3 cohort (page 29, appendix). One patient who crossed over from nivolumab-3 to nivolumab-1/ipilimumab-3 experienced treatment-related grade 3 elevations in alanine aminotransferase levels (page 3, appendix). Five patients in the nivolumab-1/ipilimumab-3 cohort had grade 3 or 4 asymptomatic lipase elevations without clinical signs of pancreatitis (table 3).

DISCUSSION

Our findings show that nivolumab monotherapy or in combination with ipilimumab provide clinically meaningful activity and an acceptable safety profile for patients with limited or extensive-stage SCLC and disease progression

after at least one prior regimen. The prognosis for patients with progression after prior treatment with platinum-based chemotherapy is poor. Patients with advanced SCLC frequently respond to first-line therapy; however, recurrence is inevitable, and effective options at the time of progression and in patients with platinum-resistant disease are limited. Patients with extensive-stage SCLC have a 2-year survival rate of <5%.[2,4,7]

Our trial enrolled a heterogeneous patient population with platinum-sensitive or platinum-resistant disease and a range of prior lines of therapy, making comparisons to second-line trials difficult. Responses and stable disease were seen in all treatment cohorts. Although the numbers of patients in subgroups were small, preliminary analysis showed similar response rates between platinum-sensitive and platinum-resistant subgroups, and similar activity in patients with one prior regimen and those with two or more prior regimens. Across treatment groups, responses were durable: 16 patients had responses lasting longer than 6 months (range 6·9 to 17·1+ months), including 13 patients with ongoing responses (range 7·0+ to 17·1+ months) at the time of database lock.

One phase 2 study evaluated temozolomide in a similar population of patients with disease progression after one or two prior chemotherapy regimens. While the objective response rates were similar to those demonstrated in our study—23% (11/48) in patients with platinum-sensitive disease and 13% (2/16) in patients with platinum-refractory disease—the median duration of response to temozolomide was lower: 3·5 months (range, 1·4–14·7 months) for all treated patients.[26] A newer agent, Rova-T, a DLL3 targeted antibody drug conjugate, demonstrated anti-tumour activity and manageable toxicity in a phase 1 study of patients with SCLC and progression after one or two previous lines of therapy.[27] The objective response rate was 44% (7/16) in patients positive for the DLL3 biomarker treated at the maximum tolerated doses.

Limitations of our study include that the study cohorts were not randomised, and the study was not powered for formal comparisons across cohorts. Baseline characteristics were generally similar across the cohorts, and although the combination cohorts showed similar response rates, responses appeared to be deeper with the nivolumab-1/ipilimumab-3 regimen. This dosing regimen has also been shown to be efficacious in previously untreated melanoma.[16]

The activity of nivolumab as monotherapy or combined with ipilimumab as observed in patients irrespective of platinum sensitivity or line of therapy is an important aspect differentiating immune-checkpoint inhibitors from topotecan or amrubicin in SCLC. Response rates to topotecan depend on chemosensitivity, driven by tumour resistance mutations.[7,8] In contrast, the genomically unstable nature of SCLC[2] may make it sensitive to immune-

checkpoint blockade via induction or restoration of a tumour antigen-driven immune response. As few lymphocytes are observed in SCLC tumours,[28] one hypothesis is that there is a greater need to target the lymphoid compartment with CTLA-4 inhibition in addition to PD-1 inhibition to maximise the treatment effect.[29]

Some studies have shown increased activity of PD-1 blockade in patients with PD-L1–expressing NSCLC. However, data, including that from this study, suggest that there is a lower prevalence of PD-L1 expression in SCLC versus NSCLC.[9,10,30] A trial of pembrolizumab, a PD-1 immune checkpoint inhibitor, reported an initial response rate of 25% (4/16) and durable responses in patients with PD-L1–positive extensive-stage SCLC.[30] In our study, objective responses were observed in patients regardless of PD-L1 expression, including deep tumour responses in patients with PD-L1 tumour expression <1%. Whether PD-L1 expression is predictive of benefit in SCLC must await analysis in a larger population.

While over half of patients in this trial had two or more prior treatments, the 1-year survival rates, 31% and 42% for nivolumab-3 and nivolumab-1/ipilimumab-3, respectively, were comparable with or better than those reported in historical trials of second-line topotecan or amrubicin.[7,8,26] Consistent with other trials with immune checkpoint inhibitors across multiple solid tumours, and unlike topotecan trials,[8] this trial demonstrated a flattening of the overall survival curves for the nivolumab-3 and nivolumab-1/ipilimumab-3 cohorts, suggesting a survival benefit in a subset of patients.[9,10,12] However, due to the small numbers in this trial, it is difficult to determine when this occurs. Also consistent with prior randomized trials of immuno-oncology agents, there appears to be more impact on overall survival than progression-free survival.

Adverse events with nivolumab monotherapy and nivolumab plus ipilimumab were managed using established safety guidelines.[9,10,13,16] Most toxicities in the nivolumab-3 and nivolumab-3/ipilimumab-1 cohorts were mild to moderate, with only four (4%) and four (7%) patients discontinuing because of toxicity, respectively. A higher rate of treatment-related grade 3 or 4 adverse events was seen in the nivolumab-1/ipilimumab-3 cohort (30% [18/61] *vs* 13% [13/98] for nivolumab-3), with seven (11%) patients discontinuing because of toxicity. This regimen was used effectively and safely in a phase 3 trial in patients with melanoma, suggesting that this schedule is feasible in patients with SCLC.[16] In all cohorts, fewer treatment-related toxicities were reported when compared with trials of topotecan or amrubicin.[7,8]

Three patients had limbic encephalitis, and one patient receiving nivolumab plus ipilimumab died of myaesthenia gravis. Autoimmune encephalitis and myaesthenia gravis have been reported, albeit rarely, with both nivolumab and

ipilimumab.[9,31-36] The frequency of these events seems to be higher in SCLC, perhaps due to the tendency for paraneoplastic neurological syndromes associated with this disease. Pneumonitis was reported in nine patients. It is critical to closely monitor for immune-related adverse events and/or unmasking of previously subclinical autoimmune disease processes, with prompt implementation of safety guidelines for effective management.

On the basis of these encouraging phase 1/2 data, phase 3 studies for nivolumab (240 mg every 2 weeks) as a flat dose and nivolumab plus ipilimumab (1 mg/kg nivolumab and 3 mg/kg ipilimumab every 3 weeks for two 42-day cycles followed by nivolumab [240 mg every 2 weeks]) as maintenance therapy (in non-progressing patients) after first-line chemotherapy (CheckMate 451, NCT02538666), and for nivolumab (240 mg every 2 weeks) versus single agent chemotherapy as second-line therapy (CheckMate 331, NCT02481830) in SCLC were initiated and are currently ongoing.

AUTHOR CONTRIBUTIONS

EC, SJA, JLM, JB, PAO, MT, JPE, DJ, MCP, DTL, FDB, MAM, PAA, LH, AA, RNP, JE, IC, PB, AA, and PS collected, analysed and interpreted data. OC designed the study, collected, analysed and interpreted the data, and designed the figures. CH collected, analysed and interpreted the data. C-SL designed the study, analysed and interpreted the data, and designed the figures. Development of the first draft was performed by SJA and EC. All authors contributed to drafting the manuscript and provided final approval to submit for publication.

DECLARATION OF INTERESTS

JLM has received personal fees from, reimbursement of trial-associated costs, and non-financial support from Bristol-Myers Squibb. PAO has received consulting fees from Amgen and Bristol-Myers Squibb, and clinical trial funding from Armo Biosciences, Bristol-Myers Squibb, Merck, and MedImmune. MT has served on advisory boards and received honoraria from Eisai and Onyx. MCP has received grant support from Bristol-Myers Squibb to conduct this study as well as personal fees from AbbVie, CelGene, Clovis Oncology, Genentech, Novartis, and grants from Novartis, OncoMed Pharmaceuticals, and Stemcentrix. DTL has received financial support from Bristol-Myers Squibb to conduct this study. FDB has served on advisory boards for and has received personal fees from Bristol-Myers Squibb, Merck, and Novartis. PAA has served as a consultant to and held an advisory role for Amgen, Bristol-Myers Squibb, Roche-Genentech, MSD, Novartis, and Ventana, as well as received research funds

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Panel: Research in context (308 words)

Evidence before this study

We searched the scientific literature for outcomes following failure of first-line treatment in patients with small-cell lung cancer (SCLC) and available subsequent treatment options. The search terms “SCLC”, “recurrent”, “relapsed”, “second-line”, “third-line”, “phase 1”, “phase 2” and/or “phase 3” were used in PubMed focusing on reports and meta-analyses during the 10-year period prior to the start of the trial. To investigate the potential for immunotherapy in SCLC, the terms “SCLC” and “immune response”, “immunotherapy”, “PD-1”, “CTLA-4”, “NSCLC”, “PD-L1”, “nivolumab”, “ipilimumab”, “MK3475”, “lambrolizumab”, “MPDL3280A”, “MEDI4736”, and “tremelimumab” were used to search PubMed, congress abstracts from the annual meetings of the American Association of Cancer Research, American Society of Clinical Oncology, European Cancer Congress, and World Conference on Lung Cancer, and for ongoing trials in Clinicaltrials.gov.

The searches revealed poor survival outcomes for patients with recurrent/relapsed SCLC and no treatment options beyond second line. The following pieces of evidence underscored the rationale for investigating nivolumab and nivolumab plus ipilimumab in SCLC: SCLC is immunogenic, ipilimumab in combination with chemotherapy was active in extensive disease-SCLC, and nivolumab and nivolumab plus ipilimumab showed encouraging activity in non-small cell lung cancer in phase 1/2 trials.

Added value of this study

Nivolumab alone and in combination with ipilimumab demonstrated durable objective responses, encouraging survival, and manageable safety in patients with advanced SCLC who had progressed after one or more prior regimens. To our knowledge, this is the first trial showing activity of nivolumab and nivolumab plus ipilimumab in SCLC, in a hard-to-treat population of patients with limited treatment options.

Implications of all the available evidence

Based on the notable rates and duration of responses and the median overall survival seen with nivolumab plus ipilimumab treatment in this patient population, phase 3 studies for nivolumab and nivolumab plus ipilimumab as maintenance therapy (in non-progressing patients) after first-line chemotherapy (CheckMate 451, NCT02538666), and for nivolumab versus chemotherapy as second-line therapy (CheckMate 331, NCT02481830) in SCLC are ongoing.

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TABLES AND FIGURES

Table 1: **Baseline patient characteristics***

	Nivolumab-3 (n=98)	Nivolumab-1/ ipilimumab-3 (n=61)	Nivolumab-3/ ipilimumab-1 (n=54)
Median age, years	62·5 (57·0–68·0)	66·0 (58·0–71·0)	61·0 (56·0–65·0)
Age ≥75 years	9 (9%)	7 (11%)	0
Male sex	61 (62%)	35 (57%)	32 (59%)
Race			
White	91 (93%)	60 (98%)	52 (96%)
Black/African American	3 (3%)	1 (2%)	0
Other	4 (4%)	0	1 (2%)
Not reported	0	0	1 (2%)
Prior treatment regimens			
1	40 (41%)	32 (52%)	23 (43%)
2–3	55 (56%)	23 (38%)	28 (52%)
>3	3 (3%)	6 (10%)	3 (6%)
First-line platinum-treated patients†			
Platinum-sensitive	55 (56%)	25 (41%)	21 (39%)
Platinum-resistant‡	30 (31%)	23 (38%)	21 (39%)
Unknown	10 (10%)	11 (18%)	8 (15%)
Smoking status			
Current/former smoker	95 (97%)	57 (93%)	48 (89%)
Never smoked	3 (3%)	4 (7%)	5 (9%)
Unknown	0	0	1 (2%)
PD-L1 expression level, §			
≥1%	10 (14%)	9 (24%)	5 (13%)
<1%	59 (86%)	28 (76%)	35 (88%)
≥5%	4 (6%)	2 (5%)	1 (3%)
<5%	65 (94%)	35 (95%)	39 (98%)
Indeterminate/not evaluable/ missing	29 (30%)	24 (39%)	14 (26%)

Data presented as n, n (%), or median (IQR) unless otherwise stated. IQR=interquartile range. PD-L1=programmed death-ligand 1. *No formal between-group comparison of incidence was performed for the baseline characteristics. †Three patients in the nivolumab-3 arm, two patients in the nivolumab-1/ipilimumab-3 arm, and four patients in the nivolumab-3/ipilimumab-1 arm did not receive first-line platinum therapy and did not meet eligibility criteria. ‡Defined as a patient who relapsed <90 days after chemotherapy. § Percentage of PD-L1 evaluable patients; may exceed 100% due to rounding.

Table 2: **Tumour response***

	Nivolumab-3 (n=98)	Nivolumab-1/ ipilimumab-3 (n=61)	Nivolumab-3/ ipilimumab-1 (n=54)
Objective response rate	10 (10%)	14 (23%)	10 (19%)
(95% CI)	(5–18)	(13–36)	(9–31)
Best overall response			
Complete response	0	1 (2%)	0
Partial response	10 (10%)	13 (21%)	10 (19%)
Stable disease	22 (22%)	13 (21%)	9 (17%)
Progressive disease	52 (53%)	23 (38%)	29 (54%)
Unable to determine†	12 (12%)	8 (13%)	6 (11%)
Not reported	2 (2%)	3 (5%)	0
Time to objective response (IQR), months‡	2·0 (1·3–2·8)	2·1 (1·4–2·8)	1·4 (1·3–2·7)
Median duration of response (95% CI), months‡	NR (4·4–NR)	7·7 (4·0–NR)	4·4 (3·7–NR)

Data presented as n or n (%) unless otherwise stated. IQR=interquartile range; NR=not reached. *All patients were enrolled at least 90 days prior to database lock. †In the nivolumab-3 cohort, seven patients died prior to disease assessment, four patients discontinued early (one due to toxicity, three due to clinical progression), and one patient withdrew consent prior to completing protocol; in the nivolumab-1/ipilimumab-3 cohort, five patients died prior to disease assessment, one patient discontinued early due to clinical progression, one patient was not evaluable as first assessment was not performed, and one patient withdrew consent for scans and follow-up visits; in the nivolumab-3/ipilimumab-1 cohort, two patients died prior to disease assessment, three patients discontinued early (two due to clinical progression and one due to toxicity), and CT scan was not performed on one patient. ‡The analysis used data from all patients who had a response (10, 14, and 10 patients, respectively, in the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 groups).

Table 3: **Treatment-related adverse events of any grade reported in ≥10% of patients in any treatment cohort***

Event	Nivolumab-3 (n=98)			Nivolumab-1/ipilimumab-3 (n=61)			Nivolumab-3/ipilimumab-1 (n=54)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any event	39 (40%)	9 (9%)	4 (4%)	30 (49%)	14 (23%)	4 (7%)	30 (56%)	8 (15%)	2 (4%)
Fatigue	10 (10%)	1 (1%)	0	16 (26%)	0	0	12 (22%)	0	0
Pruritus	11 (11%)	0	0	11 (18%)	1 (2%)	0	5 (9%)	0	0
Diarrhoea	7 (7%)	0	0	10 (16%)	3 (5%)	0	8 (15%)	1 (2%)	0
Nausea	7 (7%)	0	0	6 (10%)	1 (2%)	0	4 (7%)	0	0
Decreased appetite	6 (6%)	0	0	4 (7%)	0	0	6 (11%)	0	0
Pneumonitis	2 (2%)	1 (1%)	0	1 (2%)	1 (2%)	0	2 (4%)	0	1 (2%)
Vomiting	2 (2%)	1 (1%)	0	2 (3%)	1 (2%)	0	5 (9%)	0	0
Hypothyroidism	3 (3%)	0	0	9 (15%)	1 (2%)	0	4 (7%)	0	0
Increased aspartate aminotransferase	3 (3%)	0	0	3 (5%)	0	0	0	1 (2%)	0
Hyperthyroidism	2 (2%)	0	0	7 (11%)	0	0	3 (6%)	0	0
Hyponatraemia	2 (2%)	0	0	0	1 (2%)	0	0	0	0
Increased alanine aminotransferase	2 (2%)	1 (1%)	0	2 (3%)	0	0	0	1 (2%)	0
Increased transaminases	2 (2%)	0	0	0	0	0	1 (2%)	1 (2%)	0
Rash	2 (2%)	0	0	10 (16%)	2 (3%)	0	4 (7%)	0	0
Anaemia	1 (1%)	0	0	4 (7%)	0	0	3 (6%)	1 (2%)	0
Dyspnoea	1 (1%)	0	0	0	1 (2%)	0	1 (2%)	2 (4%)	0
Rash, maculopapular	1 (1%)	0	0	6 (10%)	2 (3%)	0	2 (4%)	0	0
Adrenal insufficiency	0	0	0	1 (2%)	0	0	1 (2%)	1 (2%)	0
Aseptic meningitis	0	0	0	0	0	0	0	0	1 (2%)
Cardiomyopathy	0	0	0	0	0	1 (2%)	0	0	0
Colitis	0	0	0	1 (2%)	1 (2%)	0	0	1 (2%)	0
Decreased neutrophil count	0	0	0	0	1 (2%)	0	0	0	0

Drug-induced liver injury	0	1 (1%)	0	0	0	0	0	0	0
Encephalitis	0	0	1 (1%)	1 (2%)	0	0	0	0	0
Eyelid ptosis	0	0	0	0	1 (2%)	0	0	0	0
Haemorrhagic gastritis	0	0	0	0	1 (2%)	0	0	0	0
Hyperglycaemia	0	0	1 (1%)	2 (3%)	0	1 (2%)	0	0	0
Hypertransaminasaemia	0	0	0	0	1 (2%)	0	0	0	0
Hypoxia	0	1 (1%)	0	0	0	0	0	0	0
Ileus	0	0	0	0	0	0	0	1 (2%)	0
Increased amylase	0	0	1 (1%)	3 (5%)	1 (2%)	0	2 (4%)	0	0
Increased gamma glutamyltransferase	0	0	1 (1%)	0	0	0	0	1 (2%)	0
Increased lipase	0	0	0	2 (3%)	4 (7%)	1 (2%)	0	0	0
Large intestine perforation	0	0	0	0	0	0	0	1 (2%)	0
Myaesthenia gravis	0	0	0	0	1 (2%)	0	0	0	0
Non-cardiac chest pain	0	1 (1%)	0	0	0	0	0	0	0
Pericardial effusion	0	1 (1%)	0	0	0	0	0	0	0
Peripheral neuropathy	0	0	0	0	0	0	0	1 (2%)	0
Renal failure	0	0	0	0	0	1 (2%)	0	0	0
Stomatitis	0	1 (1%)	0	1 (2%)	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	3 (6%)	1 (2%)	0
Tumour lysis syndrome	0	0	0	0	0	0	0	1 (2%)	0

Data presented as n or n (%). *Safety analyses included all patients who were enrolled at least 90 days prior to database lock; patients with adverse events after crossover from nivolumab monotherapy to combination treatment are excluded. Some patients had more than one adverse event. One patient in the nivolumab-1/ipilimumab-3 treatment cohort died from myaesthenia gravis considered treatment-related. This table reports any-grade treatment-related events in ≥10% of patients and all grade 3–4 events. No treatment-related grade 5 events were reported. All causality adverse events and serious adverse events are listed in pages 25–28, appendix.

Figure Legends

***Figure 1*: Study design**

Footnote to Figure 1: *Nivolumab 1 mg/kg plus ipilimumab 1 mg/kg: first patient enrolled November 20, 2013; last patient enrolled December 19, 2013. †Nivolumab monotherapy: first patient enrolled November 18, 2013; last patient enrolled July 28, 2015. ‡Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg: first patient enrolled February 3, 2014; last patient enrolled July 17, 2015. §Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg: first patient enrolled October 20, 2014; last patient enrolled April 9, 2015. Data are based on a November 6, 2015 database lock. DOR=duration of response. IV=intravenous. ORR=objective response rate. OS=overall survival. PD-L1=programmed death ligand 1. PFS=progression-free survival. Q2W=every 2 weeks. Q3W=every 3 weeks. RECIST=Response Evaluation Criteria In Solid Tumors. SCLC=small cell lung cancer.

***Figure 2*: Changes in tumour burden in individual patients treated in all lines**

Only patients with target lesions at baseline and with at least one on-treatment tumour assessment were included (nivolumab-3, n = 80; nivolumab-1/ipilimumab-3, n = 46; nivolumab-3/ipilimumab-1, n = 47). Shown is the tumour burden (assessed as the longest linear dimension) over time in patients receiving nivolumab-3 (A), nivolumab-1/ipilimumab-3 (B), and nivolumab-3/ipilimumab-1 (C). Horizontal reference line indicates the 30% reduction consistent with a Response Evaluation Criteria in Solid Tumours (RECIST), version 1·1, objective response. Tumour regression followed both conventional and immune-related patterns of response, such as a prolonged reduction in the tumour burden in the presence of new lesions. CR=complete response. PR=partial response.

***Figure 3:* Kaplan-Meier curves of overall survival and progression-free survival in all patients**

Panels show the Kaplan-Meier curves for overall survival (A) and progression-free survival (B). Symbols indicate censored observations, and the horizontal line indicates the rates of survival at 1 year. NR = not reached.

Supplementary Appendix

This appendix is a supplement to: Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone or in combination with ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a prospective, open-label, phase 1/2 trial. *Lancet Oncol*.

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Clinical trial registration number: NCT01928394

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Supplemental Text

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Criteria for dose delays and treatment discontinuation

The criteria for dose delay of nivolumab, ipilimumab, or both include the following treatment-related adverse events: grade ≥2 non-skin event (except for grade 2 fatigue), grade 3 skin, grade 3 laboratory abnormality (except for asymptomatic amylase and lipase). If the patient has normal baseline aspartate aminotransferase (AST), normal alanine aminotransferase (ALT) or normal total bilirubin levels, the dose will be delayed for grade 2 toxicity or greater. If baseline is grade 1 for these laboratory parameters, dose will be delayed for grade 3 toxicity or greater.

Criteria for permanent treatment discontinuation include the following treatment-related adverse events: grade 2 uveitis, grade 3 non-skin events lasting >7 days, grade 3 laboratory abnormalities of thrombocytopenia or liver function test, and all grade 4 events as well as laboratory abnormalities except for asymptomatic amylase or lipase elevations.

Case details: patient who died of treatment-related myaesthenia gravis in the nivolumab-1/ipilimumab-3 cohort

The patient was a 70-year-old male with a 1-year history of stage 4 SCLC, which was refractory to platinum/etoposide and radiation. The patient presented with ptosis and diplopia 16 days after starting treatment, and was hospitalised. He tested positive for acetylcholine receptor-modulating and striational antibodies. Nivolumab-1/ipilimumab-3 treatment was discontinued, and the patient was treated with prednisone, underwent three sessions of plasmapheresis, and was discharged 7 days later. The patient was readmitted 1 day later with dyspnoea and weakness, required intubation, and did not improve, despite treatment with steroids, plasmapheresis, or intravenous immunoglobulin. Complications with complete heart block, sepsis, and bleeding duodenal ulcers ensued, and medical care was withdrawn on day 22.

Treatment-related adverse events of grade 2 or higher in patients who crossed over from nivolumab monotherapy to nivolumab plus ipilimumab combination therapy

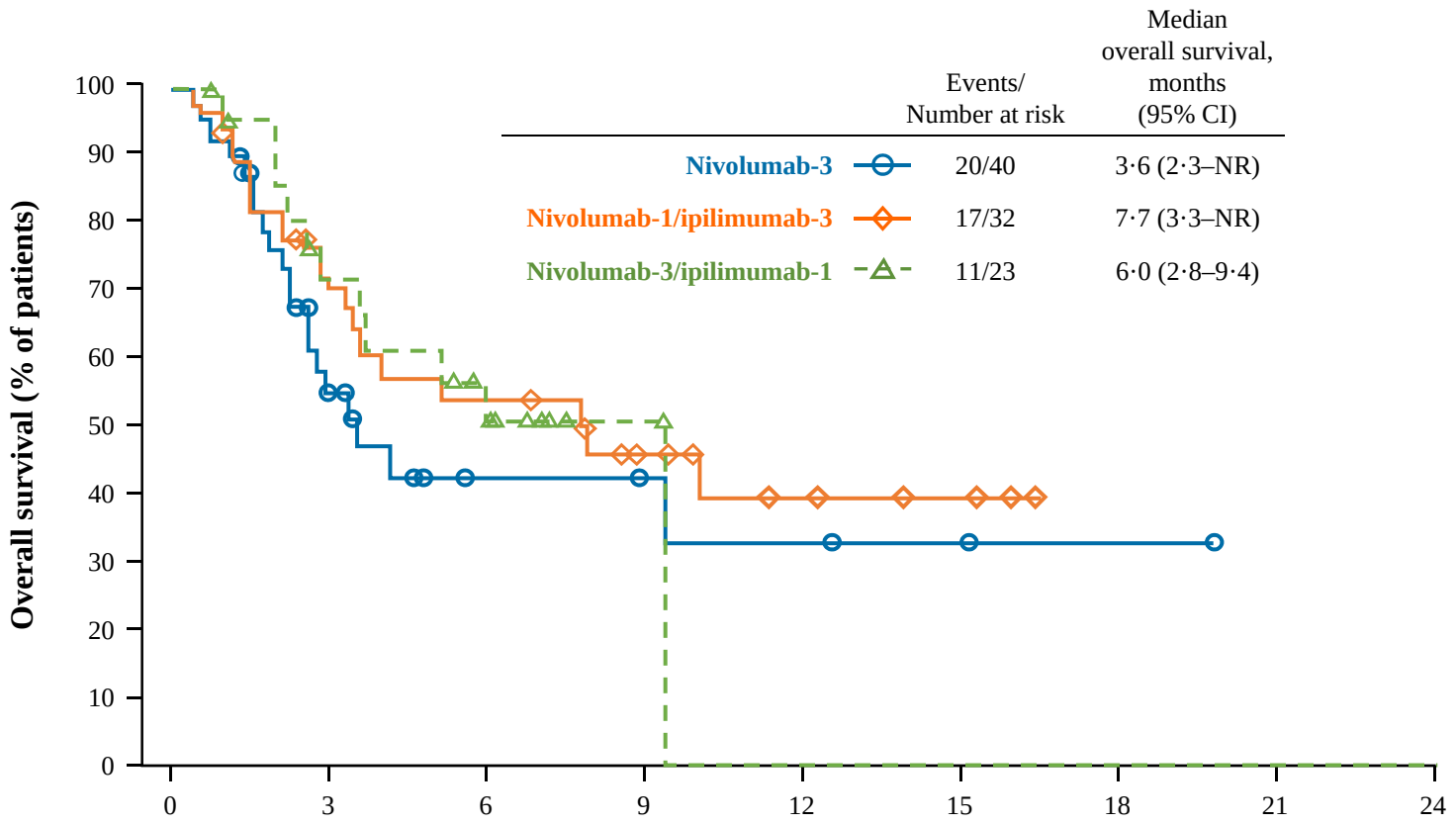
Treatment-related adverse events of grade 2 or higher occurred in three of nine patients who crossed over from nivolumab monotherapy to nivolumab plus ipilimumab combination therapy. One patient who crossed over to nivolumab-1/ipilimumab-3 treatment experienced grade 3 elevations in alanine aminotransferase levels and grade 2 elevations in aspartate aminotransferase and alkaline phosphatase levels. One patient who crossed over to nivolumab-3/ipilimumab-1 treatment experienced a grade 2 infusion-related reaction. One patient who crossed over to nivolumab-3/ipilimumab-1 treatment experienced a grade 2 maculopapular rash.

Figure S1: **Kaplan-Meier curves of overall survival for patients with one prior therapy and patients with two or more prior therapies**

Panels show the Kaplan-Meier curves for overall survival in patients with one prior therapy (A) and patients with two or more prior therapies (B). Symbols indicate censored observations, and the horizontal line indicates the rates of overall survival at 1 year (panel A only). CR=complete response; NA=not applicable; PR=partial response.

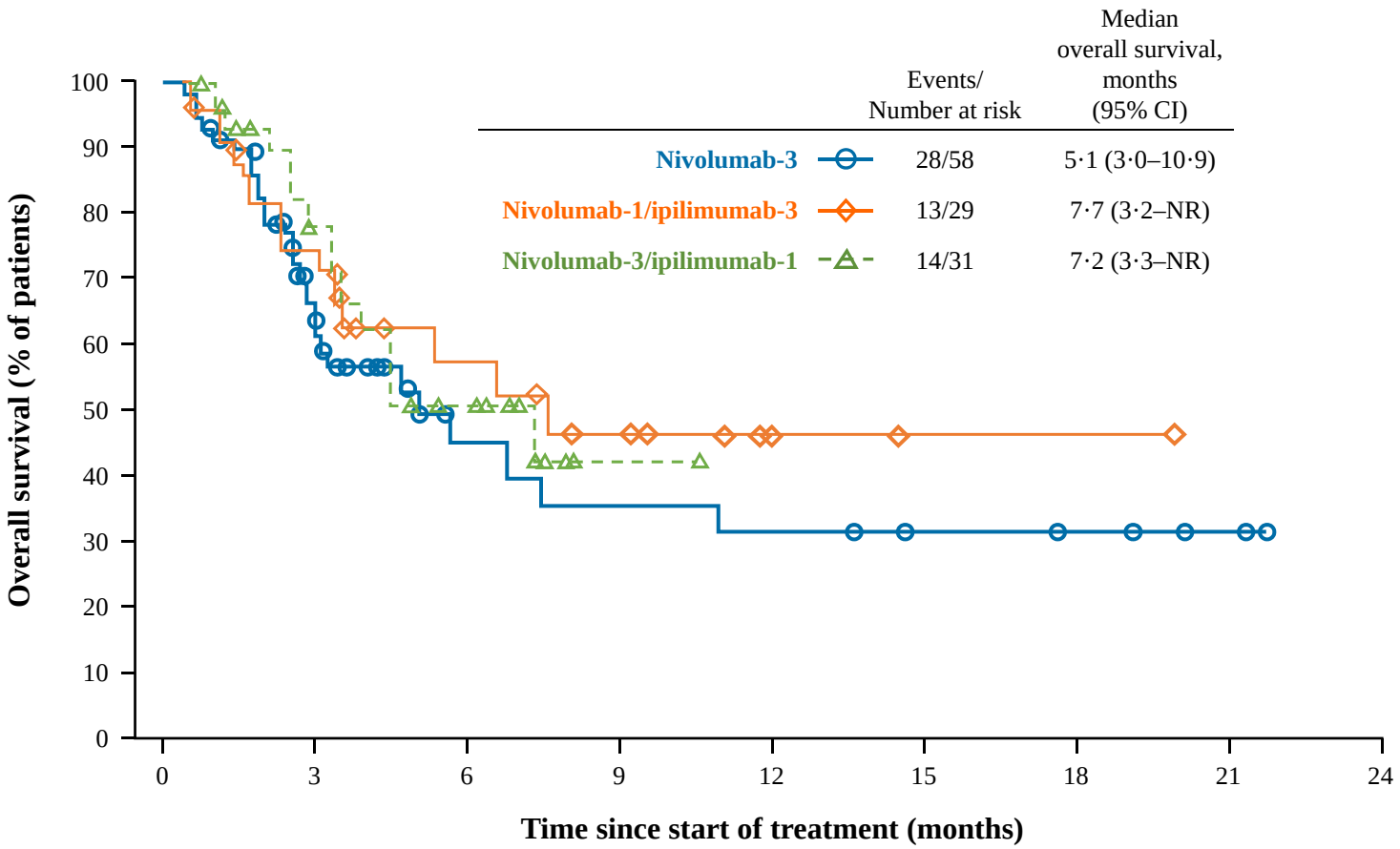
Figure S1: **Kaplan-Meier curves of overall survival for patients with one prior therapy and patients with two or more prior therapies**

A)



Number at risk									
Nivolumab-3	40	16	5	4	3	2	1	0	0
Nivolumab-1/ipilimumab-3	32	20	15	9	5	3	0	0	0
Nivolumab-3/ipilimumab-1	23	14	7	2	0	0	0	0	0
Number of censored patients									
Nivolumab-3	0	8	16	17	17	18	19	20	20
Nivolumab-1/ipilimumab-3	0	3	3	7	10	12	15	15	15
Nivolumab-3/ipilimumab-1	0	3	6	11	12	12	12	12	12

B)

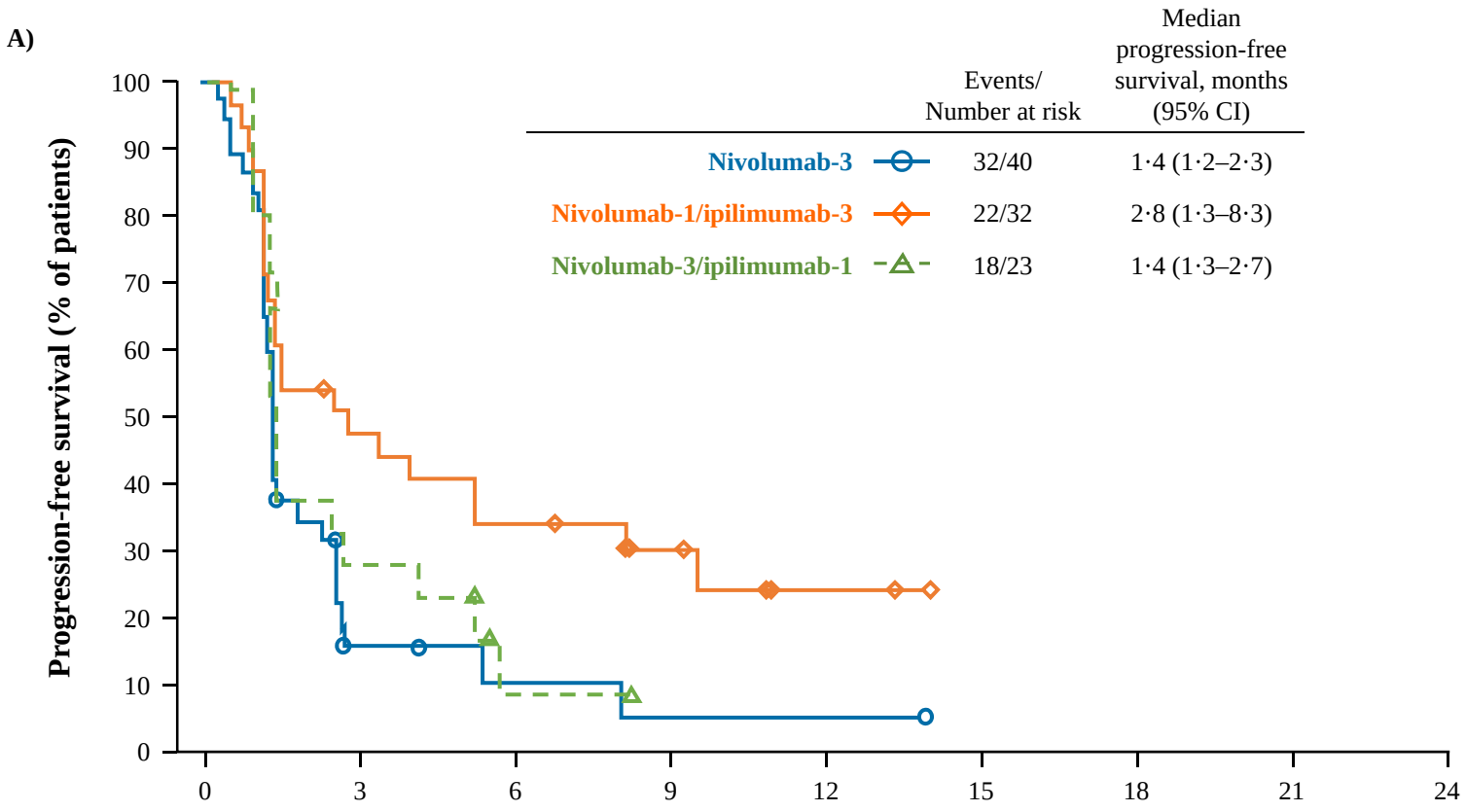


Number at risk									
Nivolumab-3	58	28	10	8	7	5	4	2	0
Nivolumab-1/ipilimumab-3	29	20	11	7	2	1	1	0	0
Nivolumab-3/ipilimumab-1	31	20	11	1	0	0	0	0	0
Number of censored patients									
Nivolumab-3	0	11	23	23	23	25	26	28	30
Nivolumab-1/ipilimumab-3	0	2	7	9	14	15	15	16	16
Nivolumab-3/ipilimumab-1	0	5	7	16	17	17	17	17	17

***Figure S2*: Kaplan-Meier curves of progression-free survival in patients with one prior therapy and patients with two or more prior therapies**

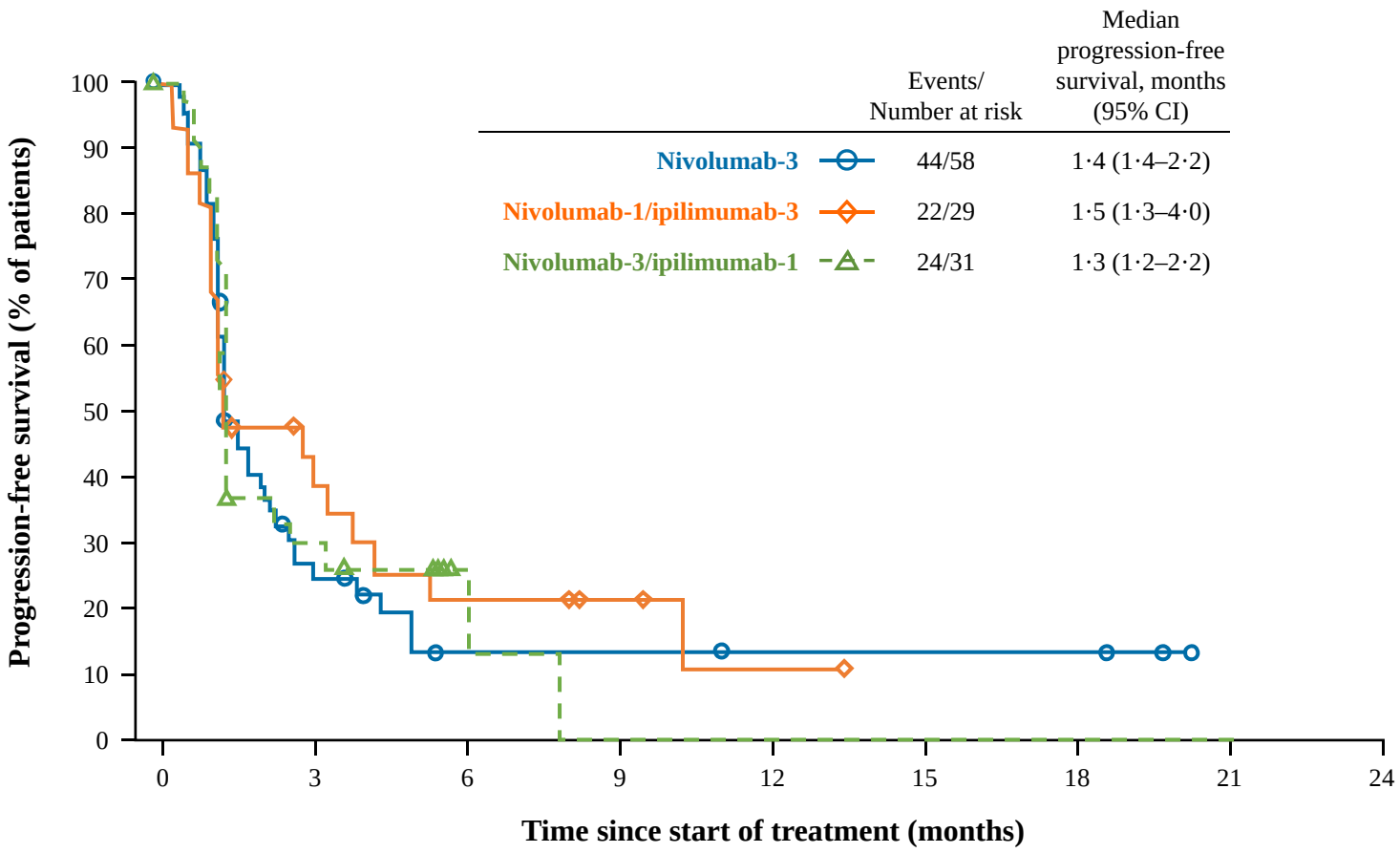
Panels show the Kaplan-Meier curves for progression-free survival in all patients (A), patients with one prior therapy (B), and patients with two or more prior therapies (C). Symbols indicate censored observations, and horizontal lines indicate the rates of progression-free survival at 1 year.

***Figure S2*: Kaplan-Meier curves of progression-free survival in patients with one prior therapy and patients with two or more prior therapies**



Number at risk								
Nivolumab-3	40	4	2	1	1	0	0	0
Nivolumab-1/ipilimumab-3	32	14	10	6	2	0	0	0
Nivolumab-3/ipilimumab-1	23	6	1	0	0	0	0	0
Number of censored patients								
Nivolumab-3	0	6	7	7	7	8	8	8
Nivolumab-1/ipilimumab-3	0	2	2	5	8	10	10	10
Nivolumab-3/ipilimumab-1	0	2	4	5	5	5	5	5

B)



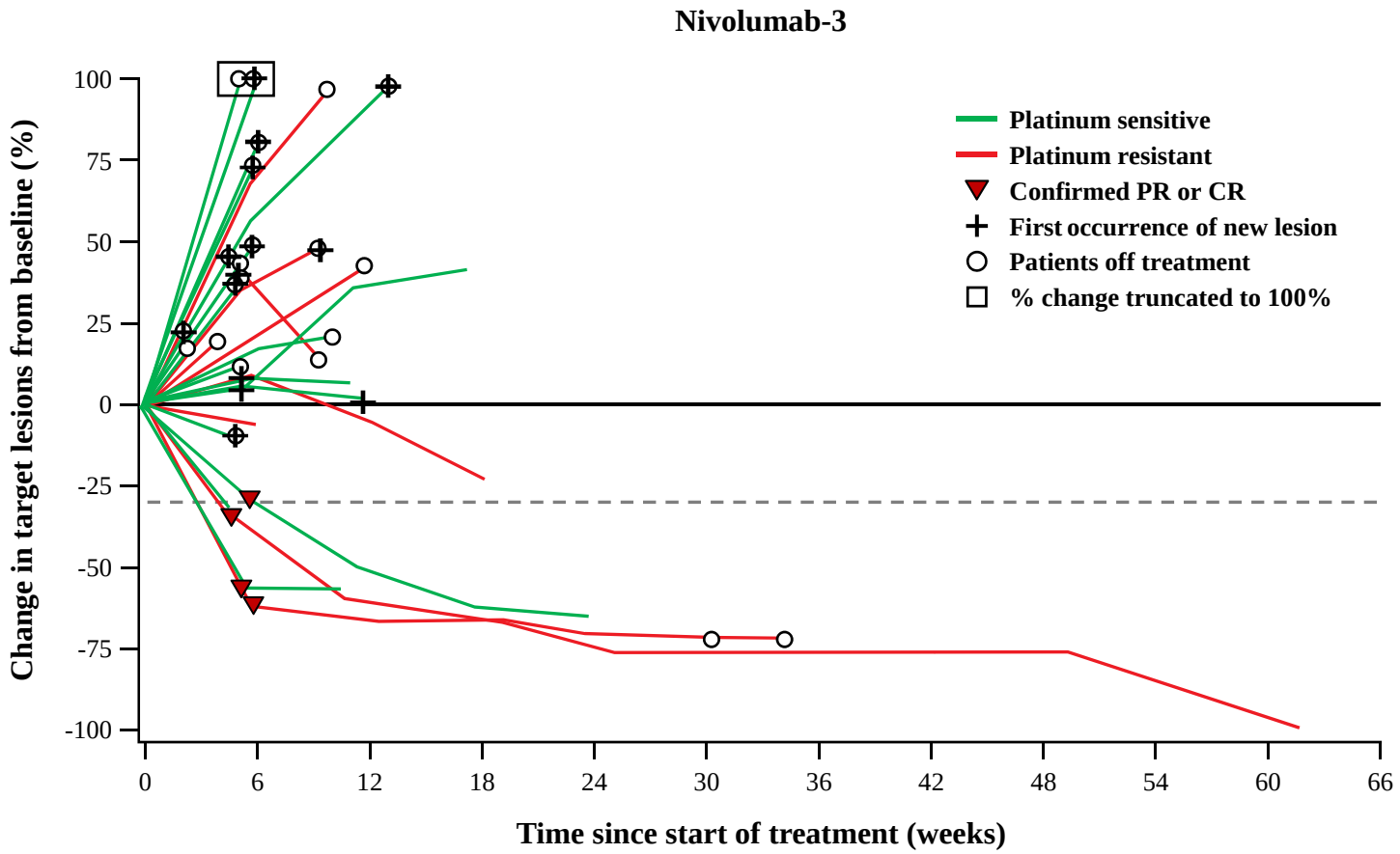
Number at risk								
Nivolumab-3	58	13	4	4	3	3	3	0
Nivolumab-1/ipilimumab-3	29	10	5	3	1	0	0	0
Nivolumab-3/ipilimumab-1	31	8	2	0	0	0	0	0
Number of censored patients								
Nivolumab-3	0	6	10	10	11	11	11	14
Nivolumab-1/ipilimumab-3	0	3	3	5	6	7	7	7
Nivolumab-3/ipilimumab-1	0	2	7	7	7	7	7	7

Figure S3: **Changes in tumour burden according to platinum sensitivity in individual patients treated in second line**

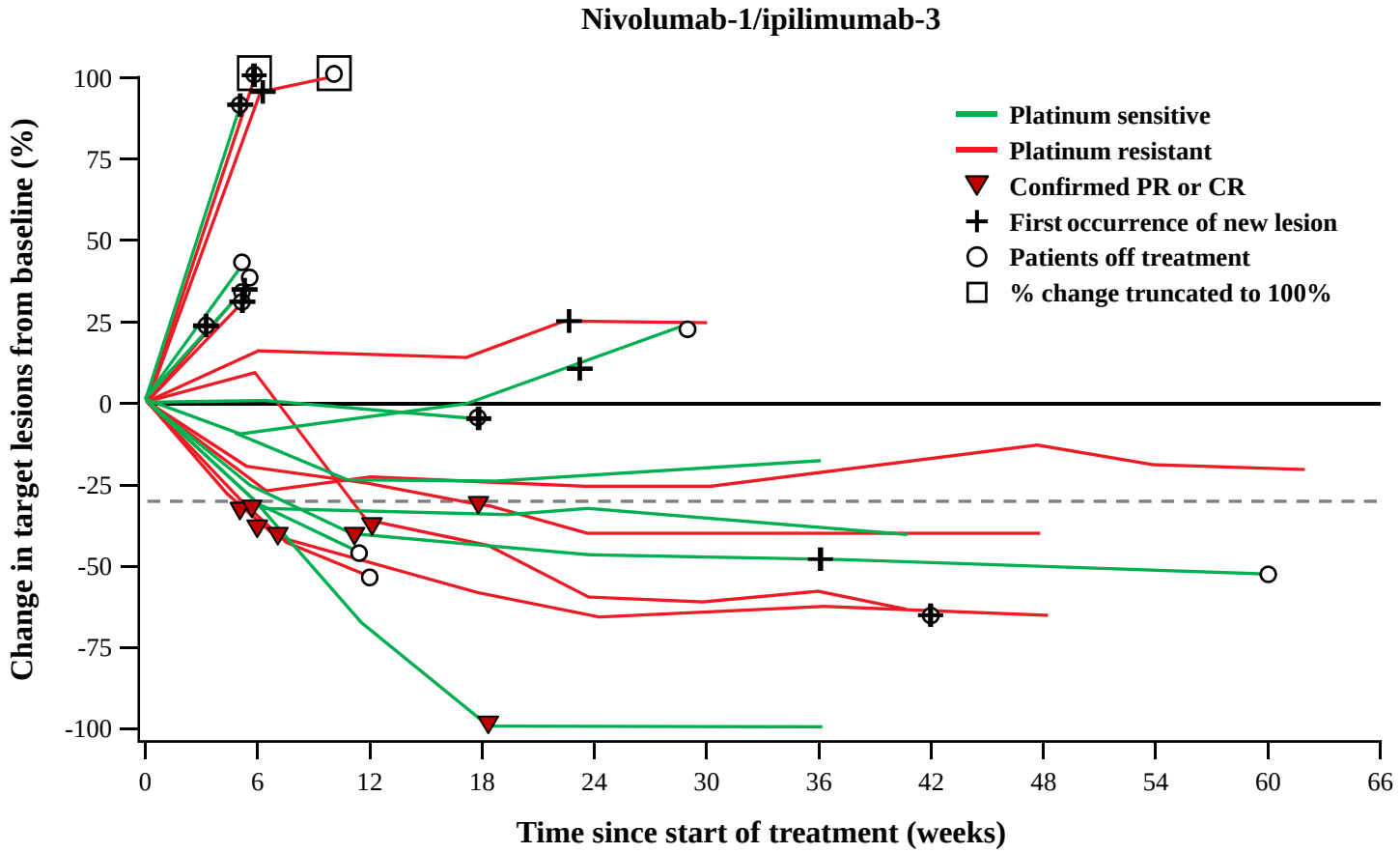
Only patients with target lesions at baseline and with ≥1 on-treatment tumour assessment were included (nivolumab-3, n=31; nivolumab-1/ipilimumab-3, n=21; nivolumab-3/ipilimumab-1, n=17). Panels show the tumour burden (assessed as the longest linear dimension) over time in patients receiving second-line nivolumab-3 (A), nivolumab-1/ipilimumab-3 (B), and nivolumab-3/ipilimumab-1 (C). Horizontal reference line indicates the 30% reduction consistent with a Response Evaluation Criteria in Solid Tumors (RECIST), version 1·1, objective response. CR=complete response; PR=partial response.

Figure S3: **Changes in tumour burden according to platinum sensitivity in individual patients treated in second line**

A)



B)


Nivolumab-1/ipilimumab-3
Platinum sensitive
Platinum resistant
Confirmed PR or CR
First occurrence of new lesion
Patients off treatment
% change truncated to 100%
Change in target lesions from baseline (%)
100
75
50
25
0
-25
-50
-75
-100
0
6
12
18
24
30
36
42
48
54
60
66
Time since start of treatment (weeks)

C)

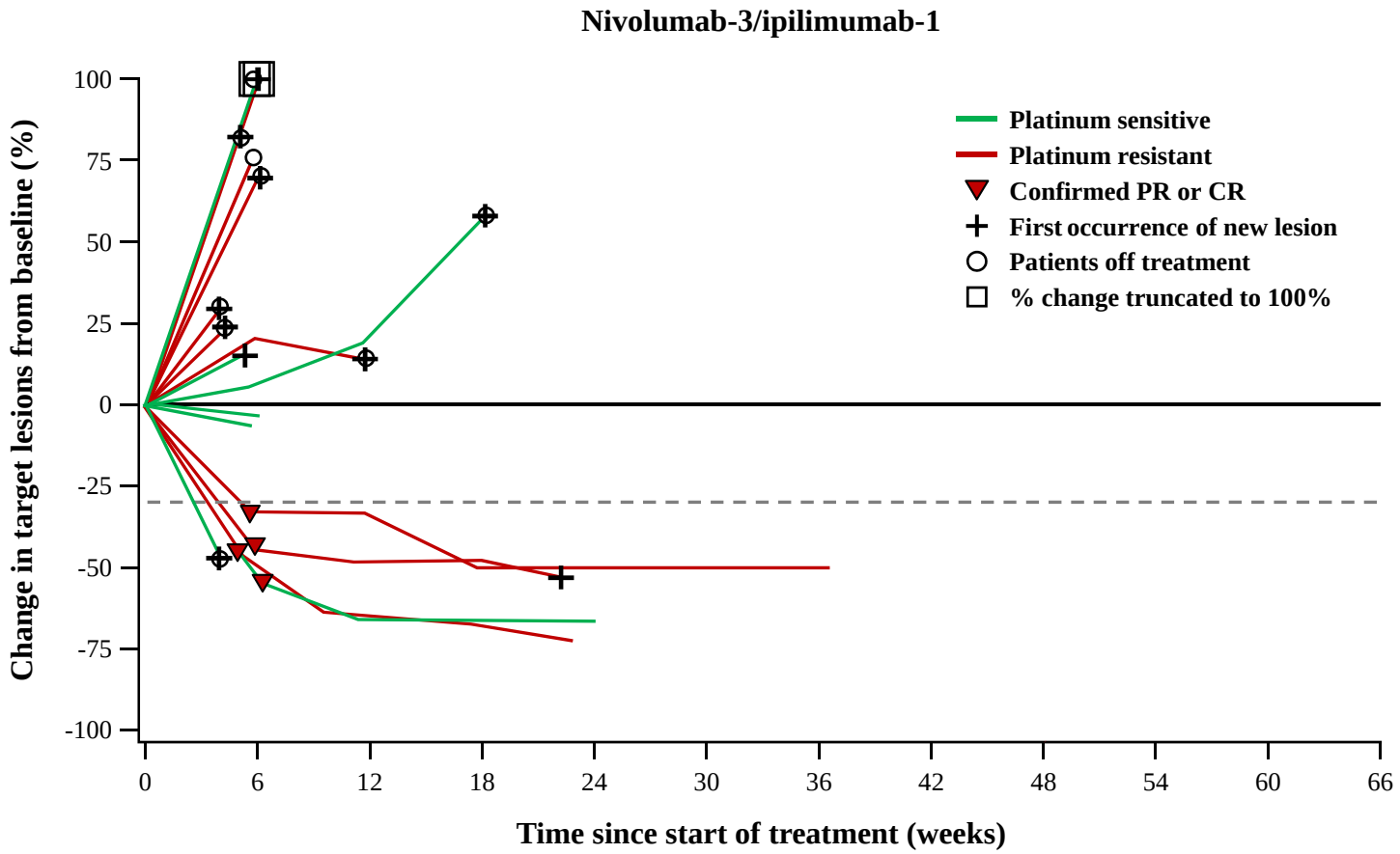
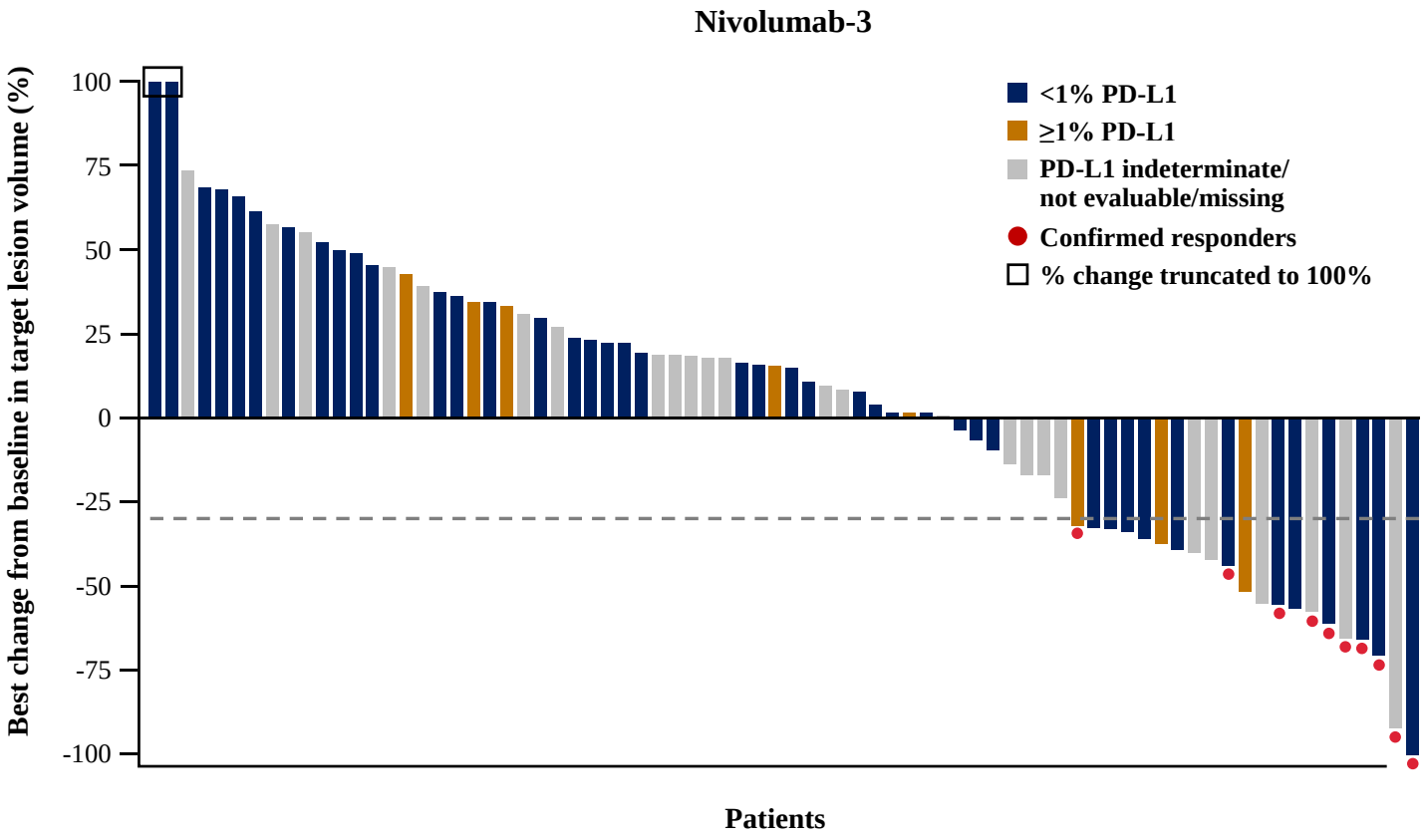

Nivolumab-3/ipilimumab-1
Change in target lesions from baseline (%)
100
75
50
25
0
-25
-50
-75
-100
0
6
12
18
24
30
36
42
48
54
60
66
Time since start of treatment (weeks)
Platinum sensitive
Platinum resistant
Confirmed PR or CR
First occurrence of new lesion
Patients off treatment
% change truncated to 100%

Figure S4: **Changes in tumour burden according to tumour PD-L1 expression status**

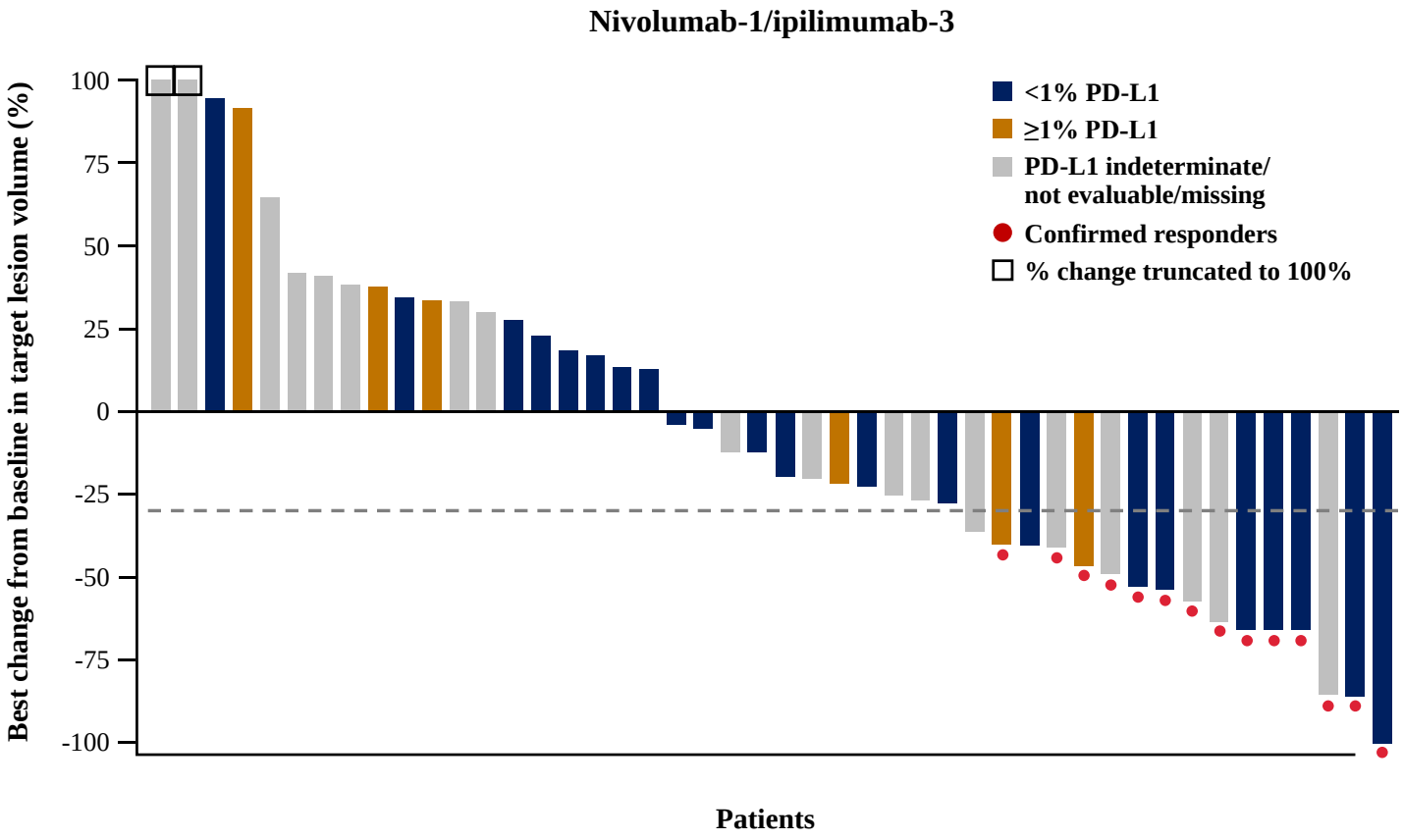
Only patients with target lesions at baseline and with ≥1 on-treatment tumour assessment were included (nivolumab-3, n=76; nivolumab-1/ipilimumab-3, n=46; nivolumab-3/ipilimumab-1, n=47). Panels show the maximum change from baseline in the target lesion according to tumour programmed death-ligand 1 (PD-L1) expression status using a 1% cut-off in patients receiving nivolumab-3 (A), nivolumab-1/ipilimumab-3 (B), and nivolumab-3/ipilimumab-1 (C). Assessments after progression or start of subsequent anticancer therapy are excluded. Negative/positive value means maximum tumour reduction/minimum tumour increase. Sixty-seven patient samples were indeterminate, nonevaluable, or missing. Horizontal reference lines indicate the 30% reduction consistent with a RECIST, version 1·1, response. The change in tumour burden was defined as the percentage decrease in the sum of the reference diameters of the target lesion from baseline to nadir, observed up to the date of progression (as assessed by the investigator per RECIST, version 1·1), subsequent anticancer therapy, or death. PD-L1=programmed death-ligand 1.

Figure S4: **Changes in tumour burden according to tumour PD-L1 expression status**

A)



B)


Nivolumab-1/ipilimumab-3
Best change from baseline in target lesion volume (%)
100
75
50
25
0
-25
-50
-75
-100
<1% PD-L1
≥1% PD-L1
PD-L1 indeterminate/
not evaluable/missing
Confirmed responders
% change truncated to 100%
Patients

C)

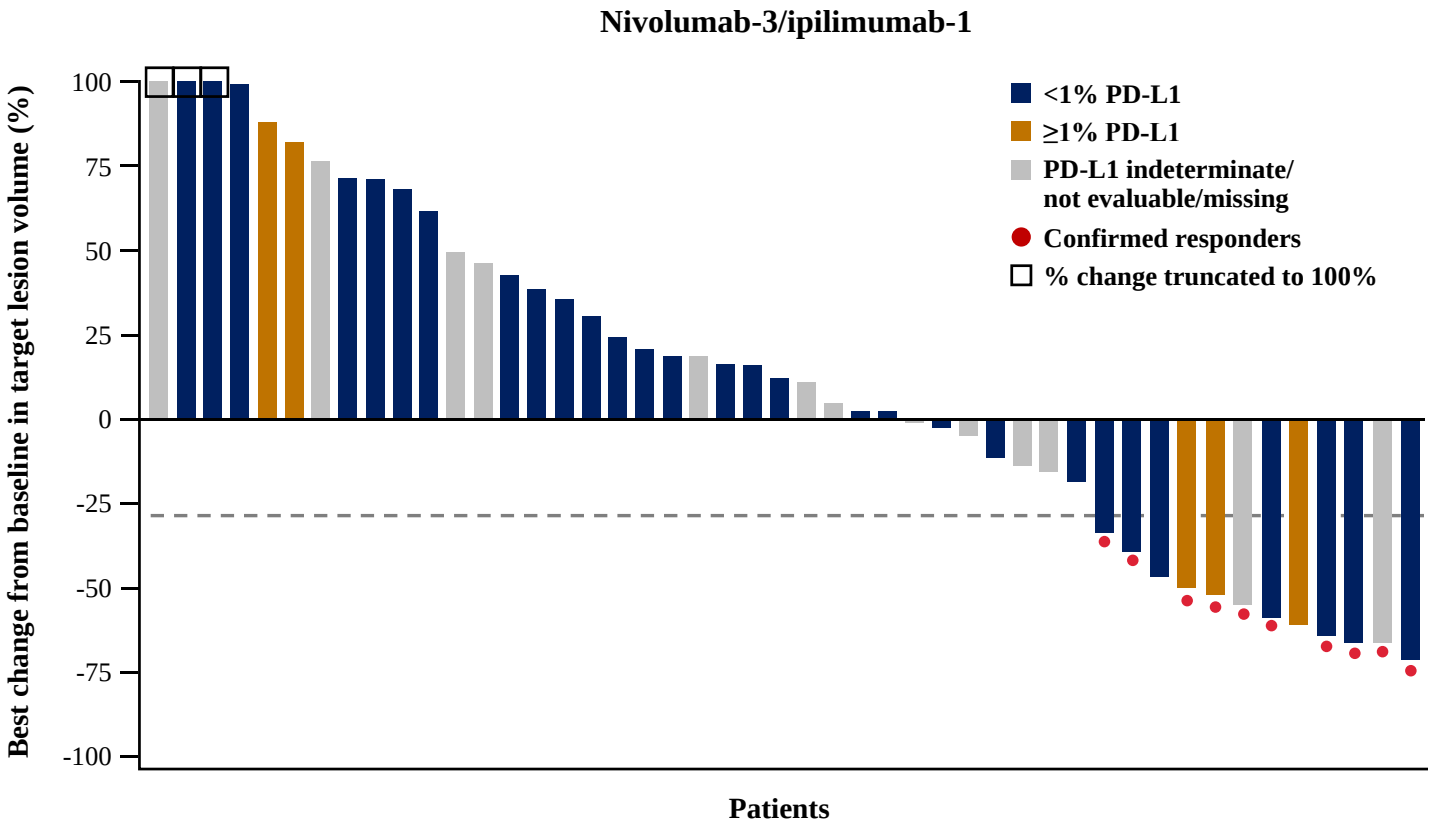

Nivolumab-3/ipilimumab-1
Best change from baseline in target lesion volume (%)
100
75
50
25
0
-25
-50
-75
-100
Patients
<1% PD-L1
≥1% PD-L1
PD-L1 indeterminate/
not evaluable/missing
Confirmed responders
% change truncated to 100%

***Table S1*: Enrolment by country and site**

Site - country	Site number	Principle investigator	Site - Institution	Number of patients treated N = 216*
Spain	0017	Lopez-Martin, Jose A	Hospital Universitario 12 de Octubre	28
United States	0021	Antonia, Scott J	H. Lee Moffitt Cancer Center & Research Institute	23
United States	0011	Bendell, Johanna	Sarah Cannon Research Institute/Tennessee Oncology	21
Spain	0010	Calvo, Emiliano	START Madrid, Centro Integral Oncológico Clara Campal	18
United States	0005	Ott, Patrick A	Dana-Farber Cancer Institute	15
United States	0007	Taylor, Matthew	Oregon Health & Science University	15
United States	0015	Eder, Joseph Paul	Yale Comprehensive Cancer Center	13
Germany	0016	Jaeger, Dirk	Nationales Centrum für Tumorerkrankungen (NCT), University Medical Center	13
United States	0006	Pietanza, M. Catherine	Memorial Sloan Kettering Cancer Center	10
Italy	0019	De Braud, Filippo	Fondazione IRCCS Istituto Nazionale dei Tumori Milano	8
United States	0004	Le, Dung T	The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University	8
United States	0008	Morse, Michael A	Duke University Medical Center	8
Italy	0020	Ascierto, Paolo A	Istituto Nazionale Tumori Fondazione Pascale	7
United States	0003	Amin, Asim	Levine Cancer Institute, Carolinas Medical Center	6
United States	0002	Horn, Leora	Vanderbilt-Ingram Cancer Center	6
United Kingdom	0012	Evans, Jeff	Beatson West Of Scotland Cancer Centre	5
United States	0001	Pillai, Rathi	Winship Cancer Institute of Emory University	5
Germany	0026	Atmaca, Akin	Krankenhaus Nordwest UCT-University Cancer Center	2
Finland	0014	Bono, Petri	Comprehensive Cancer Center, Helsinki University Hospital	2
United Kingdom	0013	Chau, Ian	Royal Marsden Hospital	2
United States	0009	Sharma, Padmanee	The University of Texas M.D. Anderson Cancer Center	1

*Enrolment numbers are based on the November 6, 2015 database lock.

Table S2*: On-study safety assessment schedules in nivolumab and nivolumab/ipilimumab cohorts

Safety assessment	**Timing considerations**	**Nivolumab monotherapy**	**Nivolumab/ipilimumab week 1 to week 12**	**Nivolumab/ipilimumab week 13 onward**
		Day 1 Week 1, 3, 5, 7, 9, etc	**Day 1 Week 1, 4, 7, 10**	**Day 1 Week 13, 15, 17, 19, 21, etc**
Targeted physical examination	72 hours prior to dosing	X	X (+day 4, week 2,5)	X
Vital signs and oxygen saturation	72 hours prior to dosing	X	X (+day 4, week 2,5)	X
Physical measurements	Weight prior to dosing	X	X (+day 4, week 2,5)	X
Adverse events assessment		continuously	continuously	continuously
Review of concomitant medications		continuously	continuously	continuously
Laboratory tests*	72 hours prior to dosing	X	X (+day 4, week 2,5)	X
Pregnancy test	24 hours prior to dosing, for WOCBP only	X (baseline and every 4 weeks)	X (baseline and every 3 weeks)	X (baseline and every 4 weeks)

*Complete blood count with differential, liver function tests, blood urea nitrogen or serum urea level, creatinine, albumin, calcium, magnesium, sodium, potassium, chloride, lactic acid dehydrogenase, glucose, amylase, lipase, and thyroid stimulating hormone. WOCBP=women of child-bearing potential. X=assessment to be performed.

Table S3: **Patient baseline characteristics in the nivolumab-1/ipilimumab-1 cohort**

Baseline characteristics	**Nivolumab-1/ipilimumab-1 (n=3)**
Median age (IQR), years	61 (52–65)
Age ≥75	0
Male sex	2 (67%)
Race	
White	2 (67%)
Black/African American	1 (33%)
Other	0
Prior treatment regimens	
1	1 (33%)
2–3	2 (67%)
>3	0
Sensitivity to first-line platinum treatment	
Platinum sensitive	1 (33%)
Platinum resistant	0
Unknown	2 (67%)
Current/former smoker	3 (100%)
PD-L1 expression level*	
≥1%	1 (50%)
<1%	1 (50%)
≥5%	0
<5%	2 (100%)
Indeterminant/not evaluable/missing	1 (33%)

Data presented as n or n (%), unless otherwise stated. All patients were enrolled at least 90 days prior to database lock. PD-L1=programmed death-ligand 1. *Percentage of PD-L1 evaluable patients.

***Table S4*: Tumour response in the nivolumab-1/ipilimumab-1 cohort**

	Nivolumab-1/ipilimumab-1 (n=3)
Objective response rate (95% CI)	1 (33%) (0·8–91)
Best overall response	
Complete response	1 (33%)
Partial response	0
Stable disease	2 (67%)
Progressive disease	0
Time to objective response (IQR), months*	2·7 (2·7 – 2·7)
Median duration of response (95% CI), months*	NR

Data presented as n, or n (%) unless otherwise stated. All patients were enrolled at least 90 days prior to database lock. IQR=interquartile range. NR=not reached. *The analysis used data from the one patient who had a response.

***Table S5*: Treatment-related adverse events in the nivolumab-1/ipilimumab-1 cohort**

Event	Nivolumab-1/ipilimumab-1 (n=3)		
	Grade 1-2	Grade 3	Grade 4
Total number of patients with an event	2 (67%)	0	0
Fatigue	2 (67%)	0	0
Diarrhoea	2 (67%)	0	0
Abdominal pain	1 (33%)	0	0
Arthralgia	1 (33%)	0	0
Colitis	1 (33%)	0	0
Decreased appetite	1 (33%)	0	0
Dyspnoea	1 (33%)	0	0
Lacrimation increased	1 (33%)	0	0
Nausea	1 (33%)	0	0
Peripheral sensory neuropathy	1 (33%)	0	0
Pruritus	1 (33%)	0	0
Thyroiditis	1 (33%)	0	0
Vision blurred	1 (33%)	0	0
Treatment-related adverse events leading to discontinuation*	0	0	0

Data presented as n (%). Safety analyses include all patients who were enrolled at least 90 days prior to database lock. Some patients had more than one adverse event. *At the time of database lock, two patients had discontinued treatment; one due to disease progression, one due to an adverse event unrelated to study drug.

***Table S6*: Treatment exposure and patient disposition**

	Nivolumab-3 (n=98)	Nivolumab-1/ ipilimumab-3 (n=61)	Nivolumab-3/ipilimumab-1 (n=54)
Median number of infusions			
Nivolumab	3·5 (2·0–6·0)	3·0 (2·0–14·0)	2·0 (2·0–6·0)
Ipilimumab	NA	3·0 (2·0–4·0)	2·0 (2·0–4·0)
Median follow-up, days*	198·5 (163·0–464·0)	361·0 (273·0–470·0)	260·5 (248·0–288·0)
Patients continuing treatment	21 (21%)	19 (31%)	11 (20%)
Patients not continuing treatment	77 (79%)	42 (69%)	43 (80%)
Progressive disease	57 (58%)	26 (43%)	36 (67%)
AE related to study drug	4 (4%)	7 (11%)	4 (7%)
AE unrelated to study drug	10 (10%)	5 (8%)	1 (2%)
Death	0	2 (3%)	0
Patient request/withdrew consent	5 (5%)	1 (2%)	2 (4%)
Other	1(1%)	1 (2%)	0
Patients continuing to be followed†	66 (67%)	48 (79%)	44 (82%)
Deaths	48 (49%)	30 (49%)	25 (46%)

Data presented as n,n (%) or median (IQR) unless otherwise stated. All patients were enrolled at least 90 days prior to database lock. AE=adverse event. IQR=interquartile range NA=not applicable. *Patients continuing in the study at the time of database lock. †Includes patients still on treatment and patients off treatment continuing in the follow-up period.

***Table S7*: Best overall tumour response by lines of therapy**

	One prior therapy			Two or more prior therapies		
	Nivolumab-3 (n=40)	**Nivolumab-1/ ipilimumab-3 (n=32)**	**Nivolumab-3/ ipilimumab-1 (n=23)**	**Nivolumab-3 (n=58)**	**Nivolumab-1/ ipilimumab-3 (n=29)**	**Nivolumab-3/ ipilimumab-1 (n=31)**
Objective response rate §	4 (10%)	9 (28%)	5 (22%)	6 (10%)	5 (17%)	5 (16%)
(95% CI)	(3–24)	(14–47)	(8–44)	(4–21)	(6–36)	(6–34)
Best overall response ¶						
Complete response	0	1 (3%)	0	0	0	0
Partial response	4 (10%)	8 (25%)	5 (22%)	6 (10%)	5 (17%)	5 (16%)
Stable disease	8 (20%)	6 (19%)	3 (13%)	14 (24%)	7 (24%)	6 (19%)
Progressive disease	22 (55%)	10 (31%)	12 (52%)	30 (52%)	13 (45%)	17 (55%)
Unable to determine	5 (13%)	6 (19%)	3 (13%)	7 (12%)	2 (7%)	3 (10%)
Not reported	1 (3%)	1 (3%)	0	1 (2%)	2 (7%)	0

Data presented as n or n (%) unless otherwise stated. All patients were enrolled at least 90 days prior to database lock.

***Table S8*: Best overall tumour response by sensitivity to first-line platinum-based treatment**

	Platinum sensitive*			Platinum resistant†		
	Nivolumab-3 (n=55)	**Nivolumab-1/ ipilimumab-3 (n=25)**	**Nivolumab-3/ ipilimumab-1 (n=21)**	**Nivolumab-3 (n=30)**	**Nivolumab-1/ ipilimumab-3 (n=23)**	**Nivolumab-3/ ipilimumab-1 (n=21)**
Objective response rate	6 (11%)	7 (28%)	4 (19%)	3 (10%)	4 (17%)	2 (10%)
(95% CI)	(4–22)	(12–49)	(5–42)	(2–27)	(5–39)	(1–30)
Best overall response						
Complete response	0	0	0	0	1 (4%)	0
Partial response	6 (11%)	7 (28%)	4 (19%)	3 (10%)	3 (13%)	2 (10%)
Stable disease	14 (25%)	7 (28%)	5 (24%)	5 (17%)	2 (9%)	1 (5%)
Progressive disease	29 (53%)	8 (32%)	11 (52%)	16 (53%)	10 (44%)	13 (62%)
Unable to determine	5 (9%)	3 (12%)	1 (5%)	5 (17%)	5 (22%)	5 (24%)
Not reported	1 (2%)	0	0	1 (3%)	2 (9%)	0

Data presented as n (%) unless otherwise stated. All patients were enrolled at least 90 days prior to database lock. For patients with known response to platinum-based therapy, platinum sensitivity was unknown for 29 patients as follows: nivolumab-3, n=10; nivolumab-1/ipilimumab-3, n=11; nivolumab-3/ipilimumab-1, n=8. *Patient relapsed ≥90 days after platinum-based chemotherapy. †Patient failed to respond to, or relapsed <90 days after, platinum-based chemotherapy.

***Table S9*: All-causality adverse events by category reported in ≥10% of patients in any treatment cohort**

Category	Nivolumab-3 (n=98)		Nivolumab-1/ipilimumab-3 (n=61)		Nivolumab-3/ipilimumab-1 (n=54)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Total number of patients with an event	95 (96%)	21 (21%)	61 (100%)	30 (49%)	53 (98%)	15 (28%)
Gastrointestinal disorders	59 (60%)	9 (9%)	40 (66%)	9 (15%)	33 (61%)	4 (7%)
General disorders and administration site conditions	55 (56%)	5 (5%)	42 (69%)	5 (8%)	37 (69%)	4 (7%)
Metabolism and nutritional disorders	47 (48%)	15 (15%)	32 (52%)	10 (16%)	22 (41%)	3 (6%)
Respiratory, thoracic and mediastinal disorders	42 (43%)	11 (11%)	25 (41%)	6 (10%)	28 (52%)	7 (13%)
Infections and infestations	27 (28%)	6 (6%)	21 (34%)	7 (11%)	20 (37%)	5 (9%)
Investigations	26 (27%)	12 (12%)	29 (48%)	12 (20%)	16 (30%)	2 (4%)
Nervous system disorders	26 (27%)	3 (3%)	21 (34%)	6 (10%)	19 (35%)	3 (6%)
Musculoskeletal and connective tissue disorders	21 (21%)	2 (2%)	16 (26%)	0	18 (33%)	1 (2%)
Skin and subcutaneous tissue disorders	21 (21%)	0	31 (51%)	4 (7%)	20 (37%)	0
Blood and lymphatic system disorders	19 (19%)	1 (1%)	11 (18%)	3 (5%)	13 (24%)	5 (9%)
Injury, poisoning, and procedural complications	14 (14%)	2 (2%)	7 (11%)	2 (3%)	5 (9%)	0
Psychiatric disorders	11 (11%)	3 (3%)	15 (25%)	1 (2%)	10 (19%)	1 (2%)
Cardiac disorders	10 (10%)	4 (4%)	9 (15%)	6 (10%)	5 (9%)	2 (4%)
Endocrine disorders	9 (9%)	0	16 (26%)	1 (2%)	10 (19%)	1 (2%)
Eye disorders	5 (5%)	0	5 (8%)	1 (2%)	5 (9%)	0

Data presented as n (%). Safety analyses included all patients who were enrolled at least 90 days prior to database lock; nivolumab-1/ipilimumab-1 cohort is excluded; patients with adverse events after crossover from nivolumab monotherapy to combination treatment are excluded. Some patients had more than one adverse event. Grade 5 events (deaths) occurred in 36 (37%), 16 (26%), and 14 (26%) patients in the nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1 cohorts, respectively. One patient in the nivolumab-1/ipilimumab-3 treatment cohort died from myaesthenia gravis that was considered treatment-related; there were no other treatment-related deaths.

***Table S10*: All-causality serious adverse events reported by category**

Category	Nivolumab-3 (n=98)				Nivolumab-1/ipilimumab-3 (n=61)				Nivolumab-3/ipilimumab-1 (n=54)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Total number of patients with an event	8 (8%)	13 (13%)	4 (4%)	36 (37%)	3 (5%)	14 (23%)	6 (10%)	16 (26%)	10 (19%)	9 (17%)	3 (6%)	14 (26%)
Neoplasms, benign, malignant, and unspecified	1 (1%)	2 (2%)	1 (1%)	35 (36%)	0	0	0	14 (23%)	3 (6%)	0	1 (2%)	14 (26%)
Respiratory, thoracic, and mediastinal disorders	2 (2%)	9 (9%)	1 (1%)	0	2 (3%)	3 (5%)	1 (2%)	0	5 (9%)	3 (6%)	1 (2%)	0
Gastrointestinal disorders	3 (3%)	6 (6%)	1 (1%)	0	1 (2%)	6 (10%)	0	0	3 (6%)	3 (6%)	0	0
Infections and infestations	0	4 (4%)	1 (1%)	1 (1%)	2 (3%)	4 (7%)	2 (3%)	0	0	4 (7%)	1 (2%)	0
Cardiac disorders	1 (1%)	2 (2%)	2 (2%)	1 (1%)	0	5 (8%)	1 (2%)	0	0	1 (2%)	0	0
General disorders and administration site conditions	5 (5%)	1 (1%)	0	0	1 (2%)	3 (5%)	0	2 (3%)	1 (2%)	3 (6%)	0	0
Metabolism and nutrition disorders	0	4 (4%)	1 (1%)	0	1 (2%)	2 (3%)	2 (3%)	0	0	1 (2%)	0	0
Injury, poisoning, and procedural complications	3 (3%)	1 (1%)	0	0	0	1 (2%)	1 (2%)	0	0	0	0	0
Investigations	0	3 (3%)	0	0	0	3 (5%)	0	0	0	1 (2%)	0	0
Nervous system disorders	2 (2%)	1 (1%)	0	0	2 (3%)	4 (7%)	1 (2%)	0	2 (4%)	2 (4%)	0	0
Musculoskeletal and connective tissue disorders	0	2 (2%)	0	0	0	0	0	0	0	1 (2%)	0	0
Psychiatric disorders	0	2 (2%)	0	0	1 (2%)	0	0	0	0	1 (2%)	0	0
Vascular disorders	0	2 (2%)	0	0	1 (2%)	0	0	0	0	1 (2%)	0	0

Hepatobiliary disorders	1 (1%)	1 (1%)	0	0	0	1 (2%)	0	0	0	0	0	0
Endocrine disorders	2 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)	0	0
Blood and lymphatic system disorders	0	1 (1%)	0	0	0	0	0	0	0	0	1 (2%)	0
Ear and labyrinth disorders	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Renal and urinary disorders	0	1 (1%)	0	0	0	0	1 (2%)	0	0	0	0	0
Eye disorders	0	0	0	0	0	0	0	0	1 (2%)	0	0	0

Data presented as n (%). Safety analyses included all patients who were enrolled at least 90 days prior to database lock; nivolumab-1/ipilimumab-1 cohort is excluded; patients with adverse events after crossover from nivolumab monotherapy to combination treatment are excluded. Some patients had more than one adverse event. One patient in the nivolumab-1/ipilimumab-3 treatment cohort died from myaesthenia gravis that was considered treatment-related; there were no other treatment-related deaths.

***Table S11*: Treatment-related elevations in liver function tests**

Event	Nivolumab-3 (n=98)			Nivolumab-1/ipilimumab-3 (n=61)			Nivolumab-3/ipilimumab-1 (n=54)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Increased alanine aminotransferase	2 (2%)	1 (1%)*	0	2 (3%)	0	0	0	1 (2%)	0
Increased aspartate aminotransferase	3 (3%)	0	0	3 (5%)	0	0	0	1 (2%)	0
Increased blood alkaline phosphatase	2 (2%)	0	0	2 (3%)	0	0	0	0	0
Increased transaminases	2 (2%)	0	0	0	0	0	1 (2%)	1 (2%)	0
Increased gamma glutamyltransferase	0	0	1 (1%)*	0	0	0	0	1 (2%)	0

Data presented as n (%). Safety analyses included all patients who were enrolled at least 90 days prior to database lock; patients with adverse events after crossover from nivolumab monotherapy to combination treatment are excluded. Some patients had more than one adverse event. *Patient discontinued treatment.