original reports

Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non–Small-Cell Lung Cancer (NADIM phase II trial)

Mariano Provencio, MD, PhD[1]; Roberto Serna-Blasco, MSc[1]; Ernest Nadal, MD[2]; Amelia Insa, MD[3]; M. Rosario García-Campelo, MD[4]; Joaquín Casal Rubio, MD[5]; Manuel Dómine, MD[6]; Margarita Majem, MD[7]; Delvys Rodríguez-Abreu, MD[8]; Alex Martínez-Martí, MD[9]; Javier De Castro Carpeño, MD[10]; Manuel Cobo, MD[11]; Guillermo López Vivanco, MD[12]; Edel Del Barco, MD[13]; Reyes Bernabé Caro, MD[14]; Nuria Viñolas, MD[15]; Isidoro Barneto Aranda, MD[16]; Santiago Viteri, MD[17]; Eva Pereira, MSc[18]; Ana Royuela, PhD[1]; Virginia Calvo, MD[1]; Javier Martín-López, MD[1]; Francisco García-García, PhD[19]; Marta Casarrubios, MSc[1]; Fernando Franco, MD[1]; Estela Sánchez-Herrero, MSc[1,20]; Bartomeu Massuti, MD[21]; Alberto Cruz-Bermúdez, PhD[1]; and Atocha Romero, PhD[1]

abstract

PURPOSE Neoadjuvant chemotherapy plus nivolumab has been shown to be effective in resectable non–small-cell lung cancer (NSCLC) in the NADIM trial (ClinicalTrials.gov identifier: NCT03081689). The 3-year overall survival (OS) and circulating tumor DNA (ctDNA) analysis have not been reported.

METHODS This was an open-label, multicenter, single-arm, phase II trial in which patients with stage IIIA NSCLC, who were deemed to be surgically resectable, were treated with neoadjuvant paclitaxel (200 mg/m^2 once a day) and carboplatin (area under curve 6) plus nivolumab (360 mg) once on day 1 of each 21-day cycle, for three cycles, followed by adjuvant nivolumab monotherapy for 1 year (240 mg once every 2 weeks for 4 months, followed by 480 mg once every 4 weeks for 8 months). The 3-year OS and ctDNA analysis were secondary objectives of the trial.

RESULTS OS at 36 months was 81.9% (95% CI, 66.8 to 90.6) in the intention-to-treat population, rising to 91.0% (95% CI, 74.2 to 97.0) in the per-protocol population. Neither tumor mutation burden nor programmed cell death ligand-1 staining was predictive of survival. Conversely, low pretreatment levels of ctDNA were significantly associated with improved progression-free survival and OS (hazard ratio [HR], 0.20; 95% CI, 0.06 to 0.63, and HR, 0.07; 95% CI, 0.01 to 0.39, respectively). Clinical responses according to RECIST v1.1 criteria did not predict survival outcomes. However, undetectable ctDNA levels after neoadjuvant treatment were significantly associated with progression-free survival and OS (HR, 0.26; 95% CI, 0.07 to 0.93, and HR, 0.04; 95% CI, 0.00 to 0.55, respectively). The C-index to predict OS for ctDNA levels after neoadjuvant treatment (0.82) was superior to that of RECIST criteria (0.72).

CONCLUSION The efficacy of neoadjuvant chemotherapy plus nivolumab in resectable NSCLC is supported by 3-year OS. ctDNA levels were significantly associated with OS and outperformed radiologic assessments in the prediction of survival.

J Clin Oncol 40:2924-2933. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

See accompanying article on page 2871

Data Sharing Statement

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 4, 2022 and published at ascopubs.org/journal/jco on May 16, 2022: DOI https://doi.org/10.1200/JCO.21.02660

INTRODUCTION

Lung cancer is a devastating disease, being the leading cause of cancer deaths worldwide.[1] Nevertheless, immunotherapy-based treatments have dramatically improved outcomes and become established as a major modality for the treatment of metastatic non–small-cell lung cancer (NSCLC).[2-5] Yet, its role in earlier stages needs to be established. In this regard, we previously published the results from the primary analysis of the NADIM trial, in which patients with resectable stage IIIA NSCLC were treated with neoadjuvant nivolumab plus chemotherapy, which showed a progression-free survival (PFS) at 24 months of 77.1% in the intention-to-treat (ITT) population.[6] In addition, a pathologic complete response (pCR) rate of 63.4% was reported. These are unprecedented results that outperform outcomes with the standard-of-care preoperative chemotherapy.[7] Consequently, currently, there is intense research ongoing focused on the efficacy of chemoimmunotherapy in the neoadjuvant setting. Without long-term survival data available, methodologies for the early measurement of treatment

CONTEXT

Key Objective

Our objectives were to evaluate the long-term clinical benefit of neoadjuvant nivolumab plus chemotherapy in operable stage IIIA non–small-cell lung cancer (NSCLC) and to assess the utility of circulating tumor DNA (ctDNA) as an early surrogate end point for treatment efficacy.

Knowledge Generated

Overall survival at 36 months was 81.9% in the intention-to-treat population, rising to 91.0% in the per-protocol population. Additionally, we report for the first time a significant association between ctDNA levels after neoadjuvant chemo-immunotherapy and survival outcomes in operable NSCLC. Indeed, ctDNA outperformed clinical responses, assessed on computed tomography scans and according to RECIST criteria v.1.1, in the prediction of survival.

Relevance

The efficacy of neoadjuvant chemotherapy plus nivolumab in resectable NSCLC is supported by unprecedentedly high survival rates. Overall survival was almost three times that reported in the historical series. Our data support the usefulness of ctDNA as an early surrogate end point in the context of neoadjuvant treatment.

efficacy are of particular interest. Scoring approaches for pathologic response assessments for neoadjuvant immunotherapy in NSCLC have been reported.[8] Specifically, Cottrell et al[9] proposed quantitative immune-related pathologic response criteria on the basis of the histologic features of the regression bed in the tumors. Similarly, Stein et al[10] have proposed a pan-tumor immune-related pathologic response score system. Yet, its capacity to predict long-term survival has not been established.

Here, we report the results of the planned secondary end point of 3-year overall survival (OS) of the NADIM trial. Finally, we evaluate the prognostic value of the circulating tumor DNA (ctDNA) and compare its capacity to predict long-term survival with classical survival surrogates.

METHODS

Study Design and Participants

This is an open-label, multicenter, single-arm phase II trial. The trial was conducted in accordance with the precepts established in the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable regulatory requirements. The study Protocol (online only) was approved by the ethics committee of Hospital Puerta de Hierro and the Spanish Agency of Medicines and Medical Devices. Full details of the NADIM trial (ClinicalTrials.gov identifier: NCT03081689) have been published elsewhere.[6] Briefly, eligible patients included patients age $\geq$ 18 years, with operable stage IIIA NSCLC (American Joint Committee on Cancer seventh edition criteria) and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were treated with neoadjuvant intravenous paclitaxel (200 mg/m^2 once a day) and carboplatin (area under the curve 6; 6 mg/mL per min) plus nivolumab (360 mg) once on day 1 of each 21-day cycle, for three cycles before surgical resection, followed by adjuvant intravenous nivolumab monotherapy for 1 year (240 mg once every 2 weeks for 4 months, followed by 480 mg once every 4 weeks for 8 months). The primary end point was PFS at 24 months and it has been previously published.[6] Secondary end points included 3-year OS and the analysis of tissue and plasma biomarkers.

Peripheral blood and tissue from all patients were prospectively collected. Plasma samples were collected before and after neoadjuvant treatment. Post-treatment plasma samples were collected before surgery in all cases. Informed consent for the collection of research samples was obtained.

Procedures

Patients were assessed every 21 days for clinical response. Computed tomography (CT) scans were performed locally before and after neoadjuvant treatment, after surgery, every 3 months during the first-year follow-up, every 4 months during the second year of follow-up, and every 6 months thereafter. The tumor response to neoadjuvant treatment was evaluated by comparing before and after neoadjuvant treatment CT scans, and according to RECIST version 1.1.

The pathologic response was locally assessed in the pulmonary resection specimen (lobectomies, bilobectomies, or pneumonectomies) according to the pathologist of each of the 18 participating hospitals. A second evaluation was performed by two independent pathologists with 100% agreement. The number of sections reviewed for pathologic response assessment ranged from 8 to 28 (median 10, mean 12). In all cases, the pathologist was blinded to the patient's identity and outcome. pCR was defined as the absence of any viable tumor cell in the resected lung specimen and all regional lymph nodes. Major pathologic response was defined as the presence of 10% or fewer tumor cells in the primary tumor, and incomplete pathologic response was considered when there were 10% or more viable tumor cells present in the primary tumor.

Next-generation sequencing analysis of formalin-fixed paraffin-embedded and plasma samples is described in the Data Supplement (online only). Briefly, DNA from formalin-fixed paraffin-embedded samples was sequenced using the Oncomine Tumor Mutation Load Assay. Likewise, cfDNA, from plasma samples, was analyzed using the Oncomine Pan-Cancer Cell-Free Assay kit.

Mutant allele fraction (MAF) was defined as the number of mutant molecules at a specific nucleotide location relative to the sum of total DNA molecules (mutant plus wild-type). A cutoff of MAF $\geq$ 0.1% was established as the limit of detection.

Statistical Analysis

Median follow-up time was estimated by the reverse Kaplan-Meier (KM) method.[11] Estimation of the median follow-up and the ratio of the expected variance of S(t) to the current variance of S(t) at 36 and 42 months were used to quantify data maturity.[12]

OS was defined as the time from the start of neoadjuvant treatment to death from any cause. PFS was defined as the time between the start of neoadjuvant treatment and disease progression, as assessed by RECIST criteria v1.1, or death from any cause, whichever occurred first. Patients who were alive or without the event at the end of follow-up were censored at the time of the last contact. PFS and OS were assessed in the ITT population, which included all patients who received neoadjuvant treatment, and in the per-protocol (PP) population, which included all patients who underwent tumor resection and received at least one cycle of adjuvant therapy (Data Supplement). Cox proportional-hazards models were used to determine the association of each of the study variables with survival outcomes. The models were adjusted by surgery. Two patients died of COVID-19 disease, which represents a competing event for cause-specific mortality. Thus, competing risk analysis was also performed. Specifically, cumulative incidence functions and subhazard ratios on the basis of the Fine and Gray approach are presented to estimate the risks of progression and cancer-related death.

To avoid potential bias in the association of PFS and OS with response to treatment assessed by pathologic response, radiologic response, and ctDNA detection after neoadjuvant treatment, the landmark analysis approach[13] was used with the landmark chosen as the date of the end of neoadjuvant treatment.

The discrimination ability for each model was evaluated using Harrell's concordance index (C-index).[14,15] The C-index can take values from 0 to 1, with higher values indicating better discrimination. A value of 0.5 corresponds to no better discrimination than by chance. Likelihood ratio statistics of tumor response to treatment assessed by CT scans and ctDNA were also evaluated after accounting for surgery status. Models were first conditioned on one predictor, and then the significance of the other was tested. P values of $< .05$ were considered to be statistically significant.

Role of Funding Source

The study was sponsored by the Spanish Lung Cancer Group.[16] The study funders had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

RESULTS

Clinical Outcomes

The demographic characteristics of the patients at baseline have been reported previously.[6] All patients (N = 46) were stage IIIA. Regarding nodal status, nine (19.6%) patients were N0, three (6.5%) patients were N1, and 34 (73.9%) were N2. The median follow-up time was 38.0 months (95% CI, 36.7 to 40.7), with 94% maturity at 36 months and 90% maturity at 42 months. There were no events (death or disease progression) during neoadjuvant treatment. Among the ITT population (N = 46), 41 patients underwent tumor resection and 37 patients, constituting the PP population, received subsequent adjuvant therapy (90.2% of the planned population; Data Supplement). Of these, 29 (78.4%) patients completed the adjuvant treatment (14-17 cycles), eight (21.6%) patients received between three and 13 cycles of adjuvant therapy. There was no interruption of nivolumab administration in any of the 17 cycles. KM curve according to completion of adjuvant therapy is presented in the Data Supplement. Details of the patients who did not undergo surgery (n = 5) or did not receive adjuvant treatment (n = 4) are available in the Data Supplement.

At the time of data cutoff (March 2021), disease progression had been diagnosed in 12 patients and nine deaths had been recorded. Three of these deaths were of patients who did not undergo surgery and had disease progression, four were of patients who underwent surgery and had disease progression, and two were of patients diagnosed as being disease-free after surgery but who died of COVID-19 disease. The Data Supplement shows the cumulative incidence function curves for each cause of death. The median PFS and the median OS were not reached in the ITT or PP population (Fig 1). The median time to progression for patients who had progressive disease was 19.4 months (P25-P75: 10.6-25.1 months; Data Supplement).

PFS at 36 and 42 months in the ITT population was 69.6% (95% CI, 54.1 to 80.7) in both cases. Similarly, PFS at 36 and 42 months in the PP population was 81.1% (95% CI, 64.4 to 90.5) in both cases. OS at 36 and 42 months in the ITT population was 81.9% (95% CI, 66.8 to 90.6) and 78.9% (95% CI, 63.1 to 88.6), respectively. Likewise, OS at 36 and 42 months in the PP population was 91.0% (95%

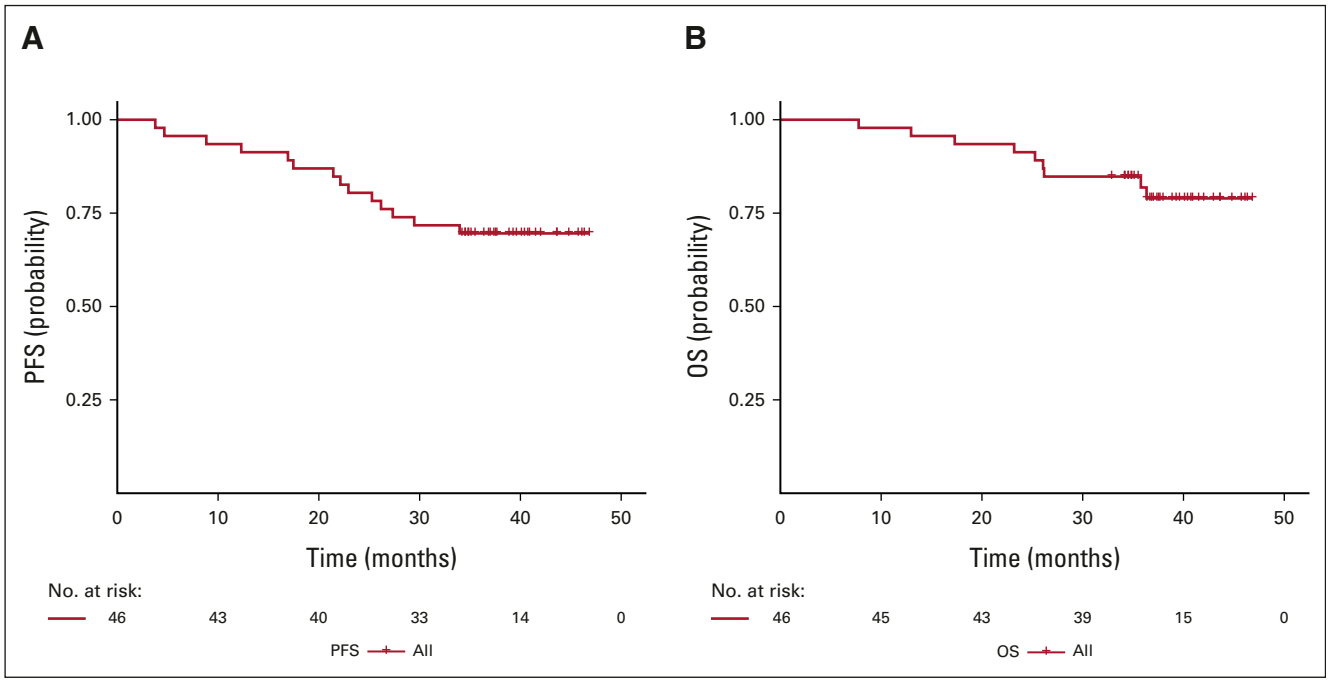

FIG 1. Kaplan-Meier curves for (A) PFS and (B) OS in the ITT population (N = 46). ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

CI, 74.2 to 97.0) and 87.3% (95% CI, 69.3 to 95.1), respectively.

In univariate Cox regression analyses, no statistically significant associations were noted between the baseline characteristics of the patients and PFS or OS, except for Eastern Cooperative Oncology Group performance status (0 *v* 1) and the tumor lesion size (maximum diameter), which were both associated with inferior OS (hazard ratio [HR], 4.91; 95% CI, 1.01 to 23.80; and HR, 1.03; 95% CI, 1.01 to 1.06, respectively; Data Supplement). Finally, patients who underwent surgery had significantly improved OS (HR, 0.14; 95% CI, 0.04 to 0.59; Data Supplement).

Treatment-related adverse events (AEs) during neoadjuvant treatment have been reported previously.[6] Of note, any of them were associated with surgery delays or deaths. There was no intraoperative or in-hospital mortality either at 30 or 90 days after surgery. AEs of grade 1 or 2 during adjuvant treatment were noted in 27 (73.0%) patients. The most common grade 1 or 2 AE was fatigue that was noted in 10 patients (27.0%; Data Supplement). AEs of grade 3 or 4 during adjuvant treatment were notified in five (13.5%) patients, being the most common toxicity increased lipase which was reported in four (10.8%) patients (Data Supplement). No long-term toxicities were noted.

Baseline Biomarkers

Of the 46 patients included in the trial, 35 (76.1%) had a biopsy sample available for next-generation sequencing analysis and 29 (63.0%) had valid data for tumor mutation burden (TMB) assessment. Similarly, programmed cell death ligand-1 (PD-L1) data were available for 28 (60.9%) samples. In total, 43 pretreatment plasma samples were collected.

TABLE 1. HR and Corresponding 95% CI According to Each Biomarker (TMB, PD-L1, and ctDNA levels at baseline)

Biomarker	No.	Deaths	Progressions	HR (PFS)[a]	95% CI[a]	*P*[a]	HR (OS)[a]	95% CI[a]	*P*[a]
Basal ctDNA < 1%	43	9	12	0.20	0.06 to 0.63	.006	0.07	0.01 to 0.39	.002
TMB ≥ 10 mut/Mb	29	6	6	1.67	0.41 to 6.83	.474	2.13	0.37 to 12.40	.399
PD-L1 ≥ 1%	28	5	8	0.64	0.17 to 2.40	.508	0.35	0.06 to 2.12	.252

NOTE. A cutoff of MAF ≥ 1% was established. Among patients with low ctDNA (MAF < 1%), 77.4% (95% CI, 58.4 to 88.5) were progression-free, and 93.6% (95% CI, 76.6 to 98.4) were alive at 36 months, whereas only 41.7% (95% CI, 15.3 to 66.5) and 46.7% (95% CI, 16.8 to 72.2) patients with baseline ctDNA ≥ 1% were progression-free and alive, respectively.

Abbreviations: ctDNA, circulating tumor DNA; HR, hazard ratio; MAF, mutant allele fraction; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; TMB, tumor mutation burden.

[a]Multivariate analyses adjusted by surgery.

The expression of PD-L1 in tumor cells was not associated with improved PFS or OS (Data Supplement). Similarly, TMB assessment was not associated with survival outcomes (Data Supplement; Table 1).

Baseline ctDNA was detected in 30 of 43 (69.8%) of the pretreatment plasma samples (Data Supplement). ctDNA levels at baseline were significantly associated with tumor size (maximum diameter; Data Supplement).

To explore the prognostic value of the amount of ctDNA at baseline, for each positive plasma sample, we calculated the sum of MAFs for all detected mutations. Different MAF thresholds were evaluated (Data Supplement), and 1% MAF was selected (Table 1). In the multivariate analysis, patients with low ctDNA levels (< 1% MAF), at baseline, had significantly improved PFS and OS than patients with high ctDNA levels (adjusted HR, 0.20; 95% CI, 0.06 to 0.63; $P = .006$; and adjusted HR, 0.07; 95% CI, 0.01 to 0.39; $P = .002$ for PFS and OS, respectively; Fig 2; Data Supplement).

Tumor Response to Treatment Assessment: Comparative Analysis of Different Surrogates for the Prediction of Long-Term Survival

Tumor response to treatment was evaluated by CT scans in all patients (N = 46), the pathologic response was assessed in all patients who underwent surgery (n = 41), and a plasma sample collected after neoadjuvant treatment but before surgery was available in 40 cases (Data Supplement).

According to RECIST v1.1 criteria, two (4.3%) patients had a complete response, 33 (71.7%) had a partial response, and 11 (23.9%) showed stable disease. Regarding pathologic response, 34 (82.9%) patients had a major pathologic response, including 26 (63.4%) patients who showed pCR, and seven (17.1%) had an incomplete response.

Radiologic response according to CT scans did not show any association with PFS or OS ($P = .698$ for PFS and 0.848 for OS). Likewise, pCR was not significantly associated with survival ($P = .111$ for PFS and 0.102 for OS; Table 2). However, when treating COVID-19 deaths as competing risk events, pCR (but not radiologic response) identified patients with improved PFS (adjusted subHR, 0.23; 95% CI, 0.06 to 0.86; $P = .030$ for PFS and adjusted subHR: not estimable for OS because of lack of events). Of note, two of the 26 patients diagnosed as having pCR were deceased. Both patients died of COVID-19 disease and did not show disease progression according to CT scans during the study. ctDNA dynamics at the individual level and according to pathologic response are available in the Data Supplement.

Improved PFS and OS were observed for patients with undetectable ctDNA (limit of detection established at 0.1% MAF) after neoadjuvant treatment (adjusted HR, 0.26; 95% CI, 0.07 to 0.93; $P = .038$; and HR, 0.04; 95% CI, 0.00 to 0.55; $P = .015$ for PFS and OS, respectively; Table 2; Fig 3; Data Supplement). As mentioned, 13 of 43 patients had undetectable ctDNA at baseline. Adjusted HRs remained significant when excluding patients who were ctDNA-negative at baseline (Data Supplement).

To evaluate the ability of each survival surrogate to discriminate between deceased and nondeceased patients

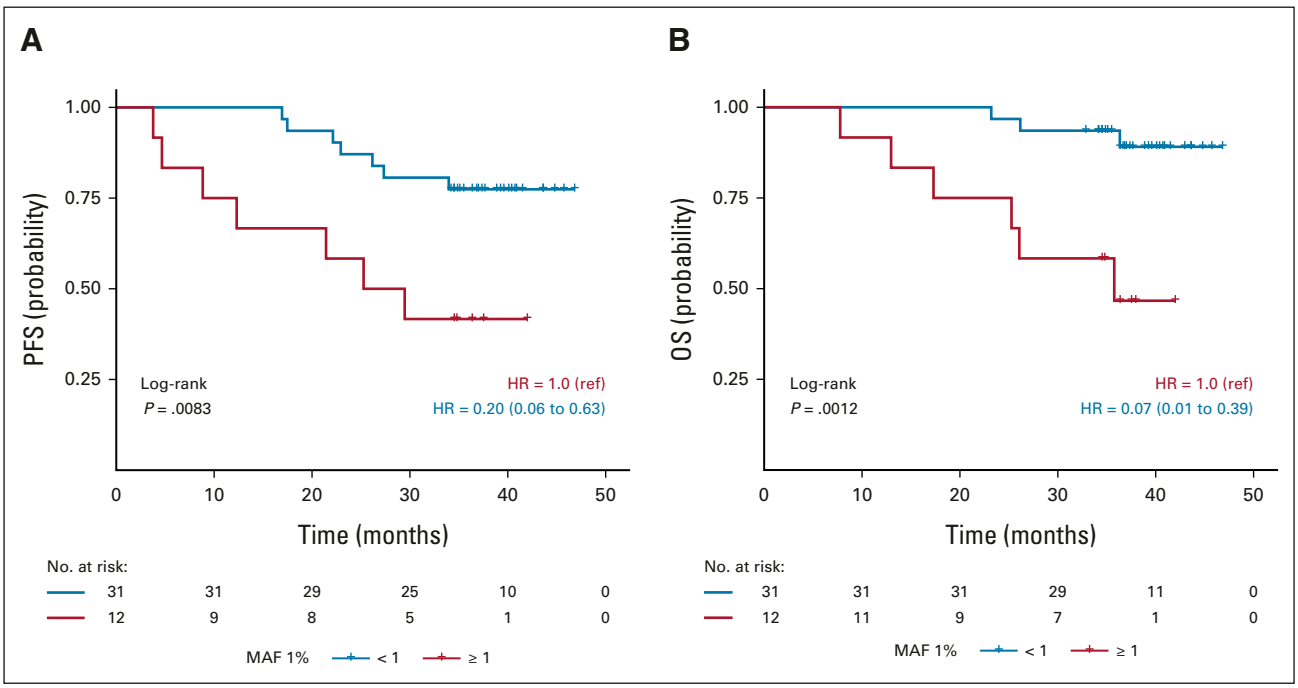

FIG 2. Kaplan-Meier curves for (A) PFS and (B) OS by ctDNA levels at baseline, using a cutoff of < 1% MAF. ctDNA, circulating tumor DNA; HR, hazard ratio; MAF, mutant allele fraction; OS, overall survival; PFS, progression-free survival; ref, reference category.

TABLE 2. Prognostic Value of Tumor Response to Treatment Assessments on the Basis of CT Scans, Pathologic Evaluation, and ctDNA (landmark analysis)

Survival surrogate	No.	HR (PFS)[a]	95% CI[a]	P[a]	C-index (PFS)	95% CI	HR (OS)[a]	95% CI[a]	P[a]	C-index (OS)	95% CI
Clinical response (CR plus PR *v* SD)	46	0.79	0.24 to 2.59	.698	0.62	0.47 to 0.77	0.87	0.20 to 3.75	.848	0.72	0.51 to 0.90
Pathologic response (pCR *v* major plus incomplete)	41	0.38	0.12 to 1.25	.111	0.63	0.47 to 0.78	0.24	0.04 to 1.33	.102	0.65	0.43 to 0.86
Undetectable ctDNA after treatment	40	0.26	0.07 to 0.93	.038	0.63	0.45 to 0.81	0.04	0.00 to 0.55	.015	0.82	0.61 to 1.00

NOTE. HR and corresponding 95% CI and C-indices and their corresponding 95% CI, to predict OS and PFS, by pathologic response, clinical response assessed according to RECIST v1.1 criteria, and ctDNA after neoadjuvant treatment. PFS and OS at 36 months in patients who showed pCR was 80.8% (95% CI, 59.8 to 91.5) and 92.3% (95% CI, 72.6 to 98.0), respectively. Among patients who showed incomplete pathologic response or major pathologic response after neoadjuvant treatment, only 60.0% (95% CI, 31.8 to 79.6) of the patients were progression-free and 61.9% (95% CI, 25.0 to 84.7) of the patients were alive. PFS and OS at 36 months for patients showing radiologic response was 71.3% (95% CI, 53.2 to 83.4) and 79.2% (95% CI, 58.4 to 90.4), respectively, compared with 63.6% (95% CI, 29.7 to 84.5) and 72.7% (95% CI, 37.1 to 90.3) in patients diagnosed as having stable disease. The probability of being alive and with no evidence of disease at 36 months in patients who showed undetectable ctDNA levels after neoadjuvant treatment (n = 27) was 96.3% (95% CI, 76.5 to 99.5) and 81.5% (95% CI, 61.1 to 91.8), respectively, compared with 57.7% (95% CI, 24.9 to 80.4) and 53.8% (95% CI, 24.8 to 76) in patients who had detectable ctDNA (n = 13) after neoadjuvant treatment.

Abbreviations: C-index; concordance index; CT, computed tomography; ctDNA, circulating tumor DNA; CR, complete response; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]Multivariate analyses adjusted by surgery.

and between progressed and nonprogressed patients, we calculated Harrell's C-index. The adjusted C-index to predict OS of ctDNA (0.82) was higher than the C-index for the RECIST criteria (0.72; Table 2).

Finally, we investigated whether the prognostic information provided by radiologic responses can improve by adding ctDNA information. In our hands, ctDNA added a significant degree of prognostic information to the radiologic response in terms of OS ($P = .003$; Data Supplement).

DISCUSSION

The main objective of any neoadjuvant study should be to contribute to the cure of the patients and increase their OS.[18] Our study shows an OS of 81.9% at 3 years in the ITT population and 91.0% in the PP population. These are unprecedentedly high survival rates in patients with stage IIIA NSCLC and have not been reported in prior studies evaluating neoadjuvant approaches.[7,19] Importantly, data maturity was 94% at 36 months. Consistent with this, a clear plateau in the KM curves for OS and PFS was observed (Fig 1). Moreover, the median time to progression was 19.4 months in patients who showed progression disease, exceeding that of the overall follow-up from the previous series.[19] We previously reported a pCR rate of 63.4% and a major pathologic response rate of 82.9%.[6] Similarly, preliminary data from the CheckMate 816 randomized phase III trial showed that neoadjuvant nivolumab plus chemotherapy increased the pCR rate compared with chemotherapy alone (24.0% *v* 2.2%; odds ratio: 13.94; 99% CI, 3.49 to 55.75).[20] Nevertheless, pathologic responses have not always resulted in prolonged OS. In this way, despite neoadjuvant treatments with chemoradiotherapy demonstrating significant benefit in terms of pathologic response rates compared with chemotherapy alone, they did not have any impact on the PFS or OS.[21]

The marked difference between the current standard of care and the NADIM-based treatments is shifting our perspective on stage IIIA NSCLC from being a lethal disease to one where it may be considered potentially curable. Accordingly, there are a significant number of ongoing clinical trials addressing the role of chemoimmunotherapy in the neoadjuvant setting. It should be acknowledged that the development of novel neoadjuvant strategies for resectable NSCLC has been hampered by a lack of surrogate end points that can be measured much faster than the end points they are meant to predict.[22] Currently, we continue to lack surrogate end points for immunotherapy-based treatment efficacy that accurately predict long-term survival. Although major pathologic response has been proposed as a surrogate end point in neoadjuvant trials for resectable NSCLC,[23] the hitherto accepted definition of major pathologic response as ≤ 10% of residual viable tumor in NSCLC regardless of histologic subtype is under debate. Several alternative approaches have been proposed so far,[8-10,24] yet its capacity to predict long-term survival has not been reported. In our study, all patients diagnosed as having pCR were alive at data cutoff, except for two patients who died of COVID-19 disease. A recent study from the International Neoadjuvant Melanoma Consortium supports the role of pCR as an early surrogate end point for recurrence-free survival and OS.[25] In this regard, it appears that pCR is a distinct biological entity being associated with specific microenvironmental features.[26,27]

In our study, neither TMB nor PD-L1 staining predicted long-term survival. Similar results have been obtained in the metastatic setting where none of these biomarkers have proved to be predictive for chemoimmunotherapy.[28]

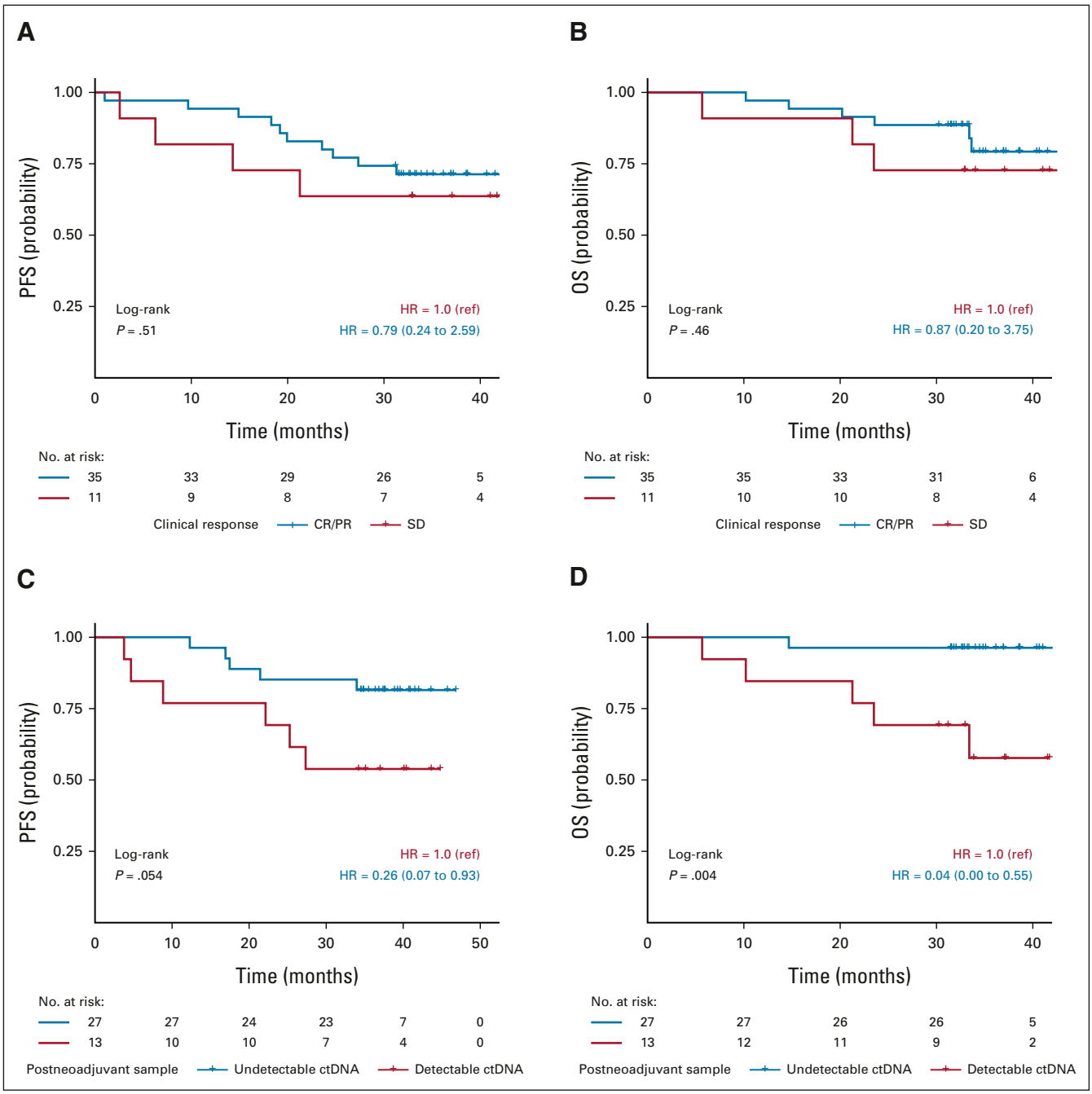

FIG 3. Kaplan-Meier curves for (A) PFS and (B) OS by clinical response assessed on CT scans and Kaplan-Meier curves for (C) PFS and (D) OS according to ctDNA detection after neoadjuvant treatment (landmark approach). Among patients who had undetectable ctDNA after neoadjuvant treatment,[17] five were diagnosed as having progression disease. All of these patients (n = 5) underwent surgery. Regarding pathology assessments, two of them were diagnosed as having pCR, one as having major pathologic response and two were diagnosed as incomplete pathologic response. One of the patients showing undetectable ctDNA after treatment but incomplete pathologic response died, representing the unique death event among patients with undetectable ctDNA after treatment. Among patients with ctDNA detection after treatment (n = 13), two patients did not undergo surgery, three patients showed an incomplete pathologic response, one patient showed a major pathologic response, and seven patients had pCR. Of these, two patients showed progressive disease despite having pCR. CR, complete response; CT, computed tomography; ctDNA, circulating tumor DNA; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; PR, partial response; ref, reference category; SD, stable disease.

Specifically, the KEYNOTE-189 trial demonstrated that the addition of pembrolizumab to chemotherapy, as a first-line treatment, significantly improved both PFS and OS in NSCLC patients with metastatic disease, regardless of status.[17] Similarly, Rothschild et al[29] reported that no significant association was found between PD-L1 expression

and major pathologic response or nodal downstaging in patients with NSCLC treated with neoadjuvant chemotherapy followed by durvalumab. However, it should be acknowledged that in our study, the sample size for PD-L1 and TMB analyses was rather low, which makes any association difficult to demonstrate as being statistically significant.

In our study, patients with low ctDNA levels (MAF < 1%) at baseline had significantly improved PFS and OS than patients with high pretreatment ctDNA levels. Currently, there is not a standardized methodology to quantify ctDNA. We hypothesize that the sum of MAFs from all detected mutations would better recapitulate the status of disease as different tumor lesions may harbor different somatic mutations. Although this approach would be dependent on the total number of genes included in the panel as well as TMB, it is plausible to think that it may be less limited by tumor heterogeneity than measuring only the mutation at the highest MAF. Anyhow, similar results were obtained when using maximum MAF (Data Supplement). This approach has been used by other researchers.[30] Consistent with our findings, numerous reports have shown that the baseline ctDNA level is a prognostic factor in a wide range of patients with lung cancer.[31-33] Indeed, it has been proposed to incorporate ctDNA levels in a modified TNM staging system.[34]

Tumor response to treatment according to RECIST criteria was not associated with survival questioning the usefulness of radiologic response as a survival surrogate or even PFS as a trial end point when evaluating the efficacy of immunotherapy-based treatments. On the contrary, undetectable ctDNA at the end of neoadjuvant treatment clearly identified patients with improved OS. Although our analysis is exploratory, the notable effect size (HR, 0.04) prompts us to postulate ctDNA as being a pivotal surrogate for long-term OS in the immunotherapy field, with a similar prognostication capacity as pCR. Prior studies have noted an association between ctDNA dynamics and response to immunotherapy in NSCLC,[35] but the NADIM set is larger and the associations are more robust. Likewise, ctDNA clearance was associated with pCR in the CheckMate 816 trial.[20] In addition, it is well established that conventional imaging cannot always reliably predict long-term OS in patients undergoing immunotherapy and it has been shown that immunotherapy-based treatments can significantly improve OS rather than PFS.[2,36,37]

Longer follow-up has not revealed any signs of any unexplained or unexpected toxicities or deaths. There have been two deaths in the context of the COVID-19 pandemic, both involving patients without active tumor disease. This is an expected outcome, considering the high morbidity and mortality of this infection in patients with lung cancer.[38]

In our study, adjuvant nivolumab was administered for up to 12 months. It remains to be determined how much this treatment contributes to the OS. In this regard, adjuvant atezolizumab following lung resection and adjuvant chemotherapy has been shown to extend disease-free survival in patients with NSCLC,[39] although this has not been replicated in other tumors.[40]

In conclusion, here we report mature OS data, with more than 3 years of follow-up, in patients with resectable stage IIIA NSCLC treated with neoadjuvant chemoimmunotherapy. Survival time was almost three times that reported in the historical series, in which the 3-year OS did not exceed 30%.[19] Pretreatment ctDNA levels were significantly associated with survival but not classical biomarkers such as TMB or PD-L1 staining. Finally, undetectable ctDNA levels after neoadjuvant treatment outperformed radiologic responses assessed according to RECIST criteria v 1.1 in the prediction of OS.

AFFILIATIONS

[1]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain
[2]Institut Català d'Oncologia, L'Hospitalet De Llobregat, Barcelona, Spain
[3]Fundación INCLIVA, Hospital Clínico Universitario de Valencia, Valencia, Spain
[4]Hospital Universitario A Coruña, A Coruña, Spain
[5]Hospital Universitario de Vigo, Pontevedra, Spain
[6]Hospital Universitario Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain
[7]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[8]Hospital Insular de Gran Canaria, Las Palmas, Spain
[9]Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Barcelona, Spain
[10]Hospital Universitario La Paz, Madrid, Spain
[11]Hospital Universitario Regional de Malaga, Spain
[12]Hospital Universitario Cruces, Barakaldo, Spain.
[13]Hospital Universitario de Salamanca, Salamanca, Spain
[14]Hospital Universitario Virgen del Rocio, Seville, Spain
[15]Hospital Clínic, Barcelona, Spain
[16]Hospital Universitario Reina Sofia, Córdoba, Spain
[17]Instituto Oncológico Dr Rosell. Hospital Universitario Quiron Dexeus, Grupo QuironSalud, Barcelona, Spain
[18]Spanish Lung Cancer Group, Barcelona, Spain
[19]Centro de Investigación Principe Felipe, Valencia, Spain
[20]Atrys Health, Barcelona, Spain
[21]Hospital General de Alicante, Alicante, Spain

CORRESPONDING AUTHOR

Mariano Provencio, MD, PhD, Medical Oncology Department, Hospital Puerta de Hierro, Calle Joaquín Rodrigo, 1, 28222 Majadahonda, Madrid, Spain; Twitter: @MARIANOPROVENCI; e-mail: mprovenciop@gmail.com.

PRIOR PRESENTATION

Presented in part at the World Conference on Lung Cancer Virtual Meeting, September 8-14, 2021.

SUPPORT

Supported by Bristol Myers Squibb. This study was supported by the European Union Horizon 2020 Research and Innovation program under grant agreement no. 875160. In addition, the project received funds from Instituto de Salud Carlos III (ISCIII) PI19/01652 (Cofunded by European Regional Development Fund/European Social Fund 'A way to

make Europe'/'Investing in your future'). R.S-B. is supported by PEJD-2018-PRE/BMD-8640 contract from European Social Fund (ESF). M.Ca. is supported by PEJD-2019-PRE/BMD-17006 contract from European Social Fund (ESF). E.S-H was funded by the Consejería de Ciencia, Universidades e Innovación of the Comunidad de Madrid (Doctorados Industriales of the Comunidad de Madrid IND2019/BMD-17258). A.C-B. is supported by Sara Borrell fellowship grant no. CD19/00170, Instituto de Salud Carlos III (ISCIII).

CLINICAL TRIAL INFORMATION

NCT03081689 (NADIM)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02660.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO.21.02660.

AUTHOR CONTRIBUTIONS

Conception and design: Mariano Provencio, Manuel Dómine, Bartomeu Massuti, Alberto Cruz-Bermúdez, Atocha Romero
Financial support: Mariano Provencio
Administrative support: Eva Pereira, Bartomeu Massuti
Provision of study materials or patients: Mariano Provencio, Ernest Nadal, Margarita Majem, Javier De Castro Carpeño, Manuel Cobo, Edel Del Barco, Santiago Viteri, Virginia Calvo, Fernando Franco, Bartomeu Massuti, Atocha Romero
Collection and assembly of data: Mariano Provencio, Roberto Serna-Blasco, Amelia Insa, Manuel Dómine, Margarita Majem, Alex Martínez-Martí, Javier De Castro Carpeño, Manuel Cobo, Reyes Bernabé Caro, Nuria Viñolas, Isidoro Barneto Aranda, Santiago Viteri, Eva Pereira, Virginia Calvo, Javier Martín-López, Marta Casarrubios, Bartomeu Massuti, Alberto Cruz-Bermúdez, Atocha Romero
Data analysis and interpretation: Mariano Provencio, Roberto Serna-Blasco, Ernest Nadal, Delvys Rodríguez-Abreu, Alex Martínez-Martí, Javier De Castro Carpeño, Edel Del Barco, Isidoro Barneto Aranda, Ana Royuela, Francisco García-García, Fernando Franco, Estela Sánchez-Herrero, Alberto Cruz-Bermúdez, Atocha Romero
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors would like to thank Phil Mason for language editing.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, et al: Cancer statistics, 2021. CA Cancer J Clin 71:7-33, 2021
2. Borghaei H, Paz-Ares L, Horn L, et al: Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 373:1627-1639, 2015
3. Herbst RS, Baas P, Kim DW, et al: Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet 387:1540-1550, 2016
4. Reck M, Rodríguez-Abreu D, Robinson AG, et al: Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 375: 1823-1833, 2016
5. Hellmann MD, Ciuleanu T-E, Pluzanski A, et al: Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 378:2093-2104, 2018
6. Provencio M, Nadal E, Insa A, et al: Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): An open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 21:1413-1422, 2020
7. NSCLC Meta-analysis Collaborative Group: Preoperative chemotherapy for non-small-cell lung cancer: A systematic review and meta-analysis of individual participant data. Lancet 383:1561-1571, 2014
8. Ling Y, Li N, Li L, et al: Different pathologic responses to neoadjuvant anti-PD-1 in primary squamous lung cancer and regional lymph nodes. NPJ Precis Oncol 4:1-7, 2020
9. Cottrell TR, Thompson ED, Forde PM, et al: Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: A proposal for quantitative immune-related pathologic response criteria (irPRC). Ann Oncol 29:1853-1860, 2018
10. Stein JE, Lipson EJ, Cottrell TR, et al: Pan-tumour pathologic scoring of response to PD-(L)1 blockade. Clin Cancer Res 26:545-551, 2020
11. Clark TG, Bradburn MJ, Love SB, et al: Survival Analysis Part I: Basic concepts and first analyses. Br J Cancer 89:232-238, 2003
12. Gebski V, Garès V, Gibbs E, et al: Data maturity and follow-up in time-to-event analyses. Int J Epidemiol 47:850-859, 2018
13. Anderson JR, Cain KC, Gelber RD: Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. J Clin Oncol 26: 3913-3915, 2008
14. Harrell FE, Califf RM, Pryor DB, et al: Evaluating the yield of medical tests. JAMA 247:2543-2546, 1982
15. White IR, Rapsomaniki E, Wannamethee SG, et al: Covariate-adjusted measures of discrimination for survival data. Biometrical J 57:592-613, 2015
16. Spanish Lung Cancer Group: www.gecp.org
17. Gadgeel S, Rodríguez-Abreu D, Speranza G, et al: Updated analysis from KEYNOTE-189: Pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non–small-cell lung cancer. J Clin Oncol 38:1505-1517, 2020
18. Blumenthal GM, Bunn PA, Chaft JE, et al: Current status and future perspectives on neoadjuvant therapy in lung cancer. J Thorac Oncol 13:1818-1831, 2018
19. Ramnath N, Dilling TJ, Harris LJ, et al: Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143:e314S-e340S, 2013 (5 suppl)
20. Forde PM, Spicer J, Lu S, et al: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIA) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial. Cancer Res 81, 2021 (suppl 13; abstr CT003)
21. Xu YP, Li B, Xu XL, et al: Is there a survival benefit in patients with stage IIIA (N2) non-small cell lung cancer receiving neoadjuvant chemotherapy and/or radiotherapy prior to surgical resection: A systematic review and meta-analysis. Medicine 94:e879, 2015
22. Mauguen A, Pignon JP, Burdett S, et al: Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: A re-analysis of meta-analyses of individual patients' data. Lancet Oncol 14:619-626, 2013

23. Hellmann MD, Chaft JE, William WN, et al: Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: Proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol 15:e42-50, 2014
24. Qu Y, Emoto K, Eguchi T, et al: Pathologic assessment after neoadjuvant chemotherapy for NSCLC: Importance and implications of distinguishing adenocarcinoma from squamous cell carcinoma. J Thorac Oncol 14:482-493, 2019
25. Menzies AM, Amaria RN, Rozeman EA, et al: Pathological response and survival with neoadjuvant therapy in melanoma: A pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). Nat Med 27:301-309, 2021
26. Casarrubios M, Cruz-Bermúdez A, Nadal E, et al: Pre-treatment tissue TCR repertoire evenness is associated with complete pathological response in patients with NSCLC receiving neoadjuvant chemoimmunotherapy. Clin Cancer Res 27:5878-5890, 2021
27. Laza-Briviesca R, Cruz-Bermúdez A, Nadal E, et al: Blood biomarkers associated to complete pathological response on NSCLC patients treated with neoadjuvant chemoimmunotherapy included in NADIM clinical trial. Clin Transl Med 11:e491, 2021
28. Paz-Ares L, Ciuleanu TE, Cobo M, et al: First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): An international, randomised, open-label, phase 3 trial. Lancet Oncol 22:198-211, 2021
29. Rothschild SI, Zippelius A, Eboulet EI, et al: SAKK 16/14: Durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non-small-cell lung cancer-A multicenter single-arm phase II trial. J Clin Oncol 39:2872-2880, 2021
30. Pairawan S, Hess KR, Janku F, et al: Cell-free circulating tumor DNA variant allele frequency associates with survival in metastatic cancer. Clin Cancer Res 26: 1924-1931, 2020
31. Provencio M, Majem M, Guirado M, et al: Phase II clinical trial with metronomic oral vinorelbine and tri-weekly cisplatin as induction therapy, subsequently concomitant with radiotherapy (RT) in patients with locally advanced, unresectable, non-small cell lung cancer (NSCLC). Analysis of survival and value of ctDNA for patient selection. Lung Cancer 153:25-34, 2021
32. Provencio M, Serna-Blasco R, Franco F, et al: Analysis of circulating tumour DNA to identify patients with epidermal growth factor receptor–positive non-small cell lung cancer who might benefit from sequential tyrosine kinase inhibitor treatment. Eur J Cancer 149:61-72, 2021
33. Giroux Leprieur E, Herbretau G, Dumenil C, et al: Circulating tumour DNA evaluated by Next-Generation Sequencing is predictive of tumour response and prolonged clinical benefit with nivolumab in advanced non-small cell lung cancer. Oncoimmunology 7:e1424675, 2018
34. Yang M, Forbes ME, Bitting RL, et al: Incorporating blood-based liquid biopsy information into cancer staging: Time for a TNMB system? Ann Oncol 29: 311-323, 2018
35. Anagnostou V, Forde PM, White JR, et al: Dynamics of tumor and immune responses during immune checkpoint blockade in non-small cell lung cancer. Cancer Res 79:1214-1225, 2019
36. Brahmer J, Reckamp KL, Baas P, et al: Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med 373:123-135, 2015
37. Motzer RJ, Escudier B, McDermott DF, et al: Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373:1803-1813, 2015
38. Provencio M, Mazarico Gallego JM, Calles A, et al: Lung cancer patients with COVID-19 in Spain: GRAVID study. Lung Cancer 157:109-115, 2021
39. Wakelee HA, Altorki NK, Zhou C, et al: IMpower010: Primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC). J Clin Oncol 39, 2021 (suppl 15; abstr 8500)
40. Bellmunt J, Hussain M, Gschwend JE, et al: Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 22:525-537, 2021

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non–Small-Cell Lung Cancer (NADIM phase II trial)

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Mariano Provencio
Consulting or Advisory Role: Bristol Myers Squibb, Roche, MSD, AstraZeneca, Takeda
Speakers' Bureau: BMS, Roche, AstraZeneca, MSD
Research Funding: Pierre Fabre (Inst), Roche (Inst), Boehringer Ingelheim (Inst), Bristol Myers Squibb (Inst)
Travel, Accommodations, Expenses: Roche, BMS, AstraZeneca

Ernest Nadal
Consulting or Advisory Role: MSD, Bristol Myers Squibb, Roche, Boehringer Ingelheim, Pfizer, Takeda, AstraZeneca, Lilly, Amgen, Bayer, Sanofi
Research Funding: Roche (Inst), Pfizer (Inst), Roche (Inst), Bristol Myers Squibb (Inst), Merck Serono (Inst)
Travel, Accommodations, Expenses: MSD, Bristol Myers Squibb, Pfizer, Roche, Lilly

Amelia Insa
Consulting or Advisory Role: Pfizer, Amgen, AstraZeneca Spain
Expert Testimony: Bristol Myers Squibb/Celgene, Roche Molecular Diagnostics, AstraZeneca Spain, MSD Oncology
Travel, Accommodations, Expenses: Roche/Genentech, Pfizer

M. Rosario García-Campelo
Consulting or Advisory Role: Roche/Genentech, MSD Oncology, AstraZeneca, Bristol Myers Squibb, Pfizer, Novartis, Takeda, Boehringer Ingelheim, Janssen Oncology
Speakers' Bureau: Roche, AstraZeneca, Bristol Myers Squibb, Pfizer, Novartis, Takeda, Boehringer Ingelheim, MSD Oncology, Sanofi/Aventis, Janssen Oncology, Amgen
Travel, Accommodations, Expenses: Roche/Genentech, MSD Oncology, Pfizer

Manuel Dómine
Consulting or Advisory Role: AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, MSD Oncology, Pfizer, Roche, Takeda

Margarita Majem
Consulting or Advisory Role: AstraZeneca, Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, Boehringer Ingelheim, Novartis, Tesaro, Helsinn Therapeutics, Takeda, Sanofi, Janssen Oncology, Pierre Fabre
Research Funding: BMS (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Roche, Lilly

Delvys Rodríguez-Abreu
Consulting or Advisory Role: Roche, Bristol Myers Squibb, MSD, AstraZeneca Spain, Novartis
Speakers' Bureau: Roche, Bristol Myers Squibb, MSD
Travel, Accommodations, Expenses: Roche, Bristol Myers Squibb, MSD

Alex Martínez-Martí
Consulting or Advisory Role: Bristol Myers Squibb, Roche, Merck Sharp & Dohme, Pfizer, Boehringer Ingelheim, MSD Oncology, AstraZeneca/MedImmune
Speakers' Bureau: Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, Boehringer Ingelheim, AstraZeneca/MedImmune
Travel, Accommodations, Expenses: Roche, Bristol Myers Squibb, Pfizer, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca/MedImmune

Javier De Castro Carpeño
Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp & Dohme, Roche, Pfizer, Takeda, GlaxoSmithKline, Janssen Oncology, Sanofi, Bayer, Lilly
Travel, Accommodations, Expenses: AstraZeneca Spain, Merck Sharp & Dohme, Roche

Edel Del Barco
Travel, Accommodations, Expenses: Bristol Myers Squibb

Nuria Viñolas
Speakers' Bureau: Pfizer, Roche, Bristol Myers Squibb/Medarex

Santiago Viteri
Consulting or Advisory Role: Roche, Bristol Myers Squibb, Janssen, Takeda, Reddy Pharma Iberia, Merck KGaA, Puma Biotechnology
Speakers' Bureau: Bristol Myers Squibb, Roche, MSD, AstraZeneca Spain
Travel, Accommodations, Expenses: Roche, MSD, Merck KGaA

Virginia Calvo
Consulting or Advisory Role: Roche/Genentech, Bristol Myers Squibb/Celgene, Merck Sharp & Dohme, Takeda, AstraZeneca Spain, Boehringer Ingelheim, Lilly, Pfizer

Javier Martín-López
Speakers' Bureau: Roche
Travel, Accommodations, Expenses: EUSA Pharma

Bartomeu Massuti
Consulting or Advisory Role: Roche, Boehringer Ingelheim, Bristol Myers Squibb, AstraZeneca, Takeda, Merck Serono, Janssen
Speakers' Bureau: Roche, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb
Travel, Accommodations, Expenses: Roche

Atocha Romero
Consulting or Advisory Role: Takeda, AstraZeneca Spain
Research Funding: Bristol Myers Squibb Foundation (Inst), Boehringer Ingelheim (Inst), Takeda (Inst)
Expert Testimony: Vivo Diagnostics

No other potential conflicts of interest were reported.