Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

Mariano Provencio, Ernest Nadal, Amelia Insa, María Rosario García-Campelo, Joaquín Casal-Rubio, Manuel Dómine, Margarita Majem, Delvys Rodríguez-Abreu, Alex Martínez-Martí, Javier De Castro Carpeño, Manuel Cobo, Guillermo López Vivanco, Edel Del Barco, Reyes Bernabé Caro, Nuria Viñolas, Isidoro Barneto Aranda, Santiago Viteri, Eva Pereira, Ana Royuela, Marta Casarrubios, Clara Salas Antón, Edwin R Parra, Ignacio Wistuba, Virginia Calvo, Raquel Laza-Briviesca, Atocha Romero, Bartomeu Massuti, Alberto Cruz-Bermúdez

Summary

Background Non-small-cell lung cancer (NSCLC) is terminal in most patients with locally advanced stage disease. We aimed to assess the antitumour activity and safety of neoadjuvant chemoimmunotherapy for resectable stage IIIA NSCLC.

Methods This was an open-label, multicentre, single-arm phase 2 trial done at 18 hospitals in Spain. Eligible patients were aged 18 years or older with histologically or cytologically documented treatment-naive American Joint Committee on Cancer-defined stage IIIA NSCLC that was deemed locally to be surgically resectable by a multidisciplinary clinical team, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients received neoadjuvant treatment with intravenous paclitaxel (200 mg/m²) and carboplatin (area under curve 6; 6 mg/mL per min) plus nivolumab (360 mg) 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 every 2 weeks for 4 months, followed by 480 mg every 4 weeks for 8 months). The primary endpoint was progression-free survival at 24 months, assessed in the modified intention-to-treat population, which included all patients who received neoadjuvant treatment, and in the per-protocol population, which included all patients who had tumour resection and received at least one cycle of adjuvant treatment. Safety was assessed in the modified intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT03081689, and is ongoing but no longer recruiting patients.

Findings Between April 26, 2017, and Aug 25, 2018, we screened 51 patients for eligibility, of whom 46 patients were enrolled and received neoadjuvant treatment. At the time of data cutoff (Jan 31, 2020), the median duration of follow-up was 24·0 months (IQR 21·4–28·1) and 35 of 41 patients who had tumour resection were progression free. At 24 months, progression-free survival was 77·1% (95% CI 59·9–87·7). 43 (93%) of 46 patients had treatment-related adverse events during neoadjuvant treatment, and 14 (30%) had treatment-related adverse events of grade 3 or worse; however, none of the adverse events were associated with surgery delays or deaths. The most common grade 3 or worse treatment-related adverse events were increased lipase (three [7%]) and febrile neutropenia (three [7%]).

Interpretation Our results support the addition of neoadjuvant nivolumab to platinum-based chemotherapy in patients with resectable stage IIIA NSCLC. Neoadjuvant chemoimmunotherapy could change the perception of locally advanced lung cancer as a potentially lethal disease to one that is curable.

Funding Bristol-Myers Squibb, Instituto de Salud Carlos III, European Union's Horizon 2020 research and innovation programme.

Copyright © 2020 Elsevier Ltd. All rights reserved.

Introduction

Non-small-cell lung cancer (NSCLC) accounts for 80–85% of all lung cancer cases. Approximately 20% of patients with NSCLC are diagnosed with stage IIIA (N2) disease.[1] Outcomes remain poor for this subset of patients, even in patients with potentially operable tumours, with a median progression-free survival of 13 months and a 3-year overall survival of 30%, with no major treatment advances made in the past 25 years.[2]

Pathological response to neoadjuvant treatment is a potential surrogate endpoint for survival; however, considering the low proportion of patients who achieve complete pathological response with induction chemotherapy (median 4%; range 0–16%), a definitive association has been difficult to establish, and has not been validated in NSCLC.[3]

In a 2018 study, neoadjuvant administration of two doses of nivolumab was associated with major pathological response in nine (45%) of 20 evaluable patients with NSCLC tumours, with two (10%) of 20 patients achieving a complete pathological response.[4] Furthermore, in a 2020 study of neoadjuvant chemoimmunotherapy, 17 (57%) of

Lancet Oncol 2020

Published Online
September 24, 2020
https://doi.org/10.1016/S1470-2045(20)30453-8

Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain (M Provencio MD, A Royuela PhD, M Casarrubios MSc, C Salas Antón MD, V Calvo MD, R Laza-Briviesca MSc, A Romero PhD, A Cruz-Bermúdez PhD); **Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Institute of Health Carlos III, Madrid, Spain** (A Royuela); **Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain** (E Nadal MD); **Fundación INCLIVA, Hospital Clínico Universitario de Valencia, Valencia, Spain** (A Insa MD); **Hospital Universitario A Coruña, A Coruña, Spain** (M R García-Campelo MD); **Hospital Universitario de Vigo, Pontevedra, Spain** (J Casal-Rubio MD); **Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD), Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain** (M Dómine MD); **Hospital de la Santa Creu I Sant Pau, Barcelona, Spain** (M Majem MD); **Hospital Insular de Gran Canaria, Las Palmas, Spain** (D Rodríguez-Abreu MD); **Hospital Universitario e Instituto de Oncología Vall d´Hebron (VHIO), Barcelona, Spain** (A Martínez-Martí MD); **Hospital Universitario La Paz, Madrid, Spain** (J De Castro Carpeño MD); **Hospital Universitario Regional de Málaga, Málaga, Spain** (M Cobo MD); **Hospital Universitario Cruces, Barakaldo, Spain** (G López Vivanco MD); **Hospital**

Universitario de Salamanca, Salamanca, Spain (E Del Barco MD)**; Hospital Universitario Virgen del Rocio, Seville, Spain** (R Bernabé Caro MD)**; Hospital Clínic de Barcelona, Barcelona, Spain** (N Viñolas MD)**; Hospital Universitario Reina Sofia, Córdoba, Spain** (I Barneto Aranda MD)**; Instituto Oncológico Dr Rosell, Hospital Universitari Dexeus-Grupo Quironsalud, Barcelona, Spain** (S Viteri MD)**; Spanish Lung Cancer Group, Barcelona, Spain** (E Pereira MSc)**; Department of Translational Molecular Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA** (E R Parra PhD, I Wistuba MD)**; and Hospital General de Alicante, Alicante, Spain** (B Massuti MD)

Correspondence to: Dr Mariano Provencio, Hospital Universitario Puerta de Hierro-Majadahonda, 28222 Madrid, Spain **mprovenciop@gmail.com**

Research in context

Evidence before this study

We searched PubMed from Jan 1, 2010, to May 11, 2020, for clinical trials published in English using the search terms "neoadjuvant", "lung cancer", and "PD-L1" or "PD-1". Our search yielded two studies. The first study described neoadjuvant nivolumab treatment in patients with stage I–IIIA non-small-cell lung cancer (NSCLC) with the primary endpoints of safety and feasibility; however, no survival data were reported. The second study assessed neoadjuvant atezolizumab plus chemotherapy for patients with stage II–IIIA NSCLC, and the authors identified no association between major pathological response and survival after a median of 1-year follow-up. Additionally, using the same search terms and date restrictions, we examined the websites of three major international conferences (American Society of Clinical Oncology, European Society for Medical Oncology, and World Conference on Lung Cancer) and ClinicalTrials.gov, and identified several ongoing phase 2 and phase 3 trials of different neoadjuvant immunotherapy approaches with estimated primary completion dates ranging from 2020 to 2024.

Added value of this study

To our knowledge, our study is the first published trial to assess the feasibility, safety, antitumour activity, and survival outcomes of neoadjuvant nivolumab plus standard chemotherapy in patients with resectable stage IIIA NSCLC. One of the main concerns regarding neoadjuvant therapy is risk of preoperative complications; however, we showed that treatment was well tolerated, was not associated with delays in surgery, and led to complete resection in all patients who had surgery. Our results showed that in this high-risk patient group, which included a high proportion of patients with multiple stage IIIA (N2) disease, favourable pathological responses and downstaging, and progression-free survival and overall survival at 24 months were observed after neoadjuvant nivolumab plus standard chemotherapy.

Implications of all the available evidence

Our results combined with existing evidence could support the addition of neoadjuvant nivolumab to platinum-based chemotherapy in patients with resectable stage IIIA NSCLC, and encourage the use of pathological response as an early surrogate endpoint for survival, while considering specific somatic mutations that might limit its survival-predictive value. These observations have important implications for future clinical trial design and could improve outcomes for patients with resectable stage IIIA NSCLC.

30 patients achieved a major pathological response, with ten (33%) of 30 patients achieving a complete pathological response.[5] However, both studies included patients with stage I or II NSCLC, and disease-free survival (median duration of follow-up 12·9 months [IQR 6·2–22·9]) was not associated with pathological response.[5]

We hypothesised that neoadjuvant chemoimmunotherapy could increase the proportion of patients with resectable stage IIIA NSCLC who achieve a complete pathological response, and that this approach would increase the number of patients that can ultimately be cured. We designed our study to investigate the nivolumab plus paclitaxel-carboplatin regimen, as this regimen was associated with a 2-year overall survival of 62% in patients with advanced NSCLC (both squamous and non-squamous) in the Checkmate012 trial.[6] We aimed to assess the feasibility, safety, antitumour activity, and survival outcomes of neoadjuvant nivolumab plus standard chemotherapy in treatment-naive patients with potentially resectable stage IIIA NSCLC.

See Online for appendix 1

Methods

Study design and participants

This open-label, multicentre, single-arm, phase 2 trial was done at 18 hospitals in Spain. Eligible patients were aged 18 years or older and had histologically or cytologically documented, treatment-naive NSCLC of stage IIIA (American Joint Committee on Cancer 7th edition criteria)[7,8] that was deemed locally to be surgically resectable by a multidisciplinary clinical team.[9] Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1,[10] adequate organ function, and a forced expiratory volume in 1 s of at least 1·2 L.[11] Exclusion criteria were the presence of known *EGFR* mutations or *ALK* translocations; active autoimmune or infectious disease; ongoing systemic corticosteroid or other immunosuppressive therapy; history of symptomatic grade 3 or 4 interstitial lung disease; clinically significant concurrent malignancies; previous malignancies unless a complete remission was achieved at least 2 years before study entry and no additional therapy was required during the study; any medical, mental, or psychological condition which would affect study completion in the opinion of the investigator; previous treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways; acute or chronic infection with hepatitis B or C virus; patients who are HIV positive; and patients with history of allergy to study drug components. Full details of the inclusion and exclusion criteria are listed in the protocol (appendix 1 pp 41–45).

All patients had tumour staging, including diagnostic biopsy, pathological evaluation of mediastinal lymph nodes by endobronchial ultrasound, and mediastinoscopy or thoracotomy at baseline.[12] N2 disease was not required for patient inclusion. PET-CT and contrast-enhanced CT or MRI of brain and chest were mandatory at patient inclusion.

The study was done in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of

Helsinki. All patients provided written informed consent before enrolment. The protocol was approved by the clinical research ethics committee of Hospital Puerta de Hierro (Madrid, Spain). The full study protocol is available in appendix 1 (pp 20–98).

Procedures

Patients received the following drugs intravenously, as neoadjuvant treatment: nivolumab (360 mg), paclitaxel (200 mg/m²), and carboplatin (area under the curve 6; 6 mg/mL per min), on day 1 of each 21-day cycle, for three cycles before surgical resection. After completion of neoadjuvant chemoimmunotherapy, surgery was planned 42–49 days after the first day of the third treatment cycle. Resection of the primary tumour and lymph nodes was done according to standard institutional procedures. Once the patients were deemed fully recovered from surgery, adjuvant treatment with nivolumab was scheduled to commence 3–8 weeks after surgery. Patients received intravenous nivolumab as adjuvant treatment at a fixed dose of 240 mg every 2 weeks for 4 months, followed by a fixed dose of 480 mg every 4 weeks, until month 12.

Tumour CT imaging was done locally every 3 months during the first year of follow-up, every 4 months during the second year, and every 6 months thereafter. Tumour response was assessed after three cycles of treatment and before surgery; all changes in tumour size were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Morbidity and mortality and surgical complications were monitored during the first 30 days after surgery.

Patients had laboratory blood tests before each 21-day treatment cycle to monitor complete blood cell counts and biochemical parameters. Adverse events and abnormal laboratory findings were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Investigators determined whether adverse events were treatment related according to the study protocol and standard regulatory requirements.

Dose reductions were not permitted for nivolumab; however, nivolumab treatment could be interrupted, delayed, or discontinued depending on tolerability. Reductions were permitted for paclitaxel and carboplatin in accordance with two levels of dosage specified in the trial protocol (appendix 1 pp 55–58), in the event of grade 4 febrile neutropenia or neutropenia, thrombocytopenia, or anaemia. Treatment was interrupted or delayed if an adverse event occurred, and was resumed if protocol-defined criteria for treatment resumption were met (absolute neutrophil count $>1{\cdot}0\times10^9$ per L and platelet count $>75\times10^9$ per L before commencing the next treatment cycle); if haematological recovery was not achieved on day 21 (±3 days), the next treatment cycle could be delayed for up to 2 weeks.

Withdrawal criteria included patient withdrawal of consent, unacceptable toxicity, non-compliance, intercurrent illnesses, or other reasons that the investigator deemed would substantially affect the patient's safety.

Objective pathological response was assessed by local pathologists who measured the percentage of residual viable tumour in resected primary tumours, and was subsequently confirmed by 100% agreement of two masked pathologists. The entire tumour was included in the pathological study, and the number of sections reviewed for pathological response ranged from eight to 28 (median ten; mean 12). Major pathological response was defined as the presence of 10% or fewer viable tumour cells in the primary tumour, incomplete pathological response was defined as the presence of more than 10% viable tumour cells in the primary tumour, and complete pathological response was defined as tumours without any viable tumour cells in the resected lung cancer specimen and all sampled regional lymph nodes.[3,13,14]

Molecular methodology, including analysis of PD-L1 expression, CD8-positive tumour-infiltrating lymphocytes, tumour mutational burden, and multiplex immunofluorescence, is described in appendix 1 (p 2). Briefly, we assessed the baseline tumour mutational burden of formalin-fixed paraffin-embedded (FFPE) diagnostic samples using an Ion S5 Sequencer (Thermo Fisher Scientific, Palo Alto, CA, USA) with the Oncomine Tumor Mutation Load Assay (Thermo Fisher Scientific) according to the manufacturer's instructions. The PD-L1 IHC 22C3 pharmDx assay (Dako, Glostrup, Denmark) was used to assess PD-L1 tumour proportion score in FFPE tumour diagnostic samples. The number of CD8-positive tumour-infiltrating lymphocytes in FFPE surgical specimens was assessed using the CD8 Clone C8/144B assay (Dako) on a Dako Omnis platform (Agilent, Santa Clara, CA, USA). Automated multiplex immunofluorescence staining of representative FFPE tumour blocks was done using the Opal 7-Color IHC kit (PerkinElmer, Waltham, MA, USA).

Outcomes

The primary endpoint was progression-free survival at 24 months. Progression-free survival was defined as the time from diagnosis until objective tumour progression or death. Secondary endpoints were overall survival at 3 years (with overall survival defined as the time from diagnosis to date of death); pathological and imaging response (assessed per RECIST version 1.1); the proportion of patients who achieved tumour downstaging; the proportion of patients who had complete resection; proportion of patients with disease progression at 3 years; surgical outcome; and toxicity profile of the combination. Surgical outcome was defined as morbidity and mortality, and complications during the first 30 days after surgery. Toxicity profile was assessed for 100 days after the last dose of neoadjuvant or adjuvant nivolumab according to NCI-CTCAE (version 4.0) guidelines. Prespecified exploratory endpoints were investigating whether PD-L1

expression is a predictive biomarker for overall response rate, to describe progression-free survival in patients with PD-L1 tumour proportion score of 1% or more, and tumour mutational burden and immune cell populations in the tumour microenvironment to identify response biomarkers and resistance mechanisms to neoadjuvant chemoimmunotherapy.

The assessment of the proportion of patients with disease progression at 3 years (secondary endpoint) was not possible because the duration of follow-up was insufficient. Additional exploratory endpoints prespecified in the protocol (T-cell receptor immune repertoire, immunophenotyping, cell-free DNA monitoring, circulating tumour cells, and extended surgical outcomes and complications) will be published elsewhere.

Statistical analysis

Progression-free survival and overall survival were assessed in the modified intention-to-treat (ITT) population, which included all patients who received neoadjuvant treatment, and in the per-protocol population, which included all patients who had tumour resection and received at least one cycle of adjuvant treatment. All secondary outcomes were analysed in the modified ITT population. Follow-up was insufficient for the analysis of overall survival at 3 years, thus we report overall survival at 24 months, although this was not a prespecified analysis. Additionally, progression-free survival and overall survival at 24 months, and safety during adjuvant treatment were analysed in the per-protocol population.

For our sample size estimation, we used a one-sample test based on an exponential distribution. We estimated that a sample size of 46 patients would provide 80% power to detect a 15% improvement in 24-month progression-free survival, compared with that reported for these patients in previous studies (ranging from 40% in patients receiving standard therapy, considered here as the null hypothesis, to 55% in patients receiving the analysed treatment),[15–17] with a one-sided type I error of 5%. Sample size analysis was based on the assumptions of an accrual time of 18 months with an additional 36 months of follow-up.

We used the Kaplan-Meier method to estimate progression-free survival and overall survival and corresponding 95% CIs. The reverse Kaplan-Meier method was used to calculate the median follow-up time and corresponding IQR. Categorical variables were presented as absolute and relative frequencies and numerical variables as mean (SD) or median (IQR). Comparisons between groups were done using non-parametric tests (Mann-Whitney *U* test or Wilcoxon signed rank test for paired pretreatment *vs* post-treatment sample for two groups; Kruskal-Wallis with Bonferroni correction for three or more groups). We determined the association between categorical groups (specific mutations *vs* pathological responses) using Pearson's χ^2 test. The area under the receiver operating characteristic curve (AUC) was calculated to assess whether PD-L1 expression might be a biomarker of major pathological response or overall response rate. The correlation between PD-L1 and tumour mutational burden was estimated using Spearman's rank correlation coefficient. p values of less than 0.05 were considered to indicate a statistically significant difference.

The association of baseline characteristics, treatment-related adverse events, and pathological response with survival, the association between PD-L1 expression and clinical characteristics, and the association between progression-free survival and PD-L1 and tumour mutational burden combined with specific mutations were analysed post-hoc. Univariable Cox proportional hazard models were used to assess the association between baseline characteristics and progression-free survival. We tested the proportional-hazard assumption using Schoenfeld residuals. We used the Kaplan-Meier method and log-rank tests to estimate differences between post-hoc analysis groups. We estimated differences in PD-L1 tumour proportion score between patients according to clinical characteristics using Mann-Whitney tests.

Stata software was used for all statistical analyses (version 15.0). This study is registered with ClinicalTrials.gov, NCT03081689.

Role of the funding source

This study was designed by the sponsor and the study investigators. The study funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 26, 2017, and Aug 25, 2018, 51 patients were assessed for eligibility, of whom 46 patients were enrolled at 18 sites (appendix 1 pp 4, 13). Baseline characteristics of the patients are shown in table 1.

All patients received neoadjuvant treatment and thus were included in the modified ITT population. 41 (89%) of 46 patients had surgery, all of whom achieved complete tumour resection without associated morbidity or mortality. Of the 41 patients who had surgery, 37 (90%) received at least one cycle of adjuvant nivolumab and thus were included in the per-protocol population (appendix 1 p 4). Details of the patients who did not have surgery or did not receive adjuvant treatment are included in appendix 1 (p 3). Median duration of adjuvant therapy was 10·8 months (IQR 10·4–11·0). Postoperative complications were observed in 12 (29%) of 41 patients who underwent surgery. The most frequent complications were respiratory infection (four [10%] of 41 patients), cardiac arrhythmia (three [7%]), and air leakage (two [5%]; appendix 1 p 14).

At the time of data cutoff (Jan 31, 2020), 35 (85%) of 41 patients who had tumour resection were alive

and free of recurrence, with a median follow-up of 24·0 months (IQR 21·4–28·1; figure 1). Nine (20%) of 46 patients in the modified ITT population had disease progression or had died: three (7%) patients who did not undergo surgery had disease progression and died, and six (13%) patients who underwent surgery had disease progression, of whom two (4%) had died. The median duration of progression-free survival and overall survival was not reached in the modified ITT population or in the per-protocol population. In the modified ITT population, progression-free survival was 95·7% (95% CI 83·7–98·9) at 12 months, 87·0% (73·3–93·9) at 18 months, and 77·1% (59·9–87·7) at 24 months (figure 2A); in the per-protocol population, progression-free survival was 100% (95% CI not estimable) at 12 months, 91·9% (76·9–97·3) at 18 months, and 87·9% (69·8–95·3) at 24 months (appendix 1 p 4). In the modified ITT population, overall survival was 97·8% (95% CI 85·5–99·7) at 12 months, 93·5% (81·1–97·8) at 18 months, and 89·9% (74·5–96·2) and 24 months (figure 2B); in the per-protocol population, overall survival was 100% (95% CI not estimable) at 12 months, 97·3% (82·3–99·6) at 18 months, and 97·3% (82·3–99·6) at 24 months (appendix 1 p 4). 33 (89%) of 37 patients who received adjuvant nivolumab had no evidence of disease on examination or CT imaging. In a post-hoc analysis, no statistically significant associations were observed between baseline characteristics and progression-free survival (appendix 1 p 17).

43 (93%) of 46 patients had treatment-related adverse events during neoadjuvant treatment and 14 (30%) of 46 patients had adverse events of grade 3 or worse (table 2). The most common grade 1 or 2 treatment-related adverse events were asthenia or fatigue (23 [50%] of 46 patients), alopecia (16 [35%]), nausea (15 [33%]), neurotoxicity (13 [28%]), arthralgia (12 [26%]), diarrhoea (11 [24%]), and rash (ten [22%]). The most common treatment-related grade 3 or worse adverse events were increased lipase (three [7%] of 46 patients) and febrile neutropenia (three [7%]; table 2). None of the adverse events reported during neoadjuvant treatment led to treatment discontinuation, dose reduction, surgery delay, or death; however, three (7%) of 46 patients had treatment-related adverse events that prevented them from receiving adjuvant nivolumab treatment (two [4%] patients had haematological toxicity and one [2%] patient had renal insufficiency). In a post-hoc analysis, no statistically significant difference was identified between progression-free survival of patients who had grade 2–4 treatment-related adverse events (n=34) and patients who had grade 1 or no treatment-related adverse events (n=12; log-rank p=0·14). 32 (86%) of 37 patients had grade 1 or 2 treatment-related adverse events during adjuvant treatment; the most common were rash (19 [51%] of 37 patients), asthenia or fatigue (18 [49%]), and pruritus (13 [35%]). Seven (19%) of 37 patients had grade 3 or worse treatment-related adverse events. The most common grade 3 or worse treatment-related adverse events were elevated serum lipase (four [11%] of 37 patients), and increased serum amylase (three [8%]; table 3). Discontinuation of adjuvant nivolumab due to treatment-related adverse events occurred in five (14%) of 37 patients. No adverse events led to death during adjuvant treatment.

	Patients (n=46)
Age, years	63 (58–70)
Sex	
Male	34 (74%)
Female	12 (26%)
ECOG performance status	
0	25 (54%)
1	21 (46%)
Smoking status	
Former smoker (≥1 year)	25 (54%)
Current smoker	21 (46%)
Pack-years	49 (39–61)
Histology	
Adenocarcinoma	26 (57%)
Squamous cell carcinoma	16 (35%)
Not specified or undifferentiated	4 (9%)
Comorbidities	
Yes	43 (93%)
No	3 (7%)
Dyslipidaemia	16 (35%)
Hypertension	15 (33%)
Diabetes	9 (20%)
Chronic obstructive pulmonary disease	9 (20%)
Heart disease	7 (15%)
Hypercholesterolaemia	4 (9%)
Depressive disorder or anxiety	4 (9%)
Nephropathy	2 (4%)
Asthma	1 (2%)
Vasculopathy	1 (2%)
Tumour lesion size, mm	35 (23–60)
Nodal stage	
N0	9 (20%)
N1	3 (7%)
N2	34 (74%)
Single	9 (20%)
Multiple	25 (54%)
Tumour, Node, Metastasis staging classification	
T1N2M0	15 (33%)
T2N1M0	1 (2%)
T2N2M0	6 (13%)
T3N1M0	1 (2%)
T3N2M0	13 (28%)
T4N0M0	9 (20%)
T4N1M0	1 (2%)

Data are n (%) or median (IQR). ECOG= Eastern Cooperative Oncology Group.

Table 1: **Baseline demographic and clinical characteristics of the modified intention-to-treat population**

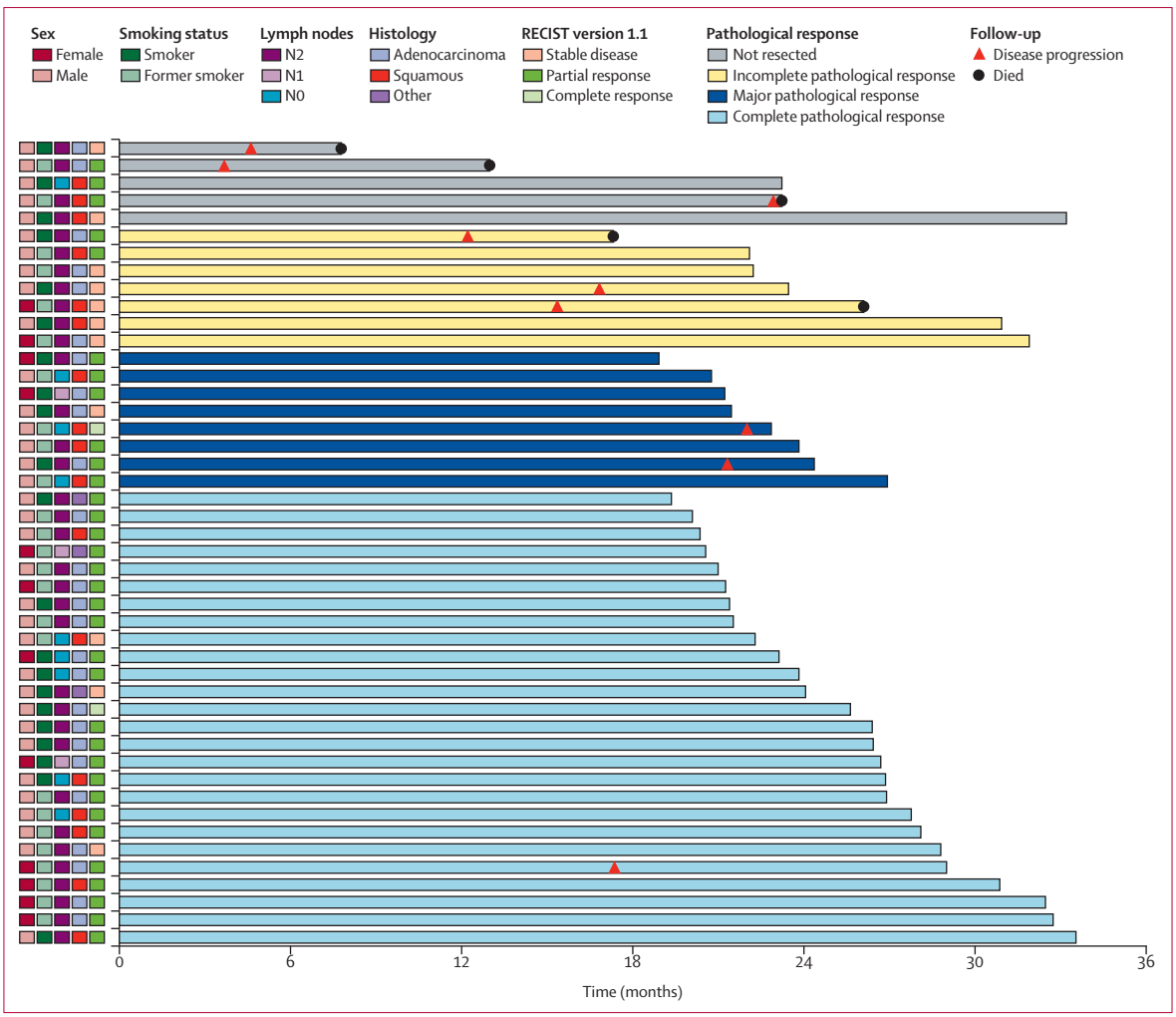

Figure 1: **Swimmer plot of progression-free survival in the modified intention-to-treat population (n=46)**
Each bar represents one patient. The left column shows clinical characteristics and radiological responses. Nine (20%) of 46 patients had disease progression or died; three (7%) patients who did not undergo surgery had disease progression and died, and six (13%) patients who underwent surgery had disease progression, two (4%) of whom died. Of the 26 patients who achieved a complete pathological response, one patient (4%) had disease progression, and this patient had an *EGFR* mutation (exon 19 deletion; Glu746_Ala750del) in the baseline biopsy that was not known at the trial inclusion. Of the seven patients with a major pathological response, two (29%) had disease progression and harboured baseline mutations in *STK11* (465-2A→T) and *KEAP1* (Lys287_Gln292dup, 876_877insLysCysGluIleLeuGln). RECIST=Response Evaluation Criteria in Solid Tumors.

According to RECIST 1.1 criteria, 35 (76%) of 46 patients had an overall response; two (4%) had a complete response, 33 (72%) had a partial response, and 11 (24%) had stable disease. No patients had progressive disease during neoadjuvant therapy (appendix 1 p 15). 34 (83%; 95% CI 68–93) of 41 patients who underwent surgery had a major pathological response, of whom 26 (63%; 62–91) had a complete pathological response (appendix 1 p 15). Three (33%) of nine patients with stable disease and 22 (73%) of 30 patients with a partial response had a complete pathological response (appendix 1 p 15). Of the 41 patients who underwent resection, 37 (90%) achieved pathological downstaging of clinical disease stage (appendix 1 p 16). No significant associations were identified between any clinical parameter and pathological response (data not shown).

In a post-hoc analysis, of the 41 patients who had surgery, six (15%) patients had disease progression (three [7%] patients had an incomplete pathological response, two [5%] had a major pathological response, and one [2%] had complete pathological response) and two (5%) died (both had incomplete pathological response). Of the 34 patients who had a major pathological response, including those who had a complete pathological response, 97·1% (95% CI 80·9–99·6) of patients were progression free at 18 months and 88·4% (67·1–96·1) at 24 months; and of the seven patients with an incomplete pathological response, 57·1% (17·2–83·7) of patients were progression

free at 18 and 24 months (log-rank p=0·010). Among 26 patients who had a complete pathological response, 96·2% (95% CI 75·7–99·5) of patients were progression free at 18 and 24 months, which was significantly higher than that for patients with incomplete pathological response (log-rank p=0·0023) or major pathological response (log-rank p=0·041). No significant differences in progression-free survival were observed between patients with an incomplete pathological response and major pathological response (log-rank p=0·52). In patients with major pathological response or complete pathological response, overall survival at 18 and 24 months was 100% (95% CI not estimable) compared with 85·7% (95% CI 33·4–97·9) in patients with incomplete pathological response at 18 and 24 months (log-rank p=0·0020). No differences in overall survival were observed between patients with a major pathological response and an incomplete pathological response (log-rank p=0·24), but a significant difference was identified between patients with a complete pathological response and an incomplete pathological response (log-rank p=0·0046; appendix 1 p 5).

In terms of the exploratory endpoints, among the 18 patients with a PD-L1 tumour proportion score of 1% or higher, 94·4% (95% CI 66·6–99·2) of patients were progression free at 12 months, 83·3% (56·7–94·3) at 18 months, and 75·8% (46·9–90·3) at 24 months. For the 28 patients with available PD-L1 data, the AUC for PD-L1 tumour proportion score to predict overall response rate was 0·719 (95% CI 0·533–0·904), with an optimal PD-L1 tumour proportion score cutoff of at least 45%. The AUC for PD-L1 tumour proportion score to distinguish between major pathological response and incomplete pathological response (n=25) was 0·785 (95% CI 0·622–0·948). A tumour proportion score of 25% or higher predicted a major pathological response with 65% sensitivity and 100% specificity, and was also associated with a major pathological response by χ^2 test (p=0·015). Additionally, 11 (73%) of 15 patients who achieved a complete pathological response had a PD-L1 tumour proportion score of 25% or higher, and two (40%) of five of the patients who achieved a major pathological response had a PD-L1 tumour proportion score of 25% or higher. Thus, PD-L1 tumour proportion score was significantly higher in patients who had a complete pathological response than in patients who had incomplete pathological response (p=0·042); however, no significant differences were identified between patients who had a major pathological response alone and incomplete pathological response (appendix 1 p 6). By contrast, no significant association was found between PD-L1 tumour proportion score and progression-free survival or overall survival (data not shown). In a post-hoc analysis, no significant differences in PD-L1 tumour proportion score were identified by histology, lymph node involvement, or sex (data not shown).

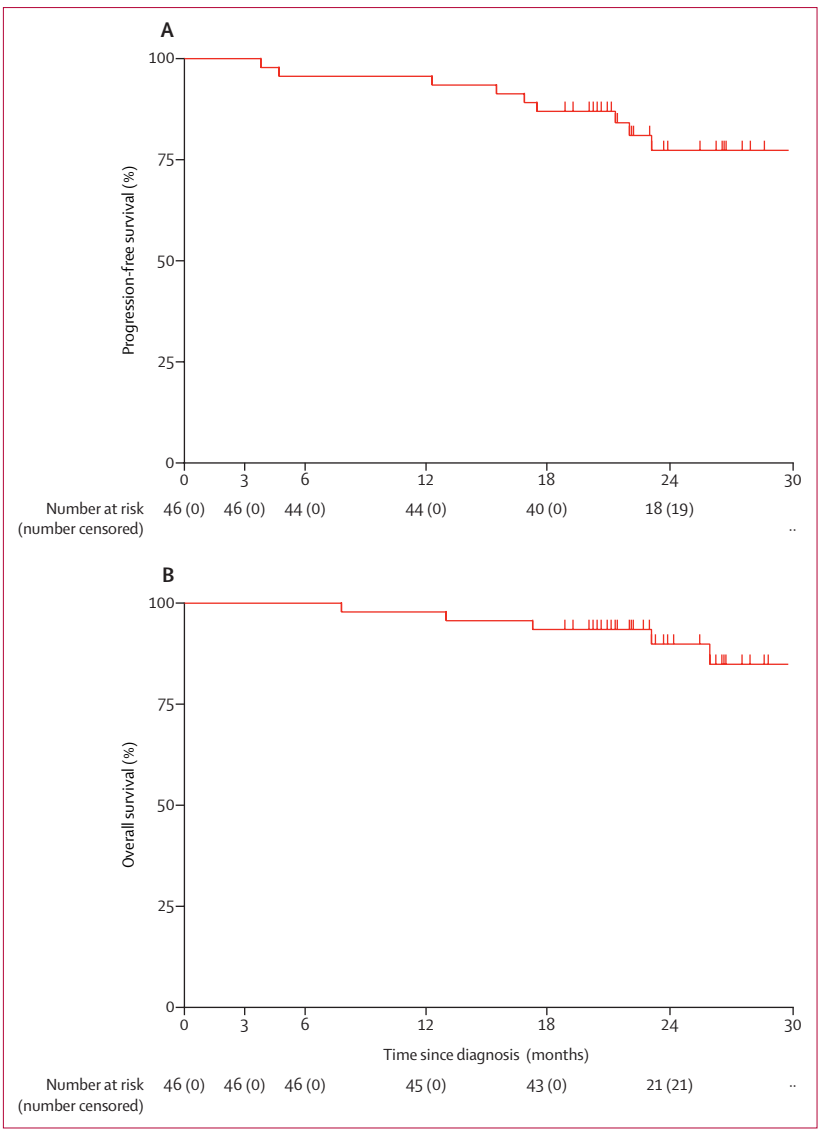

Figure 2: **Kaplan-Meier curves of progression-free survival (A) and overall survival (B) in the modified intention-to-treat population (n=46)**

29 (63%) of 46 patients had valid data for tumour mutational burden calculation, of whom 25 (54%) had pathological response data and eight (17%) had disease progression (appendix 1 p 7). No significant differences in the median number of somatic alterations were identified between any of the groups when stratified by pathological response (incomplete pathological response [n=6], 5·5 alterations [IQR 2·97–8·18]; major pathological response including complete pathological response [n=19], 6·7 alterations [3·4–16·8]; and complete pathological response alone [n=14], 6·3 [3·99–18·71]; appendix 1 p 6). No significant differences in progression-free survival were identified when patients were classified according to different tumour mutational burden thresholds (data not shown). Several somatic mutations were identified

	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	43 (93%)	14 (30%)	2 (4%)
Asthenia or fatigue	23 (50%)	1 (2%)	0
Alopecia	16 (35%)	1 (2%)	0
Nausea	15 (33%)	0	0
Neurotoxicity	13 (28%)	2 (4%)	0
Arthralgia	12 (26%)	0	0
Diarrhoea	11 (24%)	0	0
Skin disorders (rash)	10 (22%)	1 (2%)	0
Myalgia	9 (20%)	0	0
Vomiting	8 (17%)	0	0
Decreased appetite or anorexia	8 (17%)	1 (2%)	0
Constipation	8 (17%)	0	0
Paraesthesia	8 (17%)	0	0
Pruritus	7 (15%)	0	0
Anaemia	7 (15%)	0	0
Increased aminotransferases	4 (9%)	1 (2%)	0
Neutropenia	2 (4%)	1 (2%)	1 (2%)
Increased serum amylase	1 (2%)	2 (4%)	0
Increased creatinine	1 (2%)	2 (4%)	0
Increased lipase	0	2 (4%)	1 (2%)
Febrile neutropenia	0	3 (7%)	0
Pemphigoid of the hand	0	1 (2%)	0

Data are n (%). Toxicity was monitored continuously for 100 days after the last dose of neoadjuvant nivolumab. No grade 5 treatment-related adverse events were observed.

Table 2: **Treatment-related adverse events during neoadjuvant treatment in the modified intention-to-treat population (n=46)**

	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	32 (86%)	7 (19%)	1 (3%)
Skin disorders (rash)	19 (51%)	1 (3%)	0
Asthenia or fatigue	18 (49%)	0	0
Pruritus	13 (35%)	0	0
Decreased appetite or anorexia	7 (19%)	0	0
Diarrhoea	7 (19%)	0	0
Arthralgia	7 (19%)	0	0
Myalgia	5 (14%)	0	0
Nausea	5 (14%)	0	0
Vomiting	4 (11%)	0	0
Constipation	4 (11%)	0	0
Paraesthesia	4 (11%)	0	0
Increased lipase	1 (3%)	3 (8%)	1 (3%)
Increased serum amylase	1 (3%)	3 (8%)	0
Adrenal insufficiency	0	1 (3%)	0
Pemphigoid of the hand	0	1 (3%)	0

Data are n (%). No grade 5 treatment-related adverse events were observed.

Table 3: **Treatment-related adverse events during adjuvant treatment in the per-protocol population (n=37)**

See Online for appendix 2

(appendix 2). Nine tumours harboured baseline mutations in genes associated with poor immunotherapy prognosis, specifically *STK11, KEAP1, RB1,* and *EGFR*. The presence of these mutations was not associated with pathological response, but was associated with shorter progression-free survival (median 21·4 months [95% CI 3·8–not estimable] for patients harbouring mutations [n=9, five events] *vs* not reached in patients without the mutations [n=20, three events]; log-rank p=0·027). Furthermore, no association was identified between tumour mutational burden and tumour PD-L1 expression (n=25; Spearman's rank correlation coefficient –0·18; p=0·38). A post-hoc analysis suggested that the absence of mutations in *STK11, KEAP1, RB1,* or *EGFR* combined with a high tumour mutational burden could help to identify patients with longer progression-free survival in this cohort (log-rank p=0·038), whereas patients without these specific mutations and with high PD-L1 expression did not have significantly longer progression-free survival compared with all other patients (log-rank p=0·136; appendix 1 p 12). In a further exploratory analysis of the tumour microenvironment, 34 samples were sent to MD Anderson Cancer Center for multiplex immunofluorescence; 29 (85%) samples were adequate for staining (12 at diagnosis and 17 at surgical resection) from 20 patients. Paired samples (pre-treatment and post-treatment) were available for nine patients. The number of most immune populations analysed was lower in post-neoadjuvant samples than pre-neoadjuvant samples. By contrast, the number of memory and regulatory T cells seemed to be maintained, or even increased, after treatment (appendix 1 pp 8–9). Additionally, we identified statistically significant differences in the levels of certain immune populations between tumours with major pathological response and incomplete pathological response, and between those with complete pathological response and major pathological response (appendix 1 pp 10–11).

Discussion

To our knowledge, this is the first study to assess the feasibility, safety, antitumour activity, and survival outcomes of neoadjuvant chemoimmunotherapy specifically in patients with resectable stage IIIA NSCLC. The addition of neoadjuvant nivolumab to chemotherapy was well tolerated, and the frequency of treatment-related adverse events was similar to that commonly observed with induction chemotherapy, and that described in the KEYNOTE-189 trial.[18] Furthermore, treatment with neoadjuvant nivolumab did not delay planned surgery, and at 24 months, progression-free survival was 77% and overall survival was 90%.

Compared with adjuvant strategies, the presence of the full tumour mass at the initiation of immunotherapy allows the induction of a stronger adaptive antitumour response and early development of immune memory that might provide long-term protection.[19] We identified lymphoid follicles in post-treatment samples compatible with tertiary lymphoid structures, which are associated with improved responses to immunotherapy.[20] However, the post-treatment reduction of several lymphocyte

populations would indicate that, at the time of surgery, the lymphocytes would have eliminated most tumour cells and then would have partially declined after the tumour mass was reduced or completely eliminated. This hypothesis is supported by the high proportion of tumours that achieved a major or complete pathological response; the significantly lower amounts of cytotoxic T cells in tumours with complete pathological response than in those with major or incomplete pathological responses (appendix 1 p 10); and the significantly higher numbers of memory and regulatory T cells (associated with advanced and strong antitumour immune responses)[19,21,22] present in tumour areas that had major or complete pathological responses compared with those that had incomplete pathological response (appendix 1 p 10).

Complete surgical resection,[15,16] tumour downstaging,[17] and major pathological response or complete pathological response have been associated with improved survival in patients with resectable NSCLC.[3,14] The criteria for resection are a matter of debate in patients with stage IIIA NSCLC. In our study, 25 (54%) of 46 patients had multiple level N2 disease, which is considered unresectable by some, and therefore reinforces the potential antitumour activity of this combination. All patients who achieved a major pathological response or complete pathological response were alive at 24 months, and progression-free survival in patients with a complete pathological response was significantly higher than that achieved in patients with an incomplete pathological response or major pathological response. Our data reinforce the relevance of the pathological response as a potential survival surrogate and highlight that the presence of specific mutations could limit its predictive value.

No significant associations were identified between any clinical or molecular parameters analysed at diagnosis and pathological response. A PD-L1 tumour proportion score of 25% or more was associated with major pathological response or complete pathological response; however, this was insufficiently sensitive since 58% of patients with a PD-L1 tumour proportion score of less than 25% had a major pathological response or complete pathological response. Similar associations between PD-L1 expression and major pathological response have been observed in ongoing neoadjuvant immunotherapy trials with similar limitations in biomarker sensitivity.[23,24]

PD-L1 expression and tumour mutational burden were not associated with survival, extending to the neoadjuvant setting the finding of an absence of association between tumour mutational burden and survival in patients treated with chemoimmunotherapy combinations.[25] The presence of specific mutations (*STK11*, *KEAP1*, *RB1*, and *EGFR*) was associated with reduced progression-free survival, reinforcing their negative role in terms of survival observed in previous studies,[26–29] and supporting their future consideration in clinical trials.

The limitations of our study include the small sample size, the intrinsic heterogeneity of patients with stage IIIA NSCLC, and the absence of a randomised control group. However, we believe that neoadjuvant chemoimmunotherapy represents a promising therapeutic option for patients with resectable stage IIIA NSCLC, which requires confirmation in future randomised clinical trials, such as the ongoing phase 2 NADIM II trial (NCT03838159) and phase 3 Checkmate 77T trial (NCT04025879).[30]

Contributors

MP conceived the study. MP, VC, EN, AI, MRG-C, JC-R, MD, MM, DR-A, AM-M, JDCC, MCo, GLV, EDB, RBC, NV, IBA, SV, and BM recruited and treated patients. EP collected the data. MP and ARoy analysed the data. AC-B, RL-B, MCa, ARom, CSA, ERP, and IW did pathology and translational studies. MP, AC-B, RL-B, MCa, ARoy, and ARom interpreted the data. MP wrote the first draft of the manuscript. All authors read and contributed to the final version of the manuscript and approved its submission for publication.

Declaration of interests

MP reports grants, personal fees, and travel expenses from Bristol-Myers Squibb, Roche, and AstraZeneca; and personal fees from Merck Sharpe & Dohme and Takeda, outside the submitted work. EN reports personal fees from Bristol-Myers Squibb, Merck Sharpe & Dohme, AstraZeneca, Lilly, Amgen, and Boehringer Ingelheim; and grants and personal fees from Roche and Pfizer, outside the submitted work. AI reports personal fees from Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharpe & Dohme, Pfizer, Roche, and AstraZeneca, outside the submitted work. MRG-C reports personal fees from Bristol-Myers Squibb, Merck Sharpe & Dohme, Roche, Pfizer, and AstraZeneca, outside the submitted work. MD reports personal fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharpe & Dohme, Pfizer, and Roche, outside the submitted work. MM reports grants and personal fees from Bristol-Myers Squibb, Kyowa Kyrin, and Pierre Fabre; and personal fees and travel expenses from Merck Sharpe & Dohme, Boehringer Ingelheim, AstraZeneca, and Roche, outside the submitted work. DR-A reports grants and personal fees from Bristol-Myers Squibb; and personal fees from Genetech/Roche, Merck Sharpe & Dohme, AstraZeneca, Boehringer Ingelheim, Novartis, and Lilly, outside the submitted work. AM-M reports personal fees and travel expenses from Bristol-Myers Squibb, F Hoffmann-La Roche, Merck Sharp & Dohme, Pfizer, Boehringer Ingelheim, MSD Oncology, and AstraZeneca, outside the submitted work. JDCC reports personal fees from AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, F Hoffmann-La Roche, Bristol-Myers Squibb, Takeda, Pfizer, and Novartis, outside the submitted work. EDB reports travel expenses from Roche, Bristol-Myers Squibb, Pfizer, AstraZeneca, and Merck Sharpe & Dohme, during the conduct of the study. IBA reports consulting or advisory board fees from Bristol-Myers Squibb, Takeda, Roche, AstraZeneca, and Boehringer Ingelheim. SV reports personal fees and travel expenses from Bristol-Myers Squibb and Roche; personal fees from Merck Sharpe & Dohme and AbbVie; and travel expenses from OSE Immunotherapeutics, and Merck KGaA, outside the submitted work. IW reports grants and personal fees from Genentech/Roche, Bayer, Bristol-Myers Squibb, AstraZeneca/Medimmune, Pfizer, HTG Molecular Diagnostics, Merck, GlaxoSmithKline, Guardant Health; personal fees from Merck Sharpe & Dohme and Oncocyte; and grants from Oncoplex, DepArray, Adaptive, Adaptimmune, EMD Serono, Takeda, Amgen, Johnson & Johnson, Karus, Iovance, 4D, Novartis, and Akoya, outside the submitted work. VC reports personal fees from Roche, Bristol-Myers Squibb, Merck Sharpe & Dohme, AstraZeneca, and Boehringer Ingelheim. ARom reports personal fees from Boehringer Ingelheim, outside the submitted work. BM reports grants and personal fees from Roche; personal fees and travel expenses from Bristol-Myers Squibb and Takeda; travel expenses from Merck Sharpe and Dohme; and personal fees from Boehringer Ingelheim, outside the submitted work; JC-R, MCo, GLV, RBC, NV, EP, MCa, CSA, ERP, RL-B, ARoy, and AC-B declares no competing interests.

Data sharing

De-identified individual data might be made available following publication by reasonable request to the corresponding author. A research proposal should be included, which will be evaluated by the Spanish Lung Cancer Group and the ethics committee for clinical investigation.

Acknowledgments

This study was funded by Bristol-Myers Squibb, Instituto de Salud Carlos III (ISCIII; grant PI19/01652), and the European Union's Horizon 2020 research and innovation programme (CLARIFY 875160). RL-B was supported by the European Social Fund and Comunidad de Madrid (PEJ16/MED/AI-1972, PEJD-2018-PRE/SAL-8641), which were both granted to MP. AC-B received a Spanish Lung Cancer Group grant and is supported by a ISCIII-"Sara Borrell" contract (CD19/00170). MCa is supported by a PEJD-2019-PRE/BMD-17006 contract granted to AC-B. We thank the patients, their families, all the participating clinical teams, and all the staff at the Spanish Lung Cancer Group and Bristol-Myers Squibb for making this study possible. We also would like to thank Maria del Rocio Moreno Villa and Auriole Tamegnon for their technical assistance.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70:** 7–30.

2 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* 2013; **143** (suppl 5)**:** e314S–340S.

3 Hellmann MD, Chaft JE, William WN Jr, 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* 2014; **15:** e42–50.

4 Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med* 2018; **378:** 1976–86.

5 Shu CA, Gainor JF, Awad MM, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2020; **21:** 786–95.

6 Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2016; **34:** 2969–79.

7 Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007; **2:** 706–14.

8 Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th edn. New York, NY: Springer International Publishing, 2010.

9 Tan WL, Chua KLM, Lin C-C, et al. Asian Thoracic Oncology Research Group Expert Consensus Statement on optimal management of stage III NSCLC. *J Thorac Oncol* 2020; **15:** 324–43.

10 Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5:** 649–55.

11 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

12 Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28** (suppl 4)**:** iv1–21.

13 Travis WD, Dacic S, Wistuba I, et al. IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens following neoadjuvant therapy. *J Thorac Oncol* 2020; **15:** 1–32.

14 Pataer A, Kalhor N, Correa AM, et al. Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. *J Thorac Oncol* 2012; **7:** 825–32.

15 Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378:** 2078–92.

16 Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *Science* 2020; **367:** eaax0182.

17 Helmink BA, Reddy SM, Gao J, et al. B cells and tertiary lymphoid structures promote immunotherapy response. *Nature* 2020; **577:** 549–55.

18 Yost KE, Satpathy AT, Wells DK, et al. Clonal replacement of tumor-specific T cells following PD-1 blockade. *Nat Med* 2019; **25:** 1251–59.

19 Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. *Cell* 2008; **133:** 775–87.

20 Kirn DH, Lynch TJ, Mentzer SJ, et al. Multimodality therapy of patients with stage IIIA, N2 non-small-cell lung cancer. Impact of preoperative chemotherapy on resectability and downstaging. *J Thorac Cardiovasc Surg* 1993; **106:** 696–702.

21 Sugarbaker DJ, Herndon J, Kohman LJ, Krasna MJ, Green MR. Results of cancer and leukemia group B protocol 8935. A multiinstitutional phase II trimodality trial for stage IIIA (N2) non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 1995; **109:** 473–83.

22 Choi YS, Shim YM, Kim J, Kim K. Recurrence-free survival and prognostic factors in resected pN2 non-small cell lung cancer. *Eur J Cardiothorac Surg* 2002; **22:** 695–700.

23 Kwiatkowski DJ, Rusch VW, Chaft JE, et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3). *Proc Am Soc Clin Oncol* 2019; **37:** 8503 (abstr).

24 Cascone T, William WN, Weissferdt A, et al. Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): clinical and correlative results from the NEOSTAR study. *Proc Am Soc Clin Oncol* 2019; **37:** 8504 (abstr).

25 Garassino M, Rodriguez-Abreu D, Gadgeel S, et al. OA04.06 Evaluation of TMB in KEYNOTE-189: pembrolizumab plus chemotherapy vs placebo plus chemotherapy for nonsquamous NSCLC. *J Thorac Oncol* 2019; **14:** S216–17.

26 Anagnostou V, Niknafs N, Marrone K, et al. Multimodal genomic features predict outcome of immune checkpoint blockade in non-small-cell lung cancer. *Nat Can* 2020; **1:** 99–111.

27 Rizvi H, Sanchez-Vega F, La K, et al. Molecular determinants of response to anti-programmed cell death (PD)-1 and anti-programmed death-ligand 1 (PD-L1) blockade in patients with non-small-cell lung cancer profiled with targeted next-generation sequencing. *J Clin Oncol* 2018; **36:** 633–41.

28 Frank R, Scheffler M, Merkelbach-Bruse S, et al. Clinical and pathological characteristics of *KEAP1*- and *NFE2L2*-mutated non-small cell lung carcinoma (NSCLC). *Clin Cancer Res* 2018; **24:** 3087–96.

29 Bhateja P, Chiu M, Wildey G, et al. Retinoblastoma mutation predicts poor outcomes in advanced non small cell lung cancer. *Cancer Med* 2019; **8:** 1459–66.

30 Cascone T, Provencio M, Sepesi B, et al. Checkmate 77T: a phase III trial of neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) followed by adjuvant nivo in resectable early-stage NSCLC. *Proc Am Soc Clin Oncol* 2020; **38:** TPS9076 (abstr).