Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial

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Summary

Background Perioperative immunotherapy improves short-term outcomes in resectable non-small-cell lung cancer (NSCLC). We now report 5-year survival from the NADIM trial to assess its long-term benefit.

Methods NADIM was a multicentre, single-arm, phase 2 trial conducted across 18 hospitals in Spain. Patients were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had histologically or cytologically confirmed, treatment-naive, resectable stage IIIA NSCLC (American Joint Committee on Cancer, 7th edition criteria). The neoadjuvant treatment consisted of three cycles of intravenous paclitaxel (200 mg/m²) and carboplatin (area under the curve 6 mg/mL per min) with nivolumab (360 mg). After surgery, 1 year of adjuvant treatment with intravenous nivolumab monotherapy was administered (240 mg every 2 weeks for 4 months, followed by 480 mg every 4 weeks for 8 months). The primary endpoint was 24-month progression-free survival, with 5-year progression-free survival and overall survival as secondary endpoints, assessed in the intention-to-treat population (ie, all patients who received neoadjuvant treatment). Toxicity profile was also assessed as a secondary endpoint. This trial is registered at ClinicalTrials.gov (NCT03081689) and is complete; this is the final report of the trial.

Findings Between April 26, 2017, and Aug 25, 2018, 51 patients were assessed for eligibility, of whom 46 comprised the intention-to-treat population (34 [74%] male and 12 [26%] female, median age 63 years [IQR 58–70]). Follow-up was concluded at 60 months (data cutoff July 11, 2023; median follow-up 60·0 months [IQR 60·0–60·0]). 5-year progression-free survival in the intention-to-treat population was 65·0% (95% CI 49·4–76·9), and overall survival was 69·3% (53·7–80·6). Disease progression occurred in 11 (24%) patients; 14 (30%) patients died, including nine (20%) from disease relapse and five (11%) from non-tumour-related causes. Treatment-related adverse events (TRAEs) of grade 3 or worse occurred in 14 (30%) of 46 patients during neoadjuvant treatment and in seven (19%) of 37 during adjuvant treatment. The most common grade 3 or worse TRAEs were increased lipase and febrile neutropenia (three [7%] each) during neoadjuvant treatment, and elevated serum lipase (four [7%]) and elevated serum amylase (three [8%]) during adjuvant treatment. Serious TRAEs included elevated serum lipase and neutropenia (one [2%] each) during neoadjuvant treatment, and elevated serum lipase (one [3%]) during adjuvant treatment. No treatment-related surgery delays, deaths, or unexpected long-term toxicities were reported.

Interpretation Perioperative chemoimmunotherapy showed a promising long-term benefit with no concerning safety data, reinforcing its use in resectable stage IIIA NSCLC.

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Introduction

Lung cancer is the leading cause of cancer-related mortality globally,[1] with non-small-cell lung cancer (NSCLC) accounting for approximately 85% of all cases. Nearly 30% of individuals with NSCLC present with disease that is amenable to surgical resection, but they show poor 5-year survival.[2] Immunotherapy based on PD-1 or PD-L1 axis blockade has revolutionised the treatment of resectable NSCLC,[3] using either a neoadjuvant[4,5] or adjuvant[6,7] approach.

Combining the advantages of neoadjuvant and adjuvant immunotherapy within perioperative regimens holds the potential to further enhance long-term outcomes. To our knowledge, the NADIM study was the first to evaluate the activity of perioperative chemoimmunotherapy in potentially resectable stage IIIA NSCLC, resulting in 2-year progression-free survival of 77·1% (95% CI 59·9–87·7) and 36-month overall survival of 81·9% (66·8–90·6) in the intention-to-treat population, with 36-month overall survival increasing to 91·0% (74·2–97·0)

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Research in context

Evidence before this study

We searched PubMed from Jan 1, 2018, to July 15, 2024, for clinical trials on perioperative chemoimmunotherapy in lung cancer published in English using the search terms "perioperative" and "lung cancer" and "immunotherapy" or "PD-L1" or "PD-1" or "chemotherapy". We identified several ongoing phase 2 and phase 3 trials exploring various perioperative immunotherapy approaches with different follow-up periods published, all with follow-up periods no longer than 2 years.

Added value of this study

To our knowledge, NADIM is the first trial investigating the value of perioperative immunotherapy in patients with resectable stage IIIA NSCLC providing information on 5-year survival. No concerning safety data or unexpected long-term toxicities were observed. Despite the limitations of this being a phase 2 single-arm trial, with a relatively small patient cohort, our results support the long-term benefit of perioperative chemoimmunotherapy, offering crucial insights for future clinical trial design and patient management. Progression-free survival reached a plateau without tumour relapses from the 3-year mark. Additionally, our findings suggest sustained 5-year survival benefit after attaining pathological complete response and highlight the potential role of adjuvant treatment compliance in the prognosis of patients with non-complete pathological responses.

As far as we are aware, this academic trial is the most comprehensive in terms of translational studies including predictive biomarkers and mechanisms of acquired resistance. Neither PD-L1 tumour proportion score nor tumour mutational burden alone were associated with 5-year survival. However, our results support circulating tumour DNA (ctDNA) baseline levels and ctDNA response after neoadjuvant treatment as valuable biomarkers in the perioperative chemoimmunotherapy scenario.

Implications of all the available evidence

The results of the final analysis of the NADIM study, with a minimum follow-up of 5 years, along with the evidence generated by other phase 3 studies with shorter follow-up periods, support the safety and long-term benefit of the perioperative chemoimmunotherapy strategy, reinforcing its use as the standard of care for patients with potentially resectable stage IIIA NSCLC.

in the per-protocol population. These survival rates were accompanied by a high rate of complete pathological responses.[8,9] Previous trials had shown a median event-free survival of no more than 15 months and a 3-year overall survival of 35% with neoadjuvant chemotherapy.[10] The randomised, phase 2 NADIM II trial showed the favourable efficacy in terms of complete pathological response, progression-free survival, and overall survival with the combination of chemotherapy and immunotherapy in the perioperative setting.[11]

Over time, these results have been widely reproduced in large, randomised trials (Checkmate 77T,[12] AEGEAN,[13] KN671,[14] NeoTORCH,[15] RATIONALE-315[16]) in the perioperative setting, with a consistent increase in complete pathological response rates, event-free survival, and, in some cases, overall survival when chemoimmunotherapy is used compared with chemotherapy alone. However, these studies still have short follow-up periods, ranging from 1 to 2 years, which might raise doubts about the consistency of perioperative immunotherapy data in the longer term.

Consequently, the role of established immunotherapy biomarkers, including PD-L1 tumour proportion score (TPS), tumour mutational burden (TMB), circulating tumour DNA (ctDNA), and pathological response, in predicting long-term survival within the perioperative setting remains uncertain.[3,17]

See Online for appendix 1

Here we describe the 5-year survival outcomes and main biomarker results of the NADIM trial, which evaluated the activity of perioperative nivolumab plus standard chemotherapy in patients with resectable stage IIIA NSCLC.

Methods

Study design and participants

NADIM was a multicentre, single-arm, phase 2 trial done at 18 hospitals in Spain assessing feasibility, safety, and activity of perioperative chemoimmunotherapy in resectable NSCLC.[8,9] Participants were aged 18 years or older and had histologically or cytologically confirmed operable stage IIIA NSCLC (American Joint Committee on Cancer, 7th edition criteria) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. All patients had tumour staging, including diagnostic biopsy, pathological evaluation of mediastinal lymph nodes by endobronchial ultrasound, and mediastinoscopy or thoracotomy at baseline. PET-CT and contrast-enhanced CT or MRI of the brain and chest were mandatory at patient inclusion. Data on race or ethnicity were not collected. Participant sex was self-reported. Exclusion criteria included documented *EGFR* mutations or *ALK* translocations; active autoimmune or infectious disease; current treatment with immunosuppressive drugs; and a history of symptomatic interstitial lung disease classified as grade 3 or 4. Complete details regarding the inclusion and exclusion criteria can be found in the protocol (appendix 1).

The study was conducted in adherence to the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of

Helsinki. All patients provided written informed consent before enrolment. The protocol received approval from the Clinical Research Ethics Committee of Hospital Puerta de Hierro (Madrid, Spain; reference 20.16). This study is registered with ClinicalTrials.gov, NCT03081689.

Procedures

Patients received intravenous neoadjuvant chemotherapy with paclitaxel (200 mg/m²) and carboplatin (area under the curve 6 mg/mL per min) and immunotherapy with nivolumab (360 mg) every 3 weeks for three cycles, followed by surgery and adjuvant intravenous nivolumab for 1 year (240 mg every 2 weeks for 4 months then 480 mg every 4 weeks for 8 months).

Tumour clinical response was determined after three cycles of treatment and before surgery; all changes in tumour size were assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Tumour CT imaging during follow-up visits after adjuvant treatment was done every 3 months for 1 year, every 4 months in the second year, and every 6 months thereafter. Progression-free survival was centrally reviewed. Pathological response was assessed locally and confirmed centrally by two masked pathologists. A complete response was defined as 0% residual viable tumour cells in the resected specimen and sampled lymph nodes. A non-complete response was defined as presence of any residual viable tumour cells in the resected specimen and sampled lymph nodes, including major pathological responses (ie, ≤10% residual viable tumour cells) and incomplete pathological responses (ie, >10% residual viable tumour cells).

Patients underwent laboratory blood tests (complete blood cell counts and biochemical parameters) before each 21-day treatment cycle. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used to grade adverse events and abnormal laboratory results. The investigators assessed treatment-related adverse events per protocol and regulatory guidelines.

Dose reductions were allowed for paclitaxel and carboplatin but not for nivolumab (specifically for grade 4 neutropenia, neutropenic fever, thrombocytopenia, or anaemia, in accordance with two levels of dosage specified in the trial protocol). Treatment was either interrupted or delayed in the event of an adverse reaction and could be resumed once the criteria for treatment continuation, as specified in the protocol (appendix 1), were satisfied.

Criteria for withdrawal included patient consent withdrawal, development of intolerable toxicity, failure to comply with study requirements, emergence of concurrent illnesses, or any other circumstances that could critically compromise the patient's safety (investigator decision).

Formalin-fixed paraffin-embedded specimens obtained at diagnosis were used to centrally determine the PD-L1 TPS (using the PD-L1 IHC 22C3 pharmDx assay [Dako, Glostrup, Denmark]) and TMB (using the Oncomine Tumour Mutation Load Assay [ThermoFisher Scientific, Palo Alto, CA, USA]). ctDNA at baseline, pre-surgery, and at 6 months of adjuvant treatment were analysed using the amplicon-based Oncomine Pan-Cancer Cell-Free Assay kit (ThermoFisher Scientific). Additional details regarding molecular analyses are provided in appendix 1 (pp 2–5).

Outcomes

The primary endpoint was progression-free survival at 24 months, as reported previously.[1] Secondary endpoints reported here are toxicity profile and progression-free survival and overall survival at 5 years. Survival analysis at 5 years was a protocol amendment approved by the institutional review board on June 8, 2022. Previously published secondary endpoints were downstaging, complete resection rate, surgical outcomes, pathological response, and imaging response.[8,9,18] Progression-free survival was defined as the time from diagnosis to objective tumour progression or death from any cause. Overall survival was defined as the time from diagnosis to date of death by any cause. Prespecified exploratory endpoints involved the determination of whether PD-L1, TMB, or ctDNA serve as predictive biomarkers for survival. Additional exploratory endpoints prespecified in the protocol have been published elsewhere.[8,9,19–22]

Statistical analysis

Progression-free survival and overall survival estimates, along with the corresponding 95% CIs, were evaluated using the Kaplan–Meier method in the intention-to-treat population, which included all patients who received neoadjuvant treatment. Informative censoring was not observed in the study data (only one patient was lost to follow-up due to withdrawal of consent). A sample size of 46 patients was estimated based on providing 80% power to detect a 15% net improvement in 24-month progression-free survival rate, compared with a 40% rate reported in previous studies for patients with NSCLC treated with chemotherapy alone.[23,34] No interim or sensitivity analyses were planned or conducted. Extended statistical methods are provided in the statistical analysis plan (appendix 1).

Post-hoc analyses were the progression-free survival and overall survival analysis in the per-protocol population (which included all patients who had tumour resection and received at least one cycle of adjuvant treatment); the differences in progression-free survival and overall survival between the per-protocol and non-per-protocol populations; progression-free survival and overall survival analysis in the intention-to-treat population considering only cancer-related events (ie, censoring patients at the time of non-cancer-related death); the median time to progression for patients who had progressive disease status, overall and excluding

non-lung-cancer-related deaths; and the exploratory role of clinical aspects and molecular biomarkers in progression-free survival and overall survival considering only cancer-related events. For this last post-hoc analysis, clinical aspects comprised baseline characteristics, local relapses, CNS relapses, resection status, pathological and clinical response attained, and adherence to adjuvant treatment, and molecular biomarkers comprised PD-L1; TMB; presence of any pathogenic mutation in *STK11*, *KEAP1*, *EGFR*, or *RB1*; baseline tumour T-cell receptor repertoire clonality; Tumor-Immune Prognostic Score (an additive score, newly created for this study, based on PD-L1, TMB, specific mutations, and T-cell receptor clonality at baseline; appendix p 5); ctDNA mutant allelic fraction at baseline; ctDNA clearance; and emerging or baseline mutations in *KRAS* and *PIK3CA*.

Univariable Cox proportional hazards models were used to assess the association between baseline characteristics and survival. We tested the proportional hazards assumption using Schoenfeld residuals. We used the Kaplan–Meier method and log-rank tests to estimate differences between post-hoc analysis groups. Fisher's exact test was used to determine if there were associations between two categorical variables. p values of less than 0·05 were considered statistically significant (two-sided). Patients with missing information were excluded for that specific analysis. PD-L1 and TMB were analysed using various exploratory thresholds; PD-L1 TPS cutoffs were 1%, 1–49%, and 50%, and TMB cutoffs were 5·89 mutations per megabase (cohort median), 10 mutations per megabase, and as a continuous variable. GraphPad Prism software, version 8.0 was used for statistical analyses.

This study is registered with ClinicalTrials.gov, NCT03081689.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The study was designed by the sponsor (Spanish Lung Cancer Group, which did not provide funding) and the study investigators.

Results

Between April 26, 2017, and Aug 25, 2018, 51 patients were assessed for eligibility and 46 patients (34 [74%] male and 12 [26%] female, median age 63 years [IQR 58–70]) were enrolled at 18 sites. The entire patient cohort exhibited a uniform stage IIIA diagnosis. Baseline characteristics are shown in appendix 1 (pp 8, 9).

All patients received three neoadjuvant cycles of nivolumab plus chemotherapy (except for a single patient who decided to withdraw from the study and completed only two cycles). Five (11%) patients did not undergo surgery. Among 41 patients who underwent surgery, four (10%) did not receive adjuvant treatment, whereas 37 (90%) received at least one cycle of adjuvant nivolumab (median number of cycles 16 [IQR 16–16]). Of these 37 patients, 33 (89%) received at least half (nine or more) of the scheduled adjuvant cycles, and 29 (78%) completed the scheduled adjuvant cycles (appendix 1 p 12).

Follow-up was ended for all patients when they reached 60 months after inclusion. This follow-up duration was reached for the last recruited patient alive on July 10, 2023. One (2%) patient was lost to follow-up at 36·4 months (due to withdrawal of consent).

With a median follow-up of 60·0 months (IQR 60·0–60·0), disease progression was reported in 11 (24%) of 46 patients. Salvage therapies after disease progression are summarised in appendix 1 (p 10). Additionally, 14 (30%) patients died; nine (20%) were a result of disease relapse and five (11%) were deaths not associated with lung tumour progression (three [7%] due to COVID-19, one [2%] due to pneumonia, and one [2%] due to pancreatic cancer).

Three (7%) cancer-specific deaths occurred among five patients who did not undergo surgical intervention and developed disease progression, whereas six (13%) deaths were registered among 41 patients who underwent surgical intervention and subsequently exhibited disease progression (three had an incomplete pathological response, two had a major pathological response, and one had a complete pathological response; figure 1A).

5-year progression-free survival in the intention-to-treat population was 65·0% (95% CI 49·4–76·9), and 5-year overall survival was 69·3% (53·7–80·6; figure 1B). In a post-hoc analysis censoring the five patients who died from non-lung-cancer-related causes without active disease, 5-year progression-free survival was 75·8% (60·6–58·8), and 5-year overall survival was 82·2% (67·6–90·7; appendix 1 p 13). In a post-hoc analysis, the median time to progression for patients who had progressive disease status was 22·5 months (IQR 13·5–28·7) overall, and 17·3 months (8·8–22·9) excluding non-lung-cancer-related deaths.

In further post-hoc analyses, the per-protocol population (37 patients) had 5-year progression-free survival of 75·4% (95% CI 58·0–86·4) and 5-year overall survival of 78·0% (60·8–88·4; appendix 1 p 14). Compared with these patients, the non-per-protocol population (nine patients) showed worse prognosis, with a 5-year progression-free survival of 22·2% (95% CI 3·4–51·3; hazard ratio [HR] 5·7, 95% CI 1·3–23·6; p<0·0001) and overall survival of 33·3% (7·8–62·3; HR 5·3, 95% CI 1·1–26·1; p=0·0005; appendix 1 p 15).

All treatment-emergent adverse events were determined to be treatment-related adverse events (TRAEs). During neoadjuvant treatment, 43 (93%) of 46 patients developed TRAEs, with 14 (30%) patients having grade 3 or worse TRAEs (table 1). In the adjuvant setting, 32 (86%) of 37 patients reported grade 1 or 2 TRAEs, while seven (19%) patients had grade 3 or 4 TRAEs (table 2). The most common grade 3 or worse TRAEs were increased lipase (three [7%] of 46) and febrile neutropenia (three [7%]

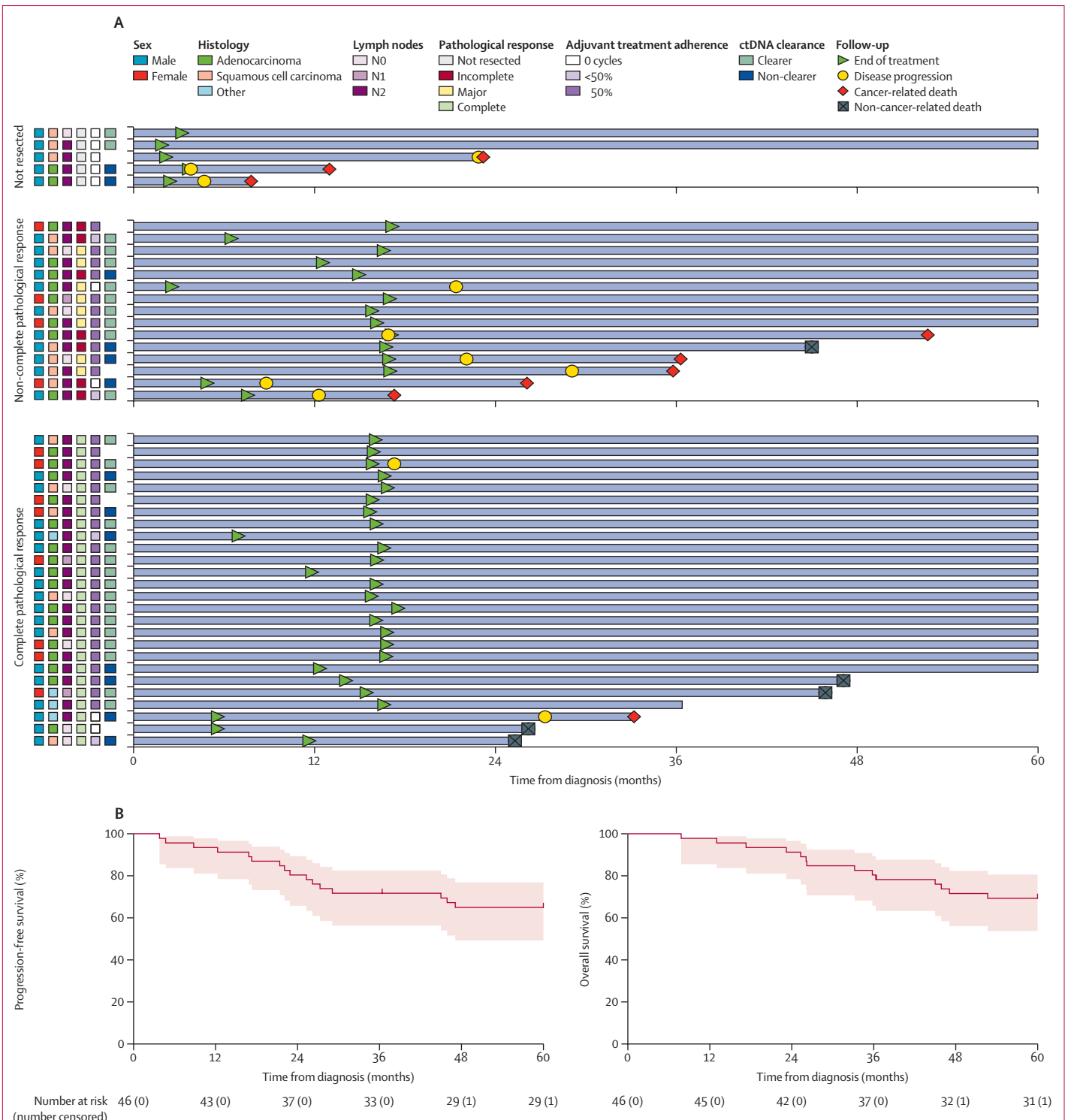

Figure 1: **Long-term survival analysis of the intention-to-treat population of the NADIM trial**
(A) Swimmer plot summarising follow-up and relevant events (end of treatment, disease progression, cancer-related death, and non-cancer-related death) for patients (n=46). Each bar represents one patient. The left column shows clinical and molecular characteristics (from left to right: sex, histology, lymph node status, pathological response, adherence to adjuvant treatment, and ctDNA clearance. (B) Progression-free survival and overall survival Kaplan–Meier curves of the intention-to-treat population (n=46) considering all events. Shaded areas represent 95% CIs.

	Grade 1–2	Grade 3	Grade 4
≥1 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 (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
Transaminase increased	4 (9%)	1 (2%)	0
Neutropenia	2 (4%)	1 (2%)	1 (2%)
Serum amylase increased	1 (2%)	2 (4%)	0
Creatinine increased	1 (2%)	2 (4%)	0
Lipase increased	0	2 (4%)	1 (2%)
Febrile neutropenia	0	3 (7%)	0
Hand pemphigoid	0	1 (2%)	0

Data are n (%). Data are based on continuous toxicity evaluation within 100 days of the last dose of nivolumab. No treatment-related deaths were observed.

Table 1: **Treatment-related adverse events during neoadjuvant treatment with paclitaxel–carboplatin–nivolumab (n=46)**

	Grade 1–2	Grade 3	Grade 4
Developed ≥1 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 (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
Lipase increased	1 (3%)	3 (8%)	1 (3%)
Serum amylase increased	1 (3%)	3 (8%)	0
Adrenal insufficiency	0	1 (3%)	0
Hand pemphigoid	0	1 (3%)	0

Data are n (%). Treatment-related adverse events during adjuvant treatment in the per-protocol population (n=37) are shown. The events are listed in descending order of frequency for grade 1–2 adverse events. No treatment-related deaths were observed.

Table 2: **Treatment-related adverse events during adjuvant treatment with nivolumab (n=37)**

of 46) during neoadjuvant treatment, and elevated serum lipase (four [11%] of 37) and elevated serum amylase (three [8%] of 37) during the adjuvant phase. Serious adverse events included elevated serum lipase (one [2%] of 46) and neutropenia (one [2%] of 46) during the neoadjuvant period, and elevated serum lipase (one [3%] of 37) during adjuvant treatment. Additionally, one (2%) patient was diagnosed with pancreatic cancer during follow-up. None of the adverse events during neoadjuvant therapy led to treatment discontinuation, dose reduction, surgery delay, or death. However, three (7%) patients were unable to receive adjuvant nivolumab due to TRAEs that developed during neoadjuvant treatment (two [4%] had haematological toxicity, and one [2%] had renal insufficiency). Adjuvant nivolumab was discontinued in five (14%) patients due to TRAEs. No treatment-related deaths were reported throughout the entire follow-up period, and no unexpected long-term toxicities were observed.

Regarding the pattern of relapses, three (27%) of 11 were solely local, three (27%) were both local and distant, four (36%) were exclusively distant, and one (9%) was clinically determined (ie, based on worsening of clinical symptoms). A post-hoc analysis suggested that there was no difference in time to progression or overall survival between the exclusively local relapses and the rest of the cases (appendix 1 p 16).

In a subsequent post-hoc evaluation, the two patients who had disease relapse after complete pathological response (patients 13 and 51) showed exclusively a distant relapse pattern (CNS in both cases). By contrast, six (67%) of nine relapses had a local component among the patients who did not have a complete pathological response (Fisher test p=0·18). Furthermore, four (36%) of the relapses were in the CNS (two complete pathological responses, one major pathological response, and one not resected) with a time-to-event and patient survival similar to non-CNS relapses. Median progression-free survival for patients with CNS relapses was 17·3 months (95% CI 0–39·5), and median overall survival was 33·2 months (5·8–60·6), compared with 16·9 months (5·1–28·7) and 26·1 months (18·6–33·5) for patients with non-CNS relapses (appendix 1 p 17). Data for baseline tumour genomic variants were available for three patients with CNS relapses; patient 13 with an *EGFR* exon 19 deletion detected both in tissue and blood, patient 51 with a *KEAP1* mutation in tissue and *KRAS* mutation in blood, and patient 52 with no relevant mutations except one *TP53* mutation detected in tissue and blood.

Post-hoc analysis of baseline clinical characteristics showed no statistically significant correlations with progression-free survival or overall survival, except for ECOG performance status 1, which was associated with worse overall survival compared with ECOG performance status 0 (figure 2, appendix 1 p 11).

Post-hoc analysis of clinical features developed during the treatment showed that the five (11%) patients who did not undergo surgery had a poorer prognosis than the

41 (89%) patients who underwent tumour resection. However, this worse prognosis observed in patients who did not undergo tumour resection appeared to diminish when compared with the four (9%) patients who underwent surgery but did not receive adjuvant therapy (appendix 1 p 18).

Through post-hoc examination, patients whose tumours were resected and had a major or incomplete pathological response (ie, non-complete pathological response; 15 [37%] of 41 patients who underwent tumour resection) had a worse long-term prognosis than those who had a complete pathological response (ie, 0% viable tumour cells; 26 [63%] of 41 patients; figure 3A). 5-year progression-free survival and overall survival for patients with a complete pathological response were 92·0% (95% CI 70·5–97·9) and 95·8% (73·9–99·4), respectively, compared with 60·0% (31·8–79·7) and 66·0% (36·5–84·3) for patients with a non-complete pathological response. Only two (8%) of 26 patients with a complete pathological response had disease progression (patients 13 and 51 with mutations in *EGFR* and *KEAP1*, respectively). Clinical responses by RECIST criteria (complete response and partial response *vs* stable disease) were not associated with progression-free survival or overall survival in a post-hoc evaluation (appendix 1 p 19).

To analyse the role of the duration of adjuvant treatment on survival, the type of pathological response observed was taken into account in post-hoc analyses given the importance of these responses in long-term survival. 22 (85%) of 26 patients with a complete pathological response completed at least 50% of adjuvant cycles, with this proportion being similar in patients without a complete response (11 [73%] of 15). In five (63%) of the eight patients who received less than 50% of adjuvant treatment cycles, the cause for treatment cessation was toxicity (appendix 1 p 20).

Regarding the survival analysis of the subgroup with complete pathological responses, only four (15%) of 26 patients received less than 50% of adjuvant treatment cycles. Two of them died of COVID-19 and were censored, one of them had disease progression at 27·3 months and died at 33·2 months, and the other remains without evidence of disease at data cutoff. The patients with a complete pathological response who received at least 50% of adjuvant treatment cycles showed a 5-year progression-free survival of 95·5% (95% CI 71·9–99·3) and no deaths at data cutoff (appendix 1 p 21).

In the subgroup with non-complete pathological responses (ie, incomplete and major pathological

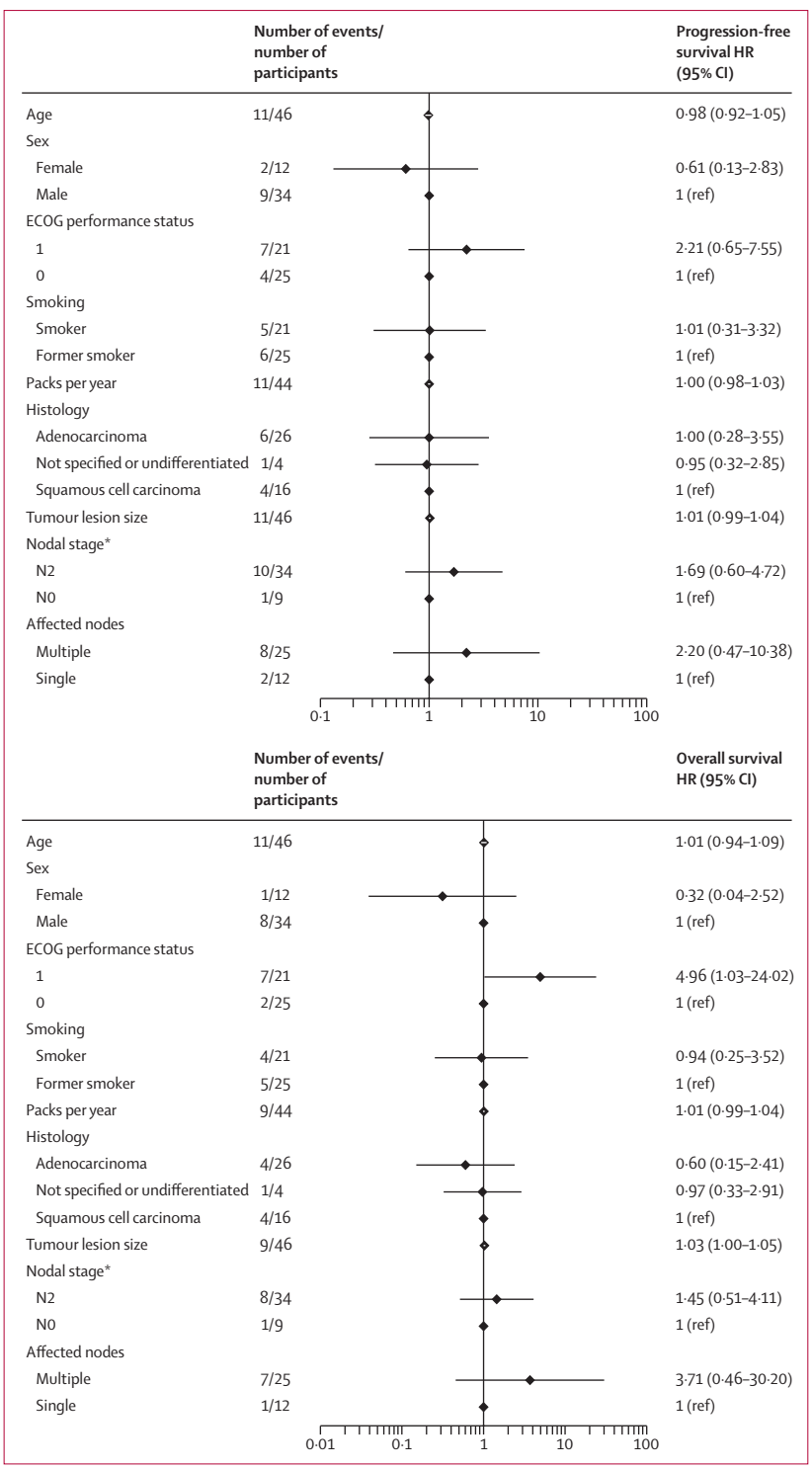

Figure 2: **Baseline clinicopathological characteristics and long-term survival**
Forest plot of univariate Cox proportional HR for progression-free survival and overall survival by clinicopathological features at diagnosis in the intention-to-treat population (n=46) considering cancer-specific events. Number of events (disease progressions or deaths) and total number of patients for each group are shown. The reference categories for each variable are: sex, male (n=34); ECOG performance status, 0 (n=25); smoking, former smoker (n=25); histology, squamous-cell carcinoma (n=16); nodal stage, N0 (n=9); affected nodes, single (n=12). Age (n=46), packs per year (n=44), and tumour lesion size (n=46) are continuous variables. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. *N1 not included as there were only 3 patients with N1 disease, meaning too much error to calculate the Cox model.

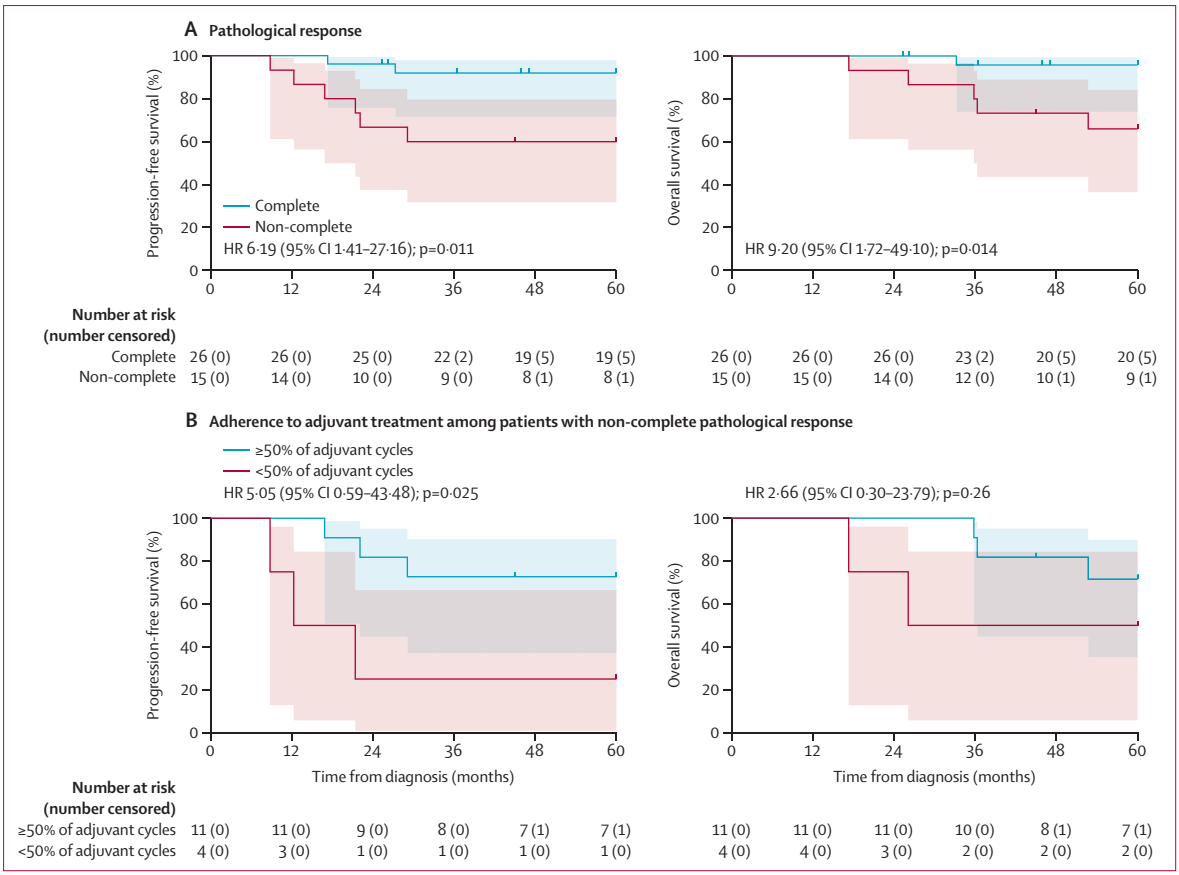

Figure 3: **Post-hoc survival analyses by pathological response and adjuvant treatment adherence**
(A) Progression-free survival and overall survival Kaplan–Meier curves of patients who underwent tumour resection (n=41) who had a complete pathological response (n=26) versus those with a major or incomplete pathological response (non-complete pathological response, n=15). (B) Progression-free survival and overall survival Kaplan–Meier curves of patients who had a non-complete pathological response (n=15) and completed ≥50% of adjuvant treatment cycles (n=11) versus those who completed <50% of adjuvant treatment cycles (n=4). Curve comparison was carried out using the log-rank test. p values are two-sided; p<0·05 was considered statistically significant. Shaded areas represent 95% CIs of the survival function. HR=hazard ratio.

response; n=15), patients who received less than 50% of the cycles (n=4) seemed to exhibit worse progression-free survival. No statistically significant differences were observed for overall survival. Among patients with a non-complete pathological response, 5-year progression-free survival and overall survival in those who received less than 50% of adjuvant treatment cycles were 25·0% (0·9–66·5) and 50·0% (5·8–84·5), respectively, compared with 72·7% (37·1–90·3) and 71·6% (35·0–89·9) in those who received at least 50% of adjuvant cycles (figure 3B).

Post-hoc analyses of baseline tumour characteristics and survival are as follows. Neither PD-L1 levels (TPS ≥1% cutoff) nor TMB (cohort median 5·89 mutations per megabase cutoff) at diagnosis were associated with progression-free survival or overall survival (figure 4A, B). Additional thresholds for PD-L1 and TMB were also not associated with progression-free survival nor overall survival (appendix 1 p 22). The presence of *STK11*, *KEAP1*, *RB1*, or *EGFR* mutations was associated with worse progression-free survival, but no statistically significant differences in overall survival were observed. Considering only *KEAP1* status, three (75%) of four patients with tumours harbouring mutations in *KEAP1* had disease progression and died (appendix 1 p 23). Patients with tumours with low T-cell receptor clonality showed numerically lower overall survival (appendix 1 p 24). A Tumor-Immune Prognostic Score of 3 or higher was significantly associated with improved progression-free survival and overall survival, with 5-year progression-free survival and overall survival rates of 100% (95% CI undefined) compared with 46·2% (19·2–69·6) and 53·8% (24·8–76·0) in patients with a score of 2 or lower (appendix 1 p 25).

Post-hoc analyses of ctDNA showed that higher baseline mutant allelic fraction (summatory mutant allelic fraction [sumMAF] ≥1%) was associated with shorter progression-free survival and overall survival (figure 4C). 5-year progression-free survival and overall survival for patients with sumMAF of 1% or higher were 48·6% (19·2–73·0) and 56·3% (24·4–79·1), respectively, compared with 83·8% (65·3–92·9) and 86·2% (67·1–94·6) for patients with sumMAF less

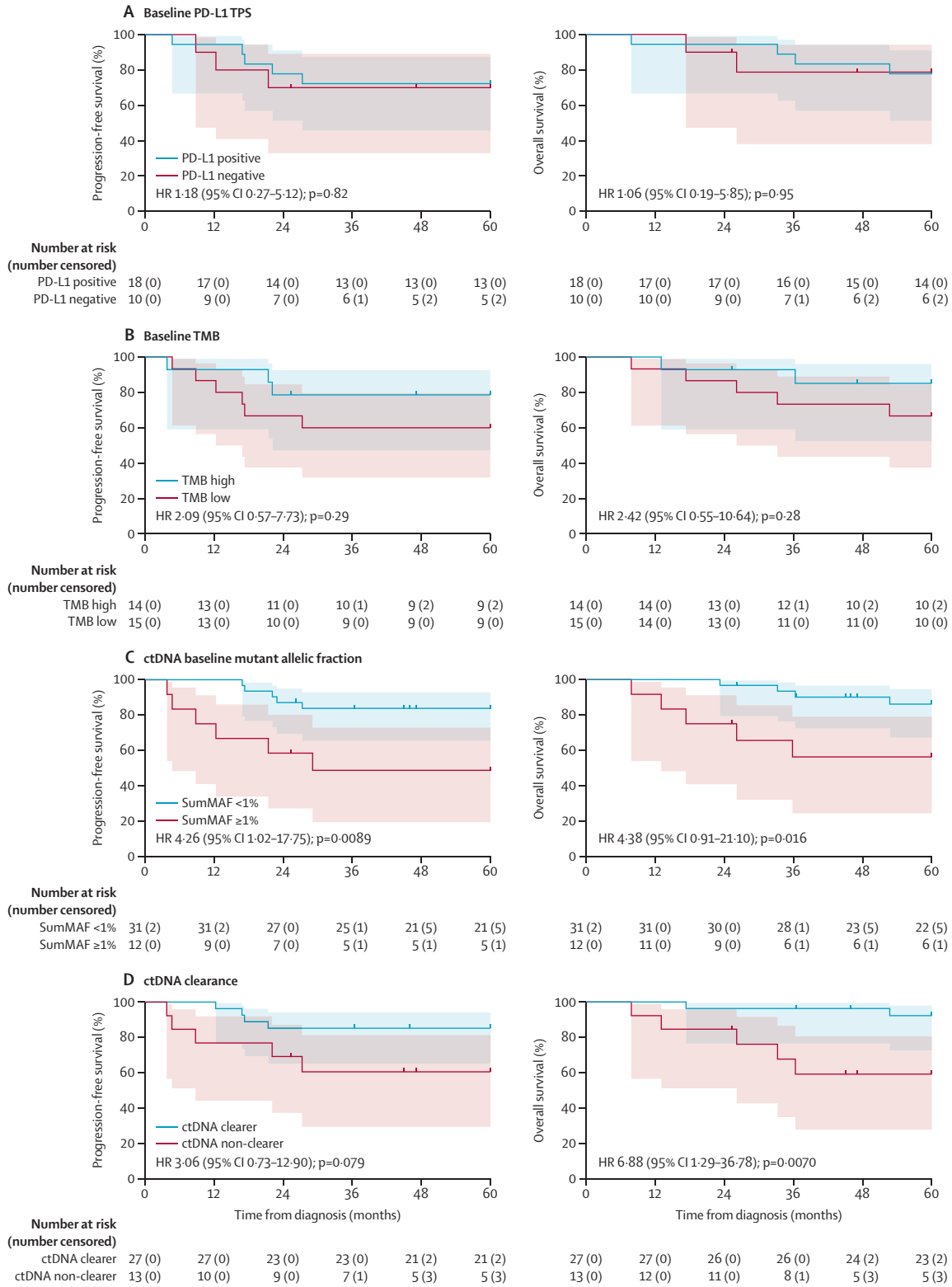

Figure 4: **Post-hoc survival analyses by molecular parameters**
Progression-free survival and overall survival Kaplan–Meier curves of patients with available data for different endpoints. (A) PD-L1 TPS (n=28), stratified into two categories: positive (≥1%, n=18) and negative (<1%, n=10). (B) TMB (n=29), categorised as high (n=14) or low (n=15) based on cohort median (5·89 mutations per megabase). (C) ctDNA status (n=43), stratified according to mutant allelic fraction from all detected mutations in blood with a threshold of 1% (sumMAF ≥1%, n=12; sumMAF <1%, n=31). (D) ctDNA clearance after neoadjuvant treatment (n=40), stratified according to detection of ctDNA at the end of neoadjuvant treatment (ctDNA clearer, n=27; ctDNA non-clearer, n=13). Curve comparison was carried out using the log-rank test. p values are two-sided; p<0·05 was considered statistically significant. Shaded areas represent 95% CIs of the survival function. ctDNA=circulating tumour DNA. HR=hazard ratio. SumMAF=summatory mutant allelic fraction. TMB=tumour mutational burden. TPS=tumour proportion score.

than 1%. Remarkably, of the five patients who had disease progression with baseline sumMAF less than 1%, four (80%) had mutations associated with poor prognosis (one *EGFR*, three *KEAP1*). In addition, clearance of ctDNA (ie, undetectable or less than 0·1% sumMAF after neoadjuvant treatment) was associated with better overall survival when compared with patients without ctDNA clearance (figure 4D). 5-year progression-free survival and overall survival for patients with ctDNA clearance were 85·2% (95% CI 65·2–94·2) and 92·3% (72·5–98·0), respectively, compared with 60·6% (29·4–81·4) and 59·2% (27·9–80·7) for patients with ctDNA detection after neoadjuvant treatment. Moreover, ctDNA clearance was not associated with pathological response attained. Additionally, ctDNA clearance was not associated with progression-free survival nor overall survival in patients who had a complete pathological response; however, the prognostic value of ctDNA clearance in terms of overall survival was evident in patients without a complete pathological response (appendix 1 p 26).

Finally, emerging mutations in *KRAS* or *PIK3CA* during treatment, but not baseline mutations, were associated with worse progression free survival and overall survival in a post-hoc evaluation (appendix 1 pp 7, 27–29 and appendix 2).

See Online for appendix 2

Discussion

Our results support the long-term benefits of chemoimmunotherapy in terms of 5-year progression-free survival and overall survival in the intention-to-treat population, which were 65·0% (95% CI 49·4–76·9) and 69·3% (53·7–80·6), respectively.

From 29 months onwards in the NADIM trial, there were no tumour-related relapses, suggesting that patients disease-free beyond the 3-year mark might be considered cured. This aspect is highly informative, as there is uncertainty about the long-term benefit and clinical relevance of neoadjuvant chemoimmunotherapy, given that none of the current pivotal studies (CM816,[5] 77T,[12] AEGEAN,[13] or KN671[14]) extend to our minimum follow-up. We also did not observe signs of late toxicity nor treatment-related deaths.

Considering NSCLC-specific events, patients who had a complete pathological response had better 5-year survival, suggesting complete pathological response as a potential surrogate for long-term survival and a useful factor in planning adjuvant studies.[17]

In this sense, ctDNA sumMAF of 1% or higher before treatment was associated with poor prognosis, and after neoadjuvant treatment, ctDNA clearance was a good predictor of improved progression-free survival and overall survival. Overall survival in patients with undetectable ctDNA is six-times better than in patients with detectable ctDNA, positioning ctDNA response as a valuable tool in decision making,[25] especially in patients with worse prognosis such as those with a non-complete pathological response or those who have not undergone surgery, who additionally lack the prognostic information of the pathological response attained. Similarly, the fact that patients who did not undergo surgery but had cleared ctDNA are still alive without disease progression after 5 years of follow-up opens an interesting area of research regarding the role of surgery in those patients.

The value of adjuvant treatment after neoadjuvant chemoimmunotherapy is currently a matter of debate. In the subgroup of patients with non-complete pathological responses, those who received less than 50% of the adjuvant cycles seemed to exhibit worse progression-free survival. These results would be in line with those presented in the recently conducted CheckMate-77T study.[12] Although we cannot rule out the benefit of adjuvant treatment adherence for patients with a complete pathological response due to the low number, it seems that adherence to adjuvant treatment could improve prognosis in patients with a non-complete pathological response.

Regarding biomarkers, neither PD-L1 TPS nor TMB alone seem to reliably predict progression-free survival or overall survival. Similar findings for these biomarkers in 5-year follow-up of neoadjuvant immunotherapy[26] underscore the need for new biomarkers[19–21] in the perioperative setting, where combining different markers into a score, such as the Tumor-Immune Prognostic Score provided here, could prove valuable.

The limitations of the study include the small sample size, the lack of a control group, and the exploratory nature of the translational studies and their multiplicity, which necessitates cautious interpretation of the subgroup analyses. However, our results represent an important step towards future phase 3 trials, providing valuable insights in this area.

In conclusion, to our knowledge, NADIM is the first trial investigating the value of perioperative immunotherapy to provide information on 5-year survival. Our results showed an encouraging long-term benefit and support the use of perioperative immunotherapy as a standard of care for patients with potentially resectable stage IIIA NSCLC. No alarming safety data or unexpected long-term toxicities were observed.

Contributors

MP conceived the study. MP, EN, AI, RGC, JC, MD, BM, MM, DR-A, AM-M, JdC, DGdA, IM, SF, LFV, VC, and RP recruited and treated patients. MP, EN, AI, RGC, JC, MD, BM, MM, DR-A, AM-M, JdC, DGdA, IM, SF, LFV, VC, and RP collected the data. MP, BS-R, CM-T, MM-A, RS-B, AR, and AC-B analysed the data. BS-R, CM-T, MM-A, RS-B, AR, and AC-B did the translational studies. MP, AR, and AC-B interpreted the data. MP and AC-B wrote the first draft of the manuscript. MP and AC-B accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study, contributed to the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

MP reports non-financial support (reagents for T-cell receptor sequencing) from ThermoFisher Scientific; grants, consulting fees, and non-financial support from Bristol Myers Squibb, Roche, and

AstraZeneca; and consulting fees from MSD and Takeda; outside the submitted work. EN reports grants from Roche, Pfizer, Bristol Myers Squibb, Merck, and Nanostring; consulting fees from Roche, Bristol Myers Squibb, Merck Sharpe & Dohme, Merck-Serono, Sanofi, Pfizer, Lilly, Amgen, Janssen, Daiichi-Sankyo, Boehringer-Ingelheim, AstraZeneca, Takeda, Sanofi, Pierre Fabre, Qiagen, and Bayer; payment of honoraria from Roche, Bristol Myers Squibb, Merck Sharpe & Dohme, Sanofi, Pfizer, Lilly, Amgen, Janssen, Daiichi-Sankyo, Boehringer-Ingelheim, AstraZeneca, Takeda, Sanofi, and Qiagen; support for attending meetings or travel from Takeda, MSD, Janssen, and Roche; and participation on advisory boards for Apollomics, Roche, and Pfizer. AI reports consulting fees from Pfizer, Amgen, and Astra Zeneca; payment for expert testimony from Bristol Myers Squibb, Roche, Pfizer, Astra Zeneca, and Takeda; support for attending meetings or travel from Roche, Takeda, and Pfizer; and participation on advisory boards for Roche and Bristol Myers Squibb. RG-C reports consulting fees from Bristol Myers Squibb, MSD, Roche, Pfizer, and AstraZeneca. MD reports consulting fees from AstraZeneca, Bristol Myers Squibb, MSD Oncology, Pfizer, Roche, and Takeda; and support for attending meetings or travel from AstraZeneca, MSD Oncology, Pfizer, and Takeda. BM reports consulting fees from Astra Zeneca and Amgen; payment or honoraria from Roche, Bristol Myers Squibb, and MSD; and support for attending meetings or travel from MSD and AstraZeneca. MM reports grants from Roche and Astra Zeneca; payment of honoraria from Roche, AstraZeneca, MSD, Pfizer, Helsinn, Cassen, Amgen, Janssen, Sanofi, Pierre Fabre, Bristol Myers Squibb, and Takeda; and support for attending meetings or travel from MSD, Roche, and AstraZeneca. DR-A reports honoraria for lectures from MSD, Roche, Bristol Myers Squibb, Novartis, Takeda, Lilly, and AstaZeneca; support for attending meetings or travel from Roche, MSD, Novartis, and Sanofi; and participation on advisory boards for Merck Sharpe & Dohme, Regeneron, Bristol Myers Squibb, GSK, and Lilly. AM-M reports consulting fees from AstraZeneca/MedImmune, Bristol Myers Squibb, F. Hoffmann La Roche, Merck Sharpe & Dohme, MSD Oncology, Pfizer, and Janssen; payment for expert testimony from AstraZeneca, MedImmune, Bristol Myers Squibb, and F. Hoffmann La Roche; support for attending meetings or travel from AstraZeneca, MedImmune, Bristol-Myers Squibb, F. Hoffmann La Roche, Merck Sharpe & Dohme, MSD Oncology, Pfizer, Janssen, and Lilly; and participation on advisory boards for AstraZeneca, MedImmune, Merck Sharpe & Dohme, F. Hoffmann La Roche, and Bristol-Myers Squibb. JdC reports consulting fees from AstraZeneca, Bristol Myers Squibb, Roche, MSD, Boehringer, Janssen, Lilly, Sanofi, Takeda, Pfizer, and GSK; support for attending meeting or travel from AstraZeneca, MSD, and Roche; participation on advisory boards for AstraZeneca, Bristol Myers Squibb, Roche, MSD, Glaxo, Janssen, and Gilea; and speaker's bureau fees from AstraZeneca/MedImmune, Bristol-Myers Squibb, F. Hoffmann La Roche, Merck Sharpe & Dohme, MSD Oncology, Pfizer, and Janssen. DG reports payment or honoraria from Astra Zeneca and Bristol Myers Squibb. VC reports consulting fees from Roche, AstraZeneca, MSD, Bristol Myers Squibb, Takeda, Sanofi, and Amgen; payment or honoraria from Roche, AstraZeneca, MSD, Bristol Myers Squibb, Takeda, SanofiI, and Amgen; and support for attending meetings or travel from AstraZeneca, Roche, MSD, and Takeda. RP reports payment or honoraria from Guardant Health and Pfizer; and support for attending meetings or travel from Merck Sharpe & Dohme; participation on an advisory board for AstraZeneca. AR reports payment or honoraria from Illumina, Health in Code, and ThermoFisher Scientific; support for attending meetings or travel from ThermoFisher Scientific, Bristol Myers Squibb Foundation, and Takeda; and advisory board participation for Takeda. All other authors declare no competing interests.

Data sharing

De-identified individual participant data (including a data dictionary) may be made available upon reasonable request after publication. Researchers interested in accessing the data should submit a research proposal to the corresponding author. The proposal will be evaluated by the Spanish Lung Cancer Group and the ethics committee for clinical investigation. Additional related documents, such as the study protocol and statistical analysis plan, are available in appendix 1 (p 30).

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