ORIGINAL ARTICLE

Progression-Free and Overall Survival for Concurrent Nivolumab With Standard Concurrent Chemoradiotherapy in Locally Advanced Stage IIIA-B NSCLC: Results From the European Thoracic Oncology Platform NICOLAS Phase II Trial (European Thoracic Oncology Platform 6-14)

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ABSTRACT

Introduction: The NICOLAS study is the first completed single-arm phase II trial in stage III NSCLC evaluating hierarchically first the safety and then the efficacy of adding nivolumab concurrently to standard definitive concurrent chemoradiotherapy. The safety end point was reported earlier; here, we present the efficacy results.

Methods: Stage IIIA-B unresectable treatment-naive patients with NSCLC received three cycles of platinum-based chemotherapy and concurrent radiotherapy (66 Gy, 33 fractions), along with nivolumab (360 mg, 3-weekly).

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Nivolumab was continued as monotherapy consolidation for a maximum of 1 year (480 mg, 4-weekly). The primary end point was 1-year progression-free survival (PFS), with a target improvement compared with historical data of at least 15%, from 45% to 60%. To test this efficacy hypothesis, a sample size of 74 assessable patients provided a power of 83% with a one-sided alpha of 5%.

Results: A total of 79 patients were enrolled with a median follow-up of 21.0 months (interquartile range: 15.8–25.8 mo) for the primary PFS analysis. A total of 35.4% of the patients had stage IIIA, and 63.3% had stage IIIB disease. The 1-year PFS was 53.7% (95% confidence interval [CI]: 42.0%–64.0%) and the median PFS was 12.7 months (95% CI: 10.1–22.8 mo). Because 37 PFS events occurred in the first year posttreatment among the first 74 assessable patients, a 1-year PFS rate of at least 45% could not be rejected ($p = 0.23$). At an extended follow-up (median 32.6 mo), 37 deaths have been recorded, with a median overall survival (OS) of 38.8 months (95% CI: 26.8 mo–not estimable) and a 2-year OS rate of 63.7% (95% CI: 51.9%–73.4%). The OS of patients with stage IIIA disease was found to be significantly higher than patients with stage IIIB disease, with a 2-year OS of 81% and 56%, respectively ($p = 0.037$).

Conclusions: PFS and OS are arithmetically higher in studies involving the same population. However, on the basis of the formal hierarchical efficacy analysis, we could not reject that the 1-year PFS rate is at least 45%.

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Keywords: NSCLC; Chemoradiotherapy; Nivolumab; Immune checkpoint inhibition

Introduction

Stage III NSCLC represents approximately 25% of all patients with NSCLC at diagnosis.[1] The treatment of choice for fit patients with unresectable or multilevel N2 or any N3 disease is concurrent chemoradiotherapy (CCRT).[1] The combination of platinum-based doublet chemotherapy given together with 60 Gy to 66 Gy in 2 Gy fractions of radiotherapy (RT) is considered the standard of care.[1] Although the 5-year overall survival (OS) may reach up to 33% in highly selective patients,[2,3] most series report a more sobering 25% OS rate.[4,5] These intertrial differences may be caused by patient selection, as stage III NSCLCs represents an extremely heterogeneous group of diseases.

The addition of 1 year of durvalumab after completion of CCRT has recently been found to improve the 3-year OS by more than 10%.[6] However, as most patients still suffer from disease recurrence (with a subsequent 57% survival rate at 3 years in that study), further improvements are still necessary.

The concurrent administration of a anti–programmed cell death-protein 1 (PD-1) or anti–programmed death-ligand 1 (PD-L1) with RT may improve the response rate in preclinical models,[7] with some synergy suggested in retrospective data sets.[8,9] Similarly, in metastatic patients, concurrent platinum-based chemotherapy and anti–PD-1 or anti–PD-L1 is the treatment of choice in all frontline patients with stage IV NSCLC irrespective of any biomarker, including patients with NSCLC characterized by a low PD-L1 expression.[10]

The concurrent administration of immune checkpoint inhibitors with CCRT followed by 12 months of consolidation is a rational approach that may ultimately improve the OS compared with CCRT followed by durvalumab. The NICOLAS single-arm phase II trial combined nivolumab (delivered for the first time concurrently) with standard CCRT using definitive radiation with standard fractionation doses, followed by a maximum of 12 months of nivolumab consolidation therapy.

We hierarchically tested the safety and efficacy of this regimen. The safety analysis has been reported earlier. Here, we report the results of the hierarchically tested primary end point of 1-year progression-free survival (PFS). The updated results for safety and information on OS and secondary efficacy end points are also provided.

Materials and Methods

Patient Population

The trial included patients from 10 European centers in five countries (Belgium, Germany, Spain, Switzerland, and The Netherlands).

As previously reported,[11] patient eligibility criteria included the following: (1) age 18 years or older; (2) pathologically confirmed locally advanced stage IIIA-B NSCLC (seventh TNM classification); (3) nodal status N2 or N3; (4) Eastern Cooperative Oncology Group performance status 0 to 1; (5) life expectancy greater than 3 months; and (6) adequate hematologic, liver, and renal function. Patients with previous chemo-, radio- or molecular-targeted therapy, or with mixed small and non–small cell histologic features were excluded.

Trial Design and Treatment Administration

The history of the trial and corresponding amendments have been previously described in detail.[11] Protocol version 3.0 called for an efficacy evaluation focusing only on patients receiving nivolumab concurrently with CCRT (Supplementary Fig. 1). Beyond the safety evaluation, the additional aim was to explore, through a hierarchical design, the efficacy of the

combination treatment. A corresponding increase of sample size was planned to enable the efficacy analysis in 74 assessable patients. The primary efficacy end point, 1-year PFS rate, was to be tested on the condition that adequate safety was proven with the concurrent addition of nivolumab to CRT.

Three cycles of chemotherapy with cisplatin or carboplatin combined with either vinorelbine, etoposide, or pemetrexed (nonsquamous histologic subtype) were required. The delivery of the first induction cycle of platinum-based chemotherapy before inclusion in the trial was part of the protocol to homogenize treatment and take into account potential RT planning delays in some participating centers. RT (66 Gy in 33 once-daily fractions to the primary tumor and the involved lymph nodes[12]) were delivered concurrently with the second and third chemotherapy cycle. Patients received four doses of nivolumab of 360 mg at a 3-week cycle, the first two concurrently with standard platinum-based chemotherapy and RT, starting from the first day of CRT, followed by 480 mg at a 4-week cycle for up to 1 year from the start of nivolumab treatment.

Ethics committees and relevant health authorities approved the trial protocol. This trial was registered with ClinicalTrials.gov (number NCT02434081).

End Points

The primary end point, to be hierarchically tested after safety was proven, was PFS rate at 1-year. The start date for time-to-event end points was the date of the first chemotherapy cycle. PFS was defined as the time from the start date until a documented progression of disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or death if no documented progression had occurred. Tumor assessments (TAs) by computed tomography scans were performed every 9 weeks for the first year from enrolment, every 12 weeks for the second year, and every 6 months afterward.

Secondary end points were the following: (1) OS (time from the start date to death from any cause); (2) objective response rate (ORR) of patients according to RECIST version 1.1 criteria (best overall response, complete response (CR), or partial response across all assessment time points from enrolment to the termination of protocol treatment); (3) duration of response (time from first objective response documentation until documented progression); (4) time to treatment failure (TTF) (time from enrolment until any kind of treatment failure, including discontinuation because of toxicity, progression, death, withdrawal, or lost to follow-up); and (5) time to first pneumonitis incidence of grade 3 or higher (TFP3) (time from enrolment until the first documented pneumonitis).

Statistical Analysis

According to the hierarchical design of the trial, the efficacy hypothesis would only be tested if the safety null hypothesis was rejected, either at the interim or the final safety analysis. This condition was satisfied, as the safety null hypothesis has been rejected at the interim analysis, as previously published.[11]

The aim of the efficacy testing was to detect an increase in the 1-year PFS rate from less than or equal to 45% to at least 60% under concurrent nivolumab administration with CCRT. Using a 5% one-sided type I error and 83% power, a sample size of 74 patients was needed for testing this efficacy hypothesis according to the exact binomial test for a single proportion. At least 41 of the 74 patients had to reach 1 year without a PFS event to reject the null hypothesis. No formal efficacy interim analysis was planned for the trial.

The event date for PFS was the first of either the imaging date of the first TA exhibiting the progression of disease or the date of death. The censoring date for PFS was the date of the last TA without event, whereas for OS, the date of the last available contact with the patient while still alive. The estimation of all time-to-event end points was based on the product-limit Kaplan-Meier method.

Further analysis of PFS, OS, and other secondary efficacy end points was performed on all patients enrolled in the CCRT cohort, whereas adverse events (AEs) (classified according to the Common Terminology Criteria for Adverse Events version 4.0) were presented for the safety cohort. More details on statistical analysis are provided in the Supplementary Data.

All statistical results were produced using the Statistical Analysis System version 9.4 (SAS Institute, Cary, NC).

Interim safety analyses were performed at 3-month intervals and reviewed by the European Thoracic Oncology Platform Independent Data Monitoring Committee.

Results

Analysis Cohorts

The primary efficacy analysis was performed on the cohort consisting of the first 74 assessable patients on CCRT up to the primary efficacy analysis cutoff in August 2019. These patients had either reached a 1-year TA without a PFS event or had earlier experienced a PFS event. For the purposes of completeness, all other results except for the primary analysis were presented for all 79 patients on the CCRT regimen (full CCRT cohort) (Fig. 1). This cohort included all patients enrolled on CCRT irrespective of whether they received any dose of the study treatment (intention-to-treat population). The safety

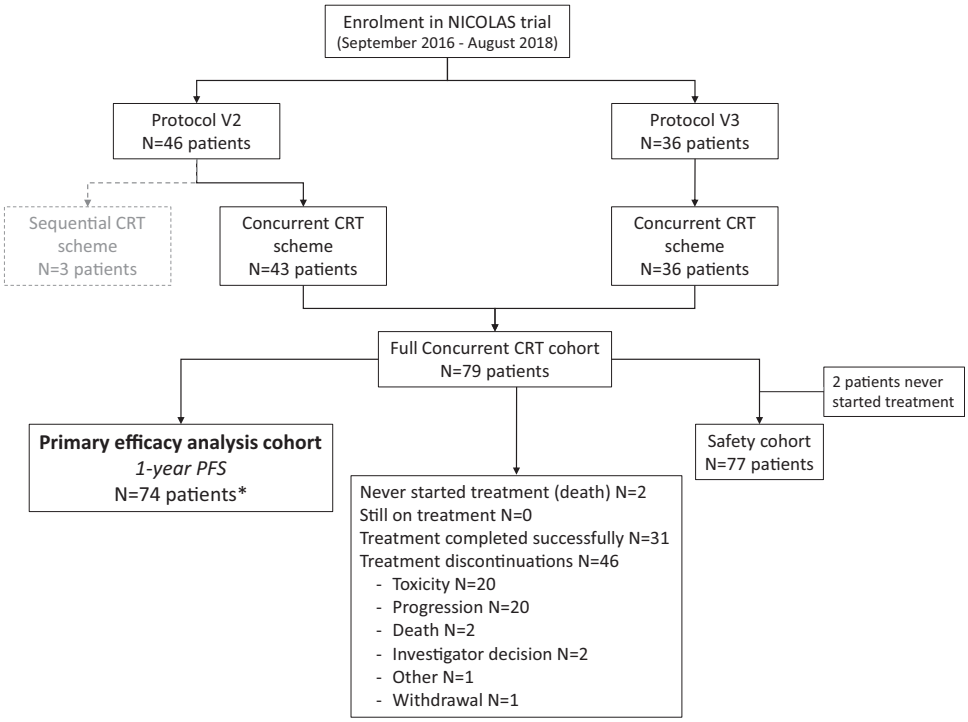


Figure 1. Patient flowchart. *The primary efficacy analysis cohort consists of the first 74 assessable patients under concurrent CRT who had either reached a 1-year tumor assessment without a PFS event or had earlier experienced a PFS event. CRT, chemoradiotherapy; PFS, progression-free survival; V2, version 2; V3, version 3.

cohort consisted of the 77 patients who received at least one dose of treatment after enrolment.

Patient and Treatment Characteristics

A total of 79 patients were enrolled in the study from September 14, 2016 to August 6, 2018. The patient and treatment characteristics for the full CCRT cohort are presented in Table 1. The median follow-up of 21 months (interquartile range [IQR]: 15.8–25.8 mo) captured all follow-up up to the completion of 1 year on the study of the last enrolled patient (database cutoff: August 21, 2019; queried, final: September 18, 2019).

Of the 79 patients in the full cohort of the NICOLAS trial, 77 started treatment as per protocol (two died before treatment started). The median age of patients was 62 years (IQR: 41–78 y), most were men (67.1%), had nonsquamous histologic subtype (59.5%), with stage IIIB disease (63.3%), were former smokers (68.4%), and with an Eastern Cooperative Oncology Group performance status of 1 at enrolment (51.9%). Chemotherapy constituted a cisplatin-based combination with etoposide, pemetrexed, or vinorelbine in 65 patients (84.0%), whereas a carboplatin-based combination was used for 12 patients (15%). After completion of the CCRT and nivolumab, most patients (54.5%) had a performance status of 1.

All three chemotherapy cycles were completed for 73 and RT (at least 60 Gy) for 72 patients. Per protocol, the treatment of nivolumab was completed successfully in 31 patients (39.2%). The overall median number of nivolumab doses was 11 (IQR: 1–15). From the 46 treatment discontinuations, five occurred during the CCRT-nivolumab phase (two toxicities, stroke and febrile neutropenia; two disease progressions; and one investigator's decision). Of the 41 treatment discontinuations during the nivolumab-alone phase, the recorded reasons were 18 toxicities, 18 progressions, two deaths, one withdrawal, one investigator's decision, and one unspecified (a patient without treatment for longer than 6 wk). A total of 49 (62%) patients were still on follow-up at the final analysis time.

Primary Efficacy Analysis: 1-year PFS

As previously mentioned, the 1-year PFS analysis was based on the primary efficacy analysis cohort, which, according to the design, included the first 74 assessable patients who either completed 1 year of follow-up without an event or had a PFS event up to the 1-year time-point. This cohort did not take into consideration the two patients who died before the treatment started, one who withdrew 2.6 months after enrolment, and the last two enrolled patients who reached a 1-year follow-up at a later timepoint.

Table 1. Patient and Treatment Characteristics (Full CCRT Cohort; N = 79)

Characteristic	All Patients
Before treatment start (N = 79)	
Age (y)	
n (%)	79 (100.0)
Mean (95% CI)	62.3 (60.3-64.3)
Median (Min-Max)	62 (41-78)
Sex, n (%)	
Male	53 (67.1)
Female	26 (32.9)
Histologic subtype, n (%)	
Nonsquamous	47 (59.5)
Squamous	28 (35.4)
Missing	4 (5.1)
Stage, n (%)	
IIIA	28 (35.4)
IIIB	50 (63.3)
Missing	1 (1.3)
Smoking history, n (%)	
Current (patient still smokes)	22 (27.8)
Former (≥100 cigarettes in the past during the whole life)	54 (68.4)
Never (0-99 cigarettes during the whole life)	3 (3.8)
ECOG performance status at enrolment, n (%)	
0	37 (46.8)
1	41 (51.9)
Unknown or missing	1 (1.3)
After treatment start (N = 77)	
Chemotherapy regimen, n (%)	
Cisplatin	
Etoposide	24 (31.2)
Pemetrexed	20 (26.0)
Vinorelbine	21 (27.3)
Carboplatin (etoposide, pemetrexed, vinorelbine)	12 (15.6)
ECOG performance status after CRT phase, n (%)	
0	26 (33.8)
1	42 (54.6)
2	3 (3.9)
3	1 (1.3)
4	1 (1.3)
Unknown or missing	4 (5.2)

CI, confidence interval; CCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; Max, maximum; Min, minimum.

To reject the null efficacy hypothesis, at least 41 patients (from a total of 74 patients) on CCRT treatment should be progression-free at 1 year. The required number was not reached. Only 37 patients were free of progression at 1 year. Thus, the null hypothesis of a 1-year PFS rate of less than or equal to 45% could not be rejected (exact binomial test $p = 0.23$). Even if the analysis took into account the two patients who died before treatment or the withdrawn patient, the conclusion still remains the same.

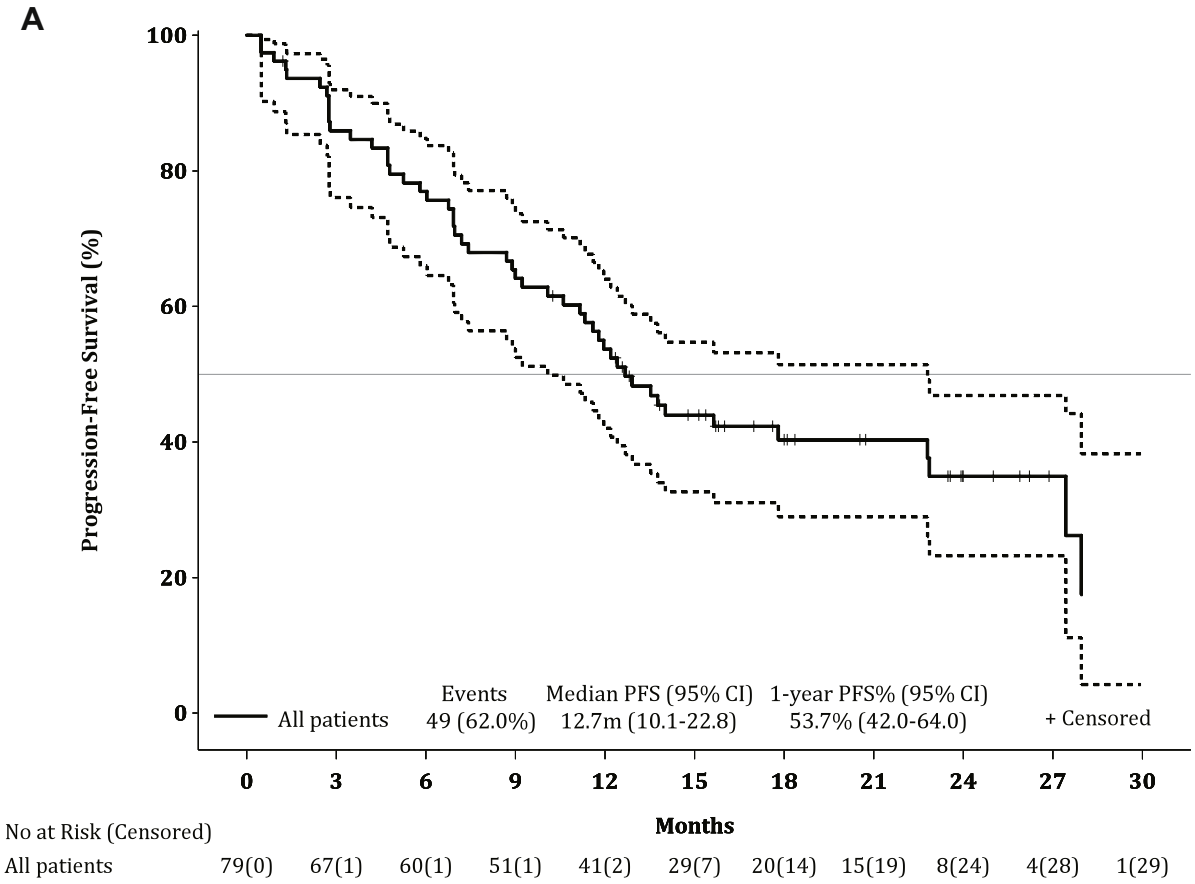
For the primary efficacy cohort of 74 patients, the estimated PFS at 1-year from the Kaplan-Meier curve was 50.0% (95% confidence interval [CI]: 39.9%–60.1%) (Supplementary Fig. 1).

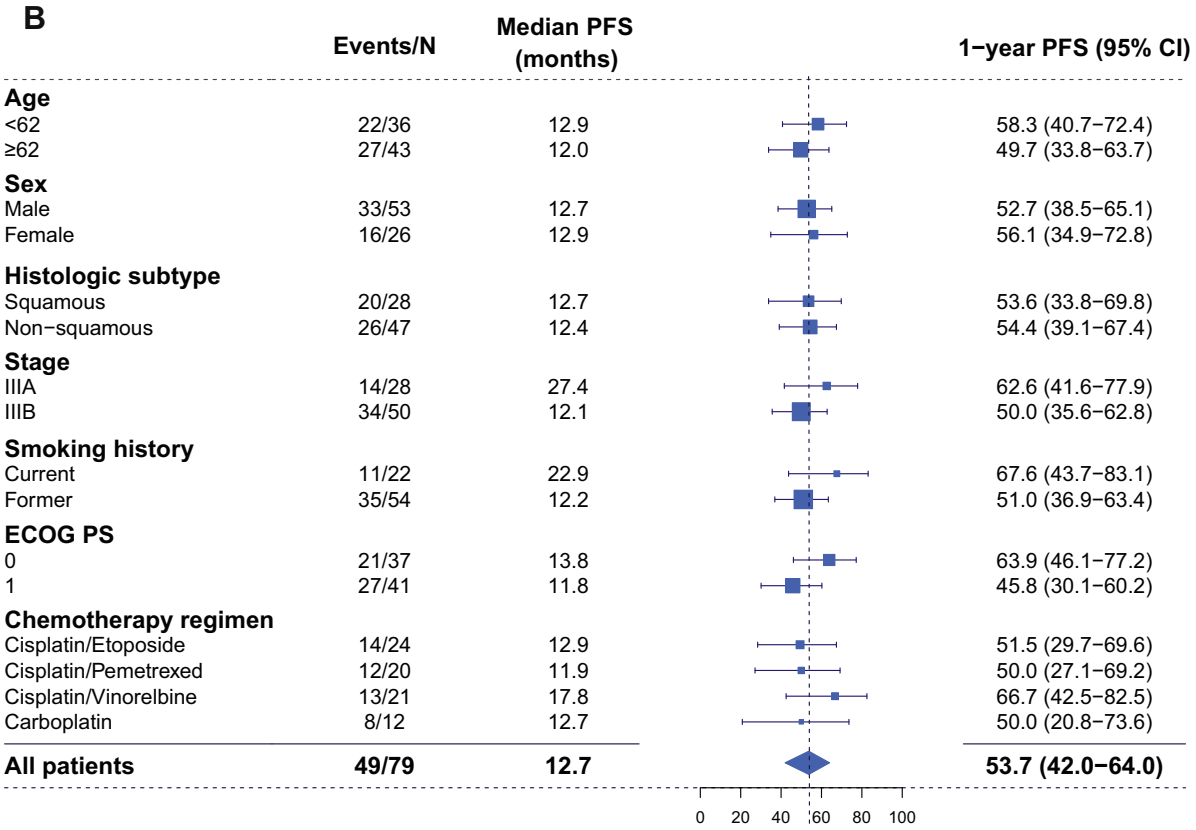
Secondary Analyses (Full CCRT Cohort)

PFS. Among all the 79 patients enrolled in the CCRT regimen, 49 (62.0%) PFS events were observed, with 40 occurring by the first year. Progression was documented for 36 patients, 15 of whom subsequently died, whereas 13 patients died without documented progression (cause of death: lung cancer [3], stroke [2], toxicity [pneumonitis], sepsis [infection], myocarditis, and other [5]). The PFS at 1 year was estimated to be 53.7% (95% CI: 42.0%–64.0%), and the median PFS was 12.7 months (95% CI: 10.1–22.8 mo) (Fig. 2*A*). For the 28 patients with squamous histologic subtype, 20 (71.4%) PFS events were recorded, with a 1-year PFS of 53.6% (95% CI: 33.8%–69.8%) and a median PFS of 12.7 months (95% CI: 10.1–22.8 mo); whereas among the 47 patients with nonsquamous histologic subtype, 26 (55.3%) events occurred, with a 1-year PFS of 54.4% (95% CI: 39.1%–67.4%) and a median PFS of 12.4 months (95% CI: 7.2 mo–not estimable [NE]) (Supplementary Fig. 2*A*). A total of 14 (50.0%) PFS events were recorded among the 28 patients with stage IIIA disease (1-year PFS: 62.6% [95% CI: 41.6%–77.9%]; median PFS: 27.4 mo [95% CI: 7.2 mo–NE]) and 34 (68.0%) events out of the 50 patients with stage IIIB disease (1-year PFS: 50.0% [95% CI: 35.6%–62.8%]; median PFS: 12.1 mo [95% CI: 8.9–17.8 mo]) (Supplementary Fig. 2*B*). Statistically significant differences were observed, neither between the histologic subtypes nor between the stage subgroups ($p = 0.59$ and 0.11, respectively).

None of the variables evaluated using univariate or multivariate Cox models yielded any statistically significant effect on the PFS (all p values > 0.05) (Fig. 2*B* and Supplementary Fig. 2).

OS. *The* OS results are presented here as of September 2020, analyzed beyond the cutoff for the primary PFS analysis, with a median follow-up of 32.6 months (IQR: 26.3–39.4 mo). Among the 79 patients, 37 (46.8%) deaths were observed, with a median OS of 38.8 months (95% CI: 26.8 mo–NE), a 1-year OS rate of 75.7% (95% CI: 64.6%–83.7%), and a 2-year OS rate of 63.7% (95% CI: 51.9%–73.4%). Most deaths (20 cases or 54.1%) were attributed to lung cancer and one to toxicity (pneumonitis along with tumor progression), whereas other reported reasons included stroke (n = 2), sepsis, cardiac cause, esophageal ulcer with hemorrhage, myelodysplastic syndrome, pericarditis carcinomatosa, pneumonia, pulmonary embolism (uncertain whether it


A
Progression-Free Survival (%)
100
80
60
40
20
0
Events
Median PFS (95% CI)
1-year PFS% (95% CI)
All patients
49 (62.0%)
12.7m (10.1-22.8)
53.7% (42.0-64.0)
+ Censored
0 3 6 9 12 15 18 21 24 27 30
Months
No at Risk (Censored)
All patients 79(0) 67(1) 60(1) 51(1) 41(2) 29(7) 20(14) 15(19) 8(24) 4(28) 1(29)


B
Events/N
Median PFS (months)
1−year PFS (95% CI)
Age
<62 22/36 12.9 58.3 (40.7−72.4)
≥62 27/43 12.0 49.7 (33.8−63.7)
Sex
Male 33/53 12.7 52.7 (38.5−65.1)
Female 16/26 12.9 56.1 (34.9−72.8)
Histologic subtype
Squamous 20/28 12.7 53.6 (33.8−69.8)
Non−squamous 26/47 12.4 54.4 (39.1−67.4)
Stage
IIIA 14/28 27.4 62.6 (41.6−77.9)
IIIB 34/50 12.1 50.0 (35.6−62.8)
Smoking history
Current 11/22 22.9 67.6 (43.7−83.1)
Former 35/54 12.2 51.0 (36.9−63.4)
ECOG PS
0 21/37 13.8 63.9 (46.1−77.2)
1 27/41 11.8 45.8 (30.1−60.2)
Chemotherapy regimen
Cisplatin/Etoposide 14/24 12.9 51.5 (29.7−69.6)
Cisplatin/Pemetrexed 12/20 11.9 50.0 (27.1−69.2)
Cisplatin/Vinorelbine 13/21 17.8 66.7 (42.5−82.5)
Carboplatin 8/12 12.7 50.0 (20.8−73.6)
All patients 49/79 12.7 53.7 (42.0−64.0)
0 20 40 60 80 100

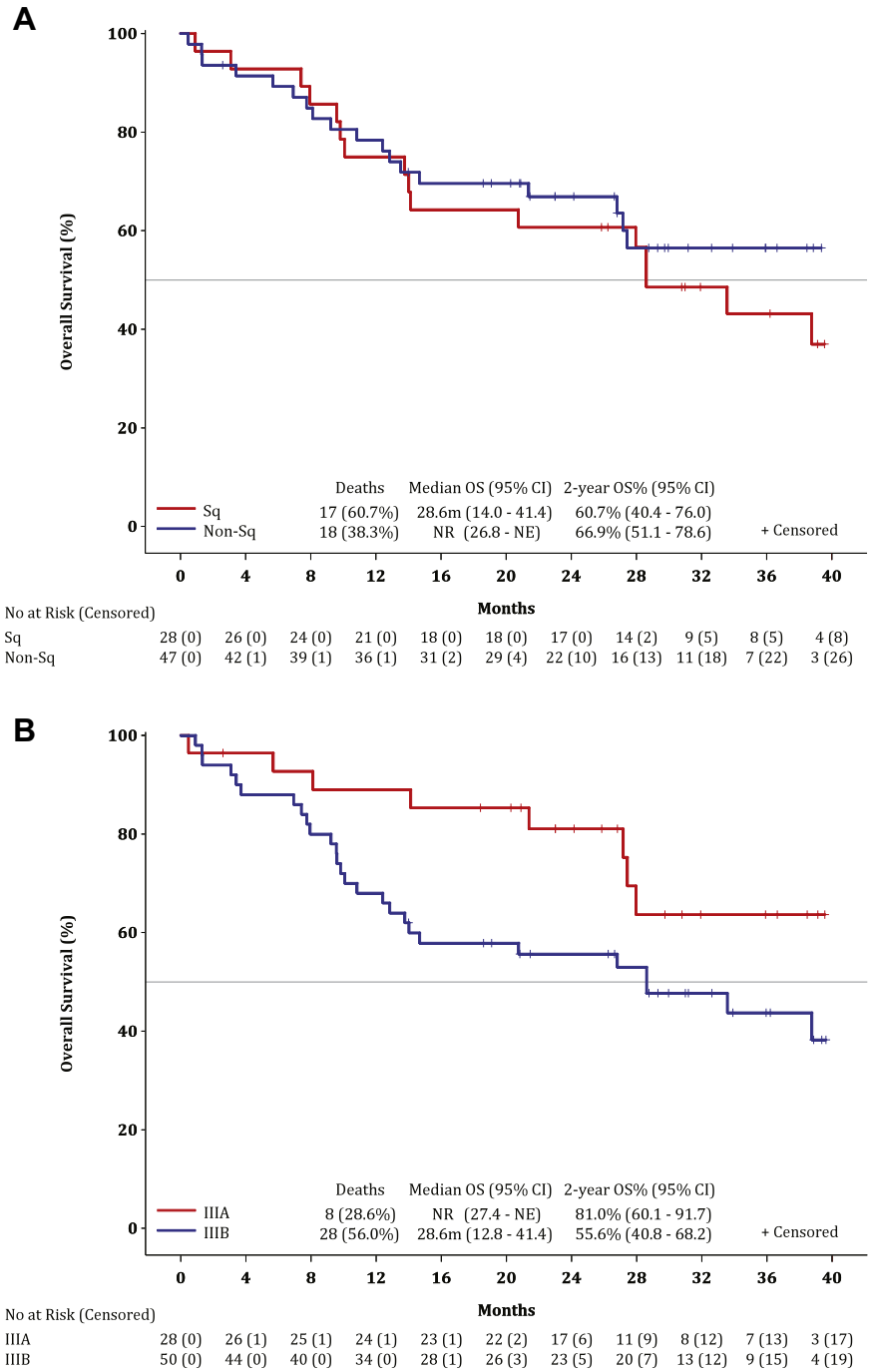


Figure 3. OS by histologic subtype and stage. (*A*) OS by histologic subtype. (*B*) OS by stage (full CCRT cohort; N = 79) (Note: missing, histologic subtype n = 4; stage n = 1). CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival; Sq, squamous.

was death because of pulmonary fibrosis or myocarditis), necrotizing colitis, and severe anemia (one case each). The cause of death was not reported in five cases. The relationship to study treatment was assessed for deaths recorded as AEs (eight fatal AEs at least possibly related to one of the treatments administered).

Figure 2. PFS. (*A*) PFS (full CCRT cohort; N = 79) (CI band is indicated with dashed lines). (*B*) The 1-year PFS rate by patient and treatment characteristics (full CCRT cohort; N = 79). All *p* values from separate Cox models are not significant at α equals 5% (not provided: never-smokers n = 3; missing observations: histologic subtype n = 4, stage n = 1, ECOG PS n = 1, chemotherapy regimen n = 2). CCRT, concurrent chemoradiotherapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival.

In univariate analyses, no statistically significant difference in OS was found between the histologic subgroups ($p = 0.35$) (Fig. 3*A*) or other variables except for stage when comparing stage IIIA with IIIB (log-rank $p = 0.037$) (Fig. 3*B*). Eight (28.6%) deaths occurred among the 28 patients with stage IIIA disease, with a 2-year OS of 81.0% (95% CI: 60.1%–91.7%), whereas 28 (56.0%) deaths occurred among the 50 patients with stage IIIB disease, with a 2-year OS of 55.6% (95% CI: 40.8%–68.2%). The median OS was 28.6 months for the IIIB patient subgroup (95% CI: 12.8–41.4 mo), whereas, for the IIIA subgroup, the OS was not reached (95% CI: 27.4 mo–NE).

In the multivariate Cox model, stage remains significant (Cox Wald $p = 0.029$) along with age ($p = 0.046$) (Fig. 3 and Supplementary Fig. 3).

ORR. The ORR was 73.4% (95% CI: 62.3%–82.7%), with five (6.3%) CRs. For these five patients, only the baseline TA was available before treatment discontinuation. For the 58 patients with documented objective response, the median duration of response was 11.0 months (95% CI: 8.6–20.7 mo), with 33 (56.9%) patients progressing afterward (Supplementary Fig. 4). A total of 60 of 79 (76.0%) patients achieved at least a partial remission of their target lesions, with 58 patients achieving objective response (53 partial response and five CR per RECIST version 1.1) during treatment. The change from baseline of targeted lesion size is presented in Figure 4.

TTF. A total of 58 (73.4%) treatment failures were observed, with a 1-year TTF of 41.8% (95% CI: 30.8%–52.3%) and a median of 9.2 months (95% CI: 6.4–12.4 mo). For the 10 of 31 (32.3%) patients who completed the 1-year nivolumab treatment per protocol, treatment failure was because of progression (seven patients), death (two patients), or withdrawal (one patient).

TFP3. A total of nine (11.7%) pneumonitis events of grade 3 or higher occurred among the 79 patients. All occurred within 1 year of follow-up, with a corresponding 1-year TFP3 of 87.0% (95% CI: 76.4%–93.0%, median: not reached) (Supplementary Table 1).

Site of Progression and Tumor Change. In most of the 36 documented progressions (27 cases; 75.0%), distant metastases (appearance of new lesions) were recorded (seven cases [19.4%] also involved local and, or regional progression). Three cases were local metastases, whereas the remaining six cases were locoregional (three cases), local (two cases), and regional disease progression (one case).

Metastases were detected in only one site for 21 patients (70.0% of the 30 patients with distant or local metastases), two sites in eight patients (26.7%), and three sites in one (3.3%) patient. The lungs were the most frequent metastatic site (25.0%), followed by the brain (17.5%), the lymph nodes (15.0%), and the liver (12.5%) (Supplementary Tables 2 and 3).

Safety

AEs. The safety cohort consisted of the 77 patients who received at least one dose of treatment, with 76 (98.7%) patients experiencing at least one AE. A detailed account of the AEs by grade is provided in Supplementary Table 4.

Of the 780 AEs, 91 (11.6%) were severe, 20 (2.6%) were life-threatening, and 10 (1.3%) were fatal (Table 2). Seven of the 10 fatal events were considered at least possibly related to nivolumab, with pneumonitis reported as definitely attributed to nivolumab and possibly related to RT, whereas esophageal fistula was noted as definitely related to RT.

In total, 361 AEs were related to at least one treatment, with 168 (21.5%) related to RT and 249 (31.9%) to nivolumab (Table 2). For the 84.5% of these RT- or nivolumab-related events, no action was taken, whereas for 31 events (8.6%), the dose was delayed. In eight (2.2%) cases, the dose was temporarily discontinued and in 16 cases (4.4%) permanently discontinued (one of grade 1, nine of grade 2, five of grade 3, and one of grade 5). For 1.6% of cases, no information on the action taken was available.

Serious AEs. Almost half of the patients in the safety cohort experienced one to four serious AEs (48.1%). Of the 61 recorded serious AEs, 15 (24.6%) were of grade 2, 29 (47.5%) of grade 3, and eight each were of grade 4 (life-threatening) and grade 5 (fatal). Most cases were resolved (75.4%). Only four events (6.6%) were attributed to nivolumab.

In total, nine (11.7%) patients experienced a pneumonitis event of grade 3 or higher (eight of grade 3 and one of grade 5), six of which occurred within 6 months post-RT. Seven were resolved completely, one was resolved with sequelae, whereas one (although initially resolved) reoccurred, leading to the patient's death. The median time-to-event's resolution was 11 days (range: 6–53). All cases of pneumonitis were attributed to nivolumab (three with possible, four with probable, and two with definite relation), whereas four cases were also attributed to RT with a probable relation.

Discussion

Radical, curative-intent treatment of stage III NSCLC, although extensively studied, has remained a medical

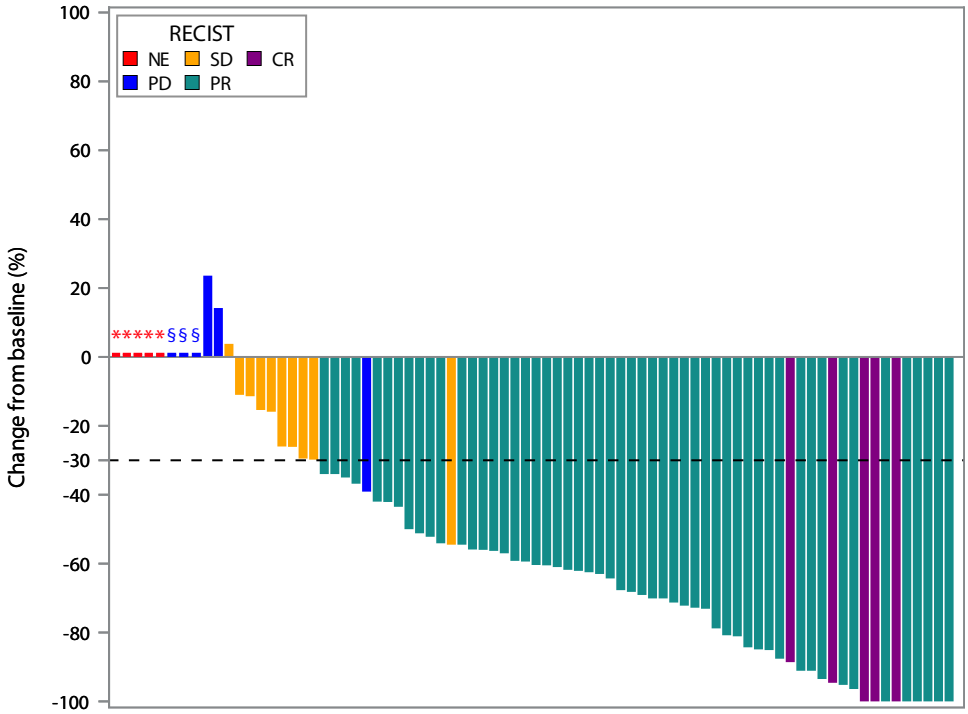


Figure 4. Best percent change from baseline for target lesion size (sum of tumor diameters for targeted lesions) by RECIST best overall response (among patients with available information in the full CCRT cohort; N = 79) *non evaluable patients, §patients with missing information on tumor diameters. CCRT, concurrent chemoradiotherapy; CR, complete response; NE, non evaluable; PD, progression of disease; PR, partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

challenge. Whereas CCRT has been the standard of care for inoperable disease for a long time, the results of the recent PACIFIC study have defined a new standard by combining CCRT with consolidation durvalumab for 12 months. Despite these clinically meaningful advances, most patients will eventually still die from lung cancer.[6,13] As there is preclinical evidence that the administration of a PD-1 or PD-L1 or antagonist immediately after or preferably during RT may be the most efficient[7] way to combine treatment, the NICOLAS trial investigated the concurrent administration of nivolumab with CCRT followed by 12 months of nivolumab. In this trial, we reported the CCRT cohort having a 1-year PFS of 53.7%, a median PFS of 12.7 months, a 1-year OS of 75.7%, a 2-year OS of 63.7%, and a median OS of 38.8 months.

These results could also be viewed in relation to other recent studies such as RTOG 0617,[2] PROCLAIM,[5] and PACIFIC[6] (Supplementary Tables 5 and 6). The 1-year PFS was 48% in the 60-Gy arm of RTOG 0617, 48% in the cisplatin-pemetrexed arm of PROCLAIM, and 55.9% in the durvalumab arm of PACIFIC. The 1-year OS and median OS for RTOG 0617, PROCLAIM, and PACIFIC was 78%, 76%, 83.1%, and 28.7 months, 26.8 months, and not reached, respectively (at median follow-up times of 32.4, 22.2, and 33.3 months accordingly). However, major differences between these studies should be emphasized, using substantially distinct upfront

Table 2. Treatment-Related AEs (Safety Cohort; N = 77)

Information on Treatment-Related AEs	Radiotherapy	Nivolumab
Safety cohort: number of patients	77	76
Any AE (SAE)	780 (61)	
Treatment-related AEs (SAEs)	168 (14)	249 (26)
Treatment-related AEs (SAEs) grade 3-5	32 (9)	44 (18)
Treatment-related AEs (SAEs) leading to death	2 (1)	7 (6)
Treatment-related AEs (SAEs) leading to permanent discontinuation of treatment	6 (-)	16 (-)

AE, adverse event; SAE, severe adverse event.

selection criteria. In the PACIFIC study, patients were randomized after having received CCRT, which was 2 to 3 months later than the other studies RTOG, PROCLAIM, and NICOLAS—all of which included patients before CCRT. In the PACIFIC study, only the fittest patients without disease progression after completion of CCRT were enrolled, whereas in the NICOLAS study, similar to RTOG 0617 and PROCLAIM studies, the patients had to be in a good general condition at the time of enrolment before starting CCRT. In the PROCLAIM study, only patients with nonsquamous histologic subtype (mainly adenocarcinoma) were eligible in view of the use of pemetrexed. In the same study, patients with pleural effusion required a puncture. In the case of documented exudate, even in the absence of malignant cells, patients were not eligible for the trial. In RTOG 0617, patients with involvement of supraclavicular lymph nodes were not eligible for the study. In this study, patients with pleural exudates were also excluded regardless of the cytology. In addition, patients' demographics also seem to be different between these studies. In the NICOLAS study, patients with stage IIIB disease (generally characterized with a poorer outcome) were representing 63% of the intention-to-treat population—a substantially higher proportion than in PACIFIC (45%), RTOG 0617 (34%), and PROCLAIM (52%) studies. As the inclusion criteria of the present NICOLAS trial were less stringent than in the two other studies, with an NSCLC population characterized by a possibly worse outcome, an intertrial comparison is not possible. Nevertheless, the 1-year PFS of 53.7% in the NICOLAS trial compared with 48% in RTOG 0617 and 38% in PROCLAIM, and the median OS of 38.8 months compared with 28.7 and 26.8 months, respectively, support continuous investigations of concurrent immunotherapy with CCRT.

As previously published, it is reassuring that the toxicity of nivolumab given together with CCRT was within the predefined limits.[11] Of note, 89% of treatment discontinuations happened during the consolidation phase, with 44% of the cases being attributed to treatment toxicity. Although we could not reject the null hypothesis that the 1-year PFS rate is 45% or lower, the safety, PFS, and OS outcomes support continued investigation of concurrent nivolumab with CCRT.

Ultimately, the impact of using immune checkpoint inhibitors concomitantly with CRT will be determined in larger randomized trials using durvalumab (NCT04092283, NCT03519971) or nivolumab (NCT04026412).

In conclusion, at the present time, the use of checkpoint inhibitors given concurrently with CCRT remains experimental, but this strategy is promising enough to warrant further investigation.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.10.129.

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