Tumor and nodal pathological response after neoadjuvant nivolumab plus chemotherapy in a cohort of 622 patients with resectable NSCLC: Results from a French multicenter study

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Introduction

- The randomized, phase 3 CheckMate 816 trial demonstrated that neoadjuvant nivolumab plus platinum-based chemotherapy provides statistically significant and clinically meaningful improvements in pathological complete response (pCR), event-free survival (EFS), and overall survival (OS) in patients with resectable non-small cell lung cancer (NSCLC).[1-3]
- Based on the finding of this study, an early access program (EAP) was authorized by the Haute Autorité de Santé in France in 2023 to provide access to nivolumab plus platinum-based chemotherapy as neoadjuvant therapy for adults with resectable NSCLC at high risk of recurrence, whose tumors expressed PD-L1 ≥1%, and without known sensitizing *EGFR* mutations or *ALK* translocations.[4]
- Given the limited real-world data available, the aim of this study was to evaluate the feasibility and effectiveness of neoadjuvant nivolumab plus chemotherapy in patients with resectable NSCLC.
- Initial results of this study in the first 101 patients enrolled showed that neoadjuvant nivolumab plus chemotherapy was associated with a pCR rate of 32% (95% confidence interval [CI] 23, 42) and a major pathological response (MPR) rate of 50% (95% CI 39, 60).[2] Patients were more likely to achieve pCR if they had ≥50% vs. <50% PD-L1 expression (odds ratio [OR] 3.32; 95% CI 1.31, 8.74; p=0.011).[2]
- This analysis included data from a larger cohort of patients with NSCLC receiving nivolumab plus chemotherapy, recruited from multiple sites in France.

Methods

- This was a retrospective, multicenter analysis of real-world data from patients aged ≥18 years with resectable stage II-III NSCLC treated with neoadjuvant nivolumab plus platinum-based chemotherapy between 2021 and 2025 in France.
- Patients were followed up for ≥4 months until death, loss to follow up, or the end of the study observation period (1 November 2025).
- Patients were excluded from the analysis if they had any primary tumor other than NSCLC (on or before the date of NSCLC diagnosis) that required treatment within the 12 months before starting nivolumab plus chemotherapy.
- The primary study endpoints were pCR rate and EFS.
- Secondary endpoints included surgery and neoadjuvant treatment characteristics, MPR rate, and subsequent treatments received. Exploratory endpoints included the association between PD-L1 expression level and pCR, between PD-L1 expression level and EFS, and between pCR and EFS.
- Subgroup analyses were conducted to evaluate pCR according to PD-L1 expression level and disease stage.
- Safety evaluation included the frequencies and characteristics of adverse events.

Results

Baseline demographic and clinical characteristics

- Data from 622 patients were collected from 56 centers between 1 April 2022 and 1 June 2025.
- At the time of NSCLC diagnosis, patients had a mean (standard deviation [SD]) age of 64.3 (8.8) years, 62.6% had stage III disease, 65.8% had non-squamous histology, and 97.3% were current or former smokers. PD-L1 expression was assessed in 606 patients (97.4%; Table 1).
- More than two-thirds of patients (69.2%; 430/621) had at least one comorbidity. Among these, cardiovascular disease (60.2%), pulmonary disorders (28.6%), and endocrine disorders (26.5%) were the most frequent. Fifty-five patients (12.8%) had a history of other cancers without treatment in the 12 months prior to the initiation of nivolumab plus chemotherapy.
- Around half of patients (51.3%) had a PD-L1 expression level <50%. Four patients (1.1%) were positive for *EGFR* mutation, but were not targetable by therapy and were therefore included.
- At the start of nivolumab plus chemotherapy, 98.8% of patients for whom data were available had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1.

Table 1. Patient characteristics.

Characteristic	N=622*
Male sex	396 (63.7%)
Age at diagnosis	
<65 years	289 (46.5%)
65-74 years	274 (44.1%)
≥75 years	59 (9.5%)
Disease stage at diagnosis (TNM 8th Edition)	n=611
Ib	7 (1.1%)
IIa	36 (5.9%)
IIb	175 (28.6%)
IIIa	290 (47.5%)
IIIb	92 (15.1%)
Other	11 (1.8%)
ECOG PS (at start date of nivolumab plus chemotherapy)	n=586
0	340 (58%)
1	239 (40.8%)
≥2	7 (1.2%)
Node status	n=620
Nx	13 (2.1%)
N0	193 (31.1%)
N1	190 (30.6%)
N2 mono-site	143 (23.1%)
N2 multi-sites	76 (12.3%)
N3	5 (0.8%)
Histology at diagnosis	n=617
Squamous	211 (34.2%)
Non-squamous	406 (65.8%)
PD-L1 expression assessed	
Yes	606 (97.4%)
No	16 (2.6%)
PD-L1 expression level	n=606
<50%**	311 (51.3%)
≥50%	295 (48.7%)

*Data were available for the total population (N=622) unless stated otherwise; **31 patients (5.1%) had a PD-L1 expression <1%. ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; TNM, tumor, node and metastasis.

Treatment characteristics

- The mean (SD) time from NSCLC diagnosis to the start of neoadjuvant treatment was 38.4 (25.2) days, and 560 patients (90.1%) received ≥3 cycles of nivolumab. A total of 62 patients (9.9%) received 1 or 2 cycles of nivolumab.
- Chemotherapies administered with nivolumab included pemetrexed-based regimens (55.8%), paclitaxel-based regimens (39.7%), and other platinum doublets (4.5%). Carboplatin was the most frequently used platinum-based chemotherapy (90.9%).

Surgical data

- Overall, 550 patients underwent surgery (88.4%; Table 2). The mean (SD) time from diagnosis to surgery was 4.0 (1.0) months and time to surgery from the last dose of neoadjuvant therapy was 1.3 (0.6) months.
- Lymph node resection was performed in 94.7% of patients who underwent surgery (n=514/543).
- Among the 72 patients who did not undergo surgery, the most frequent reasons were disease progression (19.4%), major comorbidities contraindicating surgery (18.1%), impaired lung function (16.7%), and unresectability (15.3%). Other reasons patients did not proceed to surgery were an ECOG PS >1 (9.8%), patient refusal (8.3%), adverse events (4.2%), or death prior to surgery (4.2%).

Table 2. Extent of resection and procedure type in patients who underwent surgery.

Number of patients who underwent surgery	n=550 (88.4%)
Extent of resection	n=548
R unspecified	5 (0.9%)
R0	529 (96.5%)
R1	13 (2.4%)
R2	1 (0.2%)
Type of surgical procedure	n=546
Lobectomy	452 (82.8%)
Segmentectomy	8 (1.5%)
Bilobectomy	36 (6.6%)
Wedge resection	3 (0.5%)
Pneumonectomy	44 (8.1%)
Lymph node dissection	3 (0.5%)

Pathological response

- The pCR rate in the overall population was 31.2% (95% CI 27.6, 35.0; Figure 1). The MPR rate was 51.0% (95% CI 47.0, 55.0).
- With the exception of two patients who did not have surgery due to achieving complete response, patients who did not receive surgery (n=70) were considered as non-responders.
- Multivariate analysis revealed that PD-L1 ≥50% was independently associated with achieving pCR (adjusted OR 2.13; 95% CI 1.47, 3.11; p<0.001).
- pCR was consistent across nodal stages, with pCR rates of 29.5% (95% CI 23.2, 36.5), 32.6% (26, 39.8), 28.7% (21.4, 36.8), and 35.5% (24.9, 47.3) across N0, N1, monostation N2, and multistation N2, respectively.

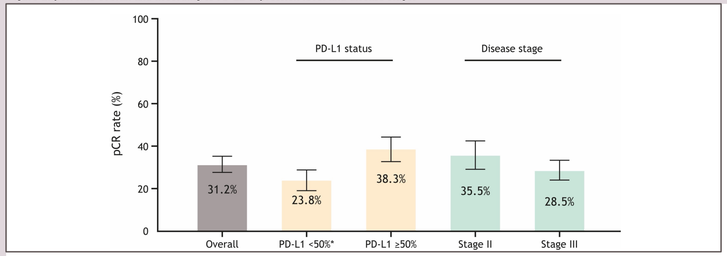
Survival

- Patients had a median follow-up of 10 months (range 1-39).
- The EFS rate at 12 months was 79.3% (95% CI 75.4, 83.4).
- Patients without pCR had significantly higher risk of EFS events than those with pCR (hazard ratio [HR] 5.58; 95% CI 2.91, 10.69; p<0.001; Figure 2). In addition, failure to undergo surgery was independently associated with shorter EFS (adjusted HR 3.3; 95% CI 2.1, 5.2; p<0.001).
- Multivariate analyses revealed that PD-L1 ≥50% was not associated with achieving EFS (HR 0.8; 95% CI 0.54, 1.16; p=0.2).
- The OS rate at 12 months was 94.0% (95% CI 91.8, 96.3).

31.2% of patients (n=194) experienced pCR after receiving neoadjuvant nivolumab plus chemotherapy

The pCR rate was higher in patients with a PD-L1 expression ≥50% (38.3%; 95% CI 32.7, 44.1) vs. <50% (23.8%; 19.2, 28.9).

Figure 1. pCR rate overall and according to PD-L1 expression level and disease stage.

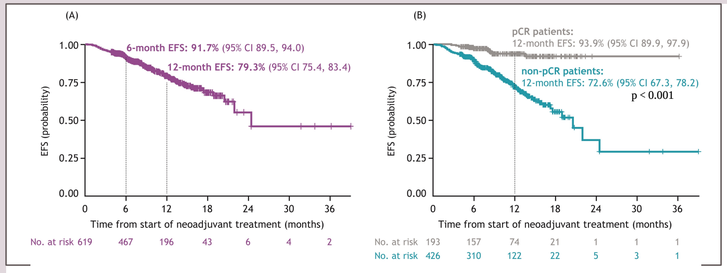


*pCR rate was 32.3% in patients with PD-L1 expression<1%. pCR, pathological complete response; PD-L1, programmed death-ligand 1.

The EFS rate at 12 months was 79.3% in the overall population (95% CI 75.4, 83.4)

A total of 93.9% of patients who had pCR did not have any EFS events at 12 months.

Figure 2. EFS (A) overall and (B) according to achievement of pCR.

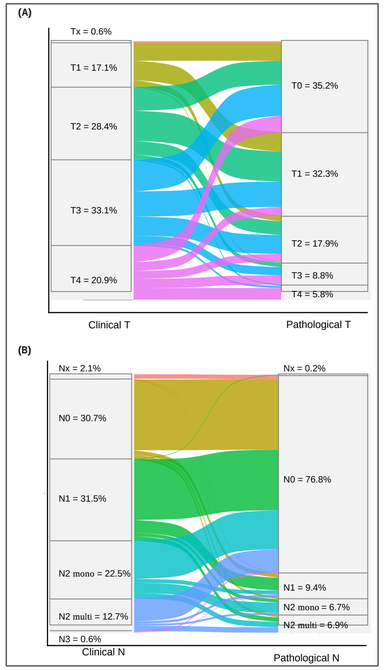


EFS, event-free survival; pCR, pathological complete response.

Downstaging

- Tumor downstaging was observed in 78.2% (95% CI 74.5, 84.6) of patients with evaluable pathological T stage after surgery (Figure 3A).
- Downstaging was observed across all baseline clinical T categories, including transitions to ypT0 in 40.7%, 32.5%, 36.4%, and 30.6% from cT1, cT2, cT3, and cT4, respectively.
- Nodal downstaging was observed in 62.8% (95% CI 58.6, 66.9) of patients with evaluable nodal status after surgery (Figure 3B).
- Transitions from cN+ disease to ypN0 status were common, including 66.7% of patients with initial monostation N2 disease and 70.6% of those with initial multistation N2 disease achieving ypN0 status post-treatment. By convention, patients with pCR were classified as having nodal downstaging.

Figure 3. Tumor and nodal downstaging. Tumor (A) and nodal (B) stage at the initial clinical stage and at the post-treatment pathological stage.



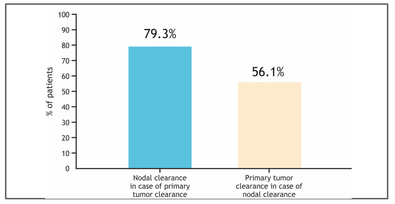
N2 mono: N2 monostation; N2 multi: N2 multistation

Association between tumoral and nodal responses

- Among patients with clinical nodal disease, 79.3% of those with primary tumor clearance* also had nodal clearance (Figure 4). In patients with clinical nodal disease who experienced nodal clearance, 56.1% also had primary tumor clearance.

*Nodal clearance: No residual viable tumor cells in nodes; Primary tumor clearance: No residual viable tumor cells in the primary tumor.

Figure 4. Probability of nodal clearance in patients with primary tumor clearance (left) and probability of primary tumor clearance in patients with nodal clearance (right; cN+ patients only).



cN+, clinically node-positive NSCLC.

Adjuvant treatment

- Among resected patients (n=550), 44 (8.0%) received adjuvant treatment.
- The main indications for adjuvant treatment were nodal involvement (n=15; 34.1%), R1 resection (n=6; 13.6%), capsular rupture (n=3; 6.8%), or other reasons (n=20; 45.5%).
- Adjuvant therapy consisted of chemotherapy alone in 14 patients (31.8%), radiotherapy alone in 14 (31.8%), immunotherapy alone in 4 (9.1%), combined chemotherapy plus immunotherapy in 3 (6.8%), radiotherapy plus chemotherapy in 2 (4.5%), radiotherapy plus chemotherapy plus immunotherapy in 4 (9.1%), and radiotherapy plus immunotherapy in 1 (2.3%).

Safety

- Grade 3-4 treatment-related adverse events occurred in 14.5% of treated patients. Hematologic toxicities were most common, while severe immune-related events (hepatitis, pneumonitis) were reported in <1% of patients each.
- Two treatment-related deaths were reported. One patient died due to "septic shock in the context of aplasia and multiorgan failure" and did not proceed to surgery. The second patient died due to "possible interstitial lung disease related to nivolumab or amiodarone". This patient proceeded to surgery and died 3.3 months later.

Conclusions

- Neoadjuvant nivolumab plus chemotherapy resulted in pCR in approximately one-third of patients and favorable early EFS in a large cohort of real-world patients in France receiving treatment. pCR was highly associated with EFS, which indicates that pCR is a clinically meaningful early outcome measure.
- The high percentage of patients undergoing surgery demonstrates the feasibility of this approach in a larger cohort in real-world settings in France.
- In patients with nodal disease, nodal clearance was observed in close to 80% of those with primary tumor clearance, with a high correlation between nodal and tumor responses.
- The effectiveness and tolerability of neoadjuvant nivolumab plus chemotherapy in this analysis were in line with the findings of the initial analysis;[2] taken together, these analyses highlight the real-world benefits of neoadjuvant chemoimmunotherapy in patients with resectable NSCLC.

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