Neoadjuvant nivolumab plus platinum-doublet chemotherapy for resectable non-small cell lung cancer: 3-year update from CheckMate 816 with exploratory analyses of event-free survival by pathologic complete response

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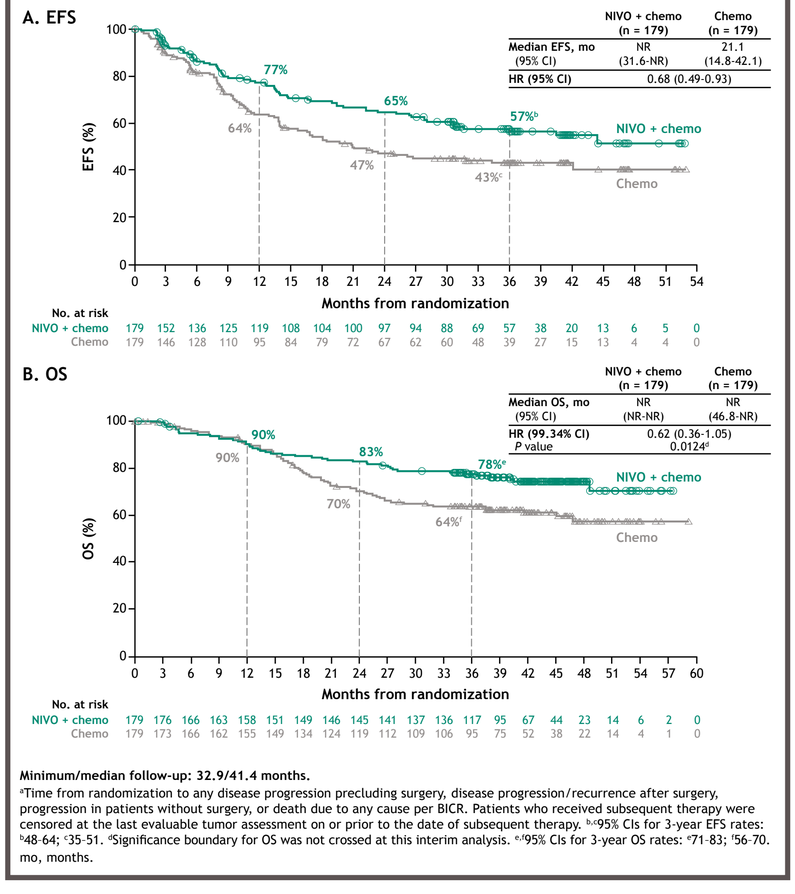
Background

- In the randomized phase 3 CheckMate 816 study, neoadjuvant nivolumab (NIVO) + platinum-based chemotherapy (chemo) demonstrated statistically significant and clinically meaningful improvements in event-free survival (EFS) and pathologic complete response (pCR) vs chemo in patients with resectable non-small cell lung cancer (NSCLC)[1-3]
- Based on these results, NIVO + chemo has been approved as a neoadjuvant therapy in the United States and several other countries for adult patients with resectable NSCLC (tumors ≥ 4 cm or node-positive) and in the EU for resectable NSCLC at high risk of recurrence in patients with tumor programmed death ligand 1 (PD-L1) expression ≥ 1%[4]
- Adding NIVO to neoadjuvant chemo did not impact feasibility of surgery; definitive surgery rates were 83% vs 75%, respectively[1]
  - Overall, the timing of surgery and completeness of resection were not impacted by the addition of neoadjuvant NIVO to chemo
  - No increase in postsurgical complications was observed with NIVO + chemo vs chemo
- Here we report 3-year efficacy and safety results from CheckMate 816, including exploratory analyses of EFS by pCR

Methods

- Adults with stage IB (tumors ≥ 4 cm) to IIIA (per American Joint Committee on Cancer [AJCC], 7th edition staging) resectable NSCLC, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1, and no known epidermal growth factor receptor (*EGFR*)/anaplastic lymphoma kinase (*ALK*) mutations were randomized 1:1 to NIVO 360 mg + platinum-based chemo every 3 weeks (Q3W) or chemo Q3W for 3 cycles, followed by definitive surgery within 6 weeks of treatment (**Figure 1**)
- Primary endpoints were EFS per blinded independent central review (BICR) and pCR per blinded independent pathologic review (BIPR)
- Exploratory analyses included EFS by surgical approach and extent/completeness of resection, and EFS and overall survival (OS) by pCR

Figure 1. CheckMate 816 study design[a]



Database lock: October 14, 2022; median follow-up, 41.4 months.

[a]NCT02998528. [b]Tumor-Node-Metastasis (TNM) Classification of Malignant Tumors 7th edition. [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [d]Included patients with PD-L1 expression status not evaluable and indeterminate. [e]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin. [f]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin. [g]Per healthcare professional choice. [h]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy.

IHC, immunohistochemistry; MPR, major pathologic response; NSQ, non-squamous; RT, radiotherapy; SQ, squamous.

Adapted from Forde PM, et al. *N Engl J Med* 2022;386:1973-1985.

Results

Event-free survival and overall survival in the concurrently randomized patient population

- With a median follow-up of 41.4 months, median EFS was not reached (NR) (95% confidence interval [CI], 31.6-NR) in the NIVO + chemo arm vs 21.1 months (95% CI, 14.8-42.1) in the chemo arm (hazard ratio [HR], 0.68; 95% CI, 0.49-0.93) (**Figure 2A**)
  - 3-year EFS rates were 57% (95% CI, 48-64) and 43% (95% CI, 35-51) for patients who received NIVO + chemo or chemo, respectively
- Median OS was not yet reached for either study arm (**Figure 2B**)
  - 3-year OS rates were 78% (95% CI, 71-83) and 64% (95% CI, 56-70) for patients who received NIVO + chemo or chemo, respectively

Figure 2. A) EFS and B) OS with neoadjuvant NIVO + chemo vs chemo: 3-year update[a]

Minimum/median follow-up: 32.9/41.4 months.

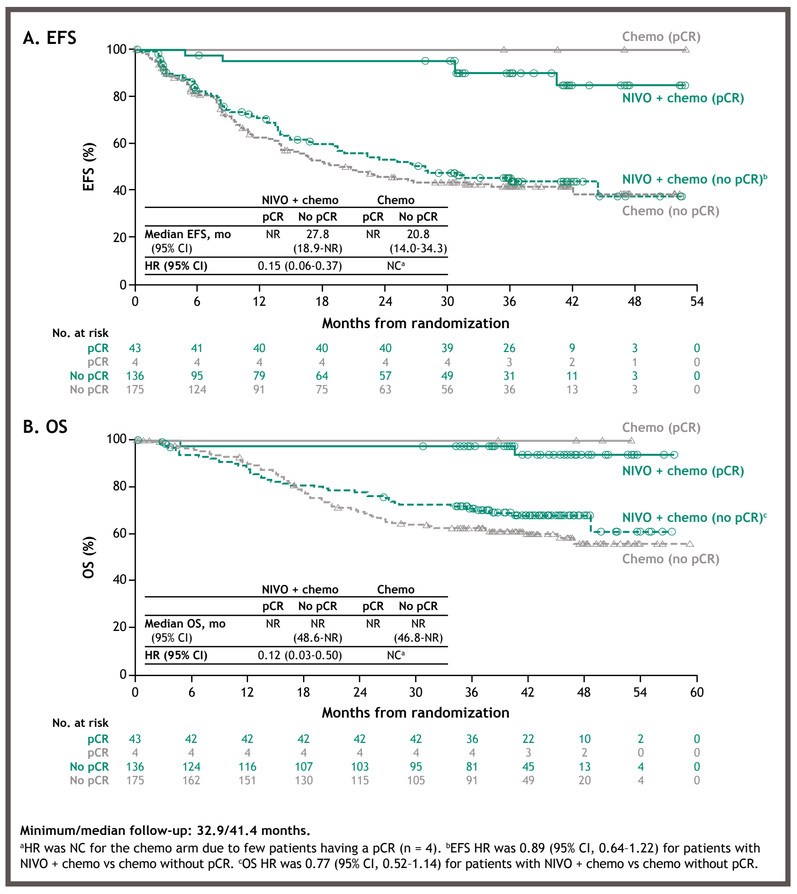
[a]Time from randomization to any disease progression precluding surgery, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b,c]95% CIs for 3-year EFS rates: [b]48-64; [c]35-51. [d]Significance boundary for OS was not crossed at this interim analysis. [e,f]95% CIs for 3-year OS rates: [e]71-83; [f]56-70.

mo, months.

Efficacy by pathologic complete response

- In the NIVO + chemo arm, EFS and OS were improved in patients with a pCR compared to those without (EFS: HR, 0.15; 95% CI, 0.06-0.37; OS: HR, 0.12; 95% CI, 0.03-0.50) (**Figure 3**)
- A similar trend was observed in the chemo arm (HR was not calculated [NC] due to the small number of patients with a pCR)
- Among patients without a pCR, EFS and OS appeared to favor NIVO + chemo vs chemo

Figure 3. Efficacy outcomes by pCR status in concurrently randomized patients



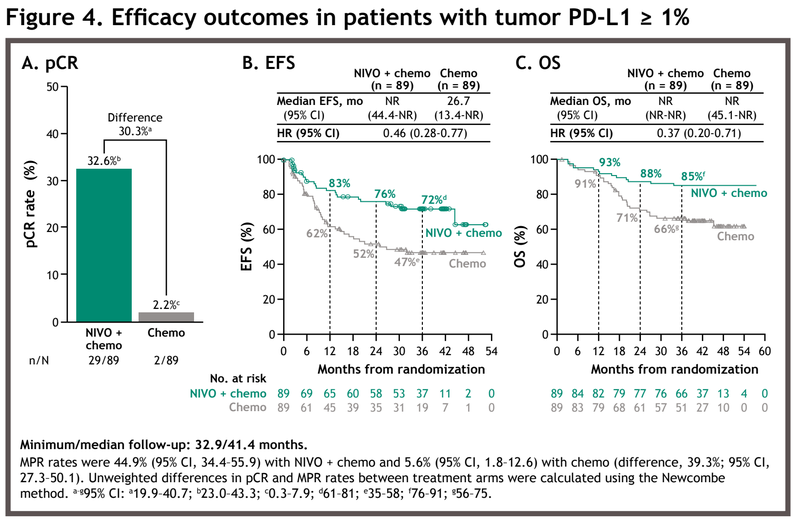
Minimum/median follow-up: 32.9/41.4 months.

[a]HR was NC for the chemo arm due to few patients having a pCR (n = 4). [b]EFS HR was 0.89 (95% CI, 0.64-1.22) for patients with NIVO + chemo vs chemo without pCR. [c]OS HR was 0.77 (95% CI, 0.52-1.14) for patients with NIVO + chemo vs chemo without pCR.

Efficacy by tumor PD-L1 expression

- Baseline characteristics were generally similar between tumor PD-L1 subgroups and treatment arms, although a higher proportion of patients with tumor PD-L1 < 1% had ECOG PS 1 (both arms)
- NIVO + chemo showed improvement vs chemo across all efficacy endpoints in patients with tumor PD-L1 ≥ 1% (pCR: 32.6% vs 2.2%, respectively; EFS: HR, 0.46; 95% CI, 0.28-0.77; OS: HR, 0.37; 95% CI, 0.20-0.71) (**Figure 4**) and in patients with tumor PD-L1 ≥ 1% and stage II-IIIA disease (pCR: 32.1% vs 2.3%, respectively; EFS: HR, 0.49; 95% CI, 0.29-0.83; OS: HR, 0.43; 95% CI, 0.22-0.83) (**Figure 5**)
- NIVO + chemo showed a trend for improvement vs chemo across all efficacy endpoints in patients with tumor PD-L1 < 1% (pCR: 16.7% vs 2.6%, respectively; EFS: HR, 0.87; 95% CI, 0.57-1.35; OS: HR, 0.81; 95% CI, 0.48-1.36) (**Figure 6**)

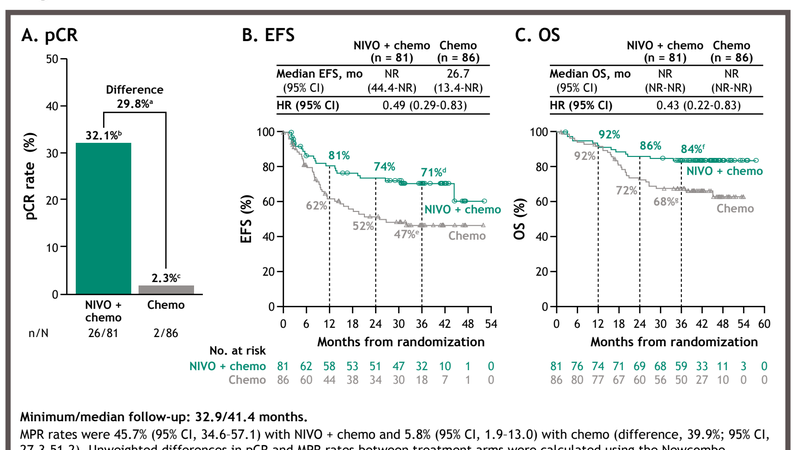
Figure 4. Efficacy outcomes in patients with tumor PD-L1 ≥ 1%



Minimum/median follow-up: 32.9/41.4 months.

MPR rates were 44.9% (95% CI, 34.4-55.9) with NIVO + chemo and 5.6% (95% CI, 1.8-12.6) with chemo (difference, 39.3%; 95% CI, 27.3-50.1). Unweighted differences in pCR and MPR rates between treatment arms were calculated using the Newcombe method. [a-g]95% CI: [a]19.9-40.7; [b]23.0-43.3; [c]0.3-7.9; [d]61-81; [e]35-58; [f]76-91; [g]56-75.

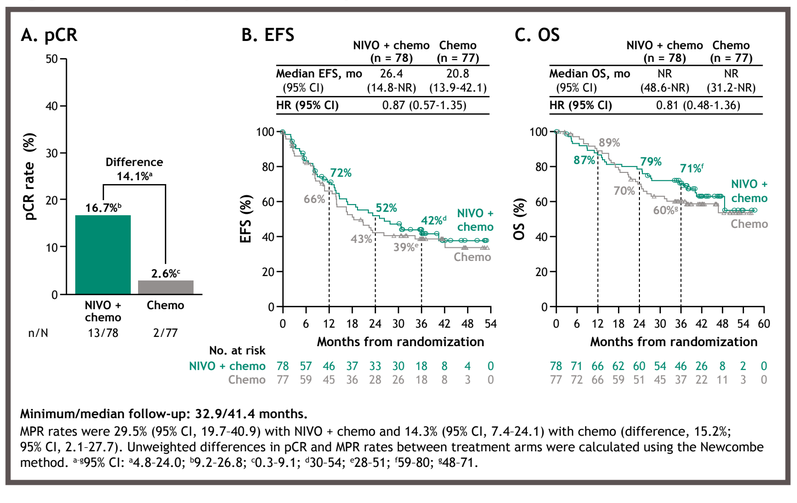
Figure 5. Efficacy outcomes in patients with tumor PD-L1 ≥ 1% and stage II-IIIA disease



Minimum/median follow-up: 32.9/41.4 months.

MPR rates were 45.7% (95% CI, 34.6-57.1) with NIVO + chemo and 5.8% (95% CI, 1.9-13.0) with chemo (difference, 39.9%; 95% CI, 27.3-51.2). Unweighted differences in pCR and MPR rates between treatment arms were calculated using the Newcombe method. [a-g]95% CI: [a]19.0-40.7; [b]22.2-43.4; [c]0.3-8.1; [d]59-80; [e]35-58; [f]74-90; [g]56-77.

Figure 6. Efficacy outcomes in patients with tumor PD-L1 < 1%



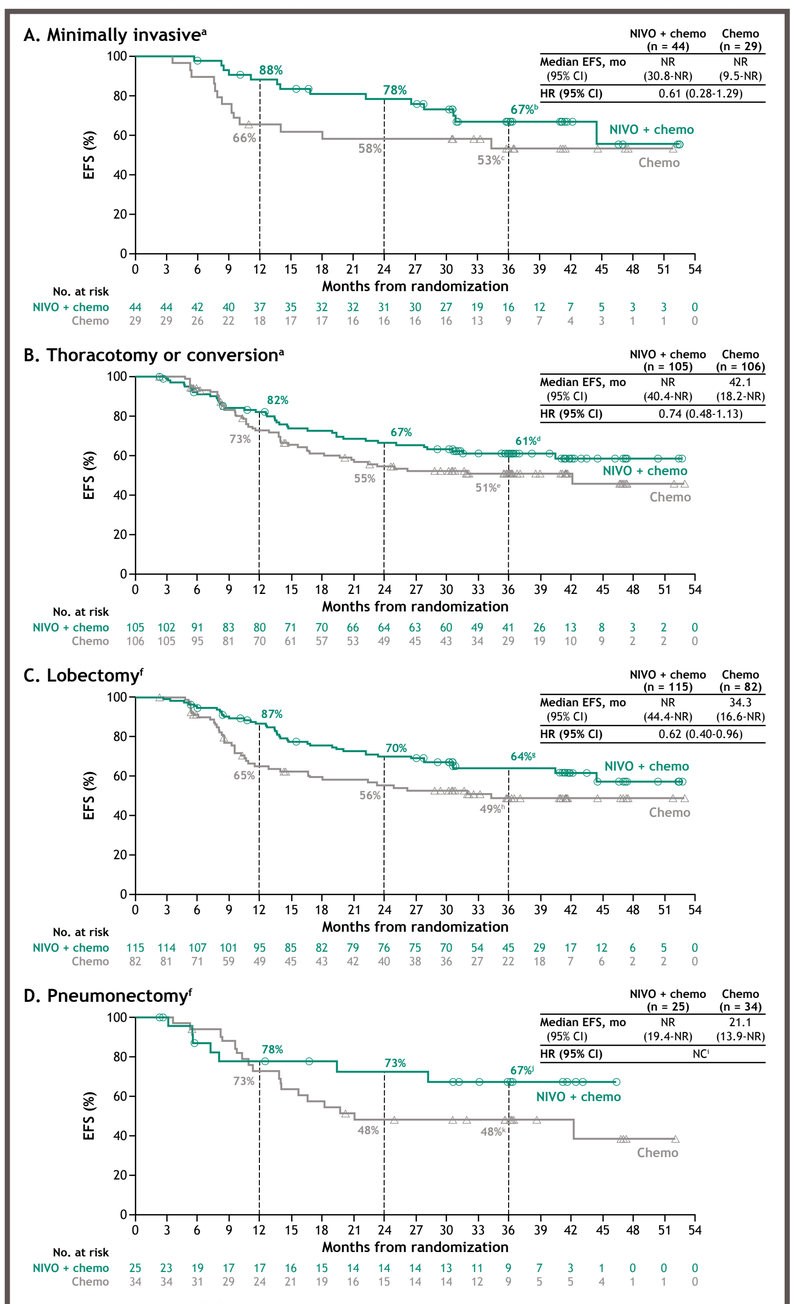
Minimum/median follow-up: 32.9/41.4 months.

MPR rates were 29.5% (95% CI, 19.7-40.9) with NIVO + chemo and 14.3% (95% CI, 7.4-24.1) with chemo (difference, 15.2%; 95% CI, 2.1-27.7). Unweighted differences in pCR and MPR rates between treatment arms were calculated using the Newcombe method. [a-g]95% CI: [a]4.8-24.0; [b]9.2-26.8; [c]0.3-9.1; [d]30-54; [e]28-51; [f]59-80; [g]48-71.

Efficacy by surgical approach

- NIVO + chemo improved EFS vs chemo in patients who had surgery, regardless of surgical approach or extent of resection (**Figure 7**)
- In patients with no residual tumor (R0 resection), 3-year EFS rates were 64% (95% CI, 55-72) vs 51% (95% CI, 40-60) for NIVO + chemo vs chemo, respectively (HR, 0.65; 95% CI, 0.43-0.98)
- Recurrence occurred in 28% and 42% of patients who had surgery in the NIVO + chemo (n = 149) and chemo arms (n = 135), respectively

Figure 7. EFS by surgical approach and extent of resection: 3-year update



Minimum/median follow-up: 32.9/41.4 months.

[a]Among patients with definitive surgery in the NIVO + chemo and chemo arms, respectively, 30% and 21% had minimally invasive surgery; 70% and 79% had thoracotomy or conversion. [b-e]95% CIs for 3-year EFS rates: [b]50-80; [c]33-70; [d]51-70; [e]40-61. [f]Patients may have had ≥ 1 type of surgery. In the respective NIVO + chemo and chemo arms, surgery types included lobectomy (77% and 61%) and pneumonectomy (17% [11 right; 14 left] and 25% [12 right; 22 left]); patients with R0 resection: 83% and 78%. [g,h]95% CIs for 3-year EFS rates: [g]54-72; [h]37-60. [i]HR was NC due to insufficient event numbers (< 10 per arm). [j,k]95% CIs for 3-year EFS rates: [j]43-83; [k]31-64.

Safety and surgical outcomes

- Among patients with tumor PD-L1 ≥ 1%, 84% underwent definitive surgery in the NIVO + chemo arm vs 74% of patients with chemo alone; among patients with tumor PD-L1 < 1%, 81% underwent definitive surgery in the NIVO + chemo arm vs 77% with chemo alone
- Grade 3-4 treatment-related adverse events (AEs) were reported in 36% vs 38% of patients in the NIVO + chemo vs chemo arms, respectively
- Grade 3-4 surgery-related AEs reported within 90 days after surgery occurred in 11% vs 15% of patients in the NIVO + chemo vs chemo arms, respectively
- Grade 5 surgery-related AEs (1 each due to pulmonary embolism and aortic rupture) were reported in 2 patients in the NIVO + chemo arm and were deemed unrelated to treatment
- Treatment-related deaths occurred in 3 patients in the chemo arm (pancytopenia, diarrhea, acute kidney injury [all in 1 patient], enterocolitis [n = 1], and pneumonia [n = 1])

Conclusions

- In this 3-year analysis from CheckMate 816, neoadjuvant NIVO + chemo showed long-term EFS benefit and favorable OS trend vs chemo in patients with resectable NSCLC
  - Benefit was seen regardless of surgical approach or extent of resection, and in patients with R0 resection
- Patients with a pCR had improved EFS and OS compared to those without, in both treatment arms
- A greater magnitude of benefit with NIVO + chemo vs chemo was seen for patients with tumor PD-L1 ≥ 1% compared to those with tumor PD-L1 < 1%
  - pCR rate: 32.6% vs 2.2% (PD-L1 ≥ 1%), 16.7% vs 2.6% (PD-L1 < 1%)
  - 3-year EFS rate: 72% vs 47% (PD-L1 ≥ 1%), 42% vs 39% (PD-L1 < 1%)
  - 3-year OS rate: 85% vs 66% (PD-L1 ≥ 1%), 71% vs 60% (PD-L1 < 1%)
- Neoadjuvant NIVO + chemo showed a manageable safety profile and did not impact the feasibility of surgery vs chemo alone, regardless of tumor PD-L1 expression
- These results reinforce the role of NIVO + chemo as a standard neoadjuvant treatment for eligible patients with resectable NSCLC and tumor PD-L1 ≥ 1% or PD-L1 < 1%

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