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Neoadjuvant PD-1 and PD-L1 Blockade With Chemotherapy for Borderline Resectable and Unresectable Stage III Non–Small Cell Lung Cancer

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IMPORTANCE Patients with borderline resectable or unresectable stage III non–small cell lung cancer (NSCLC) with T4 and/or N2-N3 involvement face limited treatment options and poor outcomes. Neoadjuvant chemoimmunotherapy has shown promise in improving resectability and pathological responses.

OBJECTIVE To evaluate the efficacy of neoadjuvant programmed cell death 1 protein (PD-1) or programmed cell death 1 ligand 1 (PD-L1) blockade combined with chemotherapy in enhancing surgical outcomes and pathological responses in patients with T4 and/or N2-N3 stage III NSCLC.

DESIGN, SETTING, AND PARTICIPANTS This multicenter cohort study analyzed data from patients treated between February 2018 and January 2024 with neoadjuvant PD-1/PD-L1 inhibitors plus chemotherapy at academic and tertiary care centers across the US and Italy. Pathological and survival outcomes were assessed. Patients with stage III NSCLC and T4 and/or N2-N3 involvement were included. Data were collected from February 2018 to January 2024.

EXPOSURES Neoadjuvant PD-1/PD-L1 blockade combined with platinum-based chemotherapy.

MAIN OUTCOMES AND MEASURES Pathological complete response (pCR), major pathological response, surgical resectability, and event-free survival (EFS).

RESULTS Of 112 patients, 58 (51.8%) were female, and the median (range) age was 66 (41-84) years. A total of 84(75.0%) underwent surgical resection, achieving a pCR rate of 29.0% (24 of 83 with available final pathology) and a major pathological response rate of 42.2% (35 of 83). Patients with both PD-L1 expression of 50% or more and high tumor mutational burden achieved the highest pCR rate (4 of 9 [44.4%]; $P = .03$). Conversely, covariants in *KRAS*/*STK11* or *KRAS*/*KEAP1* were associated with lack of pCR. Patients with single-station or multistation N2/N3 disease exhibited comparable pathological outcomes. The median EFS for all resected patients was 52.6 months (95% CI, 27.8 to not reached), and this was significantly longer in patients with pCR (not reached vs 27.8 months [95% CI, 19.5 to not reached]; $P < .001$).

CONCLUSIONS AND RELEVANCE In this study, neoadjuvant PD-1/PD-L1 blockade combined with chemotherapy resulted in high pathological response rates and surgical resectability in patients with T4 and/or N2-N3 stage III NSCLC. This approach offers a viable treatment option for patients with borderline resectable or unresectable NSCLC but requires further validation through prospective studies.

Supplemental content

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Stage III non-small cell lung cancer (NSCLC) with T4 and/or N2-N3 involvement remains a major clinical challenge due to extensive local invasion and high recurrence rates. While concurrent chemoradiotherapy followed by durvalumab (PACIFIC trial[1]) is standard for unresectable NSCLC, neoadjuvant chemoimmunotherapy offers an emerging alternative for borderline resectable stage III tumors. Recent trials (CheckMate 816 and 77T, AGEAN, KEYNOTE-671)[2-6] demonstrated that adding immune checkpoint inhibitors to chemotherapy significantly improves pathological complete response (pCR), event-free survival (EFS) in stage, and overall survival (OS) in stage II to III NSCLC. However, patients with T4 and/or N2-N3 disease often have worse outcomes and were underrepresented or excluded from these studies, and a recent EORTC-Lung Cancer Group survey across multiple societies showed no consensus on the resectability of this subset of patient.[7] This underscores the urgent need for robust clinical data on neoadjuvant immune checkpoint inhibitor–based approaches in this high-risk subgroup.

Here, we present a multicenter analysis of patients with T4 and/or N2-N3 NSCLC treated with neoadjuvant chemoimmunotherapy to address the current evidence gap for optimizing treatment in these challenging, locally advanced cases.

Key Points

Question Is neoadjuvant programmed cell death 1 protein (PD-1) or programmed cell death 1 ligand 1 (PD-L1) blockade combined with chemotherapy effective in borderline resectable or unresectable stage III non–small cell lung cancer (NSCLC)?

Findings In this cohort study including 112 patients with stage III NSCLC treated with neoadjuvant PD-1/PD-L1 inhibitors and chemotherapy, 75% underwent surgical resection; pathological complete response was achieved in 29%, with a major pathological response in 42.2%. The median event-free survival was 52.6 months for patients who underwent resection.

Meaning In this study, neoadjuvant PD-1/PD-L1 blockade combined with chemotherapy was associated with high resectability and pathological responses, offering a promising approach for selected patients with advanced stage III NSCLC.

Methods

This was an international, multicenter, retrospective study of patients with stage III (T4 and/or N2-N3) NSCLC who received neoadjuvant programmed cell death 1 protein (PD-1) or programmed cell death 1 ligand 1 (PD-L1) inhibitor plus chemotherapy at the Dana-Farber Cancer Institute, Boston, Massachusetts; Memorial Sloan Kettering Cancer Center, New York, New York; and Regina Elena Cancer Center, Rome, Italy. This study was approved by the Dana-Farber Cancer Institute Institutional Review Board, and patients provided written informed consent at each of the participating institutions prior to study entry. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and the Reporting Recommendations for Tumour Marker Prognostic Studies (REMARK) reporting guideline.

Patient Population

In this multicenter, retrospective cohort study, consecutive patients were included if they received treatment with neoadjuvant PD-1 inhibitors or PD-L1 inhibitors in combination with chemotherapy for stage III NSCLC and had baseline T4 and/or N2-N3 disease according to the *American Joint Committee on Cancer, eighth edition,* of the TNM staging system between February 2018 and January 2024. Patients at the Dana-Farber Cancer Institute who consented to institutional review board–approved protocols that allowed for conducting translational research and tumor next-generation sequencing were included. Patients at the Memorial Sloan Kettering Cancer Center and Regina Elena Cancer Center were included if they had received neoadjuvant chemoimmunotherapy for stage III NSCLC (T4 and/or N2-N3 disease) who consented to retrospective institutional review board–approved protocols. This study excluded stage IA-IIB and IIIA-IIIB disease that were not T4 and/or N2-N3 but included patients with stage IIIC or stage IIIB with N3 involvement, which were not included in landmark neoadjuvant or perioperative studies KEYNOTE-671, AGEAN, and CM816.[2-6] Data abstraction from electronic medical records was performed by 2 independent trained medical oncologists at each participating institution (Dana-Farber Cancer Institute: B.R. and E.G.; Memorial Sloan Kettering Cancer Center: A.C. and J.C.; Regina Elena Cancer Center: F.F. and F.C.).

Study Design and End Points

The primary end point of this study was the rate of pCR to neoadjuvant chemoimmunotherapy in patients with borderline resectable and unresectable NSCLC. Secondary end points included major pathological response (MPR) rate, and EFS. Exploratory analyses were conducted to correlate PD-L1 expression, tumor mutational burden (TMB), and covariants in *KRAS*, *STK11*, *KEAP1*, and *TP53* with pCR.

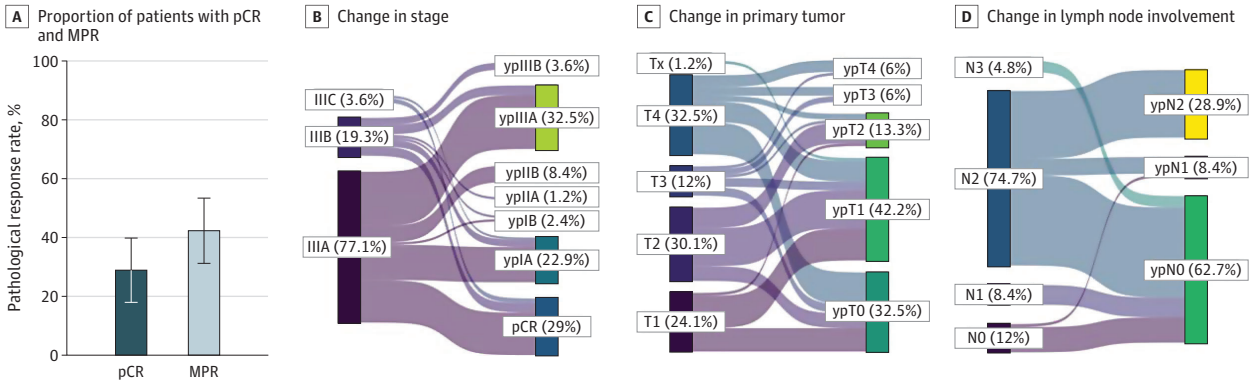
PD-1/PD-L1 Immunohistochemistry

The PD-L1 tumor proportion score (TPS) was determined by immunohistochemistry using validated anti-PD-L1 antibodies E1L3N (Cell Signaling Technology), 22C3 (Dako North America), 28-8 (Epitomics Inc), and SP263 (Roche Tissue Diagnostics) depending on local institutional practice.

Next-Generation Sequencing

NSCLC samples were sequenced by validated targeted exome sequencing platforms, including OncoPanel (Dana-Farber Cancer Institute) and MSK-IMPACT (Memorial Sloan Kettering Cancer Center), Oncomine (Thermo Fisher Scientific), and FoundationOne (Foundation Medicine), as previously described.[8-10] TMB distributions were harmonized between the 2 platforms, as previously described,[11] by applying a normal transformation followed by standardization in z scores. Clinical outcomes were examined according to TMB and *STK11*, *KEAP1*, *TP53*, and *KRAS* variant status based on previous evidence indicating significant predictive and prognostic impact of these covariant patterns on immunotherapy efficacy.[12,13]

Figure 1. Pathologic Response to Neoadjuvant Chemoimmunotherapy in Patients With Borderline Resectable and Unresectable Stage III Non–Small Cell Lung Cancer



A, Proportion of patients with pathological complete response (pCR) and major pathological response (MPR) among patients who underwent neoadjuvant chemoimmunotherapy followed by surgical resection. B-D, Sankey diagrams showing changes in stage (B), primary tumor (C), and lymph node involvement (D) before and after neoadjuvant chemoimmunotherapy followed by surgery. Error bars indicate 95% CIs.

Clinical Outcomes Assessment

The objective response rate (ORR) and EFS were determined by a dedicated thoracic radiologist (Dana-Farber Cancer Institute: M.N.; Memorial Sloan Kettering Cancer Center: M.M.P. and M.G.; Regina Elena Cancer Center: F.F.) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at each of the participating institutions. EFS was defined as the time from PD-1 inhibitor or PD-L1 inhibitor plus chemotherapy start to recurrence or death; for those without progression, censoring was done at the time of the last disease assessment scan showing no evidence of recurrence. OS was calculated from the time of start of neoadjuvant chemoimmunotherapy to death. Patients who were still alive at the time of data analysis were censored at the date of last contact. Pathological outcomes were reviewed by a dedicated thoracic pathologist at each participating institution. Mediastinal staging was performed using endobronchial ultrasonography and mediastinoscopy, according to local practice. For patients who were not candidates for invasive mediastinal staging, positron emission tomography/computed tomography was used to determine nodal involvement.

Statistical Analysis

Fisher exact or χ^2 tests were used for categorical data, Wilcoxon tests for continuous variables, and Kaplan-Meier analyses with log-rank testing for time-to-event distributions. Cox regression was used to assess hazard ratios (HRs). 95% CIs for proportions were estimated using the Clopper-Pearson method. Log-rank tests were used to test for differences in event-time distributions, and Cox proportional hazards models were fitted to obtain estimates of HRs in univariate and multivariable models after adjusting for potential confounders. The Firth penalized likelihood method was used to adjusts for small sample sizes and separation bias. All *P* values were 2-sided, and confidence intervals were at the 95% level, with significance predefined to be at $P < .05$. All analyses were conducted using R version 4.0.3 (The R Foundation).

Results

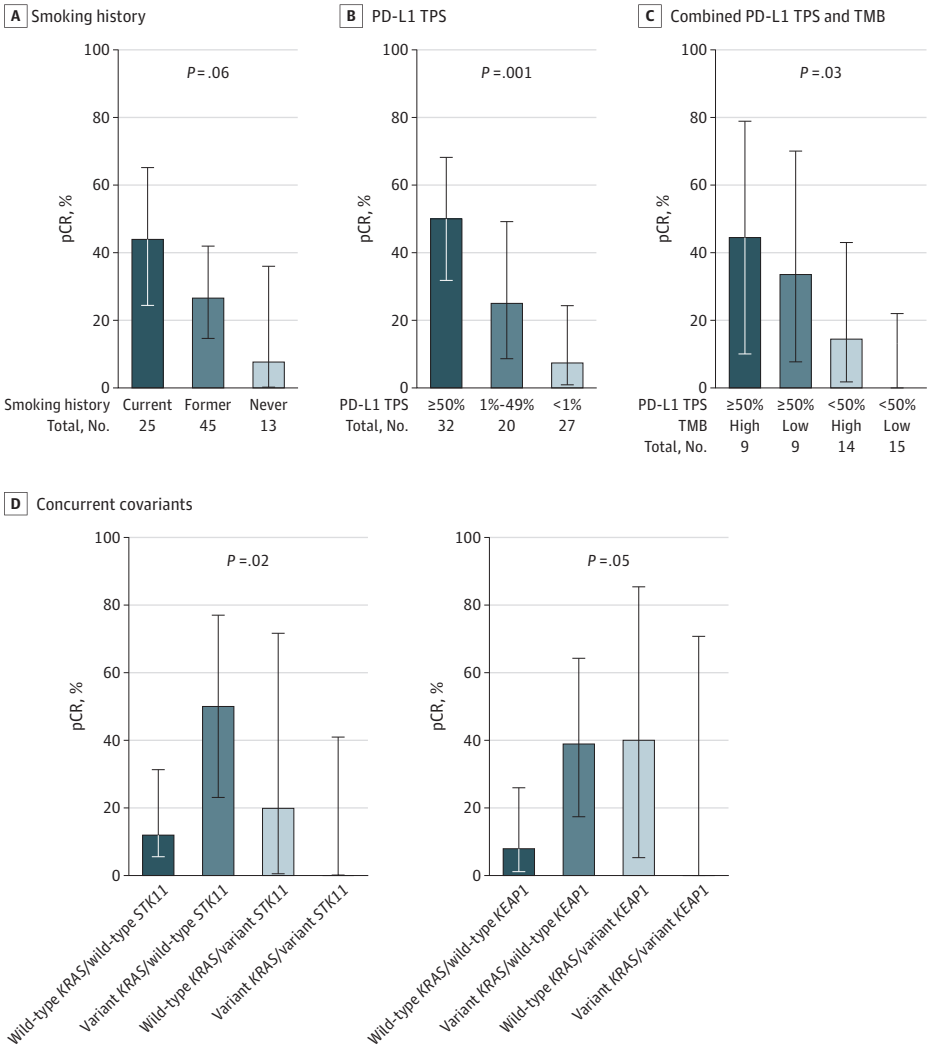
Patient Characteristics

Of 112 patients with stage III NSCLC (T4 and/or N2-N3) who received neoadjuvant or perioperative PD-1 or PD-L1 plus chemotherapy, the median (range) age was 66 (41-84) years, 58 (51.8%) were women, 78 (70.3%) had an Eastern Cooperative Oncology Group Performance Status score of 0, 99 (88.4%) had a history of tobacco use, and 76 (67.9%) had adenocarcinoma. The median (range) PD-L1 TPS was 10% (0-100), and 43 (41.7%) had a TPS of 50% or greater. Overall, 79 (70.5%) had stage IIIA, 27 (24.1%) had stage IIIB, and 6 (5.4%) had stage IIIC NSCLC, with 40 (35.7%) exhibiting T4, 78 (69.6%) exhibiting N2, and 11 (9.8%) exhibiting N3 disease. A total of 84 (75.0%) proceeded to surgery. Baseline characteristics of these patients, including TNM staging, are shown in eTables 1 to 3 in Supplement 1.

Pathological Outcomes With Neoadjuvant PD-1/PD-L1 Blockade in Combination With Chemotherapy

Among all patients who received neoadjuvant chemoimmunotherapy, the ORR was 59.4% (66 of 111 evaluable patients; eFigure 3A in Supplement 1). Patients who underwent surgery after neoadjuvant chemoimmunotherapy had a higher ORR compared with those who did not undergo surgical resection (67.5% [56 of 83] vs 35.7% [10 of 28]; $P = .003$) (eFigure 3B in Supplement 1). Baseline feature of patients who completed vs did not complete surgery are shown in eTable 4 in Supplement 1. A waterfall plot showing the depth of response in this cohort is shown in eFigure 3C in Supplement 1. Most patients underwent a lobectomy (60 of 83 evaluable patients [72.3%]), while some underwent a bilobectomy (5 of 83 [6.0%]) or a pneumonectomy (6 of 83 [7.2%]; eTable 5 in Supplement 1). The median (range) number of lymph nodes resected was 17 (2-64). A total of 80 patients (96.4%) achieved R0 resections, while only 2 (2.4%) and 1 (1.2%) had R1 and R2 resections, respectively (eTable 5 in Supplement 1).

Figure 2. Clinicopathologic and Genomic Correlates of Pathological Complete Response (pCR) in Borderline Resectable and Unresectable Stage III Non–Small Cell Lung Cancer



Clinical and pathological correlates of pCR with smoking history (A) and clinically relevant cutoffs of programmed cell death 1 ligand 1 (PD-L1) tumor proportion score (TPS) (B) as well as genomic correlates of pCR with combined PD-L1 and tumor mutational burden (TMB) (C) and concurrent *KRAS*/*STK11* and *KRAS*/*KEAP1* (D). Error bars indicate 95% CIs.

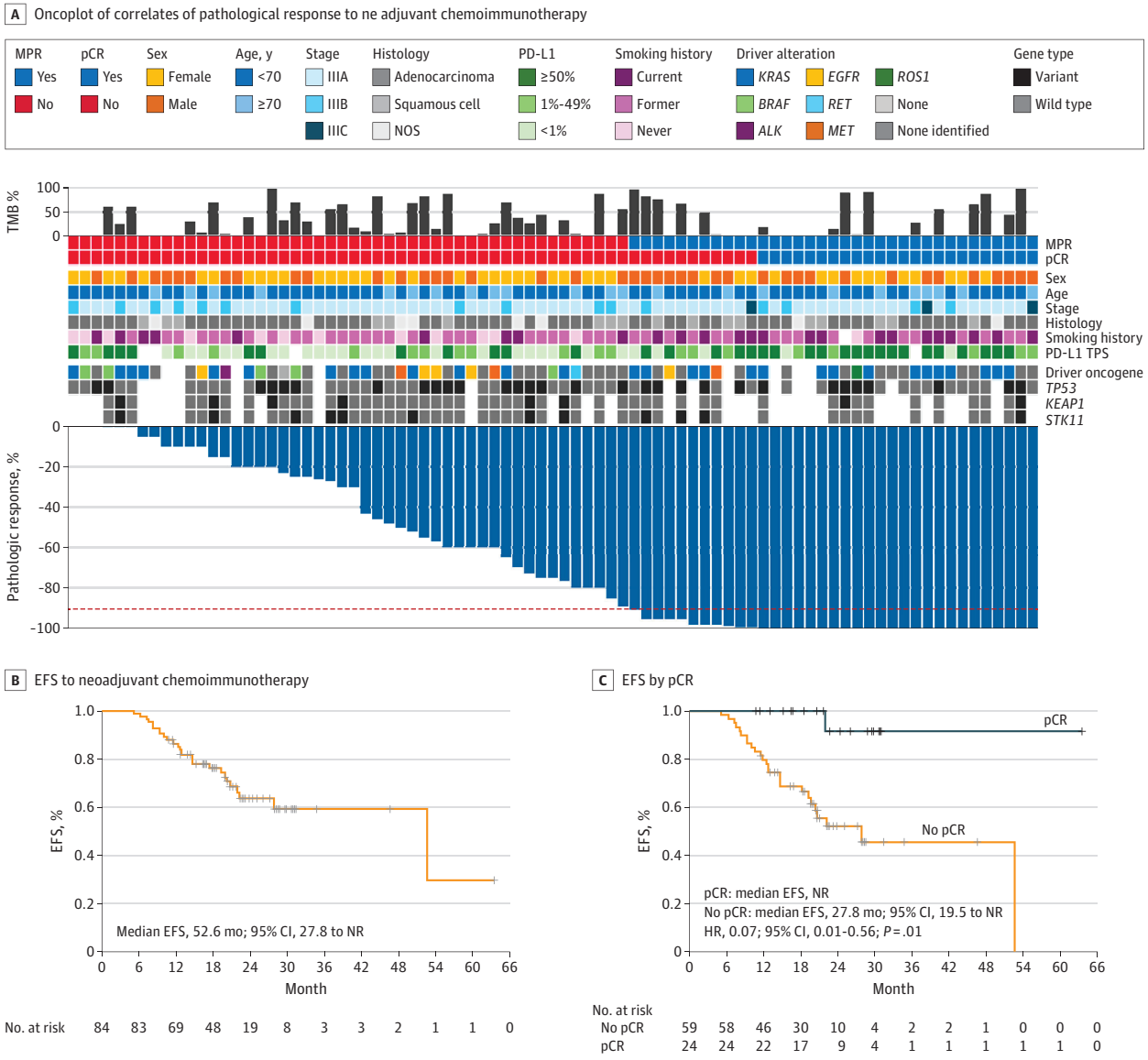
Of patients who successfully completed surgery, the pathological pCR rate was 29.0% (24 of 83 evaluable patients), while 42.2% (35 of 83) achieved an MPR (**Figure 1**A). Although radiologic and pathological responses were moderately correlated (R = 0.45; P < .01), a subset of patients achieving pCR did not show radiologic complete response or partial response, indicating that imaging may underestimate the true depth of pathological response (eFigure 4 in Supplement 1).

In examining pathological outcomes, 27 patients (32.5%) had a complete response in the primary tumor (ypT0), 35 (42.2%) had a ypT1, and 11 (13.3%) had a ypT2. Only 5 (6.0%) had a ypT3 and ypT4, indicating significant downstaging of the T parameter after neoadjuvant chemoimmunotherapy (eTable 6 in Supplement 1). Similarly, 52 patients (62.7%) had a pathological N0 (ypN0), 7 (8.4%) had an ypN1, and 24 (28.9%) had an ypN2. All patients with N3-positive lymph nodes achieved a ypN0. Sankey diagrams showing detailed changes in stage, T classification, and N classification before neoadjuvant chemoimmunotherapy vs after surgery are shown in Figure 1B-D. Key subgroup analysis showed no association between age, sex, Eastern Cooperative Oncology Group Performance Status score, histology, type of platinum, and pCR (eFigure 5 in Supplement 1). Only 4 patients received chemotherapy plus a PD-L1 inhibitor, with a pCR of 25% (1 of 4); 79 patients received chemotherapy plus PD-1/PD-L1 blockade, with a pCR of 29.1% (23 of 79). pCR rates were higher in current smokers compared with former and never smokers (11 of 25 [44.0%] vs 12 of 45 [26.6%] and 1 of 13 [7.6%], respectively; P = .06) (**Figure 2**A), while there was no difference in pCR between patients with single-station N2 disease and those with multistation N2 or N3 involvement (9 of 34 [26.4%] vs 7 of 24 [29.1%]; P = .99) (eFigure 5 in Supplement 1).

Impact of PD-L1 Expression, TMB, and Covariant Status on pCR

We next analyzed the impact of PD-L1 expression and cancer genomics on pCR rates. Median (range) PD-L1 expression was significantly higher among patients who achieved a pCR compared with those who did not (60% [0-100] vs 4% [0-100];

Figure 3. Overview of the Clinicopathologic and Genomic Determinants of Complete Pathologic Response (pCR) and Major Pathological Response (MPR) and Survival Outcomes With Neoadjuvant Chemoimmunotherapy in Borderline Resectable and Unresectbale Stage III Non–Small Cell Lung Cancer



A, Oncoplot showing the clinicopathological and genomic correlates of pathological response to neoadjuvant chemoimmunotherapy. B, Event-free survival (EFS) to neoadjuvant chemoimmunotherapy among patients with T4 and/or N2-3 non–small cell lung cancer who completed surgical resection. C, EFS according to pCR. HR indicates hazard ratio; NOS, not otherwise specified; NR, not reached; PD-L1, programmed cell death 1 ligand 1; TMB, tumor mutational burden; TPS, tumor proportion score.

P = .002) (eFigure 6 in Supplement 1). In examining clinically relevant PD-L1 subgroups, we noted a pCR of 50% (16 of 32) for patients with a PD-L1 TPS of 50% or greater, 25% (5 of 20) among those with a PD-L1 of 1% to 49%, and 7.4% (2 of 27) in patients with PD-L1 less than 1% (*P* = .001) (Figure 2B). By contrast, there was no significant association between TMB (harmonized across platforms) and pCR in this cohort (eFigure 6 B-C in Supplement 1), possibly reflecting the relatively low number of patients with available TMB (66 of 112 [58.9%]). In a combined analysis of PD-L1 (50% or greater vs less than 50%) and TMB (50th percentile or greater vs less than 50th percentile), patients with both high PD-L1 and high TMB achieved the highest pCR rate (4 of 9 [44.4%]), followed by high PD-L1 with low TMB (3 of 9 [33.3%]), low PD-L1 with high TMB (2 of 14 [14.3%]), and low PD-L1 with low TMB (0 of 15; *P* = .03) (Figure 2C). While *KRAS*, *STK11*, *KEAP1*, and *TP53* variants alone did not significantly affect pCR rates (eFigure 7 in Supplement 1), the pCR rate was 0% in patients harboring concurrent *KRAS*/*STK11* or *KRAS*/*KEAP1* variants (Figure 2D), while *KRAS*/*TP53* covariants did not impact pCR (eFigure 8 in Supplement 1). These findings highlight the importance of integrating PD-L1 and TMB for more precise pCR prediction and

identify concurrent *KRAS*/*STK11* or *KRAS*/*KEAP1* variants as key predictors of resistance to neoadjuvant chemoimmunotherapy in locally advanced NSCLC (**Figure 3**A).

EFS and OS After Neoadjuvant Chemoimmunotherapy

At a median follow-up of 23.0 months (95% CI, 21.1-24.7), patients who underwent resection had a median EFS of 52.6 months (95% CI, 27.8 to not reached) (Figure 3B), while the median OS was not reached (eFigure 9A in Supplement 1). EFS was significantly longer in those achieving pCR (not reached vs 27.8 months [95% CI, 19.5 to not reached]; HR, 0.07; 95% CI, 0.01-0.56; $P = .009$) (Figure 3C) or MPR (not reached vs 22.2 months [95% CI, 14.7 to not reached]; HR, 0.16; 95% CI, 0.05-0.57; $P < .001$) (eFigure 9B in Supplement 1). pCR and MPR were independent predictors of longer EFS in multivariable analysis (eFigure 10 in Supplement 1). OS was not reached in either group (eFigure 11 in Supplement 1).

Among 28 patients (25.0%) who did not undergo surgery, the primary reasons were unresectability without progression (18 [64.2%]), operability issues (5 [17.8%]), disease progression (4 [14.3%]), and patient preference (1 [3.5%]). Most (20 [71%]) received definitive or concurrent chemoradiotherapy plus durvalumab, while 2 received systemic therapy and 6 had no additional treatment. Notably, EFS and OS were significantly longer in patients who underwent surgical resection after neoadjvaunt immunotherapy vs those who did not (EFS: HR, 0.36; 95% CI, 0.19-0.68; $P = .001$; OS: HR, 0.33; 95% CI, 0.13-0.81; $P = .01$) (eFigure 12 in Supplement 1).

Discussion

Our findings show that neoadjuvant PD-1/PD-L1 blockade combined with chemotherapy can significantly improve outcomes in patients with locally advanced T4 and/or N2-N3 NSCLC, a population frequently underrepresented or excluded from clinical trials. The robust pCR (24 of 83 [29.0%]) and MPR (35 of 83 [42.2%]) rates align with data from large-scale studies (CheckMate 816, AGEAN, KEYNOTE-671, NADIM II)[2-6,14] that established chemoimmunotherapy as a new standard for earlier-stage disease. Importantly, these results indicate that neoadjuvant immunotherapy can facilitate successful surgical resections and long-term disease control in a subset of patients previously considered borderline resectable or unresectable.

We observed a median EFS of 52.6 months (95% CI, 27.8 to not reached), which, while not directly comparable with the PACIFIC trial (16.8 months PFS at first interim analysis),[1] is nonetheless encouraging for this high-risk group. Taken together, our data suggest that neoadjuvant chemoimmunotherapy could challenge the traditional treatment paradigm of concurrent chemoradiotherapy followed by consolidation immunotherapy in T4 and/or N2-N3 disease. However, optimal patient selection remains crucial and should involve a multidisciplinary team to evaluate resectability and potential benefit on a case-by-case basis.

In exploratory analyses, higher PD-L1 expression was strongly correlated with greater likelihood of pCR. Combining PD-L1 and TMB further enriched for responders, underscoring the need for orthogonal biomarker approaches. Additionally, covariants such as *KRAS*/*STK11* and *KRAS*/*KEAP1* were associated with reduced sensitivity to chemoimmunotherapy, consistent with emerging data in metastatic NSCLC,[12,13,15,16] although these results should be interpreted with caution given the limited number of cases.

Limitations

This study has some limitations to acknowledge, including the retrospective design and the relatively limited sample size of patients with genomic profiling and TMB, which did not allow additional subgroup analysis. In addition, while invasive mediastinal staging was performed in most of these patients, a fraction had only a positron emission tomography/computed tomography as staging imaging. However, this reflects real-world practice.

Conclusions

These results provide a rationale for further prospective investigation and support neoadjuvant chemoimmunotherapy as a potential option in borderline resectable or unresectable stage III NSCLC.

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Author Contributions: Drs Ricciuti and Cappuzzo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ricciuti, Fusco, and Cooper served as co–first authors. Drs Chaft, Awad, and Cappuzzo served as co–senior authors.
Concept and design: Ricciuti, Fusco, Cooper, Garbo, Nishino, Bott, Ramella, Minuti, Cappuzzo.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ricciuti, Cooper, Pecci, Nishino, Bott, Santo, Gallina, Landi, Ugalde Figueroa, Cappuzzo.
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Data Sharing Statement: See Supplement 2.

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