MSR63

Target Trial Emulation (TTE) Informed by Clinical Trial Data: Adjuvant Nivolumab vs Observation in Patients with Resectable Non-Small Cell Lung Cancer (rNSCLC) after Neoadjuvant Nivolumab Plus Chemotherapy and Surgery

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- In CheckMate 816, neoadjuvant nivolumab plus chemotherapy (neoNIVO+CT) improved event-free survival (EFS) and overall survival in patients with rNSCLC[1]
- CheckMate 77T extended immunotherapy (IO) into the adjuvant setting, continuing nivolumab after surgery[2]
- Despite this, the benefit of adjuvant nivolumab (adjNIVO) among patients who received neoNIVO+CT and surgery remains unclear
- Randomized controlled trials (RCTs) directly comparing adjuvant IO to observation among patients with rNSCLC who received neoadjuvant IO plus chemotherapy and surgery have been designed and are underway (e.g., Adopt-LUNG)[3]
- However, there is a need for interim evidence to guide clinical decision-making in this setting

Objective

To estimate the effect of adjNIVO versus observation on EFS after neoNIVO+CT and surgery in rNSCLC, overall and in target subpopulations defined by response outcomes defined at surgery (major pathologic response [MPR], and pathologic complete response [pCR]), by disease stage, and by PD-L1 expression at diagnosis (expressors vs non-expressors)

Study design and data sources

- This study employed a causal inference framework using TTE with clone-censor-weighting (CCW)[4]
- TTE applies the design principles of a hypothetical randomized trial to observational or secondary data sources, using methods such as CCW to reduce bias and approximate randomized comparisons[5]
- The TTE was informed by individual patient data (IPD) from the intervention arms of CheckMate 816 and CheckMate 77T (combined median follow-up of 40.9 months).
- The target trial could not be emulated precisely due to data limitations. In particular, the TTE estimated the effect of initiating adjNIVO at any time after surgery with the date of surgery (as opposed to the date of adjNIVO start) as time zero (**Figure 1**)

Figure 1. Specification of the target trial

	Target trial	Emulated trial using CheckMate data
Eligibility	• rNSCLC stage II-IIIB(N2) • Received 3-4 doses of neoNIVO+CT & definitive surgery • Progression or recurrence-free post-surgery; no unresolved toxicity/complications • No brain metastases; ECOG PS ≤1; EGFR/ALK-	• Same as target trial, except progression or recurrence during surgical recovery is counted as an outcome, and unresolved toxicity/ complications are addressed through statistical adjustment
Treatment strategies	1. ≥1 cycle adjNIVO* 2. Observation*	• *Same as target trial*
Assignment procedures	• Randomized at baseline	• Adjusted for baseline covariate differences between CheckMate 77T and CheckMate 816
Time zero	• Time at which patients are eligible for adjNIVO post-surgery (≥25 days from surgery)	• Date of surgery
Follow-up	• Up to five years from randomization or loss to follow-up	• *Same as target trial*
Outcomes	• EFS (DFS)†	• EFS per BICR (DFS)†
Casual contrasts	• Intent-to-treat effect	• Emulated effect of initiating adjNIVO at any time • Sensitivity : effect of initiating adjNIVO 30-90 days from surgery

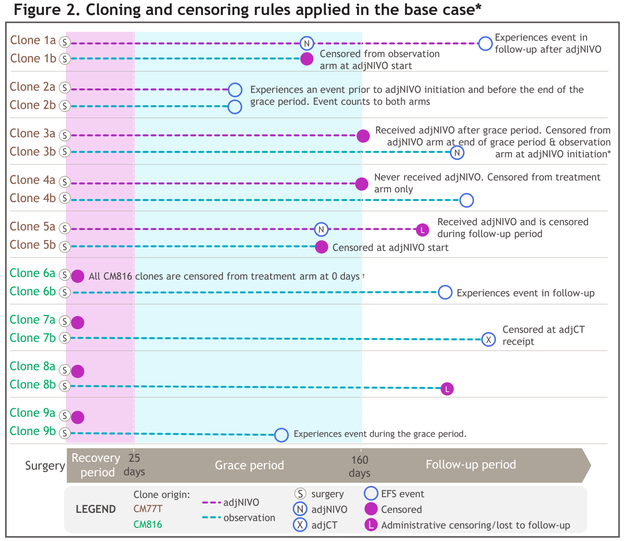
Abbreviations: adjNIVO, adjuvant nivolumab; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; N2, nodal status 2
Notes: * Adjuvant chemotherapy not allowed. † Consistent with the definition used in the source trials CheckMate 816 and CheckMate 77T. However, it should be noted that in studies enrolling patients after surgery, the relevant outcome is disease-free survival (DFS), which excludes pre-operative events.

Methods

Emulation approach: Clone-Censor-Weight

- **Cloning:** Each patient was duplicated (i.e., cloned) and assigned to both treatment strategies at time zero (the date of surgery)
- **Censoring:** Clones were artificially censored when their observed treatment deviated from the assigned strategy (**Figure 2**).
- **Weighting:** Inverse probability of censoring weights (IPCW) were estimated at 5-day intervals to adjust for potential bias due to informative censoring

Figure 2. Cloning and censoring rules applied in the base case*



Abbreviations: adjCT, adjuvant chemotherapy; adjNIVO, adjuvant nivolumab; CM77T, CheckMate 77T; CM816, CheckMate 816; EFS, event-free survival; tx, treatment
Notes: * Patients from CheckMate 77T initiated adjNIVO at different times after surgery, or not at all, so all patients contributed at least some time to both adjNIVO and observation. Only one patient started adjNIVO after the end of the grace period (246 days after surgery). † As treatment assignment was known at time zero for all patients in CheckMate 816, they did not contribute any time to the adjNIVO strategy (i.e., adjNIVO clones from CheckMate 816 were censored at time zero)

Statistical analysis

- Two separate weights models were run to account for censoring due to:
  1. Lack of adjNIVO initiation (fitted to CheckMate 77T data), and
  2. Initiation of adjuvant chemotherapy (adjCT) (fitted to CheckMate 816 data)
- Patients' overall health (EQ-5D visual analogue score [VAS]) and adverse event (AE) burden were included as time-varying in the IPCW models. AE burden was calculated overall over the past 30 days and decomposed into non-endocrine immune-mediated AE (IMAE) burden and surgical-complication AE (SCAE) burden
- Covariates included in the model for adjNIVO initiation (associated with both adjNIVO initiation and EFS) were surgery type, resection status, MPR, EQ-5D VAS, non-endocrine IMAE burden, and SCAE burden
- Covariates included in the model for adjCT initiation (associated with both adjCT initiation and EFS) were race, resection status, MPR, EQ-5D VAS, and overall AE burden
- EFS hazard ratios (HRs) were estimated using an IPCW-adjusted pooled logistic regression fitted to the cloned dataset. Baseline adjustment covariates included PD-L1 expression, stage at RCT baseline, MPR, sex, age, race, surgery type, resection status, EQ-5D VAS, non-endocrine IMAE burden, and SCAE burden
- Subgroup results were generated for PD-L1 expression, stage at RCT baseline, MPR, and pCR by adding treatment-by-covariate interactions into the model.
- The baseline hazard was modeled using a restricted cubic spline of time.
- 95% confidence intervals (CIs) were obtained via bootstrapping (1,000 iterations)
- Sensitivity analyses were conducted to test the robustness of the findings to choices in time zero, eligibility, weighting, censoring, model specification, endpoint ascertainment, and adverse event burden.

Results

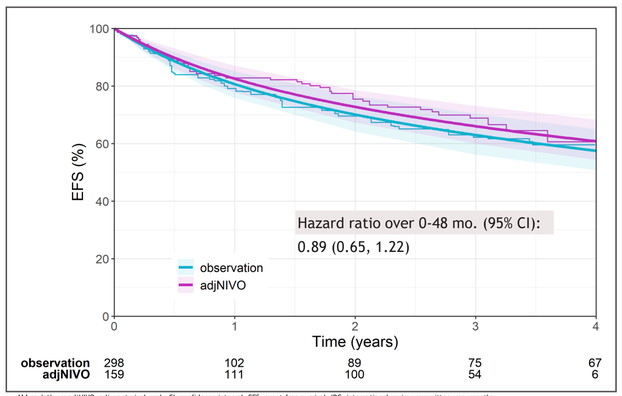
Table 1. Baseline characteristics

	Overall (n = 457)	Observation (n = 298)	adjNIVO (n = 159)
Age, mean (SD)	63.8 (7.7)	63.8 (7.7)	63.8 (7.9)
Age ≥ 65 years	232 (50.8)	149 (50.0)	83 (52.2)
Male, n (%)	338 (74.0)	217 (72.8)	121 (76.1)
Asian race, n (%)	160 (35.0)	115 (38.6)	45 (28.3)
PD-L1 expression level at RCT baseline, n (%)			
< 1% or NE	207 (45.3)	139 (46.6)	68 (42.8)
≥ 1%	250 (54.7)	159 (53.4)	91 (57.2)
Stage at RCT baseline, n (%)			
IB-II	159 (34.8)	105 (35.2)	54 (34.0)
III	298 (65.2)	193 (64.8)	105 (66.0)
MPR, n (%)	209 (45.7)	135 (45.3)	74 (46.5)
pCR, n (%)	146 (31.9)	93 (31.2)	53 (33.3)
Resection status, n (%)			
R0/RX	401 (87.7)	260 (87.2)	141 (88.7)
R1/R2	56 (12.3)	38 (12.8)	18 (11.3)
EQ-5D VAS score (last measured value prior to surgery)*			
mean (SD)	78.3 (16.9)	79.5 (16.5)	76.2 (17.4)
median (range)	80 (0, 100)	85 (0, 100)	80 (6, 100)
Surgery type, n (%)			
Pneumonectomy	51 (11.2)	36 (12.1)	15 (9.4)
Lobectomy	363 (79.4)	237 (79.5)	126 (79.2)
Other	43 (9.4)	25 (8.4)	18 (11.3)

Abbreviations: adjNIVO, adjuvant nivolumab; EQ-5D VAS, EuroQol 5-dimension visual analogue scale; MPR, major pathological response; NE, not evaluable; PCR, pathological complete response; PD-L1, programmed death-ligand 1; R0, complete resection; R1, resection with microscopically positive margins; R2, resection with macroscopically positive margins; RCT, randomized controlled trial; Rx, resection status unknown/cannot be assessed; SD, standard deviation
Notes: *Two patient-clones assigned to the observation strategy were missing EQ-5D VAS score

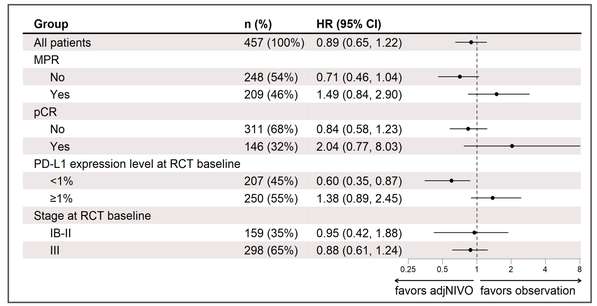
- Of 327 patients from CheckMate 816 and CheckMate 77T who received neoNIVO+CT and underwent definitive surgery, 298 were eligible for inclusion. Of the 298, 159 were from CheckMate 77T and contributed person-time to both adjNIVO and observation strategies
- Baseline characteristics of patients contributing person-time to adjNIVO and observation strategies were comparable, except for the proportion of Asian patients (~10% difference) (**Table 1**)
- Among patients who had received neoNIVO+CT followed by definitive surgery, the estimated benefit of adjNIVO initiation on EFS was modest (HR: 0.89; 95% CI: 0.65, 1.22) and did not reach statistical significance. (**Figure 3**)
- Point estimates favored adjNIVO in poorer prognosis subgroups (patients without pCR, without MPR, PD-L1 <1%, and III), though the largest and only statistically significant benefit was observed in the PD-L1 <1% subgroup (HR 0.60, 95% CI 0.35-0.87) (**Figure 4**)
- Point estimates favored observation in higher prognosis subgroups (patients with pCR, with MPR, and PD-L1 ≥1%) except for stage IB-II, though these estimates were not statistically significant (**Figure 4**)
- Across sensitivity analyses, the estimated hazard ratio for EFS in the overall population ranged from 0.82 to 0.97, suggesting robustness of the findings to various modeling choices

Figure 3. EFS curves standardized to baseline covariate distribution*



Abbreviations: adjNIVO, adjuvant nivolumab; CI, confidence interval; EFS, event-free survival; IRC, international review committee; mo, months
Notes: * 95% confidence bands of the EFS curves and weighted Kaplan Meier curves are also shown.

Figure 4. Subgroup analysis of EFS: adjNIVO vs observation



Abbreviations: adjNIVO, adjuvant nivolumab; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; MPR, major pathological response; pCR, pathological complete response; PD-L1, programmed death-ligand 1; RCT, randomized controlled trial

Discussion

- This exploratory TTE analysis leveraging IPD from two RCTs aimed to inform clinical decision-making following neoNIVO+CT and surgery for patients with rNSCLC
- After adjustment for prognostic and treatment-effect modifying baseline characteristics and time-varying confounders believed to influence the likelihood and timing of adjNIVO initiation, the estimated EFS benefit of adjNIVO in this patient population was modest overall
- Subgroup analysis by PD-L1 expression indicated a statistically significant adjNIVO benefit among patients with PD-L1<1%. All other subgroups were not statistically significant, with poorer prognosis subgroups generally trending in favor of adjNIVO and better prognosis subgroups generally trending in favor of observation. However, most subgroup estimates were associated with high uncertainty, particularly better prognosis subgroups
- The methodological contribution of this study lies in the novel application of TTE, a bias-reduction framework developed for observational research, to RCT data, demonstrating its broader utility for strengthening analyses of comparative effectiveness across study designs

Limitations

- The use of RCT data imposed sample size constraints, particularly for subgroup analyses, which had limited statistical power and resulted in imprecise estimates
- A target trial randomizing patients after surgical recovery could not be emulated due to data limitations. The analysis therefore included patients with early postoperative complications or disease progression which would have been excluded from the target trial. Still, the relative treatment effect was assumed to be similar in the target and emulated trials, in absence of strong effect modification by postoperative health status
- The two CheckMate trials differed in the number of neoadjuvant treatment cycles. Results are therefore only interpretable to the extent that 3 versus 4 cycles of neoadjuvant treatment is not believed to be a strong cause of post-surgical EFS
- The outcome model assumed a constant treatment effect over time, as fitting a time by treatment interaction was infeasible due to data limitations

Conclusions

Initiating adjNIVO after neoNIVO+CT and surgery may improve EFS among high unmet need patient subgroups, including those with PD-L1<1% at baseline, or with no MPR or pCR

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