CO202

Real-World (rw) Early Clinical Endpoints for Patients with Resectable Non-Small Cell Lung Cancer (NSCLC): A Database Evaluation Study

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Background

- The options for neoadjuvant and adjuvant systemic therapy for surgically resectable NSCLC are rapidly expanding[1]
- In the United States (US), 3 immune checkpoint inhibitors (ICI) have recently been approved for perioperative administration in combination with platinum-based chemotherapy as neoadjuvant therapy before NSCLC resection and as a single agent for adjuvant therapy postoperatively
- Perioperative pembrolizumab received US regulatory approval for resectable NSCLC in October 2023 based on KEYNOTE-671 (KN671) clinical trial results,[2,3] followed by perioperative durvalumab in August 2024 based on the AEGEAN trial[4] and perioperative nivolumab in October 2024 based on the CheckMate 77T (CM-77T) trial[5]
- Clinical trials are conducted to maximize internal validity, with selective patient populations and under idealized procedures that may differ from the heterogeneous populations and the time and economic constraints encountered in real-world oncology practice
- The need for real-world evidence, in addition to clinical trial findings, is by now well accepted[6]
- With the rapid, continuing advances in perioperative therapy for resectable NSCLC, there is a need to evaluate early clinical endpoints in real-world datasets that are analogous to clinical trial endpoints in order to benchmark the outcomes in real-world settings with newer standards of care, ie, the ICIs

Objectives

- To develop database-derived early clinical endpoints for resectable NSCLC and to evaluate how closely real-world data and associated approaches approximate control arm findings in pivotal perioperative ICI trials

Methods

Study design

- Retrospective cohort study
- Data source: Syapse Learning Health Network, Enriched Lung Cohort, a longitudinal database integrating multiple sources of patient care information at US community practices, including cancer registries, electronic medical records, laboratory reports, and external sources, enriched with manual abstraction

Patients

- Adult patients (≥18 years old) with a first NSCLC diagnosis from January 1, 2000, to June 30, 2022
  - Clinical stage II/IIIA/IIIB(T3-4N2) NSCLC, according to the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, 8th edition (AJCC-8), *or*
  - Clinical stage IB/II/IIIA NSCLC by AJCC-7
- With Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or unknown
- Who had received neoadjuvant cisplatin- or carboplatin (ie, platinum)-based chemotherapy
- Excluded: Patients participating in a clinical trial or with other primary cancer within 5 years, unknown surgical history, or prior ICI therapy
- Patients were followed through December 31, 2023

Endpoints

1. Real-world major pathologic response (rwMPR), defined as ≤10% residual viable tumor in resected tissue, as derived from pathology reports and/or clinician's notes:
   - Post-therapy pathology report indicates ≤10% residual viable tumor
   - Clinician statement indicates that patient achieved MPR or ≤10% residual viable tumor
   - MPR is not explicitly mentioned but the patient had pCR1 or pCR2
2. Pathologic complete response (rwpCR), defined as no residual invasive carcinoma in resected tissue (ypT0/Tis ypN0), as derived from pathology reports and/or clinician's notes recording complete response or pCR with in situ disease

Statistical analysis

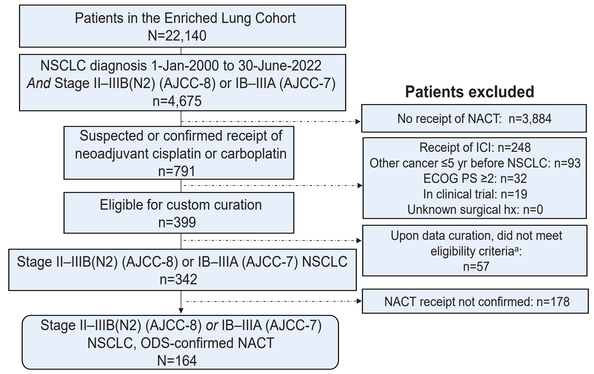
- Descriptive summaries of patient characteristics and endpoints were evaluated with respect to published findings for the platinum-based chemotherapy-treated control arms of 3 perioperative ICI trials for resectable NSCLC:
  - KEYNOTE-671[2,3] (NCT03425643)
  - AEGEAN[4] (NCT03800134)
  - CheckMate 77T[5] (NCT04025879)
- We also examined endpoints for the real-world cohort by receipt of neoadjuvant radiotherapy (yes/no) and for the subcohort of patients who received neoadjuvant cisplatin by receipt of neoadjuvant radiotherapy (yes/no)

Results

Patients

- A total of 164 patients with NSCLC were eligible for the study (**Figure 1, Table 1**)

Figure 1. Selection of eligible patients in the database with resectable NSCLC



[a]Eligibility criteria were confirmed during manual data curation.
AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; hx, history; ICI, immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1); NACT, neoadjuvant chemotherapy; ODS, Oncology Data Specialist.

Table 1. Baseline characteristics of patients who received neoadjuvant chemotherapy before NSCLC resection: Real-world cohort and control arms of 3 clinical trials

Characteristic	RW cohort (N=164)	KN671[2] (N=400)	AEGEAN[4] (N=374)	CM-77T[5] (N=232)
Age, median (range), years	65 (39–83)	64 (35–81)	65 (39–85)	66 (35–86)
Age ≥65 years	82 (50)	186 (46.5)	n/a	132 (57)
Male sex	73 (45)	284 (71)	278 (74)	160 (69)
Race[a]				
White	130 (80)	239 (62)	191 (51)	175 (75)
Black or African American	33 (20)	10 (3)	n/a	4 (2)
Asian	0	125 (33)	164 (44)	50 (22)
Other/multiple	0	10 (3)	19 (5)	3 (1)
Not documented	1	16	0	0
Positive history of smoking	151 (92)	353 (88)	318 (85)	205 (88)
Current smoker	68 (41)	103 (26)	95 (25)	n/a
Former smoker	83 (51)	250 (63)	223 (60)	n/a
ECOG PS of 1[a]	21 (33)	154 (39)	119 (32)	91 (39)
Unknown ECOG PS	101	0	0	0
Nonsquamous NSCLC	101 (62)	227 (57)	179 (48)	114 (49)
Squamous NSCLC	63 (38)	173 (43)	191 (51)	118 (51)
Clinical NSCLC stage[b]				
II	33 (20)[b]	121 (30)	110 (29)	81 (35)
III	131 (80)	279 (70)	263 (70)	149 (64)
IIIA	118 (72)	225 (56)	165 (44)	–
IIIB/N2	10 (6)	54 (14)	98 (26)	–
PD-L1 expression ≥1%[a]	70 (81)	249 (62)	249 (67)	128 (58)
PD-L1 unknown	78	0	0	11
EGFR genomic alteration[c]	0	19 (5)	0	1 (<1)
Unknown or not tested	164 (100)	381 (95)	374 (100)	231 (>99)
ALK rearrangement positive[c]	0	9 (2)	0	0
Unknown or not tested	164 (100)	391 (98)	374 (100)	232 (100)

Data are n (%) unless otherwise noted. Percentages may not add up to 100% because of rounding.
[a]Percentages for race, ECOG PS, and PD-L1 expression represent the percentages with data.
[b]Three patients (1.8%) in the real-world cohort had stage cIB NSCLC (per AJCC-7; included here with stage cII), and stage was missing for 1 patient in AEGEAN. AJCC-8 staging used in the clinical trials.
[c]Testing for *EGFR*/*ALK* genomic alterations was not required in AEGEAN, but patients with documented positive test results were excluded from the efficacy analyses. In CM-77T, testing for *EGFR* alterations was required for nonsquamous NSCLC.
CM, CheckMate; ECOG PS, Eastern Cooperative Oncology Group performance status; KN, KEYNOTE; n/a, not available; PD-L1, programmed death-ligand 1; RW, real-world.

Treatment and follow-up

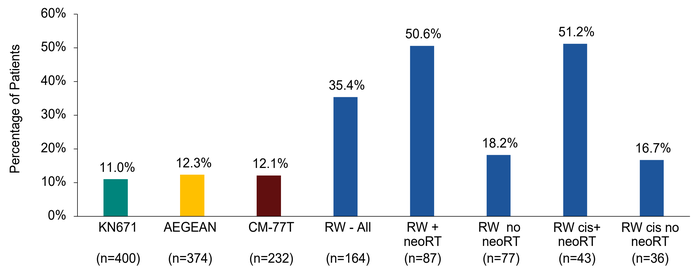
Table 2. Treatment and follow-up for the real-world cohort and control arms of 3 clinical trials

	RW cohort (N=164)	KN671[2] (N=400)	AEGEAN[4] (N=374)	CM-77T[5] (N=232)
Follow-up, median (range), mo	67.2 (45.9–92.0)	25.2 (7.5–50.6)	n/a	25.4 (15.7–44.2)
Neoadjuvant platinum agent				
Cisplatin	79 (48.2)	400 (100)	96 (25.7)	42 (18.1)[a]
Carboplatin	85 (51.8)	0	278 (74.3)	180 (77.6)[a]
Neoadjuvant radiotherapy	87 (53.0)	n/a[b]	0[b]	0[b]
Primary surgery	145 (88.4)	317 (79.4)	302 (80.7)[c]	178 (76.7)
Lobectomy/bilobectomy	125 (86.2)	264 (83.3)	241 (79.8)	151 (84.8)
Pneumonectomy	14 (9.7)	39 (12.3)	29 (9.6)	24 (13.5)
Other	6 (4.1)	14 (4.4)	32 (10.6)	3 (1.7)
Resection[d]: Complete (R0)	129 (89.0)	267 (84.2)	262 (91.3)[c]	161 (90.4)
Incomplete resection (R1)	8 (5.5)	31 (9.8)	22 (7.7)	11 (6.2)
Gross residual disease (R2)	–	4 (1.3)	2 (0.7)	6 (3.4)
Unresectable tumor	–	15 (4.7)	–	–
Unknown	8 (5.5)	0	1 (0.3)	0

Data are n (%) unless otherwise noted. Percentages may not add up to 100% because of rounding.
[a]In CM-77T, 6 patients switched from cisplatin to carboplatin, and the platinum agent was not identified for 4 patients.
[b]Neoadjuvant radiotherapy was not included in the protocols of the three clinical trials, and timing was not specified for 53 patients in KN671 who received radiotherapy.
[c]Of 302 patients who underwent surgery in AEGEAN, 287 patients completed surgery.
[d]Percentages for resection refer to patients who completed surgery. For the RW cohort, details were not available for 16 patients who did not have complete (R0) resection.
CM, CheckMate; KN, KEYNOTE; n/a, not available; RW, real-world.

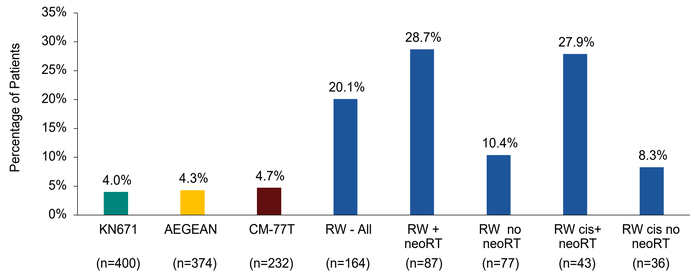
Outcomes

Figure 2. Major pathologic response in the three clinical trials[2,4,5] and rwMPR in the real-world cohort overall, by receipt of neoadjuvant radiotherapy (yes/no) and by receipt of neoadjuvant cisplatin-based regimens with/without neoadjuvant radiotherapy. Neoadjuvant radiotherapy was not administered in the three trials. The "RW cis no neoRT" subcohort received neoadjuvant therapy most aligned with that in the KN671 control arm.



cis, neoadjuvant cisplatin; CM, CheckMate; KN, KEYNOTE; neoRT, neoadjuvant radiotherapy; RW, real-world.

Figure 3. Pathologic complete response (pCR) in the three clinical trials[2,4,5] and rwpCR in the real-world cohort overall, by receipt of neoadjuvant cisplatin-based regimens with/without neoadjuvant radiotherapy. Neoadjuvant radiotherapy was not administered in the three trials.



cis, neoadjuvant cisplatin; CM, CheckMate; KN, KEYNOTE; neoRT, neoadjuvant radiotherapy; RW, real-world.

Conclusions

- Several characteristics of the US real-world population differed from those of the trial populations: namely, sex ratio (55% vs 26%–31% women, respectively), race distribution (20% vs ≤10% Black patients, respectively, and 0% vs 22%–44% Asian patients), smoking history (42% vs 25%–26% current smokers), NSCLC histologic type (62% vs 48%–57% nonsquamous), and NSCLC stages (80% vs 64%–70% stage III NSCLC)
- Over half (53%) of real-world patients received neoadjuvant radiotherapy, which was not administered in the clinical trials, while the rates of surgery and distribution of surgical procedures were similar in real-world and clinical trial settings
- The rwMPR and rwpCR rates for the real-world patients who did not receive neoadjuvant radiotherapy most closely approximated the MPR and pCR rates in the chemotherapy-treated control arms of the three clinical trials[2,4,5]
- Interpretation of our findings is limited, however, by the small size of some of the real-world subcohorts
- Moreover, differences in patient characteristics, treatment regimens, means of determining MPR and pCR, as well as the dosage, duration, and type of neoadjuvant therapy may have contributed to differences observed (vs the three trials) in rwMPR and rwpCR rates
- We plan continued study to validate rwMPR and rwpCR results with a larger real-world cohort and also to evaluate a real-world event-free survival endpoint

References

1. Spicer JD, et al. *J Thorac Oncol.* 2024;19(10):1373-1414.
2. Wakelee H, et al. *N Engl J Med.* 2023;389(6):491-503.
3. Spicer JD, et al. *Lancet.* 2024;404(10459):1240-1252.
4. Heymach JV, et al. *N Engl J Med.* 2023;389(18):1672-1684.
5. Cascone T, et al. *N Engl J Med.* 2024;390(19):1756-1769.
6. Gomes M, et al. *Value Health.* 2024;27(5):623-632.
7. N-Power Medicine. https://www.npowermedicine.com/. Accessed April 15, 2025.

Disclosures

Study sponsored by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Medical writing and editorial assistance were provided by Elizabeth V. Hillyer, DVM (freelance). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

XH, AA, PR, RK, and AS are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and hold stock in Merck & Co., Inc., Rahway, NJ, USA. CZ, GIC, AMcB, SH, and RB are employees of Syapse, which received funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, to provide data for this study. Syapse Holdings Inc. was acquired by N-Power Medicine on December 30, 2024.[7]

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Presented at ISPOR; Montreal, Canada; May 13-16, 2025.