Neoadjuvant Chemoimmunotherapy Complicates Subsequent Surgical Resection and Adjuvant Immunotherapy Is Preferable From the Surgical Standpoint

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Introduction

In April 2022, Forde et al.[1] published the CheckMate 816 trial, the first ever phase 3 trial reporting that neoadjuvant chemotherapy plus nivolumab followed by surgery offered superior pathologic complete response and event-free survival as compared with neoadjuvant chemotherapy followed by surgery in patients with clinical-stage IB to IIIA NSCLC staged using the seventh edition TNM classifications.[1] Favorable oncologic outcomes have since been reported from several additional phase 3 trials of neoadjuvant chemoimmunotherapy using immune checkpoint inhibitors (ICIs) followed by surgery in patients with resectable NSCLC.[2–4] As a result, the treatment of patients with locally advanced NSCLC is dramatically changing. Although questions regarding toxicity, surgical technical challenges, and a potential increase in perioperative surgical complications have been raised, international guidelines now recommend neoadjuvant chemoimmunotherapy followed by surgery as the standard of care. As surgeons, it is incumbent on us to evaluate the impact of neoadjuvant chemoimmunotherapy with ICIs on surgical outcomes to inform patient selection criteria, particularly in patients without N2 lymph node (LN) involvement.

Cancellation of Surgery After Neoadjuvant Chemoimmunotherapy

Carefully performed, randomized phase 3 trials of neoadjuvant therapy for resectable stage II to III NSCLC have assessed select surgical outcomes, including the number of patients who underwent surgery, while evaluating adverse effects (AEs) and mortality after neoadjuvant chemoimmunotherapy (Table 1).[1–4] Serious secondary AEs (grade 3–4) occurred after neoadjuvant treatment in 15% to 63% of patients, which is notable because AEs can interfere with treatment completion including continuing to surgery. In fact, only 40% to 71% of patients completed treatment.[1–4]

After neoadjuvant chemoimmunotherapy, 16% to 22% of patients do not undergo resection of NSCLC as planned (Table 1) because of disease progression, AEs, or becoming unfit for surgery (Table 2).[1–4] In the CheckMate 816 trial, 15.6% of patients in the intervention arm had their resection cancelled.[1] When surgical cancellation was evaluated by stage in the CheckMate 816 trial, 12% of patients with stage IB to II NSCLC and 17% of patients with stage IIIA NSCLC did not continue to surgery.[1] This level of surgical cancellation, particularly in patients with resectable, early-stage NSCLC, raises concern and warrants further investigation.

Delay in Undergoing Surgery After Neoadjuvant Chemoimmunotherapy

Patients often express the desire to rapidly remove their cancer to their thoracic surgeon, because they understand that complete resection is the cornerstone of cure. It is well documented that shorter time from investigation to surgery helps mitigate poor oncologic outcomes. In the CheckMate 816 trial, both arms had similar rates of delayed surgery. The median delay was 2 weeks with three patients (10%–12%) in each arm delayed more than 6 weeks.[1] In the Aegean trial, surgery was delayed in 58 patients (14.5%) because of

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Table 1. Summary of Clinical Results for the Main Phase 3 Trials for Neoadjuvant Chemoimmunotherapy

Specific Item	CheckMate- 816[1]	Keynote-671[4]	Aegean[2]	Neotorch[3]	CheckMate-77T[a]	Rationale-315[b]
NSCLC stage	IB-II 36 IIIA 63	II 30 IIIA-B 70	II 29 III 71	IIIA 67 IIIB 33	IIA-B 35 IIIA-B 64	II 42 IIIA 58
Cancelled surgery	16	18	23	18	22	20
Pneumonectomy	17	11	-	9	-	9
R0 resection	83	92	95	96	70	89
Adverse events (grade 3-4)	33	45	42	22	63	47
90-day surgical mortality	1	3	6	-	-	2

Note: All values are given in %.
[a]Presentation at the ESMO Congress in Madrid, Spain on October 21, 2023.
[b]Presentation at the ESMO Congress in Madrid, Spain on October 23, 2023.
ESMO, European Society for Medical Oncology.

neoadjuvant toxicity (five patients, 1.2%), logistics (31 patients, 7.7%), AEs (11 patients, 2.7%), or for other reasons (14 patients, 3.5%).[2] Thus, as surgeons, we have concerns about neoadjuvant chemoimmunotherapy causing delays in getting the patient to the operating room.

Surgical Technical Difficulties After Neoadjuvant Chemoimmunotherapy

Completeness of resection, the type of resection performed, and whether the surgery was converted from a minimally invasive approach to a thoracotomy served as indicators of surgical technical difficulty in the recent phase 2 trials of neoadjuvant ICI chemoimmunotherapy.[1–4] Pneumonectomy is typically avoided, if possible, because of a poorer prognosis. As significant downstaging allowing a less extensive resection, is not always observed after neoadjuvant therapy, pneumonectomy was still required in 9% to 17% of patients (Table 1). A higher rate of pneumonectomy was not significantly associated with disease stage.[1] Microscopically complete resection was obtained in 70% to 96% of patients, depending on the study, and also did not seem to differ on the basis of NSCLC stage (Table 1).[1] In the CheckMate 816 trial, minimally invasive surgery was performed in 30% of the patients. Conversions to open surgery from minimally invasive surgery occurred in 11% of patients and were not significantly associated with NSCLC stage.[1]

Unfortunately, none of the recent phase 3 trials of neoadjuvant chemoimmunotherapy included a thorough evaluation of technical challenges encountered during resection after neoadjuvant treatment. Some phase 1 and 2 trials of ICI immunotherapy and case series have monitored these challenges, however. Bott et al.[5] reported on the surgical outcomes of 20 patients undergoing chemoimmunotherapy with nivolumab followed by surgical resection in a phase 1 trial. In this study, 25% of the patients with stage I NSCLC, 50% of patients with stage IIA NSCLC, and 71% with stage IIB or IIIA NSCLC were converted to thoracotomy. The technical difficulties listed were related to the inflammatory response, specifically dense adhesions and fibrosis at the fissure or surrounding hilar and mediastinal nodal stations.[5] Similarly, Baek et al.[6] described surgical findings after performing resection in patients treated with ICIs. All patients had fibrotic changes and adhesions, especially in the fissure and interlobar LNs. Sepesi et al.[7] also reported on the surgical outcomes after neoadjuvant chemoimmunotherapy with ICIs in patients with NSCLC. In their cohort, 37 patients received an ICI perioperatively before lung resection by thoracotomy in 27 patients (73%), by video-assisted thoracoscopic surgery in seven (19%), and by robotic-assisted thoracoscopic surgery in three (8%). In the 12 patients approached minimally

Table 2. Reasons for Cancelled Surgery After Neoadjuvant Chemoimmunotherapy

Surgery Cancellation	CheckMate 816[1]	Keynote-671 trial[4]	Aegean[2]	Neotorch[3]
Resection cancelled after neoadjuvant chemoimmunotherapy	15.6	17.9	22.5	17.8
Reason for Cancellation				
Disease progression	6.7	4.1	8.8	2.5
AEs	1.1	6.3	1.8	3.0
Other[a]	7.8	7.5	12.3	12.4

Note: All values are given in %.
[a]Included patient refusal, physician decision, withdrawal of consent, medically unfit for surgery, cancer was deemed unresectable, and patient deaths.
AE, adverse event.

Table 3. Comparison of NI, NC, and S

Characteristics	NI	S	NC
n	37	37	37
Open procedures, %	70.3	51.4	83.8
Number of lymph nodes dissected	9	19	24
Length of stay (d)	7	6	7
Postoperative complications, %	37.8	10.8	16.2
30-d mortality, %	5.4	0	0

Modified from Zhang et al.[9]
NC, neoadjuvant chemotherapy, NI, neoadjuvant immunotherapy; S, immediate/upfront surgery.

invasively, two (17%) had a conversion to thoracotomy. The first was because of a significant intrathoracic adhesion in the pleural cavity, and the second was because of substantial hilar fibrosis that hindered an adequate nodal dissection.[7]

Surgical technical difficulties have also been evaluated in a small number of studies of neoadjuvant immunotherapy for resectable NSCLC that deserve our special attention. The French Intergroupe Francophone de Cancérologie Thoracique (IFCT)-1601 Ionesco trial was a multicenter, phase 2, single-arm study evaluating neoadjuvant durvalumab without chemotherapy for resectable NSCLC (clinical-stage IB $\geq$4 cm and IIIA non-N2 disease).[8] Adjuvant therapy after surgery was at the discretion of each investigator. The primary end point was the complete surgical resection rate, set at 95%. Secondary end points included major pathologic response and 90-day mortality. In total, 46 patients were eligible. The complete resection rate was 89%, implying that the primary end point was not met. The major pathologic response rate was 19%. This trial was stopped early because of a high 90-day mortality rate of 8.7% (four patients). A fifth patient died on the 94th postoperative day. Causes of death after lobectomy (three patients) or pneumonectomy (two patients) were arterial lesions, respiratory distress, tracheal fistula, cardiac complication, and sudden death. The authors concluded that a better selection of patients for neoadjuvant immunotherapy is required, that a technical difficulty score should be developed and that centralization of care is necessary for these patients.[8]

A total of 40 patients were enrolled in a neoadjuvant trial evaluating sintilimab in patients with resectable, clinical-stage IA to IIIB NSCLC.[9] Resection was performed in 37 patients, of whom two died postoperatively (5.4% mortality). Surgical parameters were then compared between patients receiving neoadjuvant sintilimab, patients receiving upfront surgery, and patients treated with neoadjuvant chemotherapy (Table 3).[9] LN dissection was more difficult, fewer LNs were dissected, and mortality was higher in the patients treated with sintilimab ($p < 0.001$). This study underscores the inherent difficulties of operating after neoadjuvant immunotherapy. Unfortunately, it did not include patients treated with neoadjuvant chemoimmunotherapy.

Advantages of Adjuvant Therapy

First of all, the toxicity of adding immune checkpoint blockade should be taken into consideration, especially in the neoadjuvant setting. In a recent systematic review and meta-analysis of randomized controlled trials, treatment-related AEs were evaluated in patients with solid tumors receiving neoadjuvant and adjuvant immune checkpoint blockade.[10] A total of 28 randomized controlled trials with 16,976 patients were included. The addition of immune checkpoint blockade significantly increased the incidence of grade 3 to 4 treatment-related AEs, AEs leading to treatment discontinuation, and treatment-related events of any grade, although there was no increase in treatment-related deaths.[10]

Because of additional concerns of surgical delay and disease progression, the care team may opt to perform upfront surgery followed by adjuvant ICI-based immunotherapy, especially in patients with node-negative disease or those without N2 involvement. This allows curative surgery and precise pathologic staging with a much higher likelihood of complete resection that can be performed without the risk of lung cancer progression and with fewer risks of surgical complications. Both the Impower010 and the PEARLS phase 3 trials of adjuvant immunotherapy therapy with ICIs reported significantly improved disease-free survival as compared with best supportive care in patients with stage II to IIIA NSCLC.[11,12] Currently, it remains unclear which patients will most benefit from adjuvant ICI therapy after upfront surgery, and further study in this area is needed.

Summary

Time will tell whether neoadjuvant chemoimmunotherapy with ICIs will become a common care strategy in patients with resectable NSCLC. Currently, upfront surgery followed by tailored adjuvant systemic therapy is frequently chosen for patients without N2 LN involvement, given recent advances in adjuvant therapeutic options and possibly due, in part, to surgeons' resistance to radical change. Real-world data are needed to establish the true impact of neoadjuvant chemoimmunotherapy with ICIs on thoracic surgery daily practice, to evaluate whether lymphadenectomy and rates of upstaging are affected, and to learn the scope of the surgical technical challenges faced after immunotherapy. Moreover, published phase 3 trials of neoadjuvant chemoimmunotherapy have assessed outcomes primarily in patients with stage III NSCLC, as they comprised greater than 60% of the patients studied. Whereas induction

therapy is clearly the standard of care for patients with stage III NSCLC, none the of the recent trials have addressed whether adjuvant immunotherapy might be a better option for patients with node-negative disease or those without N2 involvement. Could some of the patients with node-negative disease or those without N2 involvement in recent trials have been treated with surgery, with or without adjuvant therapy, and experienced an equivalent or better outcome? Would more patients have completed treatment using this strategy? A trial of neoadjuvant versus adjuvant chemoimmunotherapy should help us define which patients benefit from neoadjuvant chemoimmunotherapy and which benefit from upfront surgery. As we are learning about the surgical technical challenges after immunotherapy, we question whether we are at prime time for the standardized adoption of neoadjuvant chemoimmunotherapy in the treatment of resectable, early-stage NSCLC.

CRediT Authorship Contribution Statement

Paula Ugalde Figueroa: Writing original draft, Writing – review & editing.

Valérie Lacroix: Writing original draft, Writing – review & editing.

Paul E. Van Schil: Conceptualization, Writing original draft, Writing – review & editing.

Disclosure

Dr. Ugalde reports receiving honoraria from AstraZeneca, Merck Sharp & Dohme, Bristol-Myers Squibb, Medtronic, and Johnson & Johnson. Dr. Van Schil reports receiving consulting fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Janssen; honoraria from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, and Janssen; and has leadership positions at the International Association for the Study of Lung Cancer and Belgian Association of Cardiothoracic Surgery. Dr. Lacroix declares no conflict of interest.

References

1. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386:1973–1985.
2. Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative durvalumab for resectable non-small-cell lung cancer. *N Engl J Med*. 2023;389:1672–1684.
3. Lu S, Zhang W, Wu L, et al. Perioperative toripalimab plus chemotherapy for patients with resectable non-small cell lung cancer: the neotorch randomized clinical trial. *JAMA*. 2024;331:201–211.
4. Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med*. 2023;389:491–503.
5. Bott MJ, Yang SC, Park BJ, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2019;158:269–276.
6. Baek J, Owen DH, Merritt RE, et al. Minimally invasive lobectomy for residual primary tumors of advanced non-small-cell lung cancer after treatment with immune checkpoint inhibitors: case series and clinical considerations. *Clin Lung Cancer*. 2020;21:e265–e269.
7. Sepesi B, Zhou N, William WN Jr, et al. Surgical outcomes after neoadjuvant nivolumab or nivolumab with ipilimumab in patients with non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2022;164:1327–1337.
8. Wislez M, Mazieres J, Lavole A, et al. Neoadjuvant durvalumab for resectable non-small-cell lung cancer (NSCLC): results from a multicenter study (IFCT-1601 Ionesco). *J Immunother Cancer*. 2022;10:e005636.
9. Zhang F, Qiu B, Ji Y, et al. Comparison of surgical difficulty in patients with resectable non-small cell lung cancer under different neoadjuvant treatment modes: a retrospective cohort study. *J Thorac Dis*. 2021;13:5604–5616.
10. Fujiwara Y, Horita N, Adib E, et al. Treatment-related adverse events, including fatal toxicities, in patients with solid tumours receiving neoadjuvant and adjuvant immune checkpoint blockade: a systematic review and meta-analysis of randomised controlled trials. *Lancet Oncol*. 2024;25:62–75.
11. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398:1344–1357.
12. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol*. 2022;23:1274–1286.