REVIEW ARTICLE

Important Surgical and Clinical End Points in Neoadjuvant Immunotherapy Trials in Resectable NSCLC

Jay M. Lee, MD,[a,*] Anthony W. Kim, MD,[b] Tomasz Marjanski, MD, PhD,[c] Pierre-Emmanuel Falcoz, MD, PhD,[d] Masahiro Tsuboi, MD, PhD,[e] Yi-Long Wu, MD,[f] Shawn W. Sun, PharmD,[g] Barbara J. Gitlitz, MD[g]

[a]*David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California*
[b]*Keck School of Medicine, University of Southern California, Los Angeles, California*
[c]*Thoracic Surgery Department, Medical University of Gdańsk, Gdańsk, Poland*
[d]*Department of Thoracic Surgery, Strasbourg University Hospital, Strasbourg, France*
[e]*Division of Thoracic Surgery, Department of Thoracic Surgery & Oncology, National Cancer Center Hospital East, Chiba, Japan*
[f]*Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangdong, People's Republic of China*
[g]*Product Development Clinical Oncology, Genentech, Inc., South San Francisco, California*

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ABSTRACT

Neoadjuvant immunotherapy may improve outcomes in patients with resectable NSCLC and is being evaluated in phase 2 and 3 studies. Nevertheless, preoperative treatment postpones resection; the potential for increased surgical complexity and greater intra- and postoperative morbidity and mortality is an additional consideration. In studies primarily designed to evaluate efficacy, the impact of neoadjuvant immunotherapy on surgery is based on parameters that are poorly defined and reported differently between studies. Defining and reporting common end points among trials would improve understanding and facilitate cross-comparison of different immunotherapy regimens and may facilitate wider adoption of induction therapies by surgeons and oncologists. We propose several surgical end points and related metrics for neoadjuvant immunotherapy in resectable NSCLC. These include the periods from screening to treatment initiation and from last neoadjuvant dose to surgery; reporting of the allowable window for surgery to preclude masking delays caused by induction treatment-related toxicity; complete resection (R0) rate; preoperative downstaging; a standardized list of immune-related adverse events and associated delay to surgery; preoperative attrition; postoperative attrition before adjuvant therapy; and postoperative 30- and 90-day mortality and morbidity rates. Intraoperative end points

***Corresponding author.**

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Address for correspondence: Jay M. Lee, MD, Division of Thoracic Surgery, David Geffen School of Medicine at University of California Los Angeles, Box 957313, Room 64-128 CHS, 10833 Le Conte Avenue, Los Angeles, CA 90095-7313. E-mail: jaymoonlee@mednet.ucla.edu

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(blood loss, duration, and type of surgery) and our proposed system of grading complexity based on lymphadenopathy and fibrosis would allow quantitation of technical difficulty and quality of oncologic resection. In conclusion, the standardization, reporting, and prospective inclusion of these end points in study protocols would provide a comparative overview of the impact of different neoadjuvant immunotherapy regimens on surgery and ultimately clinical oncologic outcomes in resectable NSCLC.

Keywords: Early stage; Lung cancer; Neoadjuvant PD-L1 inhibitor therapy; Surgical end points

Introduction

Neoadjuvant immune checkpoint inhibitors (ICIs), such as programmed death-ligand 1 (PD-L1) and programmed cell death protein-1 (PD-1) inhibitors that enhance anticancer immunity, may improve outcomes in resectable NSCLC because T-cell function is less impaired.[1] Added potential advantages of preoperative ICI therapy include exposure to the whole tumor-antigen repertoire, leading to a broader and more diverse immune response; T-cell priming from the intact primary tumor and associated lymph nodes contributing to a durable immune response; earlier treatment of micrometastases; and potentially improved outcomes. Neoadjuvant ICIs are therefore being evaluated in patients with resectable NSCLC in phase 2 and 3 trials. Nevertheless, considerations include the delay to resection and the potential for increased intraoperative complexity and greater intra- and postoperative morbidity and mortality, particularly in locally advanced NSCLC.[2]

Although overall survival (OS) is the accepted standard efficacy outcome in phase 3 NSCLC trials,[3] the interval from enrollment to study publication can take a decade; hence, there is a critical need for surrogate efficacy end points to expedite new treatments for resectable NSCLC.[3,4] The neoadjuvant approach allows pathologic regression to be used as a potential surrogate marker of event-free survival (EFS) or OS in resectable NSCLC.[1,2] Major pathologic response (MPR; defined as $\leq$10% residual tumor)[2] after neoadjuvant chemotherapy (CT) correlated with OS[5,6] and was linked to longer disease-free survival after neoadjuvant atezolizumab plus CT.[7] MPR and EFS are key study end points in ongoing phase 3 studies of neoadjuvant CT combined with atezolizumab (IMpower030), durvalumab (AEGEAN), and tislelizumab (BGB-A317-315) (Supplementary Table 1). Pathologic complete response (pCR; defined as absence of viable tumor at resection) is a primary end point that has been met in the phase 3 CheckMate 816 study of neoadjuvant nivolumab plus CT in resectable NSCLC in the first readout from these ongoing phase 3 trials.[8] Whether MPR or pCR will be more predictive of OS in resectable NSCLC remains to be determined.

Although clinical trial design has primarily focused on treatment efficacy, surgical and other clinical end points that describe the impact of neoadjuvant ICIs on surgery and related outcomes are poorly defined. These end points are particularly relevant to surgeons and physicians who refer patients for neoadjuvant treatment. Evaluating the impact of preoperative immunotherapy on surgery using consistent measures across trials would improve understanding of the benefit-risk profile of different regimens and could inform surgeons of potential complications. In this review, we propose the standardization and reporting of several surgical end points and related metrics surrounding neoadjuvant immunotherapy for resectable NSCLC: delay to surgery measured by time end points from diagnosis to resection, preoperative attrition to surgery, postoperative attrition to adjuvant therapy, preoperative downstaging, immune-related adverse events (irAEs), rate of complete resection (R0), grading of surgical complexity, and perioperative and postoperative complications.

As this is a review of published data, no patient consent is required.

Delays to Surgery

Neoadjuvant treatment postpones resection owing to screening procedures, preoperative treatment, and treatment-related adverse events (TRAEs). Given that stage IB to IIA NSCLC is not a routine indication for neoadjuvant treatment and that these patients are candidates for immediate resection outside clinical trials, delays to potentially curative surgery pose a dilemma to patients, surgeons, and oncologists delivering the therapy.

Delays Related to Neoadjuvant Treatment

Data from large, neoadjuvant CT trials in resectable NSCLC (Table 1) serve as historical benchmarks for comparing perioperative outcomes in neoadjuvant ICI trials. A National Cancer Database study revealed that 43% of 2185 patients with stage IIIA NSCLC treated with neoadjuvant CT had long delays before surgery (>114 d), 37% had medium delays (77–114 d), and 30% had short delays (<77 d).[9] The delay to surgery did not influence 30- or 90-day mortality rates. Nevertheless, 1- and 3-year survival analyses revealed that long delays to

Table 1. Summary of Chemotherapy-Related AEs and Surgical Outcomes in Large Multicenter Studies of Neoadjuvant Chemotherapy

Study	Stage	Neoadj CT	N[a]	PD on CT	Grade ≥3 CT-Related AE (>2%)	Preop Mortality	Protocol-Defined Time From End of CT to Surgery	Pts Who Went to Surgery	Failed to Undergo Surgery/Preop Unresectable From PD[b]	Type of Surgery[c]	Intraop Unresectable	R0 rxn	Postop Mortality	Median LOS (d)	Postop Morbidity
SWOG S9900 phase 3 RCT[4]	IB-IIIA (T2N0, T1-2N1, or T3N0-1)	Platinum doublet (3 cycles)	169	6/169 (4%)	Neutropenia: 48% Febrile neutropenia: 4% Fatigue: 4% Nausea: 3% Vomiting: 3% Myalgia: 6% Arthralgia: 7% Sensory: 6% Paclitaxel-induced hypersensitivity: 3%	3/169 (2%)	3-8 wk	152/169 (90%)	17/169 (10%)/ 6/152 (4%)	Px: 24/169 (14%) Lx: 109/169 (64%) Bi-Lx: 10/169 (6%) Other: 4/169 (2%)	5/152 (3%)	142/152 (93%)	7/134 (5%)	NR	Pneumonia: 10/152 (7%) Reintubation: 11/152 (7%) ICU readmission: 8/152 (5%) Air leak: 13/152 (9%) Respiratory failure: 10/152 (7%)
		None	168	N/A	N/A	NR	N/A	165/168 (98%)	3/168 (2%)/NR	Px: 26/168 (15%) Lx: 117/168 (70%) Bi-Lx: 11/168 (7%) Other: 4/168 (2%)	7/165 (4%)	146/16 (88%)	4/147 (3%)	NR	Pneumonia: 12/165 (7%) Reintubation: 9/165 (5%) ICU readmission: 10/165 (6%) Air leak: 12/165 (7%) Respiratory failure: 7/165 (4%)
MRC LU22/NVALT 2/EORTC 08012 intergroup multicenter[10]	IA-IIIB	Platinum-based CT (3 cycles)	247	5/247 (2%)	NR	4/253 (2%)	4-6 wk from day 1 of last CT cycle	231/253 (91%)	22/253 (9%)/ 16/253 (6%)	Px: 65/231 (28%) Lx: 151/231 (65%) Other: 5/231 (2%)	NR	R0: 205/231 (89%)	NR	8	Lung infection: 24/229 (10%)
		None	259	N/A	N/A	2/259 (1%)	N/A	242/259 (93%)	17/259 (7%)/ 15/259 (6%)	Px: 80/242 (33%) Lx: 145/242 (60%) Other: 3/242 (1%)	NR	205/242 (85%)	NR	9	Lung infection: 16/240 (7%)
NATCH phase 3 multicenter[45]	IA (>2 cm)-II/ T3N1	Pac/carb (3 cycles)	199	11/193 (6%)	Neutropenia: 24/193 (12%) Fatigue: 5/193 (3%)	1/193 (<1%)	3-4 wk	181/199 (91%)	NR	Px: 42/181 (23%) Lx/Bi-Lx: 131/181 (72%) Wedge/Sx: 1/181 (1%)	7/181 (4%)	174/193 (90%) had tumor rxn[d]	9/181 (5%)	NR	NR
		None	210	N/A	N/A	N/A	N/A	200/210 (95%)	NR	Px: 52/200 (26%) Lx/Bi-Lx: 130/200 (65%) Wedge/Sx: 7/200 (4%)	11/200 (6%)	189/200 (95%)	11/200 (6%)	NR	NR
IFCT 0002[46]	IA-IIB	Cis/gem vs. Carb/pac (2-4 cycles)	267	2/267 (<1%)	Neutropenia: 110/264 (42%) Thrombocytopenia: 28/264 (11%) Nausea/vomiting: 10/264 (4%) Neuropathy: 36/264 (13%)[e]	2/267 (1%)	<5 wk	257/267 (96%)	10/267 (4%)/ 2/267 (1%)	NR for neoadj group	2/257 (1%)	244/257 (95%)	90-d: 13/264 (5%)	NR	NR
CHEST phase 3[47]	IB-IIIA	Cis/gem (3 cycles)	127	7/127 (6%)	Neutropenia: 33/127 (26%) Thrombocytopenia: 14/127 (11%) Leukopenia: 8/127 (6%)	0	2-6 wk	110/127 (87%)	17/127 (13%)/ 4/127 (3%)	Px: 14/110 (13%) Lx: 75/110 (68%) Bi-Lx: 10/110 (9%) Other: 11/110 (10%)	NR	97/110 (88%)	Perioperative: 4/110 (3%)	NR	Grade 3/4: 20/127 (16%) Bronchial fistula: 2/127 (2%)

(continued)

Table 1. Continued

Study	Stage	Neoadj CT	N[a]	PD on CT	Grade ≥3 CT-Related AE (>2%)	Preop Mortality	Protocol-Defined Time From End of CT to Surgery	Pts Who Went to Surgery	Failed to Undergo Surgery/Preop Unresectable From PD[b]	Type of Surgery[c]	Intraop Unresectable	R0 rxn	Postop Mortality	Median LOS (d)	Postop Morbidity
		None	141	N/A	N/A	N/A	N/A	136/141 (96%)	5/141 (4%)/NR	Px: 25/136 (18%) Lx: 60/136 (44%) Bi-Lx: 11/136 (8%) Other: 40/136 (29%)	NR	114/136 (84%)	Perioperative: 5/136 (4%)	NR	Grade 3/4: 15/136 (11%) Bronchial fistula: 1/136 (1%) Postop complication: 2/136 (2%)
RCT from French Cooperative Thoracic Intergroup[48]	I (except T1N0-IIIA)	Mito/ifos/cis (2 cycles)	179	10/179 (6%)	NR	3/179 (2%)	3 wk	167/179 (93%)	12/179 (7%)/4/179 (2%)	Px: 87/167 (52%) Lx: 76/167 (46%)	Exploratory thoracotomy: 4/167 (2%)	154/167 (92%)	30-d: 16/167 (10%)	NR	Bronchial fistula: 4/167 (2%) Thoracic empyema: 6/167 (4%) Pneumonia: 10/167 (6%) Hemorrhage: 3/167 (2%) Pulmonary embolism 1/167 (1%)
		None	176	N/A	N/A	N/A	N/A	171/176 (97%)	5/176 (3%)/5/176 (3%)	Px: 98/171 (57%) Lx: 68/171 (40%)	Exploratory thoracotomy: 5/171 (3%)	149/171 (87%)	30-d: 9/171 (5%)	NR	Bronchial fistula: 1/171 (1%) Thoracic empyema: 4/171 (2%) Pneumonia: 12/171 (7%) Hemorrhage: 3/171 (2%) Pulmonary embolism 1/171 (1%)

(continued)

Table 1. Continued

Study	Stage	Neoadj CT	N[a]	PD on CT	Grade ≥3 CT-Related AE (>2%)	Preop Mortality	Protocol-Defined Time From End of CT to Surgery	Pts Who Went to Surgery	Failed to Undergo Surgery/Preop Unresectable From PD[b]	Type of Surgery[c]	Intraop Unresectable	R0 rxn	Postop Mortality	Median LOS (d)	Postop Morbidity
SAKK Lung Cancer Project Group Phase 3[49]	T1-3N2M0, IIIA/N2	Cis/doc (3 cycles)	115	16/115 (14%)	73/121[f] (60%) Nausea/vomiting: 13/121 (11%) Fatigue: 7/121 (6%) Diarrhea: 15/121 (12%) Neurotoxicity: 3/121 (3%) Stomatitis: 5/121 (4%) Dyspnea: 4/121 (3%) Infection: 15/121 (12%) Febrile neutropenia: 19/121 (16%) Neutropenia: 60/121 (50%) Leukopenia: 35/121 (29%) Thrombocytopenia: 4/121 (3%)	1/115 (1%)	3-4 wk	94/115 (82%)	21/115 (18%)/ 12/115 (10%)	Px: 19/94 (20%) Lx: 59/94 (63%) Bi-Lx: 9/94 (10%)	NR	76/94 (81%)	30-d: 3/94 (3%)	NR	Reoperation: 6/94 (6%) Infection: 11/94 (12%) Other complications: 26/94 (28%)

[a]Number of patients who received neoadjuvant CT.
[b]Percentage of patients with unresectable tumors before surgery owing to PD.
[c]Other = wedge resection/segmentectomy or procedure not reported.
[d]Extent of resection (R0, R1, or R2) was not reported.
[e]Grades 1 to 4 neuropathy at 6 months.
[f]Includes six additional patients from another study arm who received CT and were assessed with the other patients who received CT.
AE, adverse event; Bi-Lx, bilobectomy; carb, carboplatin; cis, cisplatin; CT, chemotherapy; doc, docetaxel; gem, gemcitabine; ICU, intensive care unit; ifos, ifosfamide; intraop, intraoperative; LOS, length of (hospital) stay; Lx, lobectomy; mito, mitomycin; N/A, not assessed; neoadj, neoadjuvant; NR, not reported; pac, paclitaxel; PD, progressive disease; postop, postoperative; preop, preoperative; Pt, patient; Px, pneumonectomy; R0 rxn, complete resection; RCT, randomized controlled trial; Sx, segmentectomy; VATS, video-assisted thoracoscopic surgery.

surgery increased mortality compared with short delays (hazard ratio = 1.25, $p = 0.0005$), suggesting overall oncologic outcome is influenced by the timing of surgery after neoadjuvant treatment.

The interval between neoadjuvant CT and resection has rarely been reported in large multicenter studies. The mean time from randomization to surgery in the MRC LU22/NVALT 2/EORTC 08012 study was 85 days, which included 5 days from randomization to CT, 63 days on CT, and 17 days between CT and surgery.[10] In EORTC 08941, resection was performed at a median of 49 days after the last cycle of neoadjuvant CT.[11] In phase 2 neoadjuvant ICI studies, the median time between the end of neoadjuvant treatment and surgery (where reported) was 18 to 31 days (Table 2).[12–14] Time to resection after neoadjuvant therapy was shorter with an ICI alone compared with combined ICI and CT regimens or CT alone (Table 2).

Protocol-Related Delays

Clinical trial procedures such as randomization to treatment, screening, and workup, number of neoadjuvant treatment cycles and regimens, and preneoadjuvant and postneoadjuvant treatment biopsies and radiography (included in time end points A–C in Fig. 1) can all contribute to delaying resection. Because these periods often differ between study protocols or depend on the institution, it can be difficult to standardize the timing of and reasons for protocol-related delays.

The neoadjuvant CT trials SWOG S9900 and MRC LU22/NVALT 2/EORTC 08012 allowed surgery 3 to 8 weeks after completion of CT (Table 1).[4,10] In neoadjuvant ICI studies, protocol-specified windows for surgery (i.e., the earliest and latest times to surgery, illustrated by time end point D in Fig. 1) range from 7 to 10 days to 2 to 3 months and are often not clearly defined either in existing reports of phase 2 results (Table 2) or in ongoing phase 3 studies on ClinicalTrials.gov (Supplementary Table 1).

Adverse Event-Related Delays

Hematologic toxicities are the most common grade 3-4 AEs in neoadjuvant CT studies, occurring in approximately 50% of patients (Table 1). Nevertheless, it is difficult to quantitate their role in delaying surgery, given that the length of or reasons for delay to surgery after neoadjuvant CT have rarely been reported.

Grade 3 or greater TRAEs in phase 2 studies of neoadjuvant ICIs occurred in 5% to 14% of patients receiving ICI monotherapy or dual therapy and in 15% to 93% of patients receiving ICI plus CT (Table 3). Some investigator groups define a subset of immunotherapy-related AEs as "immune-related" AEs.[15] They can affect multiple organ systems, including gastrointestinal, endocrine, nervous, musculoskeletal, lung, liver, and skin. Possible mechanisms underlying irAEs such as myocarditis, colitis, thyroiditis, and pituitary inflammation include increased T-cell activity, autoantibodies, and inflammatory cytokine levels along with enhanced complement-mediated inflammation; however, the mechanisms underlying pneumonitis are poorly understood.[16,17] Typically, severe irAEs require steroid treatment, but the classification of an AE as a TRAE or an irAE varies and their definitions are often unclear.

Meta-analyses have revealed that the reporting of irAEs in clinical trials has been incomplete, as demonstrated by low rates of reporting their onset, management, and reversibility (14%, 8%, and 6% of studies, respectively).[18] Pooled analyses of ICIs in multiple cancer types revealed that the incidence of serious TRAEs (grade $\geq$3) is low (14% with PD-1 inhibitors and 21% with PD-L1 inhibitors).[19] Nevertheless, the median time to onset of grade 3 or greater irAEs is significantly longer than that of all-grade irAEs (27.5 versus 8.4 wk, $p < 0.05$).[20] In addition, the median time to resolution of grade 3 or greater versus all-grade irAEs was 6.9 versus 40.6 weeks ($p < 0.5$).[20] The different profiles of onset and resolution of irAEs pose unique challenges not found with traditional CT regimens.

In several phase 2 neoadjuvant ICI studies, the distinction between TRAEs and irAEs, also described by some groups as "AEs of special interest (AESIs)," is unclear (Table 3). This makes it difficult to determine whether delays to surgery are caused by ICI- or CT-related AEs. For example, in the LCMC3 study of atezolizumab monotherapy, 2% of patients had their surgery delayed by AESIs: hypothyroidism (10 d) and pneumonitis (43 d).[21] In the TOP1201 study of neoadjuvant ipilimumab plus CT, 15% of patients had delays of 28 and 35 days, respectively, owing to ipilimumab-related diarrhea[22] (Table 2), described as an irAE (Table 3). By contrast, in the ChiCTR-OIC-17013726 study of neoadjuvant sintilimab, 5% of patients had delayed surgery owing to TRAEs (grade 2 alanine aminotransferase and aspartate aminotransferase elevations and grade 1 hypothyroidism) but no distinction from other TRAEs was made,[23] nor was any distinction made in the MK3475-223 study of neoadjuvant pembrolizumab, in which 7% of patients had a delay owing to grade 3 treatment-related myositis.[24]

A meta-analysis revealed that ICI-associated all-grade and grade 3 or greater pneumonitis occur in approximately 3% and less than 1% of patients, respectively, in advanced cancer clinical trials, with 0.2% of patients dying.[16] The incidence was higher in patients treated outside NSCLC clinical trials: 19% all

Table 2. Summary of Surgery-Related Details of Ongoing Phase 2 Studies of Neoadjuvant Immunotherapy in Patients With Early NSCLC

Study ID Trial name Reference(s)	Stage	Neoadjuvant Therapy	Protocol-Specified Window for Surgery	No. (%) Who Had Surgery/No. of Pts Who Received Neoadjuvant Therapy	Time to Resection	Patients Who Did Not Have Surgery (Reasons)	Preoperative Mortality	Intraoperative Unresectability
Immunotherapy as monotherapy or dual therapy								
NCT02927301 LCMC3 Kwiatkowski et al. (2019)[32] Lee et al. (2019)[21]	IB-IIIB	Atezolizumab (2 cycles)	Day 40 ± 10 d after first dose of atezolizumab	90 (89%)/101	NR Surgery occurred outside 10-d protocol window (range: 2-43 d) in 10% (10 pts): TRAE (n = 2), surgeon availability (n = 2), other (n = 6)	11/101 (11%) (5/101 [5%; stage IIIA] had preoperative PD, 4/101 [4%] withdrew consent, 1/101 [1%] failed ECG, 1/101 [1%; stage IB] had involvement of pulmonary artery)	0%	5/101 (5%); these patients had stage IIIA or IIIB
NCT02994576 PRINCEPS Besse et al. (2020)[12]	I-IIIA	Atezolizumab (1 cycle)	3 wk after atezolizumab and within <15 d of that window	30 (100%)/30	Median, 24 d None delayed >15 d	0%	0%	0%
NCT02259621 CheckMate 159 Bott et al. (2019)[41] Forde et al. (2018)[14]	I-IIIA	Nivolumab (3 cycles on d −42, −28, −14 [±2 d] before surgery on d 0)	Approximately 4 wk after the first neoadjuvant dose	20 (95%)/21	Median, 18 (range: 11-29) d No treatment-related delays	0%	0%	1/21 (5%) (tracheal invasion; patient had stage IIIA)
NCT03158129 NEOSTAR Cascone et al. (2019)[13] Sepesi et al. (2019)[33]	I-IIIA	Nivolumab (3 cycles) vs. nivolumab (3 cycles) + ipilimumab (1 cycle)	Within 3-6 wk after last neoadjuvant dose	37 (84%)/44	Median, 31 (range: 21-87) d (n = 8 [22%] delayed beyond 42 d)	5/44 (11%) N: n = 1 (2%) SAE (grade 3 hypoxia) and high surgical risk NI: n = 4 (9%) PD (1), lack of resectability (1), high surgical risk (1), declined surgery (1)	1/44 (2%) (pneumonitis and BPF)	NR
NCT02938624 MK3475-223 Bar et al. (2019)[24]	I/II	Pembrolizumab (2 cycles)	1-3 wk	13 (87%)/15	NR 1/13 (8%) had delay owing to treatment-related grade 3 myositis	2/15 (13%) Treatment-related grade 3 myositis (7%); grade 3 myocardial infarction (7%; not treatment-related)	NR	NR

(continued)

Table 2. Continued

Study ID Trial name Reference(s)	Stage	Neoadjuvant Therapy	Protocol-Specified Window for Surgery	No. (%) Who Had Surgery/No. of Pts Who Received Neoadjuvant Therapy	Time to Resection	Patients Who Did Not Have Surgery (Reasons)	Preoperative Mortality	Intraoperative Unresectability
ChiCTR-OIC-17013726 Gao et al. (2020)[23]	IA-IIIB	Sintilimab (2 cycles)	29–43 d after first dose of sintilimab	37 (92.5%)/40	NR 2/37 (5%) had treatment-related delays (n = 1 grade 2 increased ALT/AST; n = 1 grade 1 hyperthyroidism)	3/40 (7.5%)	0%	0%
Combination immunotherapy plus chemotherapy								
NCT02716038 Columbia Shu et al. (2020)[7]	IB-IIIA	Atezolizumab + carboplatin + nab-paclitaxel (4 cycles)	After computed tomography scan, approximately 4 wk after last dose of chemotherapy Directly to surgery after 2 cycles if computed tomography scan revealed PD	29 (97%)/30	Median, 26.5 (IQR: 24–36) d No treatment-related delays	4/30 (13%) (3/30 [10%] had intraoperative PD; 1/30 [3%] had developed brain metastases)	0%	3/30 (10%)
NCT02572843 SAKK 16/14 Rothschild et al. (2020)[50]	IIIA (N2)	Durvalumab (2 cycles) + cisplatin/docetaxel (3 cycles)	NR	55 (82%)/67	NR	4/67 (6%) had PD before surgery	1/67 (2%; respiratory failure)	NR
NCT01820754 TOP1201 Yang et al. (2018)[22]	IB-IIIA	Ipilimumab + chemotherapy	Within 12 wk of completing neoadjuvant treatment	13 (54%)/24	<12 wk (2 patients [15%] had delay in surgery of 4 and 5 wk, respectively, owing to ipilimumab-related diarrhea)	11/24 (46%) (persistent N2 cancer: 5/24 [21%]; inadequate pulmonary function: 2/24 [8%]; PD: 2/24 [8%]; location of tumor: 1/24 [4%]; immune-related AE: 1/24 [4%])	0%	0%
NCT03081689 NADIM Provencio et al. (2019)[51]	IIIA	Nivolumab + paclitaxel + carboplatin	Nivolumab + paclitaxel + carboplatin (3 cycles)	41 (89%)/46	3–4 wk after end of neoadjuvant treatment	5/46 (11%) (patient decision: 4/46 [4%]; did not fulfill resectability criteria: 3/46 [7%])	0%	0%

(continued)

Table 2. Continued

Study ID Trial name Reference(s)	Stage	Neoadjuvant Therapy	Protocol-Specified Window for Surgery	No. (%) Who Had Surgery/No. of Pts Who Received Neoadjuvant Therapy	Time to Resection	Patients Who Did Not Have Surgery (Reasons)	Preoperative Mortality	Intraoperative Unresectability
NCT03366766 Zinner et al. (2020)[52]	I-IIIA	Nivolumab + cisplatin + pemetrexed/ gemcitabine (3 cycles)	NR	13 (100%)/13	NR	0%	0%	NR
NCT02998528 CheckMate 816 Forde et al. (2021)[8] Spicer et al. (2021)[53]	IB-IIIA	Nivolumab + pemetrexed+ cisplatin or paclitaxel + carboplatin (nsq) or nivolumab + gemcitabine + cisplatin or paclitaxel + carboplatin (sq) (3 cycles) vs. vinorelbine + cisplatin or gemcitabine + cisplatin (sq only) or pemetrexed + cisplatin (nsq only) or paclitaxel + carboplatin (3 cycles)	Within 6 wk posttreatment	N + chemo: 149 (83%)/176 Chemo: 135 (85%)/176	N + chemo: median 5.3 (IQR: 4.6-6.0) wk (n = 31 [21%] delayed beyond 6 wks) Chemo: median 5.0 (IQR: 4.6-5.9) wk (n = 24 [18%] delayed beyond 6 wk)	N + chemo[8]: 28 (16%) (disease progression: 12/176 [7%]; AE: 2/176 [1%]; other reason [patient refusal, unresectability, and poor lung function]: 14/176 [8%]) Chemo[8]: 38 (21%) (disease progression: 17/176 [9%]; AE: 2/176 [1%]; other reason [patient refusal, unresectability, and poor lung function]: 19/176 [11%])	N + chemo[8]: 0%[a] Chemo[8]: 3%[a] (enterocolitis, pneumonia, pancytopenia)	NR

[a]Describes proportion of patients who experienced treatment-related deaths; includes events reported between the first neoadjuvant dose and 30 days after last dose of neoadjuvant treatment.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BPF, bronchopleural fistula; chemo, chemotherapy; ECG, electrocardiogram; ID, identifier; IQR, interquartile range; N, nivolumab, NI, nivolumab + ipilimumab; NR, not reported; nsq, nonsquamous; PD, progressive disease; Pt, patient; SAE, serious adverse event; sq, squamous; TRAE, treatment-related adverse event.

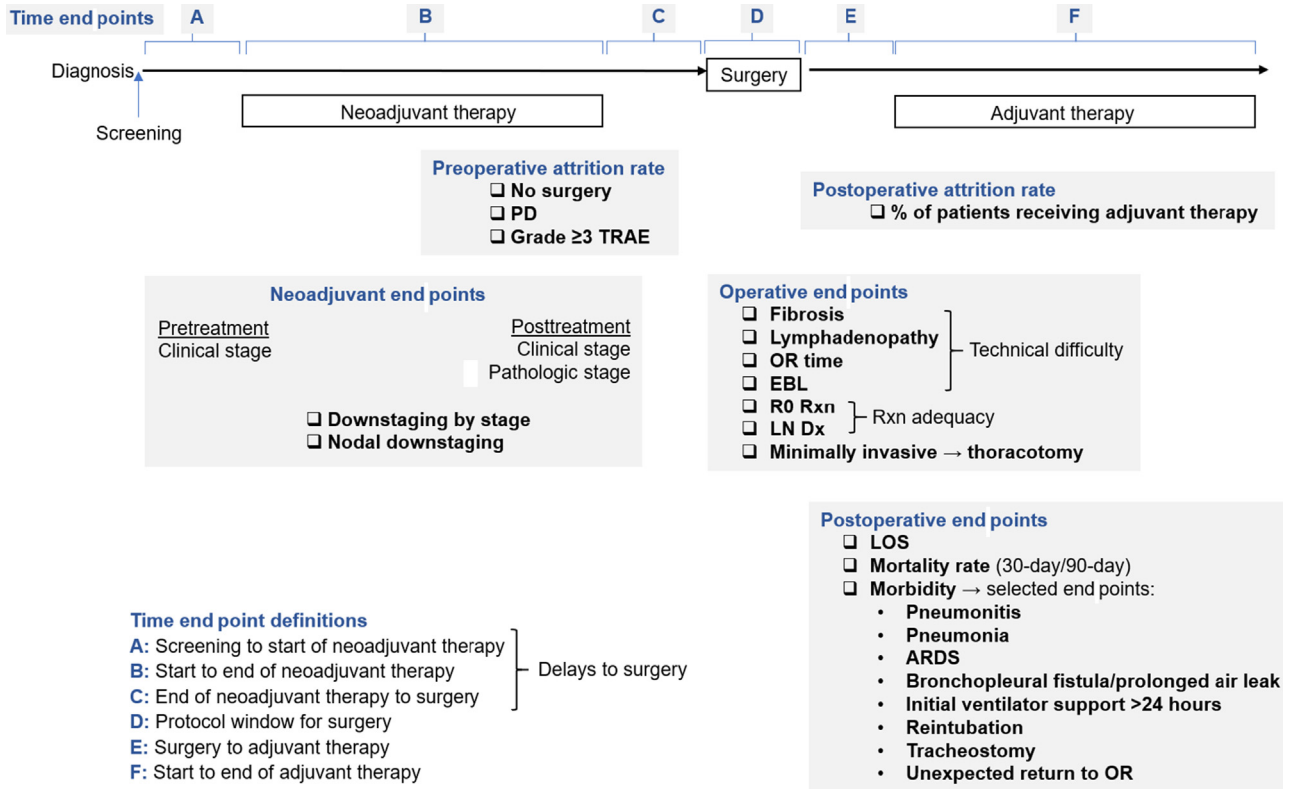

Figure 1. Proposed surgical and clinical end points for neoadjuvant immunotherapy trials in resectable NSCLC. ARDS, acute respiratory distress syndrome; EBL, estimated blood loss; LN dx, lymph node dissection; LOS, length of (hospital) stay; OR, operating room; PD, progressive disease; R0 rxn, complete resection; TRAE, treatment-related adverse event.

grade and 12% grade 3 or greater.[25] Incidence of immune-related pneumonitis varied by agent (anti–CTLA-4 versus PD-1 or PD-L1 inhibitors), regimen (combination versus monotherapy), medical history, and baseline disease characteristics.[16] Pulmonary function[26] and radiographic evidence of pneumonitis should be reevaluated after neoadjuvant immunotherapy to ensure that the patient can undergo surgery.

In a review of ICI studies in advanced NSCLC, the incidences of elevated alanine aminotransferase, elevated aspartate aminotransferase, and hepatitis were 6.2%, 5.0%, and 1.1%, respectively.[27] The relative risk of all-grade immune-related hepatitis was higher with combined ICI and CT. Immune-mediated hepatitis ranged from mild liver enzyme elevations to acute liver failure, generally without apparent radiographic change, and injury to the liver differed clinically from that with autoimmune hepatitis.[27] Immune-mediated hepatitis often becomes clinically evident 8 to 12 weeks after starting immunotherapy[27] and could affect the safety of anesthesia. Hence, liver function tests should be performed to determine fitness for surgery.

Immune-related colitis occurs more frequently with anti–CTLA-4 agents (10%–25%) and anti–CTLA-4 plus PD-1 combination therapy (≈20%) than with anti–PD-1 agents (1%–5%).[28] The onset of diarrhea or colitis varies widely and may occur after the second or third dose (5–10 wk after the start of immunotherapy) or even after treatment discontinuation.[29] In patients with severe symptoms of colitis, a computed tomography scan can reveal evidence of bowel wall thickening, fluid-filled colonic distension, mesenteric vessel engorgement, abscess, or perforation.[29]

Thyroid dysfunction is the most frequent immunotherapy-induced endocrinopathy, occurring in 5% to 10% of patients receiving anti–PD-1 monotherapy and up to 20% receiving combination anti–CTLA-4 plus anti–PD-1 therapy.[29] The median time to onset is often less than 3 months but may vary widely and even occurs several years after treatment discontinuation. Hypothyroidism is the most common thyroid dysfunction; symptomatic hyperthyroidism has also been reported. Thyroid function tests should be conducted before and after neoadjuvant immunotherapy.

A standardized list of potential irAEs with reports on incidence, time of onset, and time to resolution in trials would provide valuable information to help optimize patients for surgery after neoadjuvant immunotherapy. Oncology societies have clinical practice guidelines on

Table 3. Grade 3 or Greater TRAEs in Phase 2 Studies of Neoadjuvant Immunotherapy

Study ID Trial Name	No. of Pts	Neoadjuvant Therapy	TRAEs Grade ≥3	irAEs[a]
Immunotherapy as mono therapy or dual therapy				
NCT02927301 LCMC3[21,32]	101	Atezolizumab	6/101 (6%) Pneumonitis: 3/101 (3%), nasal congestion: 1/101 (1%), neutropenia: 1/101 (1%), anemia: 1/101 (1%)	All-grade preoperative immune-related TRAEs: 30/101 (30%) Rash: 12/101 (12%), infusion-related reaction: 11/101 (11%), hepatitis: 5/101 (5%), hyperthyroidism: 3/101 (3%), hypothyroidism: 1/101 (1%), pneumonitis: 1/101 (1% [the only grade 3 event])
NCT02259621 CheckMate 159[14]	22	Nivolumab	1/21 (5%; pneumonia)	NR
NCT03158129 NEOSTAR[13]	44	Nivolumab (N) vs. ipilimumab (I) + N	6/44 (14%) grade 3-5 N: grade 3 pneumonia, hypoxia hypermagnesemia (each 1/23 [4%]); grade 5 pneumonitis (1/23 [4%]) NI: grade 3 diarrhea (1/21 [5%]), hyponatremia (1/21 [5%])	NR
NCT02938624 MK3475-223[24]	15	Pembrolizumab	2/15 (13%) treatment-related SAEs Grade 3 myositis: 7%; grade 3 fatigue: 7%	NR
ChiCTR-OIC-17013726[23]	40	Sintilimab	4/40 (10%) Pneumonitis: 2/40 (5%), γ-glutamyltransferase increased: 1/40 (2.5%), blood creatinine phosphokinase increased: 1/40 (2.5%), lung infection: 1/40 (2.5%)	NR
Combination immunotherapy plus chemotherapy				
NCT02716038 Columbia[7]	30	Atezolizumab + carboplatin + nab-paclitaxel	28/30 (93%) Increased ALT: 2/30 (7%), increased AST: 2/30 (7%), diarrhea: 1/30 (3%), anemia: 1/30 (3%), fatigue: 1/30 (3%), febrile neutropenia: 1/30 (3%), hyperglycemia: 1/30 (3%), hyponatremia: 1/30 (3%), neutropenia: 15/30 (50%), thrombocytopenia: 2/30 (7%), weight loss: 1/30 (3%)	Possible irAEs were arthralgia or myalgia (grade 1/2; 5/30 [17%]), diarrhea (grade 1/2; 8/30 [30%]; grade 3; 1/30 [3%]), increased ALT (grade 1/2; 4/30 [13%]; grade 3; 2/30 [7%]), increased AST (grade 1/2; 3/30 [10%]; grade 3; 2/30 [7%]), hypothyroidism (grade 1/2; 3/30 [10%]), hyperglycemia (grade 4; 1/30 [3%])
NCT02572843 SAKK 16/14[50]	67	Durvalumab + cisplatin/docetaxel	Grade ≥3 all-cause AEs during neoadjuvant treatment: Chemotherapy: 45/67 (67%) Durvalumab: 8/62 (13%)	NR
NCT01820754 TOP1201[22]	13	Ipilimumab + chemotherapy	Grade 3/4: 46%	Grade 2 pneumonitis: 1/24 (4%); grade 3 adrenal insufficiency: 4/24 (17%); diarrhea/colitis (grade 1 or 2; 6/24 [25%]; grade 3; 3/24 [13%])
NCT03081689 NADIM[51]	46	Nivolumab + paclitaxel + carboplatin	Grade 3-5: 11/46 (24%) Neutropenia: 3/46 (7%), febrile neutropenia: 2/46 (2%), peripheral sensory neuropathy: 2/46 (4%), anorexia: 1/46 (2%), fatigue: 1/46 (2%), alopecia: 1/46 (2%), nephritis: 1/46 (2%)	NR
NCT03366766[52]	13	Nivolumab + cisplatin + pemetrexed or gemcitabine	Grade 3: 2/13 (15%) Neutropenia: 2/13 (15%), anemia: 1/13 (8%), renal dysfunction: 1/13 (8%)	NR

[a]Also termed "AESIs."

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ID, identifier; irAE, immune-related adverse event; N, nivolumab, NI, nivolumab + ipilimumab; NR, not reported; Pt, patient; SAE, serious adverse event; TRAE, treatment-related adverse event.

the treatment and management of irAEs after ICI therapy.[30,31]

Preoperative End Points in Neoadjuvant ICI Trials

Defining and Standardizing End Points for Timelines From Diagnosis to Surgery

To evaluate the extent to which neoadjuvant immunotherapy delays surgery, reporting of timelines from diagnosis to surgery would be informative, particularly in the ongoing phase 3 studies. The times from screening to the first neoadjuvant treatment cycle (time end point A; Fig. 1) and from the last treatment cycle to surgery (time end point C; Fig. 1) are universal in protocols and are the most relevant periods to measure. Although the time from radiographic to tissue diagnosis varies, screening duration (time end point A) may be shortened by early referral to the clinical trial team and thoracic surgery, allowing screening and preoperative workup to occur in parallel.

Duration of neoadjuvant therapy (time end point B; Fig. 1) was generally one to three cycles in phase 2 neoadjuvant ICI trials (Table 2) and three to four cycles in phase 3 neoadjuvant ICI plus CT trials (Supplementary Table 1). Hence, assessment of pathologic regression (resection) generally occurs later and after more cycles of ICI in phase 3 than in phase 2 trials.

Safety is typically measured by the frequency of TRAEs. Nevertheless, the duration from the end of neoadjuvant therapy to resection (time end point C; Fig. 1) and the protocol-defined window for surgery (time end point D) can both reflect the time to recovery from neoadjuvant therapy toxicity, and this "delay" to surgery is rarely reported. Indeed, the start of the protocol-defined window for surgery varies widely between studies. Delays to surgery owing to neoadjuvant drug toxicity are thus often masked by trial design around time end points C and D, complicating the interpretation of "no delays to surgery" in trials. Only two phase 2 studies of neoadjuvant ICIs specifically reported these types of delays to surgery. In LCMC3, non–AE-related delays outside the protocol-specified 10-day window occurred in 8% of patients.[21,32] In the NEOSTAR study of nivolumab versus nivolumab plus ipilimumab, 22% of patients had their surgery delayed beyond 42 days.[13,33]

Preoperative Attrition End Points

Progressive disease (PD) during neoadjuvant therapy that leads to unresectability is a potential disadvantage of neoadjuvant ICI therapy. As such, it is imperative to report the proportion of patients not undergoing planned surgery (preoperative attrition rate; Fig. 1). It is difficult to distinguish unresectability owing to locally advanced or metastatic disease at presentation from preoperative unresectability after delayed resection after neoadjuvant ICI therapy. Patients selected for neoadjuvant therapy should have resectable disease, with anticipated pathologic complete resection (R0) at baseline. Although controversial, preoperative identification of multistation mediastinal lymph node metastasis or direct mediastinal organ invasion may be exclusionary criteria, given the propensity for unresectability. Pathologic mediastinal staging by endobronchial ultrasound or mediastinoscopy is therefore recommended before neoadjuvant therapy. Surgical evaluation to exclude mediastinal organ invasion during screening is essential to reduce unresectability rates.

In large multicenter studies of neoadjuvant CT, less than 1% to 14% of patients had PD on computed tomography and 1% to 10% of patients did not undergo resection owing to PD (Table 1). In phase 2 studies of neoadjuvant ICI with or without CT, similar preoperative attrition (0%–8%) was due to PD (Table 2).

Neoadjuvant Therapy End Points

Although the intent of neoadjuvant therapy is not to achieve downstaging to render the disease operable, tumor downstaging after neoadjuvant therapy predicts better survival.[34] Appropriate candidates for neoadjuvant therapy should have R0 resectable disease on the basis of baseline scans, confirmed by a multidisciplinary tumor board or consilium. Nodal downstaging predicted survival after neoadjuvant CT for stage IIIA (N2) NSCLC in CALGB protocol 893: patients with resected and no residual N2 disease had superior EFS compared with patients with persistent N2 disease (47.8 versus 8.2 mo, respectively).[35] It is therefore imperative to collect data on pretreatment clinical and posttreatment clinical and pathologic stages to allow assessment of down- and upstaging after neoadjuvant therapy (downstaging end points; Fig. 1). Both clinical and pathologic staging are important, given that the agreement between clinical and pathologic TNM staging is only 46.4%, with the greatest discordance observed in stages II and IIIA.[36] Lymph node downstaging, particularly pathologic clearance or sterilization of N2 metastasis, is also an important end point. Ongoing phase 3 trials may have more stringent inclusion criteria regarding nodal staging than phase 2 studies, which may affect the proportions of patients who have PD that prevents surgery.

End Points for Surgical Complexity, Outcomes, and Complications After Neoadjuvant Immunotherapy

Intraoperative Unresectability After Neoadjuvant Therapy

In neoadjuvant CT studies, 1% to 6% of patients did not have surgery owing to intraoperative unresectability (Table 1). Rates of intraoperative unresectability in trials of neoadjuvant ICI therapy (0%–5%) and ICI plus CT (0%–10%) were comparable (Table 2). To facilitate comparison between different agents and regimens, rates of intraoperative unresectability (gross residual disease; R2 resection) or microscopic residual disease (R1 resection) should be reported for neoadjuvant immunotherapy studies (operative end points: R0 resection rate; Fig. 1). Incomplete resection negatively affects OS irrespective of stage.[37]

Although not often reported, information on the clinical characteristics of patients who are found pre- or intraoperatively to have unresectable disease would help define subgroups unlikely to respond to neoadjuvant immunotherapy, independent of pathologic response. In LCMC3, 5% of patients, all having stage IIIA disease, had preoperative PD resulting in unresectability. An additional 6% found intraoperatively to have PD had stage IIIA or IIIB disease (Table 2).[21] In CheckMate 159 (neoadjuvant nivolumab), one patient (5%) with stage IIIA disease was found intraoperatively to have tracheal invasion.[14]

End Points of Oncologic Lung Cancer Resections

Assessing the quality of NSCLC surgeries in multicenter phase 3 trials can be challenging. Nevertheless, recommendations for defining oncologic resection should be incorporated into study protocols, and these data should be collected prospectively.

Resection may be accomplished by means of an open (thoracotomy, sternotomy, clamshell, or hemiclamshell incision) or minimally invasive (video- or robot-assisted thoracoscopic surgery) approach.[26,38] R0 resection (operative end points; Fig. 1) should be the initial intent at baseline. Anatomical resection by means of segmentectomy, lobectomy, bilobectomy, or pneumonectomy is strongly preferred.

Hilar and mediastinal lymph node dissection or sampling should also be performed (operative end points; Fig. 1). For right-sided resections, this involves lymph nodes from at least levels 4R, 7, 10R, and 11R. For left-sided resections, this involves lymph nodes from at least levels 5/6, 7, 10L, and 11L. Level 8 and 9 lymph nodes should be assessed by dissection or sampling, particularly for lower lobe cancers. In addition, prospective data on intraoperative complications for bronchial or vascular injuries should be collected (operative end points; Fig. 1).

As in neoadjuvant CT studies (Table 1), lobectomy was the most common type of resection performed in phase 2 neoadjuvant ICI studies (65%–93% after monotherapy or dual immunotherapy and 73%–93% after ICI plus CT; Table 4). R0 rates ranged from 87% to 100%. In CheckMate 159, a total of 50% of conversions to thoracotomy owing to adhesions (two of four) were in patients with stage I or IIA disease.

Measures of Surgical Complexity

Resection after neoadjuvant CT can be technically demanding owing to fibrosis.[39] Fibrosis is often pronounced at sites of hilar and mediastinal lymph nodes.[40] Surgeons may have the perception that neoadjuvant immunotherapy increases the inherent complexity of resection or query whether pneumonectomy and bilobectomy are safe after neoadjuvant ICI.

To preclude subjectivity underlying these perceptions, we propose a grading system to assess intraoperative complexity (Table 5). Although this scale has not been previously reported, it is an attempt to standardize the quantification of intraoperative lymphadenopathy, peripheral fibrosis, central versus peripheral lung cancer, and perihilar or lobar adhesions (Table 5; operative end points in Fig. 1). Additional factors include cut-to-close time, estimated blood loss, and conversion rates from minimally invasive to open surgery (operative end points; Fig. 1). NEOSTAR provided data on surgical complexity.[33] On a subjective 4-point complexity scale that assumed a score of 2 as "normal dissection," representing standard lobectomy for stage I NSCLC without neoadjuvant therapy, 40% of 37 surgeries were judged to be more difficult than usual (i.e., score $\geq$3).[33] The median operative time was 147 minutes (range: 71–315 min); median blood loss was 100 mL (range: 50–1000 mL).[33]

Postoperative End Points of Surgical Outcomes and Complications

Where available, data on resection rates, surgical approach, and morbidity and mortality rates after neoadjuvant CT (Table 1) can be used as benchmarks for comparison with ongoing phase 2 neoadjuvant ICI studies (Table 4). Where reported, 30-day postoperative mortality rates after neoadjuvant CT ranged from 3% to 10% (Table 1). The most often reported postoperative complications with neoadjuvant CT were pulmonary, with pneumonia occurring in 3% to 10% and bronchopleural fistula in 2% to 5% of patients. Prolonged air leak occurred in 9% of patients with resected disease in the SWOG S9900[4] and EORTC 08941 studies.[39]

Table 4. Surgical Outcomes After Neoadjuvant Immunotherapy in Phase 2 Studies

Study ID Trial Name	No. of Surgical Pts	Neoadjuvant tx	Type of Surgery	Surgical Approach	Resection Rate	Mortality	Surgical Complications/ Morbidity	Bleeding Requiring Transfusion	Pneumonitis	Pneumonia	Bronchopleural Fistula	Prolonged Air Leak	Resp Failure	Median LOS (d)
Immunotherapy as mono therapy or dual therapy														
NCT02994576 PRINCEPS[12]	30	Atezolizumab	Pneumonectomy: 2/30 (7%) Lobectomy: 28/20 (93%)	NR	R0: 29/30 (97%) R1: 1/30 (3%)	0	7/30 (23%) (grade ≤3)	NR	0	0	0	1/30 (3%)	0	NR
NCT01820754 TOP1201[22]	13	Ipilimumab	Pneumonectomy: 1/13 (8%) Lobectomy: 10/13 (77%) Bilobectomy: 1/13 (8%) Wedge resection: 1/13 (8%)	Open: 1/13 (8%) VATS: 9/13 (69%) Converted VATS to open: 3/13 (23%)	R0: 13/13 (100%)	0	9/13 (69%)	2/13 (15%)	0	0	0	2/13 (15%)	0	5 (IQR: 4-6)
NCT02259621 CheckMate 159[41]	20	Nivolumab	Lobectomy: 15/20 (75%) Pneumonectomy: 2/20 (10%) Bilobectomy: 1/20 (5%) Wedge resection: 1/20 (5%) Sleeve lobectomy: 1/20 (5%)	Thoracotomy: 14/20 (70%) Thoracoscopy: 3/20 (14%) RATS: 3/20 (14%) Conversion rate: 7/13 (54%)	NR	0	10/20 (50%)	0	0	1/20 (5%)	0	1/20 (5%)	0	4 (range: 2-17)
NCT03158129 NEOSTAR[13,33]	37	Nivolumab	Lobectomy: 30/37 (81%) Sleeve lobectomy: 2/37 (5%) Bilobectomy: 1/37 (2%) Pneumonectomy: 2/37 (5%) Segmentectomy: 1/37 (2%) Wedge resection: 1/37 (2%)	Thoracotomy: 27/37 (73%) VATS: 7/37 (19%) RATS: 3/37 (8%) Conversion: 2/12 (17%)	R0: 37/37 (100%)	0	13/21 (62%)	0	1/21 (5%)	1/21 (5%)	1/21 (5%)	5/21 (24%)	0	4 (range: 1-18)
				Nivolumab + ipilimumab		1/21 (5%; pneumonitis; BPF/ ARDS)	6/16 (38%)	0	1/16 (6%)	1/16 (6%)	0	3/16 (19%)	0	
ChiCTR-OIC-17013726[23]	37	Sintilimab	Lobectomy: 24/37 (65%) Pneumonectomy: 13/37 (35%)	NR	R0: 36/37 (97%) R2: 1/37 (3%)	30-d: 1/37 (3%; immune-related pneumonia)	4/37 (11%)	NR	0	1/37 (3%)	0	0	0	NR
Combination immunotherapy plus chemotherapy														
NCT02716038 Columbia[7]	29	Atezolizumab + carboplatin + nab-paclitaxel	Lobectomy: 73% Bilobectomy: 15% Pneumonectomy: 12%	VATS: 12/26 (46%) Thoracotomy: 14/26 (54%)	R0: 26/29 (87%)	30-d: 1/29 (3%; pneumonia and respiratory failure)	6/29 (21%); none related to neoadjuvant treatment	2/29 (7%)	0	1/29 (3%; resulted in death)	0	0	1/29 (3%; resulted in death)	4 (IQR: 3-6)
NCT02572843 SAKK 16/14[50]	55	Durvalumab + cisplatin + docetaxel	Pneumonectomy: 5/55 (9%) Lobectomy: 43/55 (78%) Bilobectomy: 5/55 (13%)	NR	R0: 50/55 (91%) R1: 3/55 (6%) R2: 2/55 (4%)	30-d: 1/55 (2%)	Grade 3-5: 17/55 (31%)	NR	NR	NR	NR	NR	NR	NR
NCT03081689 NADIM[51]	41	Nivolumab + paclitaxel + carboplatin	Lobectomy: 38/41 (93%) Pneumonectomy: 3/41 (7%)	NR	R0: 41/41 (100%)	0	12/41 (29%)	0	0	0	Respiratory infection: 5/41 (12%)	2/41 (5%)	0	NR

ARDS, acute respiratory distress syndrome; BPF, bronchopleural fistula; IQR, interquartile range; LOS, length of (hospital) stay; NR, not reported; Pt, patient; RATS, robotic-assisted thoracoscopic surgery; tx, treatment; VATS, video-assisted thoracoscopic surgery.

Early data on postoperative complications in phase 2 neoadjuvant ICI studies should be interpreted with caution owing to the small study populations (13–55 patients; Table 4). The 30-day mortality rate was 0% to 5% and, where collectively reported, surgical complications or morbidity occurred in 11% to 69% of patients. Pneumonitis occurred in 5% and 6% in each treatment arm, respectively, in NEOSTAR and led to one death (5%).[41] Pneumonia occurred in 0% to 6% of patients (Table 4) and led to one patient death in ChiCTR-OIC-17013726.[42] Bronchopleural fistula was only reported in NEOSTAR (9% in the nivolumab arm).[13] Prolonged air leak occurred in 19% and 24% of patients, respectively, in NEOSTAR,[33] 15% of patients in TOP1201,[22] and 5% of patients in CheckMate 159.[41]

Postoperative end points that measure mortality, morbidity, and length of hospital stay after resection should be collected prospectively in clinical trials (postoperative end points; Fig. 1). To determine whether neoadjuvant immunotherapy increases the risk of prolonged air leak, defined as persisting longer than 5 days postoperatively,[43] this metric should be reported for all ongoing and planned neoadjuvant ICI studies.

Impact of Neoadjuvant Immunotherapy on Adjuvant Therapy for NSCLC

Adjuvant CT trials reveal that one-third of patients received adjuvant CT more than 8 to 12 weeks after surgery,[44] and in NATCH, one-third of patients never received adjuvant CT.[45] Hence, even without preoperative ICI therapy, adjuvant immunotherapy may be delayed or omitted. With the exception of CheckMate 816, the ongoing phase 3 neoadjuvant therapy trials in Supplementary Table 1 all include adjuvant immunotherapy maintenance therapy, which is likely to be better tolerated than adjuvant CT and could be started sooner after surgery. Adjuvant immunotherapy may potentially contribute to durable responses and improved overall OS and EFS benefits.

In comparing the different ICI regimens in phase 3 trials, the agent associated with a high proportion of patients receiving neoadjuvant immunotherapy and continuing to adjuvant immunotherapy, along with a low toxicity profile, would distinguish itself. Hence, postoperative attrition rate in patients not receiving adjuvant ICI therapy is an important end point (postoperative attrition rate; Fig. 1). It remains unclear whether preoperative treatment with ICI plus CT warrants universal application of adjuvant ICI therapy to achieve prolonged OS, particularly in patients who achieve pCR after neoadjuvant therapy. In other words, the threshold to achieve a durable response to ICI therapy with prolonged OS may be variable and predicated on the degree of pathologic regression.

Summary and Perspectives

Clinical trials in resectable NSCLC reveal the impact of neoadjuvant ICIs on surgery using parameters that are variably defined and reported. Although achieving superior clinical and oncologic outcomes should take precedence over concerns on delays to potentially curative surgery or perceptions of increased surgical complexity, these factors may reduce physician willingness to enroll patients into neoadjuvant therapy trials or recommend neoadjuvant therapy.

The reporting of time end points surrounding preoperative therapy from diagnosis to planned surgery as suggested in Figure 1 should therefore be standardized among neoadjuvant immunotherapy trials to reveal the distinguishing characteristics of different ICI regimens and varying durations of resection delay. The time from screening to first treatment cycle and the time from last neoadjuvant therapy dose to surgery are the most important periods to measure. Clearly defining and reporting the allowable window for surgery would preclude masking delays to surgery caused by neoadjuvant treatment-related toxicity. To reduce the time to resection, patient screening by clinical trial coordinators should be conducted in parallel with the presurgical workup ordered by the thoracic surgeon.

The proportion of patients in phase 2 neoadjuvant immunotherapy studies whose surgery was delayed owing to irAEs was generally small (0%–15%, where reported). Nevertheless, a standardized list of irAEs with information on their onset and resolution in clinical trials would better prepare surgeons for what to expect and which tests to perform to ensure that the patient is fit for surgery after neoadjuvant immunotherapy.

Patients with stages II to IIIA or B and possibly those with stage IB disease seem to be ideal candidates for neoadjuvant immunotherapy. More data on the clinical characteristics of patients found pre- or intraoperatively to have unresectable disease would help define the patient subgroups unlikely to respond to neoadjuvant ICI therapy, independent of pathologic response. Although controversial, patients at higher risk for unresectability, such as those with T4 tumors with direct mediastinal invasion or multistation N2 disease, may be considered for exclusion from neoadjuvant trials.

Data from intraoperative end points that allow quantitation of surgical technical difficulty and quality of oncologic resection should be collected. Standardized

Table 5. Proposed Scales for Intraoperative Quantification of Surgical Complexity in Early NSCLC After Neoadjuvant Immunotherapy

Grade	Characteristics
Nonmalignant lymphadenopathy	
0	Lymphadenopathy <1 cm
1	Lymphadenopathy 1 to <2 cm
2	Lymphadenopathy 2 to <3 cm
3	Lymphadenopathy ≥3 cm
Peripheral (pleural) fibrosis	
1	Mild fibrosis (no substantial impact on conduct of surgical resection)
2	Moderate fibrosis (requires increased effort and dissection during resection but otherwise does not severely impact the conduct of the surgery)
3	Severe fibrosis (substantially impacts the conduct of the operation by increasing the duration of or blood loss during the surgery, or requires converting minimally invasive to open surgery)
4	Severe fibrosis resulting in unresectability
Central vs. peripheral lung cancer	
1	Central (inner two-thirds of lung)
2	Peripheral (outer two-thirds of lung)
Perihilar/lobar or mediastinal adhesions	
1	Mild fibrosis (no substantial impact on conduct of surgical resection)
2	Moderate fibrosis (requires increased effort and dissection during resection but otherwise does not severely impact the conduct of the surgery)
3	Severe fibrosis (substantially impacts the conduct of the operation by increasing the duration of or blood loss during the surgery, or requires converting minimally invasive to open surgery)
4	Severe fibrosis resulting in unresectability

grading of complexity with respect to lymphadenopathy and fibrosis would address any subjectivity underlying perceptions that surgery after ICI therapy is more difficult than after CT. Demonstration of high R0 rates in phase 3 trials would further increase confidence in neoadjuvant immunotherapy. Postoperative end points measuring 30- and 90-day mortality rates and morbidity are imperative and should be reported in addition to the standard tracking of TRAEs.

In conclusion, common end points that describe how neoadjuvant immunotherapy affects surgery are needed to complement the pathologic end points emerging as potential surrogate markers of neoadjuvant treatment efficacy. These end points should be standardized, prospectively collected, incorporated into clinical trial designs, and consistently reported to shed light on the full impact of neoadjuvant immunotherapy on surgery and ultimately clinical oncologic outcomes.

CRediT Authorship Contribution Statement

Jay M. Lee: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing—original draft, Writing—review and editing, Visualization, Supervision, Project administration.

Anthony W. Kim: Conceptualization, Methodology, Writing—original draft, Writing—review and editing, Visualization.

Tomasz Marjanski, Pierre-Emmanuel Falcoz: Writing—original draft, Writing—review and editing, Visualization.

Masahiro Tsuboi: Writing—review and editing.

Yi-Long Wu: Conceptualization, Writing—review and editing.

Shawn W. Sun: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing—review and editing.

Barbara J. Gitlitz: Conceptualization, Writing—original draft, Visualization.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org/ and at https://doi.org/10.1016/j.jtocrr.2021.100221.

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