Neoadjuvant immunotherapy in patients with resectable non–small cell lung cancer

Stephen R. Broderick, MD, MPHS,^a and Matthew J. Bott, MD^b

From the ^aSidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Md; and

^bThoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY.

Dr Bott is supported in part by National Institutes of Health Cancer Center Support Grant P30 CA008748.

Received for publication Feb 26, 2019; revisions received June 7, 2019; accepted for publication June 17, 2019.

Address for reprints: Stephen R. Broderick, MD, MPHS, 600 N Wolfe St, Blalock 240, Baltimore, MD 21287

(E-mail: sbroder7@jhmi.edu).

J Thorac Cardiovasc Surg 2019;158:1471-4

0022-5223/\$36.00

Copyright © 2019 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2019.06.114>

Feature Editor's Note—Our current era will be renowned for a widespread application of immune checkpoint blockade to human malignancies. In 2018, the Nobel Prize in Medicine was jointly awarded to James Allison of the MD Anderson Cancer Center and Japanese immunologist Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation. Agents targeting immune checkpoints, including PD-1, PD-L1, and CTLA-4, block a cancer-derived inhibitory signal on effector T cells and have recently been applied to the spectrum of nearly all human solid tumors. The efficacy of checkpoint inhibition on common malignancies, such as non–small cell lung cancer (NSCLC), is so significant that it is speculated that these drugs will improve the survival of patients with cancer in general. In recent years, randomized data supporting the efficacy of checkpoint blockade in NSCLC has been explosive, and checkpoint inhibitors have become first-line therapy for the majority of patients with metastatic disease. Efficacy in stage IV NSCLC has naturally resulted in investigation of these drugs in earlier stage cancers, including locally advanced NSCLC and even stage I tumors. On the basis of randomized data, checkpoint inhibitors have recently become incorporated into the standard-of-care chemoradiotherapy regimens for patients with inoperable stage III NSCLC, and these results have been extended to recommendations of similar treatment approaches for patients with inoperable stage II disease. Neatly summarized in the Feature Expert Opinion article that follows are the 6 phase II and 3 phase III clinical trials currently evaluating survival and pathologic response by neoadjuvant checkpoint inhibitor regimens in surgically resectable NSCLC. Herein, experienced authors review the available data for neoadjuvant checkpoint blockade in NSCLC and prepare our readers for the expected proliferation of checkpoint blockade-treated patients in our operating rooms.

Bryan M. Burt, MD

Matthew J. Bott, MD (left), and Stephen R. Broderick, MD, MPHS (right).

Central Message

Results from phase II and III clinical trials suggest neoadjuvant immunotherapy is a promising strategy for patients with resectable lung cancer; however, critical questions remain to be answered.

This Invited Expert Opinion provides a perspective on the following paper: *N Engl J Med*. 2018; 378:1976-1986. <https://doi.org/10.1056/NEJMoa1716078>.

T-cell checkpoint inhibition has become an important treatment option for patients with non–small cell lung cancer (NSCLC). Recent randomized clinical trials have demonstrated a survival benefit associated with combination platinum-based chemotherapy and anti-PD-1 therapy, compared with chemotherapy alone, in patients with metastatic NSCLC.^{1,2} On the basis of these findings, T-cell checkpoint inhibition is now recommended as first-line therapy for the majority of patients with stage IV lung cancer.³ The success of these agents in patients with metastases has created enthusiasm for using them to treat patients with earlier stage disease. Further interest in this approach was generated by the publication of the results of the PACIFIC (Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non–Small Cell Lung Cancer) trial, which showed that the addition of the anti-PD-L1 drug durvalumab to definitive chemoradiation improved survival in patients with stage III disease.^{4,5} This study specifically enrolled patients with unresectable disease, however, and the benefit of this strategy in patients with resectable disease remains unknown.

The appropriate timing of surgery in relation to T-cell checkpoint inhibition for patients with NSCLC is unclear. Although data on this topic are scarce, the rationale for

using neoadjuvant treatment, rather than adjuvant treatment, is based on the premise that in situ tumor may provide a more substantial neoantigen load, thus allowing enhanced immune recognition and drug efficacy. Indeed, a preclinical study with a murine model of breast cancer demonstrated that the administration of anti-PD-1 therapy before resection of the primary tumor was associated with improved survival and a more robust tumor-specific CD8⁺ T-cell response relative to adjuvant treatment.⁶ The applicability of these findings to patients with lung cancer, however, has yet to be established.

Initial data on preoperative checkpoint inhibition in patients with lung cancer were recently published by Forde and colleagues,⁷ who performed a prospective phase II trial to evaluate the utility of induction nivolumab in patients with surgically resectable NSCLC. This pilot study was a collaboration between researchers at Johns Hopkins and Memorial Sloan Kettering. Twenty-one patients with resectable stage IB to IIIA NSCLC were treated with 2 doses of nivolumab administered 2 weeks apart, followed by resection 4 weeks after the initial dose. In accordance with the phase II status of the study, the primary end points were safety and feasibility. In addition, the investigators collected clinical and correlative data to explore novel mechanisms underlying the response to this treatment.

In general, the treatment approach appeared to be safe, as all patients proceeded to surgical resection within the expected 4-week time frame. In 5 of 22 patients (23%), treatment-related adverse events occurred, the most common of which were loss of appetite (10%) and vomiting or diarrhea (14%). Only 1 grade 3 or greater complication (postobstructive pneumonia after a single dose of nivolumab) was observed. Although this complication prevented administration of the second dose, the patient underwent resection on schedule.

On postresection pathologic evaluation, treatment response was impressive, with a major pathologic response (MPR; defined as $\leq 10\%$ of viable tumor remaining) rate of 45%. Similarly, pathologic downstaging occurred in 40% of patients. Although the study was not specifically designed to assess survival, 16 of 20 patients (80%) were alive and disease free at a median of 12 months of follow-up. Interestingly, whereas MPR was seen in both patients with PD-L1–positive and PD-L1–negative tumors, patients with higher tumor mutational burden were more likely to have MPR. Also of note, despite the high rate of pathologic response, the majority of patients (86%) had stable disease on computed tomographic scan after nivolumab treatment, which suggests there are important discrepancies between clinical and pathologic response in this context.

T-cell receptor sequencing of peripheral blood after administration of nivolumab showed expansion of

neoantigen-specific T-cell clones within 2 weeks of the initial dose, providing insight into possible mechanisms of action. Similarly, PD-1/PD-L1 expression appeared to be dynamic and varied among the cells in the tumor microenvironment; 1 patient with MPR had PD-L1–negative tumor cells, but PD-L1–positive CD8⁺ T cells and increased PD-L1 expression was seen after nivolumab treatment.

Although the prospect of neoadjuvant immunotherapy has generated excitement among surgeons, there are substantial concerns regarding the inflammatory mechanism of action of these agents and technical challenges this may pose at the time of surgery, as well as drug side effects, such as pneumonitis and endocrinopathies, that may become problematic in the postoperative period. To address this, a subsequent post hoc analysis of this trial was conducted with a particular emphasis on perioperative safety and complications. The results, published recently here in the *Journal*, demonstrate that patients treated with this approach did not have unexpected morbidity, and there were no deaths in this series.⁸ Although complications occurred in 50% of patients, serious morbidity was rare. Six patients (30%) had atrial fibrillation develop, and there was 1 instance each of postoperative pneumonia, empyema, and prolonged air leak (5% of cases for each). The median operative time was 228 minutes, which appears to be on par with other postinduction case series and does not indicate an increase in operative difficulty. Blood loss was typically low (median, 100 mL). Conversion from video-assisted thoracoscopic surgery or robotic surgery to thoracotomy, however, was performed in 54% of cases, in some instances because of difficulty with dissection and perihilar inflammation.

These safety data confirm the findings of several previous small studies. Yang and associates⁹ performed a prospective study of 13 patients with stage II to IIIA NSCLC treated with the anti-CTLA-4 agent ipilimumab as a planned neoadjuvant strategy before lung resection.⁹ Neither morbidity nor mortality was increased in their cohort relative to historical controls who received standard chemotherapy induction. Similarly, a study from Memorial Sloan Kettering that evaluated patients undergoing lung resection for previously metastatic or unresectable malignancy showed acceptable perioperative outcomes, with an overall morbidity rate of 32%.¹⁰ Although most complications were minor (grade 1 or 2), even in this heavily pretreated population, there was 1 instance of grade 4 pneumonitis 2 weeks after video-assisted thoracoscopic surgical wedge resection that required intensive care unit admission and mechanical ventilation before the patient proceeded to full recovery.

Although the results from these small series are encouraging, the safety of preoperative checkpoint inhibition still needs to be confirmed in larger trials. Additional data on

safety and efficacy will be provided by the several neoadjuvant studies that are either planned or underway, including 4 randomized phase III trials. IMPower 030 (A Study of Neoadjuvant Atezolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in Patients With Resectable Stage II, IIIA, or Select IIIB Non–Small Cell Lung Cancer; NCT03456063) is evaluating neoadjuvant platinum doublet chemotherapy in conjunction with either atezolizumab or placebo in patients with stage II or IIIA NSCLC. Select patients with stage IIIB (T3N2) tumors are also eligible for participation. CheckMate 816 (A Neoadjuvant Study of Nivolumab Plus Ipilimumab Plus Chemotherapy Versus Chemotherapy Alone in Early Stage Non–Small Cell Lung Cancer; NCT02998528) is comparing neoadjuvant platinum-based chemotherapy plus nivolumab versus chemotherapy alone in patients with stage IB (>4 cm) to IIIA NSCLC. A third arm of the study in which patients received nivolumab plus ipilimumab has been discontinued. Keynote 671 (Efficacy and Safety of Pembrolizumab [MK-3475] With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage II, IIIA, and Resectable IIIB [T3-4N2] Non–Small Cell Lung Cancer; NCT03425643) is another placebo-controlled trial that is examining standard chemotherapy with or without pembrolizumab in the neoadjuvant setting. A similar phase III study investigating preoperative and postoperative durvalumab in patients with stage III NSCLC (NCT03800134) is scheduled to open in the near future. Event-free survival is the primary end point for CheckMate 816 and Keynote 671, whereas most other studies assess MPR as the surrogate end point. The available details of these phase III studies, including additional

end points, target enrollments, and estimated completion dates, are shown in Table 1.

Multiple phase II studies investigating neoadjuvant regimens continue to enroll patients. The largest of these phase II trials (NCT02927301), which is underway at centers in the Lung Cancer Mutation Consortium, is assessing the efficacy of 2 doses of atezolizumab before resection. This study is designed to accrue 180 patients, with MPR as the primary end point. Preliminary results from the first 54 patients, presented in abstract form, suggest that neoadjuvant atezolizumab is well-tolerated, with surgery delayed in only 1 patient, because of pneumonitis. On the basis of this preliminary analysis, the MPR rate is encouraging (20%). The NEOSTAR trial (Nivolumab With or Without Ipilimumab or Chemotherapy in Treating Patients With Previously Untreated Stage I-IIIa Non–Small Cell Lung Cancer; NCT03158129), conducted at MD Anderson Cancer Center, is comparing the combination of nivolumab and ipilimumab with nivolumab monotherapy in the neoadjuvant setting in patients with stage I-IIIa NSCLC. The rationale for the addition of ipilimumab was provided by the results of the CheckMate 012 study (stage III-IV NSCLC), which demonstrated improved progression-free survival in patients treated with nivolumab and ipilimumab, compared with nivolumab monotherapy.¹⁰ Finally, the Spanish NADIM (Neo-Adjuvant Immunotherapy With Nivolumab for Non–Small Cell Lung Cancer Patients; NCT03081689) trial is evaluating the neoadjuvant combination of chemotherapy and nivolumab in patients with resectable stage IIIa NSCLC. The primary end point for this study is progression-free survival; however, preliminary results presented in abstract form demonstrate an MPR rate of 80%

TABLE 1. Select ongoing trials of neoadjuvant immunotherapeutic agents in resectable non–small cell lung cancer

Trial	Phase	Stage	Neoadjuvant intervention	Primary end point(s)	Target accrual
NCT03425643 (KEYNOTE-671)	III	IIB, IIIA	Pembrolizumab + platinum doublet vs platinum doublet	EFS, OS	786
NCT03456063 (IMpower-030)	III	II-IIIa, select IIIB (T3N2)	Atezolizumab + platinum doublet vs platinum doublet	MPR	302
NCT02998528 (CheckMate-816)	III	IB-IIIa	Nivolumab + platinum doublet vs platinum doublet	EFS, pCR	624
NCT03158129 (NEOSTAR)	II	I-IIIa	Nivolumab ± ipilimumab	MPR	66
NCT02259621	II	IB-IIIa	Nivolumab ± ipilimumab	MPR	30
NCT02927301 (LCMC3)	II	IB-IIIa	Atezolizumab	MPR	180
NCT02572843	II	IIIa (N2)	Cisplatin/docetaxel + durvalumab	EFS	68
NCT02818920 (TOP1501)	II	IB-IIIa	Pembrolizumab (neoadjuvant + adjuvant)	Surgical feasibility	32
NCT03237377	II	IIIa	Durvalumab + radiation	Safety	32

EFS, Event-free survival; OS, overall survival; MPR, major pathologic response; pCR, pathologic complete response.

and an impressive complete pathologic response rate of 60% in resected patients.¹¹

Although important clinical trials are still ongoing, data from completed and ongoing series suggest that neo-adjuvant immunotherapy is a promising treatment strategy for patients with resectable lung cancer. Nonetheless, critical questions remain to be answered, including optimal drug regimens, timing of surgery in regard to treatment, and whether additional adjuvant therapy is needed. Similarly, for patients with locally advanced disease (N2), the role of pre- or postoperative radiotherapy in this context remains to be explored. Nonetheless, this new paradigm provides hope for improved outcomes in this disease, and surgeon participation in current and future trials will be paramount in defining optimal treatment strategies.

Conflict of Interest Statement

Dr Bott is a consultant for AstraZeneca Pharmaceuticals. Dr Broderick is a consultant for Bristol-Meyers-Squibb.

References

- Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-92.
- Paz-Ares L, Luft A, Vicente D, Tafreshi A, Güümüs M, Mazières J, et al; KEYNOTE-407 Investigators. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040-51.
- National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. Version 3.2019*. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 25, 2019.
- Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al; PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919-29.
- Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al; PACIFIC Investigators. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342-50.
- Liu J, Blake SJ, Yong MC, Harjunpää H, Ngiew SF, Takeda K, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. *Cancer Discov*. 2016;6:1382-99.
- Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med*. 2018;378:1976-86. Erratum in: *N Engl J Med*. 2018;379:2185.
- Bott MJ, Yang SC, Park BJ, Adusumilli PS, Rusch VW, Isbell JM, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2019;158:269-76.
- Yang CJ, McSherry F, Mayne NR, Wang X, Berry MF, Tong B, et al. Surgical outcomes after neoadjuvant chemotherapy and ipilimumab for non-small cell lung cancer. *Ann Thorac Surg*. 2018;105:924-9.
- Bott MJ, Cools-Lartigue J, Tan KS, Dycoco J, Bains MS, Downey RJ, et al. Safety and feasibility of lung resection after immunotherapy for metastatic or unresectable tumors. *Ann Thorac Surg*. 2018;106:178-83.
- Provencio M, Nadal E, Insa A, Campelo RG, Huidobro G, Domine M, et al. Phase II study of neo-adjuvant chemo/immunotherapy for resectable stages IIIa Non-Small Cell Lung Cancer-NADIM Study-SLCG. Presented at: IASLC 19th Annual World Congress on Lung Cancer; September 24, 2018; Toronto, Canada.