ORIGINAL ARTICLE

A Phase 1 Study of Concurrent Neoadjuvant Pembrolizumab Plus Chemoradiation Followed by Consolidation Pembrolizumab in Patients With Resectable Stage IIIA NSCLC

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ABSTRACT

Introduction: Evidence supports the addition of immunotherapy to definitive chemoradiation for unresectable stage IIIA NSCLC. Adding pembrolizumab to neoadjuvant chemoradiation in patients with resectable stage IIIA NSCLC requires study for safety and feasibility.

Methods: Patients with resectable stage IIIA NSCLC received neoadjuvant cisplatin, etoposide, and pembrolizumab concurrently with thoracic radiotherapy of 45 Gy in 25 fractions. Patients without progression underwent resection followed by 6 months of consolidation pembrolizumab. Safety and feasibility were defined as less than or equal to 30% grade 3 or higher pulmonary toxicity or any grade 4 or 5 nonhematologic toxicity. A total of 10 patients were to be enrolled initially. If less than or equal to two patients had events, another 10 were to be enrolled.

Results: The study closed after enrolling nine patients. The median age was 66 (range: 49–76) years. A total of 67% were female. Median follow-up was 38.3 months. Serious adverse events occurred in seven patients, including two grade 5 events: one sudden cardiac arrest in the neoadjuvant phase and one fatal pneumocystis pneumonia after resection. Eight patients were assessable for response. The overall response rate was 67%. Six underwent complete resection. Four achieved pathologic complete response, whereas one additional patient had complete nodal clearance. Median progression-free survival has not been reached. The 3-year overall survival was 64%.

Conclusions: Adding pembrolizumab to neoadjuvant concurrent cisplatin, etoposide, and radiotherapy in resectable stage IIIA NSCLC resulted in an encouraging pathologic complete response rate. Higher-than-expected toxicities

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necessitated trial closure after meeting the rule for infeasibility. The relationship of grade 5 events to the addition of pembrolizumab is unclear.

Keywords: Neoadjuvant; Chemoradiation; Immunotherapy; NSCLC

Introduction

NSCLC remains one of the most prevalent cancers and one of the deadliest cancers in the United States. Of the newly diagnosed patients each year, approximately 20% to 30% will present with locally advanced disease with lymph node involvement. The goal of treatment in these patients remains cure, but only approximately 30% of these patients achieve long-term survival, with most recurring and ultimately having a poor outcome.[1]

For patients deemed capable of undergoing surgical resection of their cancer, neoadjuvant chemotherapy has been studied suggesting similar benefit when given either before resection or in the adjuvant setting.[2] For those with locally advanced disease, trimodality therapy with the addition of concurrent radiation to chemotherapy before surgery was found to have a progression-free survival (PFS) benefit over chemoradiation (CRT) alone, on the basis of data from the Intergroup 0139 trial, and was also effectively used for management of Pancoast tumors in the S9416 trial.[3,4] Nevertheless, recurrence and outcomes in this group remain poor and the need for new therapies or treatment paradigms is paramount.

The introduction of monoclonal antibody immune checkpoint inhibitor (ICI) therapy to the treatment of advanced-stage NSCLC has dramatically improved survival outcomes in this population.[5] In addition, a subgroup analysis of KEYNOTE-001, which tested ICI in advanced disease, suggested an improvement in PFS and overall survival (OS) in patients receiving pembrolizumab who had previously received radiation treatment compared with those who had no previous radiation.[6]

This observation has been explained by the hypothesis of radiation-induced immunogenic cellular death. This phenomenon initially leads to activation of the immune system with increased antigen presentation and lymphocyte infiltration, but over time it leads to immune exhaustion. This in turn leads to up-regulation of programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1), causing an immunosuppressive environment. Treatment with an anti–PD-1 or anti–PD-L1 ICI is thought to counter this immunosuppressive state and allow more durable immunostimulatory responses to radiation.[7,8] ICI therapy added to radiation therapy has also been observed to have benefits owing to the abscopal effect, in which increased efficacy and cancer response are noted outside of the radiation field.[9,10]

In testing the role of immunotherapy in earlier stages of NSCLC, the PACIFIC trial enrolled patients with locally advanced unresectable NSCLC and found improved survival outcomes with the addition of one year of consolidation anti–PD-L1 therapy after standard CRT.[11] More recently, several studies have evaluated the use of neoadjuvant ICI in different combinations in the neoadjuvant setting revealing promising results, particularly in major pathologic response and complete response rates.[12,13]

From this, it is reasonable to question whether the addition of ICI therapy to radiation therapy in the neoadjuvant setting could have additional benefit in the locally advanced, resectable population. Nevertheless, ICIs and radiation are known to independently increase the risk of pneumonitis, so the potential additive effect of this combination needs to be further elucidated to determine the incidence, severity, and possible consequences on the treatment course.

Herein, we present the results of a phase 1 study of the addition of the anti–PD-1 ICI pembrolizumab to neoadjuvant concurrent CRT followed by surgery and consolidation pembrolizumab for treatment in patients with stage IIIA resectable NSCLC with the hypothesis that this regimen would be both safe and feasible.

Materials and Methods

Study Population

This study enrolled patients aged more than or equal to 18 years old, with biopsy-confirmed stage IIIA (T1-3N2M0) NSCLC (adenocarcinoma, squamous cell carcinoma, large cell, or NSCLC NOS) according to the American Joint Committee on Cancer eighth edition with measurable or unmeasurable disease on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. All patients underwent pathologic mediastinal nodal staging before enrollment. Additional eligibility requirements included adequate performance status with an Eastern Cooperative Oncology Group score of 0 to 1, adequate lung and organ function for treatment, and no contraindications to pembrolizumab. Eligible patients had to have been deemed surgically resectable by a thoracic surgeon and not received previous treatment for this cancer diagnosis. Patients were also requested to provide archival tissue from a tumor lesion or undergo new biopsy if tissue was unavailable.

Exclusion criteria included previous treatment for the currently diagnosed cancer, a diagnosis of immunodeficiency or receiving systemic steroid therapy within seven days of the initial trial treatment, active autoimmune disease requiring systemic treatment within the last 2 years (excluding replacement therapy), history of active tuberculosis, or known additional malignancy requiring active treatment. Also excluded are those who were pregnant, breastfeeding, or expecting to conceive; those with a history of human immunodeficiency virus, active hepatitis B, or hepatitis C; and those who have received a live vaccine within 30 days.

All patients were required to sign informed consent to participate in the study.

Study Design

At the time of conceptualization, pembrolizumab had been safely added to platinum-doublet chemotherapy, but had not been tested concurrently with radiation therapy in NSCLC. Therefore, this phase 1 nonrandomized safety and feasibility study was designed on the basis of the risk of developing grade 3 or higher pulmonary toxicity. Ten patients were to be enrolled initially at full doses of all three systemic agents. If three or more ($\geq$30%) had grade 3 or higher pulmonary toxicity, or any grade 4 nonhematologic toxicity, the study was to be stopped. If two or fewer had grade 3 or higher pulmonary toxicity or grade 4 or higher nonhematologic toxicity, then an additional 10 patients were to be enrolled for a total population of 20. Participants would be followed during the treatment period and during surveillance for up to five years after treatment. The protocol was approved by the local institutional review board and carried out in accordance with the Declaration of Helsinki. The trial was registered with ClinicalTrials.gov number NCT02987998. Funding for the trial was provided by Merck.

Treatment Plan

Patients were to receive concurrent induction CRT with all systemic agents being given intravenously (IV). Chemotherapy with cisplatin and etoposide was chosen based off of the Intergroup 0139 trial of neoadjuvant concurrent chemoradiotherapy.[3] Cisplatin 50 mg/m^2 IV was to be given on days 1, 8, 29, and 36 and etoposide 50 mg/m^2 IV on days 1 to 5 and days 29 to 33. Thoracic radiotherapy consisted of a total dose of 45 Gy in 25 fractions beginning on day 1 of chemotherapy. In addition, patients were to receive pembrolizumab 200 mg IV on days 1, 22, and 43. Four weeks after completion of the induction course, patients were to be assessed for radiographic response to therapy by RECIST 1.1 criteria. Those with progressive disease were to be taken off study. Patients with resectable disease without progression were to undergo resection within two weeks of assessment and within six weeks of completion of induction treatment. If patients were deemed inoperable at the time of assessment for medical, anatomical, or reasons other than progressive disease, they would complete definitive radiotherapy to a total dose of 61 Gy concurrent with consolidation pembrolizumab. Consolidation pembrolizumab 200 mg IV was to be given every 21 days for 6 months (9 cycles) and was to start no more than 90 days after surgery (or within 30 d of being deemed inoperable). The six-month adjuvant pembrolizumab course was chosen to establish to a total treatment course of approximately one year.

End Points

The primary end point of safety was defined as the feasibility of delivering concurrent neoadjuvant chemoradiotherapy with pembrolizumab on the basis of the rate of pulmonary toxicity. If five or fewer ($\leq$20%) of the expected 20 patients enrolled developed grade 3 or higher pulmonary toxicity or grade 4 or higher nonhematologic toxicity, then the regimen was to be deemed safe and feasible for further study.

Secondary end points included PFS, objective response rate, complete pathologic response (pCR) rate, nodal downstaging at surgery, OS, and safety and tolerability. Radiographic response to treatment, including progression, was determined by investigator assessment using RECIST 1.1 criteria.

Toxicity Monitoring

Adverse event grading was performed according to Common Terminology Criteria for Adverse Events version 4.0. Serious adverse events for this trial were defined as any event that results in death, is life threatening, results in persistent or substantial disability or incapacity, results in or prolongs an existing hospitalization, is a congenital anomaly or birth defect, is a new cancer, is an overdose, or is another important medical event that may jeopardize the subject and may require intervention to prevent one of the previously listed outcomes.

Statistical Analysis

Analyses for safety and feasibility were descriptive. OS was calculated from the start date of treatment to the date of last follow-up or death, and PFS was calculated from the start date of treatment to the first recurrence or progression or death. Kaplan-Meier method was used to evaluate both OS and PFS. We determined the probability of stopping early if the true rate of unacceptable toxicity is more than or equal to 30% was 62% but only

7% if the true rate is less than 30%. The overall likelihood of rejecting this regimen as infeasible if it is too toxic was estimated to be 81% and 9% if it is truly feasible. All statistical analyses were performed using R Statistical Software (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of nine patients were enrolled in the study. Initial patient enrollment was in March 2017, and final data were analyzed in November 2021. Enrollment was halted with early termination of the study owing to higher-than-expected toxicity (Fig. 1). Surveillance of the enrolled participants continued after study closure. Patient demographics can be found in Table 1, with a median age of 66 (range: 49–76) years and with 67% of patients being female.

Most of the patients received the planned neoadjuvant treatment with concurrent pembrolizumab and CRT. One patient expired during the neoadjuvant phase owing to sudden cardiac arrest. The other eight patients were assessable for radiographic response after completion of induction treatment. One patient had radiologic progression of disease and was taken off study. Another patient was found to have progressive pleural and pericardial metastases at the time of resection, and surgery was aborted. The remaining six patients (75%) had a partial radiographic response to treatment and subsequently underwent surgical resection. All patients had surgical lobectomy and mediastinal lymph node dissection, with four patients undergoing

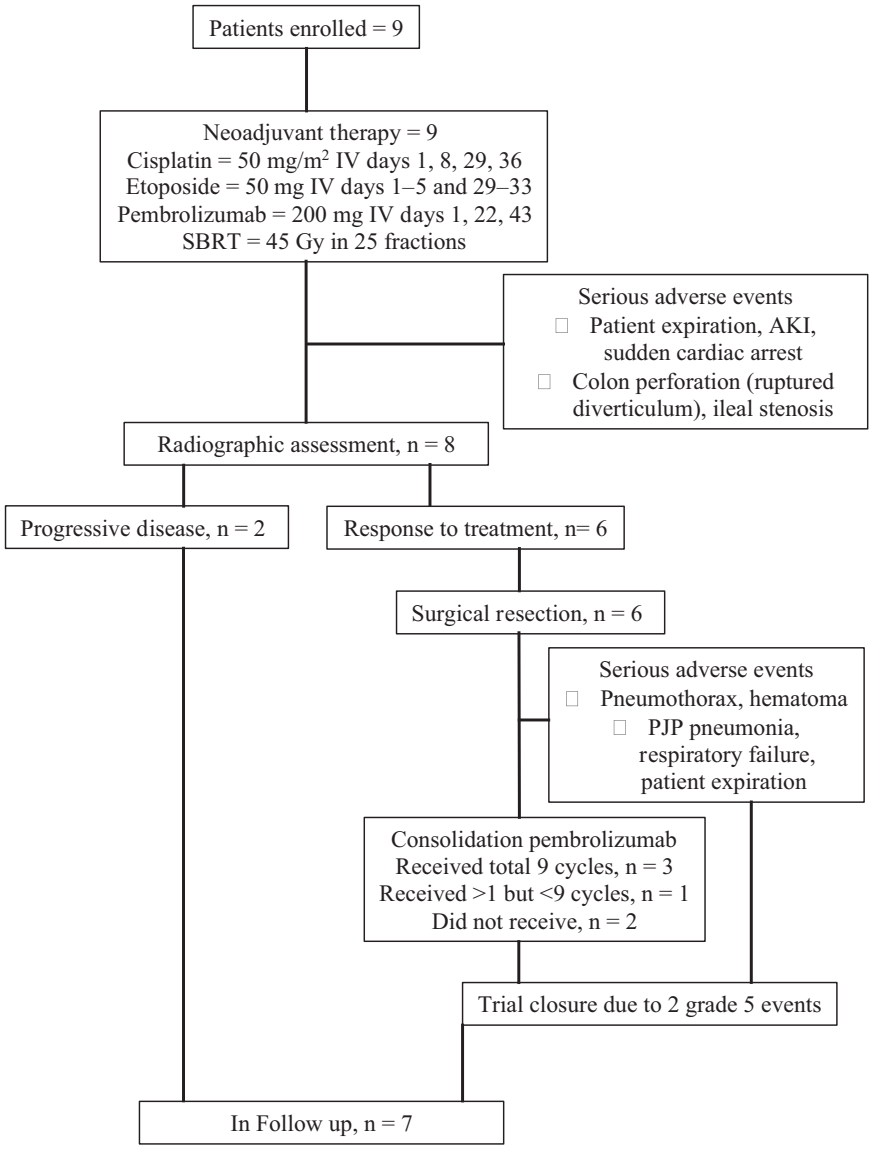

Figure 1. CONSORT diagram. AKI, acute kidney injury; IV, intravenously; PJP, *Pneumocystis jirovecii* pneumonia; SBRT, stereotactic body radiation therapy.

Table 1. Patient Demographics

Patients	N = 9	%
Age, y	Median = 66	Range 49-76
Sex	M = 3	33
	F = 6	66
Race	White = 9	100
ECOG	0 = 6	66
	1 = 3	33
Initial T stage	T1x = 3	3
	T2x = 6	66
Nonsquamous	7	77
Squamous	2	22
PD-L1 status	Low (≤1%-49%) = 6	66
	High (≥50%) = 2	22
	Not tested = 1	11

ECOG, Eastern Cooperative Oncology Group; F, female; M, male; PD-L1, programmed death-ligand 1.

thoracotomy and two patients undergoing video-assisted thoracoscopic surgery. Complete resection was achieved in all six of these patients. Four of the six (67%) had a pCR in the resected specimen with no residual viable cancer in the primary tumor or lymph nodes. One additional patient had complete nodal clearance of malignancy with small residual primary tumor. One patient did not achieve primary tumor response or nodal downstaging in the completely resected specimen (Table 2).

Four patients received at least one treatment of consolidation pembrolizumab. Of the nine total initial patients enrolled, two died before reaching this stage of the planned treatment, two patients progressed, and one patient was unable to receive consolidative therapy owing to grade 3 pneumonitis. Three of the four who received consolidation pembrolizumab completed the entire 6-month regimen. One patient elected to forego further treatment after three cycles related to progressive dyspnea from long-standing chronic obstructive pulmonary disease.

Table 2. Results and Outcomes

Patients	N = 9	%
Completed neoadjuvant treatment	7/9	77
Assessed for response	8/9	88
ORR	6/8	67
PD	2/8	25
PR	6/8	75
Complete resection	6/8	75
pCR	4/6	67
pN0[a]	5/6	83
pNx	1/6	17
Adjuvant pembrolizumab	4/8	50
Median follow-up	38.3 mo	
6-mo PFS	55.6%	95% CI: 31%-99%
Median PFS	Not reached	
3-y OS	64%	95% CI: 39%-100%
Median OS	Not reached	

[a]Including pCR.
CI, confidence interval; ORR, objective response rate; OS, overall survival; pCR, complete pathologic response; PD, progressive disease; PFS, progression-free survival; pN0, pathologic node negative; pNx, pathologic node positive; PR, partial response.

At the time of analysis, the median follow-up was 38.3 months. Median PFS had not been reached. PFS at 6 months was 55.6% (95% confidence interval: 31%–99%) with no change at the 3-year mark. At the time of analysis for most recent follow-up, no patient who underwent complete resection had disease recurrence. Median OS had not been reached. The three-year OS rate was 64% (95 confidence interval: 39%–100%) (Fig. 2).

Toxicities

A total of 14 serious adverse events as defined previously were reported in seven of nine patients (Table 3). Two grade 5 events occurred and included one episode of sudden cardiac arrest during the neoadjuvant phase, attributed to history of coronary artery disease, and one episode of *Pneumocystis jirovecii* pneumonia (PJP) occurring more than 60 days after resection and full surgical recovery, and before initiation of consolidation pembrolizumab, ultimately leading to hypoxic respiratory failure. This pneumonia occurred despite the patient only receiving steroid premedication for chemotherapy induced nausea in the neoadjuvant setting and the patient being human immunodeficiency virus negative.

Other events of note during the neoadjuvant phase included one patient with colon perforation owing to diverticulosis with abscess formation, further complicated by ileal stenosis and necessitating a partial colectomy. Owing to this, the patient did not receive the final dose of cisplatin, pembrolizumab, or the last fraction of radiation in neoadjuvant treatment before proceeding to response assessment.

Events in the postoperative setting included an episode of pneumothorax with hypoxia after complex Pancoast resection. After re-exploration, a suspected bronchopleural fistula was repaired. This patient later developed a chest wall hematoma causing severe tachycardia and requiring evacuation. A second patient underwent resection with a postoperative complication of a loculated pleural effusion with empyema formation, which was then decorticated and attributed to grade 3 pneumonitis. One additional episode of grade 1 pneumonitis occurred in a separate patient, with both fully recovering.

The most common additional adverse events included blood count abnormalities, including an

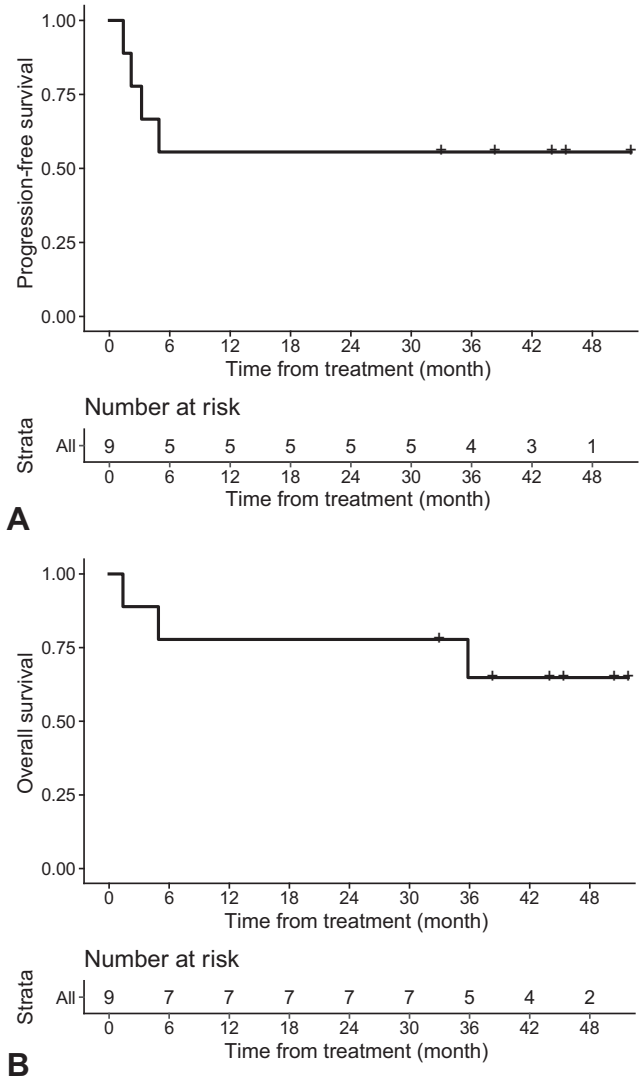

Figure 2. Kaplan-Meier curves: (*A*) Progression-free survival. (*B*) Overall survival.

episode of febrile neutropenia, gastrointestinal distress, electrolyte abnormalities, liver function aberrations, fatigue, and dermatologic changes (Table 4).

Discussion

This phase 1 safety and feasibility study was the first designed to combine ICI therapy with pembrolizumab concurrently with CRT in the neoadjuvant setting for NSCLC. This treatment protocol led to an encouraging pCR rate in this small population compared with traditional neoadjuvant strategies using CRT alone, suggesting that if tolerable this strategy could hold promise.[14] Unfortunately, there was higher-than-expected toxicity observed in this study necessitating early closure. This was triggered by meeting the technical rule for stopping and infeasibility, having recorded two grade 5 events. Nevertheless, these events could not definitively be attributed to the addition of pembrolizumab to the standard CRT treatment regimen. This study used a concurrent chemotherapy backbone of cisplatin and etoposide on the basis of the Intergroup 0139 trial that has been found to have higher rates of adverse events than other regimens, and this may have contributed to the resulting toxicity profile, but again, the relationship to grade 5 events is unclear.[15] Study of concurrent ICI and CRT with an alternative established chemotherapy regimen is underway and may provide further insight into the safety and efficacy of this strategy.[16]

Table 3. Serious Adverse Events

Serious Adverse Events—One Each
Febrile neutropenia
Sinus tachycardia
Cardiac arrest
Colonic perforation
Diarrhea
Ileal stenosis
Gastric hemorrhage
Fever
Lung infection
Pneumothorax
Pneumonitis
Respiratory failure
Hematoma
Acute kidney injury

Exploring the association of toxicities, the patient who expired owing to sudden cardiac arrest was known to have a history of coronary artery disease before enrollment, and it is unlikely that the addition of pembrolizumab aggravated this. Nevertheless, either the chemotherapy alone or the combination with the pembrolizumab may have been responsible for the acute kidney injury that developed the week before, and the contribution of this to his cardiac arrest is unknown.

With regard to the second grade 5 event of PJP causing hypoxic respiratory failure, there are rare case reports in patients of this occurring when they have been treated with pembrolizumab, but the association is not firmly established and thus difficult to ascertain causality.[17] When PJP is found with the use of ICIs, it is most often owing to the use of high-dose steroids for treatment of immune-related adverse events. This patient had received no such treatment.

Diverticular colon perforation with ICI therapy has no clear association to the use of PD-1– or PD-L1–inhibiting agents, and no relation can be made regarding the addition of pembrolizumab to this event.

Intraoperative complications by subjective description were as expected. There was noted adhesive tissue of fibrosis in four of six patients undergoing resection, consistent with findings of response to treatment. Other

Table 4. Most Common Adverse Events (Any Grade)

Most Common Adverse Events	Number Affected, n/N (%)
Anemia	8/9 (88)
Thrombocytopenia	4/9 (44)
Lymphopenia	9/9 (100)
Neutropenia	8/9 (88)
Constipation	5/9 (55)
Diarrhea	4/9 (44)
Nausea	7/9 (77)
LFT abnormalities	4/9 (44)
Hypoalbuminemia	8/9 (88)
Hypomagnesemia	6/9 (66)
Hyponatremia	4/9 (44)
Fatigue	8/9 (88)
Radiation dermatitis	4/9 (44)
Alopecia	7/9 (77)

LFT, liver function test.

postoperative complications occurred within expected rates given the patient population, the surgical complexity, and the known comorbidity of surgical resection.[18] Pneumonitis occurred at a rate and with toxicity that was not limiting to the trial progress.

Studies evaluating the safety of combining concurrent CRT and ICI therapy in patients with unresectable NSCLC include the nonrandomized phase 2 KEYNOTE-799 study and the randomized phase 3 PACIFIC2 trial (NCT03519971). Importantly, the results of KEYNOTE-799 revealed safety and efficacy of adding pembrolizumab to CRT without unexpected safety concerns.[19]

Early data in resectable NSCLC have primarily focused on using neoadjuvant immunotherapy either alone or in combination with chemotherapy, and these have revealed promising findings, especially with improvements in pCR rate compared with neoadjuvant chemotherapy alone.[12,13,20] Additional data were recently released revealing an improvement in event-free survival with neoadjuvant chemoimmunotherapy, leading to the approval of the Food and Drug Administration for resectable NSCLC.[21] Surgical outcomes of patients receiving neoadjuvant chemoimmunotherapy were also improved compared with chemotherapy alone.[22,23] Importantly, pathologic complete response rate has been found to lead to improvements in long-term survival; however, OS data from these studies remain immature.[24] These trials did not study the inclusion of concurrent radiation therapy to multimodality therapy before resection though, and any additional benefit from the incorporation of radiation in our study is unclear and will need further investigation. In addition, these trials did not incorporate adjuvant therapy either. Our protocol was conceived before resulted information from other trials of adjuvant or consolidative immunotherapy and will require further study to evaluate the potential benefit or need of adjuvant immunotherapy after incorporation to the neoadjuvant setting.

To further evaluate both the safety and efficacy of the addition of neoadjuvant immunotherapy concurrent to CRT, additional studies are planned and enrolling. Interim results from a phase one study evaluating the safety of this strategy were presented recently with promising pCR rate of 36% and major pathologic response rate of 72% in 11 resected patients (of a planned 39 total patients), and at the time of presentation, there were minimal toxicities reported (NCT03694236).[16] This disparity from our study may be due to patient selection and small sample size or may be explained by the choice of carboplatin and paclitaxel as neoadjuvant chemotherapy in that study, rather than cisplatin and etoposide as used in this protocol. Other studies enrolling include the phase 2 SQUAT trial from Japan and the phase 2 INCREASE trial from The Netherlands using combination immunotherapy added to CRT (WJOG 12119L, Netherlands Trial Register number: NL8435).[25,26] Should these studies reveal safety and efficacy, larger randomized controlled trials should be considered.

In conclusion, this first study of concurrent pembrolizumab added to neoadjuvant CRT in the treatment of locally advanced, stage IIIA NSCLC required early closure because it met the rule for infeasibility owing to the occurrence of two grade 5 events. The relationship of toxicity to the addition of pembrolizumab or choice of chemotherapy is unclear. This protocol found a promising pathologic complete response rate in this small phase 1 trial. The patients who have undergone resection seem to have achieved durable remissions. The small patient population analyzable, the need for early study closure, and the limited number of patients completing consolidation treatment preclude the ability to evaluate any role for ICI on outcomes in this treatment approach. Additional studies underway should provide additional clarity to these results.

CRediT Authorship Contribution Statement

Nathan A. Pennell, James Stevenson, Alejandro Bribriesco, Vamsidhar Velcheti, Daniel Raymond, Usman Ahmad, Marc Shapiro, Kevin L. Stephans, Sudish Murthy, Gregory M. M. Videtic: Conceptualization, Methodology.

Christopher A. Lemmon, Xuefei Jia, Nathan A. Pennell: Data curation, Formal analysis.

Christopher A. Lemmon, Gregory M. M. Videtic, Sudish Murthy, Kevin L. Stephans, Marc Shapiro, Usman Ahmad, Daniel Raymond, Vamsidhar Velcheti, Alejandro Bribriesco, Xuefei Jia, James Stevenson, Nathan A. Pennell: Investigation, Manuscript writing and editing, Final approval of manuscript.

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