ORIGINAL ARTICLE

Phase 1/2 Trial of Pembrolizumab and Concurrent Chemoradiation Therapy for Limited-Stage SCLC

James W. Welsh, MD,[a,*] John V. Heymach, MD, PhD,[b] Chunxiao Guo, MD, PhD,[c] Hari Menon, MD,[a] Katherine Klein, BS,[a] Taylor R. Cushman, MD,[a] Vivek Verma, MD,[a] Kenneth R. Hess, PhD,[d,†] Girish Shroff, MD,[e] Chad Tang, MD,[a] Ferdinandos Skoulidis, MD, PhD,[b] Melenda Jeter, MD, MPH,[a] Nathan Comeaux, RN,[a] Roshal R. Patel, BA,[a] Dawei Chen, MD,[a] Tugce Ozgen, BS,[f] Quynh-Nhu Nguyen, MD,[a] Joe Y. Chang, MD, PhD,[a] Mehmet Altan, MD,[b] Jianjun Zhang, MD, PhD,[b] Vassiliki A. Papadimitrakopoulou, MD,[b] George R. Simon, MD,[b] Lauren A. Byers, MD,[b] Bonnie Glisson, MD[b]

[a]*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[b]*Department of Thoracic Head & Neck Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[c]*Department of Interventional Radiology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[d]*Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[e]*Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[f]*Department of Radiation Oncology, Ankara University School of Medicine, Ankara, Turkey*

Received 18 June 2020; revised 18 August 2020; accepted 23 August 2020
Available online - 8 September 2020

ABSTRACT

Introduction: Few advancements in treating limited-stage SCLC (LS-SCLC) have been made in decades. We report here a phase 1/2 trial of concurrent chemoradiotherapy (CRT) and pembrolizumab.

Methods: This single-center, open-label phase 1/2 study recruited adults with LS-SCLC or other neuroendocrine tumors and good performance status (Eastern Cooperative Oncology Group ≤ 2). The primary end point was safety, as assessed by dose-limiting toxicities. Concurrent CRT consisted of etoposide and a platin with 45 Gy radiotherapy (30

*Corresponding author.

†Dr. Hess was deceased.

Disclosure: Dr. Welsh contributed as a founder, one of the board of directors, and a holder of patents, royalties of other IP, and stock or ownership of MolecularMatch; has stock or ownership with Alpine Immune Sciences, Checkmate Pharmaceuticals, Mavu Pharma, Legion Healthcare Partners, Nanorobotix, OncoResponse, Inc., and Reflexion; received travel cost from Nanobiotix S.A., Reflexion, Aileron Therapeutics, Inc., Ventana, and Varian; contributed as a consultant or advisory role with Merck, Alpine Immune Sciences, AstraZeneca Pharmaceuticals, Checkmate Pharmaceuticals, Mavu Pharma, Legion Healthcare Partners, Nanorobotix, OncoResponse, Inc., GI Innovation, MolecularMatch, Reflexion, Aileron Therapeutics, Inc., and Ventana; received research funding from Nanobiotix S.A., Checkmate Pharmaceuticals, and Mavu Pharma; and has a clinical trial-sponsored research from Bristol-Myers Squibb, Varian, and Merck. Drs. Heymach, Klein, and Cushman report receiving grants and other fees from AstraZeneca, GlaxoSmithKline, and Spectrum; and other fees from Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Catalyst, EMD Serono, Foundation Medicine, Hengrui Therapeutics, Genentech/Roche, Guardant Health, Eli Lilly, Novartis, Pfizer, Sanofi, Seattle Genetics, and Takeda outside the submitted work. Dr. Skoulidis reports receiving personal fees from Bristol-Myers Squibb outside the submitted work. Dr. Chang reports receiving grants from Bristol-Myers Squibb-MDACC; personal fees from AstraZeneca, Legion, and Varian; and other fees from Global Oncology One outside the submitted work. Dr. Altan reports receiving grants from Genentech, Nektar Therapeutics, Merck, Novartis, Jounce Therapeutics, Bristol-Myers Squibb, Eli Lilly, Adaptimmune, and GlaxoSmithKline; and personal fees from GlaxoSmithKline and Shattuck Laboratory outside the submitted work. Dr. Zhang reports receiving grants from Merck and Johnson and Johnson; and personal fees from Bristol-Myers Squibb, AstraZeneca, GenePlus, and Innovent outside the submitted work. Dr. Papadimitrakopoulou reports receiving honoraria from F. Hoffman-La Roche; receiving research funding and contributed as a scientific advisor for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Novartis, Merck, F. Hoffman-La Roche, Nektar Therapeutics, and Janssen; contributed as a scientific advisor for AbbVie, Araxes, Arrys Therapeutics, Bolt Therapeutics, Clovis Oncology, Exelixis, G2 Innovation, Gritstone, Ideaya, Leeds Biolabs, Loxo Oncology, Takeda, Tesaro, and TRM Oncology; has a research funding from Checkmate and Incyte; and has employment in Pfizer, Inc. Dr. Byers contributed as an advisor/consultant for PharmaMar, AbbVie, Bristol-Myers Squibb, Alethia, Merck, Pfizer, and Jazz Pharmaceuticals; and has received a research funding in oncology from AstraZeneca (GenMab), Sierra Oncology, and Tolero Pharmaceuticals. Dr. Glisson reports receiving research funding to her institution for clinical research from Pfizer, Inc., Medimmune, ISA Pharmaceuticals, and CUE-BIO. The remaining authors declare no conflict of interest.

Address for correspondence: James W. Welsh, MD, Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. E-mail: jwelsh@mdanderson.org

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2020.08.022

twice daily). Prophylactic cranial irradiation (25 Gy, 10 fractions) was given at the physician's discretion. Pembrolizumab was started concurrently with CRT and continued for up to 16 cycles. The phase 1 portion consisted of a 3 + 3 design. Toxicity was assessed with Common Terminology Criteria for Adverse Events version 4.0. Secondary outcomes were progression-free survival, overall survival, and tumor response as measured by the immune-related response criteria.

Results: A total of 45 patients were screened, and 40 were enrolled. All completed radiation therapy and received greater than or equal to one cycle of pembrolizumab. A total of 27 (61%) received percutaneous coronary intervention. One dose-limiting toxicity was observed in the phase 1 portion. There were no grade 5 toxicities, but there were three grade 4 events (two neutropenia, one respiratory failure). Pneumonitis rate was 15% (three grade 2 and three grade 3). All 17 esophagitis events (42.5%) were grades 1 to 2. At median follow-up time of 23.1 months, the median progression-free survival time was 19.7 months (95% confidence interval: 8.8–30.5) and the median overall survival time was 39.5 months (95% confidence interval: 8.0–71.0).

Conclusion: Concurrent CRT and pembrolizumab for LS-SCLC was well tolerated and yielded favorable outcomes, providing a basis for randomized studies.

Keywords: SCLC; Immunotherapy; PD-1; PD-L1; Radiation therapy

Introduction

SCLC is an aggressive cancer of neuroendocrine origin characterized by rapid growth and high propensity for early metastasis. SCLC accounts for 13% of the 228,150 estimated new cases of lung cancer in the United States in 2019.[1] In approximately 30% of the cases, SCLC presents as a limited-stage (LS) disease, classically defined as disease confined to one hemithorax that can be encompassed by a single radiation field.[2] LS-SCLC is both chemosensitive and radiosensitive, and several trials in the early 1990s revealed the benefit of combining these two modalities.[3] Two meta-analyses indicated that adding thoracic radiation therapy (RT) to chemotherapy increased the 3-year survival rate by 5% and intrathoracic tumor control by 25%.[4,5] Concurrent chemoRT (CRT) leads to superior outcomes over sequential CRT.[6-8] The Intergroup 0096 trial further revealed that hyperfractionated RT (45 Gy given twice daily) was superior to 45 Gy given once daily, with improved 5-year survival rates and reduced thoracic relapse.[9] More recently, the CONVERT trial revealed that, in the era of highly conformal RT, a 45-Gy twice-daily regimen should remain the standard of care rather than a 66-Gy once-daily regimen.[10] Despite notable progress over the past few decades, the prognosis for patients with LS-SCLC remains unsatisfactory, with median survival times of 16 to 30 months and 2-year survival rates of 44% to 56%.[2,6,9,10]

Because ipilimumab was approved to treat metastatic melanoma in 2011, immune checkpoint blockade therapy has transformed the landscape of cancer therapy.[11] However, despite relatively high initial response rates to immunotherapy, many patients still develop progressive disease.[12] The addition of RT to immunotherapy can help to prime the adaptive immune system by stimulating the release of immunogenic tumor-specific antigens.[13] Trials to evaluate the benefits of combining immune checkpoint blockade with chemoradiation for NSCLC have included the phase 3 double-blind, placebo-controlled international PACIFIC trial, which found that adjuvant durvalumab treatment after CRT improved both progression-free survival (PFS) and overall survival (OS) in patients with stage III NSCLC.[14] A phase I trial of pembrolizumab with concurrent CRT in patients with unresectable, stage III NSCLC has also revealed promising results with respect to outcomes and toxicities.[15] Similarly, a phase 2 trial of concurrent chemoradiation with consolidation pembrolizumab for patients with unresectable stage III NSCLC (LUN 14-179) revealed better PFS in terms of mean time to metastatic disease or death relative to historical controls.[16] Pembrolizumab and nivolumab, both humanized anti–PD1 antibodies, have been approved by the U.S. Food and Drug Administration to treat recurrent SCLC based on the results of CheckMate 032 and KEYNOTE-028 trials.[17,18] However, the role of anti–programmed cell death-protein 1 (anti–PD-1) therapy for patients with LS-SCLC undergoing concurrent chemoradiation has yet to be evaluated. Given the high risk of systemic failure in SCLC, agents focused on reducing systemic failure are of particular relevance. We therefore designed this phase 1/2 trial to evaluate the safety and efficacy of concurrent pembrolizumab with CRT for LS-SCLC.

Materials and Methods

Study Design and Participants

This single-institution, open-label phase 1/2 trial was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center. Eligible patients were aged greater than or equal to 18 years; had a histologic diagnosis of LS-SCLC or other neuroendocrine tumor; had a performance status score of 0 to 2

on the Eastern Cooperative Oncology Group performance scale; and had adequate organ function as determined within 10 days of treatment. Exclusion criteria were as follows: diagnosis of immunodeficiency or receipt of immunosuppressive therapy within 7 days before the first dose of trial treatment (except for physiological steroid replacement); receipt of monoclonal antibody therapy (including anti–PD1, anti–programmed death-ligand 1, anti–programmed death-ligand 2, or anti–CD137 agent) within 2 weeks before study entry; not having recovered from adverse events from agents given more than 4 weeks earlier; having another malignancy that was progressing or required active treatment (except for nonmelanomatous skin or in situ cervix carcinoma); and having active central nervous system metastases or carcinomatous meningitis. In addition, patients with an active autoimmune disease requiring systemic treatment within the previous 3 months, or a documented history of clinically severe autoimmune disease, or a syndrome requiring systemic steroids or immunosuppressive agents were excluded.

The participants gave written informed consent to participate, and the study was conducted according to the Declaration of Helsinki and Good Clinical Guidelines.

Procedures

All patients underwent baseline investigations before treatment, which included history and physical examination; performance status assessment; pregnancy test; prothrombin time, international normalized ratio, and partial thromboplastin time; complete blood count with differential, comprehensive serum chemistry panel; thyroid function tests (T3, FT4, and thyroid-stimulating hormone); pulmonary function tests; and blood biomarker testing. Baseline tumor images of the brain, chest, abdomen, and skeleton by magnetic resonance imaging, computed tomography (CT), bone scan, or positron emission tomography were obtained from all patients without contraindications. The disease was staged according to the Union for International Cancer Control. LS disease was defined as intrathoracic disease that can be encompassed by a single radiation field.

All radiotherapy procedures were overseen by a radiotherapy quality assurance program managed by the MD Anderson Cancer Center's Department of Radiation Oncology. Radiation was given as 45 Gy in twice-daily fractions for 15 days as CT planning−based intensity-modulated radiation therapy. Concurrent chemotherapy consisted of four 21-day cycles of etoposide and cisplatin or carboplatin. Induction chemotherapy was allowed. Etoposide (100 mg/m^2) was given intravenously (IV) for approximately 4 hours on days 1, 2, and 3 of each 3-week cycle. Cisplatin was given IV at a dose of 80 mg/m^2 for approximately 2 hours on day 1 of each 3-week cycle; carboplatin was given IV at a dose of area under the curve of 5 for approximately 30 minutes on day 1 of each 3-week cycle. Prophylactic cranial irradiation (25 Gy in 10 fractions) was allowed at the discretion of the treating physician and was given after chemotherapy was completed.

Pembrolizumab was started concurrently with chemotherapy and continued in 21-day cycle after completion of chemotherapy. In the dose-escalation portion of the trial, pembrolizumab was first given at 100 mg (half of the maximum tolerated dose [MTD] of 200 mg every 3 weeks). The dose was modified per 3 + 3 dose-escalation rules, being either reduced to 70 mg, continued at 100 mg, or increased to 150 mg and eventually 200 mg, for up to 16 cycles. Pembrolizumab was withheld for drug-related grade 4 hematologic toxic effects, grade greater than or equal to 3 nonhematologic toxicity (including laboratory abnormalities), or severe or life-threatening adverse events. Pembrolizumab could also be withheld for up to 21 days at the treating physician's discretion for percutaneous coronary intervention (PCI) or other clinically pertinent reasons.

The first follow-up visit was scheduled for 1 month after the completion of chemoradiation and included new imaging studies (chest CT) to assess response to treatment, including physical examination, review of medications, and assessment for treatment-related side effects. The same assessment was done every 3 months for the next 2 years and every 6 months thereafter.

Outcomes

The primary outcome of the study was safety, that is, to establish the MTD of pembrolizumab with concurrent chemotherapy and radiation. In accordance with the 3 + 3 phase 1 study design, dose-limiting toxicities were defined as any grade greater than or equal to 3 nonlaboratory events or any grade greater than or equal to 4 events (except transaminitis or total bilirubin elevation) possibly, probably, or definitely related to protocol therapy within 22 days of initiation. Overall toxicity was scored with the Common Terminology Criteria for Adverse Events version 4.0. Secondary outcomes were OS, PFS, and tumor response (assessed according to the Immune-Related Response Criteria [irRC][19]).[20]

Statistical Analyses

Our primary hypothesis was that pembrolizumab with chemoradiation for LS-SCLC would have an acceptable toxicity profile, that is, toxicity comparable to that in previous trials. Our secondary hypothesis was that pembrolizumab would extend PFS time compared with historical controls with LS-SCLC and that adding

pembrolizumab would lead to T-cell activation, which in turn would help to improve both local and distant disease progression. Time-to-event distributions for PFS and OS were estimated by Kaplan-Meier analysis. PFS was calculated from the date of first protocol treatment (radiotherapy or pembrolizumab, whichever came first) to the date of progression, death, or last follow-up (whichever came first). Between-group comparisons were evaluated in an exploratory manner for patients receiving PCI versus no PCI. Summary statistics were computed along with confidence intervals (CIs). The limited sample size precluded formal statistical comparison with historical controls.

Role of the Funding Source

Merck & Co. provided funding for and access to pembrolizumab; other support was provided by the Cancer Center Support (core) grant P30 CA016672 from the National Cancer Institute, National Institutes of Health. These funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

From March 30, 2015, to November 18, 2018, 45 patients were screened, and five were excluded (three for screening failures, one who declined protocol therapy, and one who withdrew consent) (Fig. 1). Thus, a total of 40 patients were enrolled. All patients were naive to immunotherapy, and all completed protocol radiotherapy with a least one cycle of pembrolizumab (median 10 cycles, range: 1−29). Induction chemotherapy was given to 13 patients (range 1–3 cycles, median 2 cycles). One patient received first dose of pembrolizumab 1 day before the end of the protocol chest RT. Another underwent RT to the right buttock eight years before owing to another malignancy. A total of 27 patients (61%) received prophylactic cranial irradiation. The baseline characteristics of all 40 enrolled patients are illustrated in Table 1. Median patient age was 64 years (range: 41−79). Most patients (92.5%) were former smokers, 11 (27.5%) were current smokers, and 32 (80%) had a smoking history of greater than 30 pack-years. A total of 36 patients (90%) had high-grade small-cell neuroendocrine carcinoma. Other pathologies were two intermediate-grade neuroendocrine carcinoma, one large-cell neuroendocrine carcinoma, and one poorly differentiated NSCLC with neuroendocrine features. One patient presented with stage IV disease (T3N1M1b, an isolated rib metastasis).

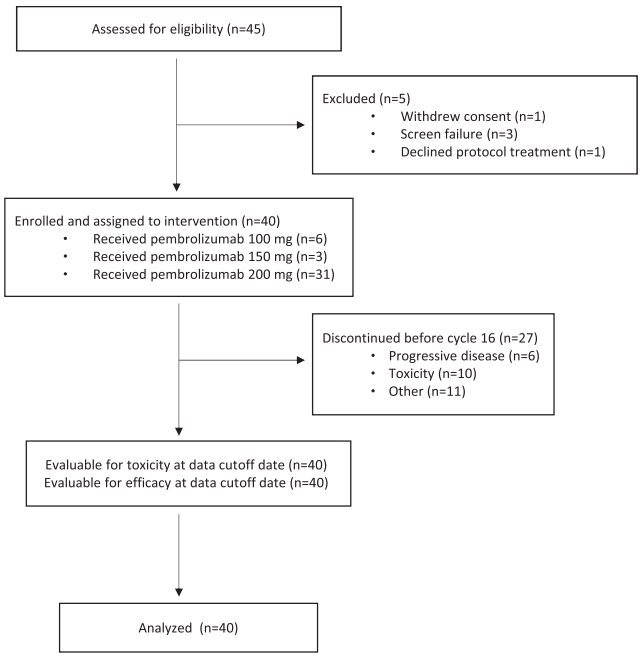

Figure 1. CONSORT diagram illustrating the derivation of numbers of patients evaluated in this trial.

The MTD of pembrolizumab could not be determined during the 3 + 3 dose-escalation portion of the trial, and so all patients enrolled in the phase 2 portion were given 200 mg of pembrolizumab every 21 days. One dose-limiting toxicity, a grade 3 radiation-related pericarditis, was reported in a patient who received an average of 29 Gy radiation to the heart. In this patient, the V40 Gy and V50 Gy to the heart were 24% and 0%, respectively. We then implemented a 26 Gy heart constraint, and no pericarditis was observed thereafter. All 40 patients experienced some form of toxicity (Table 2). Although none were grade 5, three were grade 4 (two neutropenia and one respiratory failure) and 41 were grade 3. The most common grade 3 toxic effects were neutropenia and anemia, both reported in five patients. Treatment-associated pneumonitis was found in 15% of patients (three grade 2 and three grade 3). The V20 Gy and mean lung dose in these patients were 31% (range: 23%–37%) and 15.1 Gy (range: 11.4–18.7 Gy), respectively. The patients with grade 3 pneumonitis seemed to have higher average V5 Gy (63% versus 47%) and V10 Gy (49% versus 37%) than those experiencing grade 2 pneumonitis. Of the 17 cases of esophagitis (42.5%), all were grade 1 or 2. The mean esophageal dose in these patients was 22.0 Gy (range: 9.6–34.0 Gy). Maximum point doses averaged to 50.1 Gy (range: 44.2–57.4 Gy). Only three patients had esophageal V50 Gy above 1.1% (range: 0%–12%). A list of all other treatment-related adverse events is illustrated in Supplementary Table 1.

According to irRC, treatment response should be confirmed by a repeat, consecutive assessment no less than 4 weeks after initial documentation. Seven patients

Table 1. Patient Characteristics

Characteristic	No. of Patients (%) or Median (Range)
Sex	
Male	16 (40)
Female	24 (60)
Median age, y	64 (41-79)
Histologic diagnosis	
SCLC	36 (90)
Other neuroendocrine carcinoma	4 (10)
Eastern Cooperative Oncology Group performance status	
0	13 (33)
1	24 (60)
2	3 (8)
UICC/AJCC stage	
I	2 (5)
II	4 (10)
III	33 (83)
IV (T3N1M1b)	1 (2)
Ethnicity	
White	36 (90)
Asian	1 (3)
African American	3 (8)
Smoking history	
Never smoker	3 (8)
Former smoker	26 (65)
Current smoker	11 (28)
Previous therapy	
RT	2 (8)
Induction systemic therapy	13 (33)
Immunotherapy	0
Completed per-protocol RT	40 (100)
Cycles of pembrolizumab	10 (1-29)
Received prophylactic cranial irradiation	27 (68)

AJCC, American Joint Committee on Cancer; RT, radiation therapy; UICC, Union for International Cancer Control.

are excluded from response analysis because confirmatory scans were not obtained owing to a variety of reasons, including death (two), disease progression (three), other treatment options (one), and toxicity (one). Thus, there were a total of 33 patients assessable for response. The best responses (according to the irRC) were complete response for three patients (9.1%), partial response for 23 (69.7%), stable disease for six (18.2%), and progressive disease (irPD) for one (3.0%) The objective response rate was 79%. A waterfall plot revealing the best response in all the assessable patients with available follow-up imaging is illustrated in Figure 2.

The median follow-up time as of May 30, 2019, was 23.1 months (95% CI: 13.5−32.7). In addition, 12 patients (30.0%) had died at the last follow-up, but not of treatment-related causes. At the time of analysis, 20 patients (50%) had disease progression, for a median PFS interval of 19.7 months (95% CI: 8.8−30.5) (Fig. 3*A*). The median OS was 39.5 months (95% CI: 8.0–71.0), and the 2-year OS rate was 65.8% (95% CI: 45.8−79.8) (Fig. 3*B*). Median PFS of patients with high-grade small-cell neuroendocrine carcinoma was 22.2 months (95% CI: not reached [NA]−NA [CI was not reached]), and median OS was not reached. The other four patients reached a median PFS of 13.0 months (95% CI: 4.0−22.0) and a median OS of 14.2 months (95% CI: 0.0−34.4). A total of 15 patients had relapse, including one with simultaneous local and distant recurrences. No infield recurrences were noted, and 13 patients had remote recurrence at the time of analysis, most often in the brain (six cases) (Table 3).

A total of 27 patients (67.5%) received PCI. The median OS time for the 27 patients who received PCI was not reached; that for the 13 patients who did not receive PCI was 39.5 months (hazard ratio: 3.9, 95% CI: 1.1−13.6, $p < 0.05$). The apparent difference in median PFS intervals was not significant (NR versus 14.2 mo; hazard ratio: 2.5, 95% CI: 0.97−6.5, $p = 0.06$).

Discussion

Few advancements in treating LS-SCLC have been made in the past few decades.[21] Because SCLC is

Table 2. Treatment-Related Select Adverse Events Among 40 Patients Assessed for Toxicity

	No. (%)			
Adverse Event	Grades 1-2	Grade 3	Grade 4	Grade 5
General				
Fatigue	24 (60)	1 (3)	0 (0)	0 (0)
Flushing	0 (0)	1 (3)	0 (0)	0 (0)
Hypokalemia	1 (3)	2 (5)	0 (0)	0 (0)
Hyponatremia	1 (3)	2 (5)	0 (0)	0 (0)
Pruritus	3 (8)	1 (3)	0 (0)	0 (0)
Rash acneiform	2 (5)	1 (3)	0 (0)	0 (0)
Arthralgia	6 (15)	0 (0)	0 (0)	0 (0)
Arthritis	2 (5)	0 (0)	0 (0)	0 (0)
Extremity edema	5 (13)	0 (0)	0 (0)	0 (0)
Radiation dermatitis	5 (13)	0 (0)	0 (0)	0 (0)
Neurologic				
Neuropathy (sensory)	2 (5)	0 (0)	0 (0)	0 (0)
Confusion	0 (0)	1 (3)	0 (0)	0 (0)
Gastrointestinal				
Anorexia	7 (18)	0 (0)	0 (0)	0 (0)
Duodenitis	0 (0)	1 (3)	0 (0)	0 (0)
Esophagitis	17 (43)	0 (0)	0 (0)	0 (0)
Diarrhea	6 (15)	1 (3)	0 (0)	0 (0)
Dysphagia	23 (58)	0 (0)	0 (0)	0 (0)
Nausea	14 (35)	0 (0)	0 (0)	0 (0)
Pancreatitis	0 (0)	1 (3)	0 (0)	0 (0)
Respiratory				
Cough	14 (35)	0 (0)	0 (0)	0 (0)
Chest wall pain	0 (0)	1 (3)	0 (0)	0 (0)
Dyspnea	20 (50)	2 (5)	0 (0)	0 (0)
Lung infection	2 (5)	3 (8)	0 (0)	0 (0)
Pneumonitis	3 (8)	3 (8)	0 (0)	0 (0)
Respiratory failure	0 (0)	0 (0)	1 (3)	0 (0)
Hematologic				
Anemia	17 (43)	5 (13)	0 (0)	0 (0)
Febrile neutropenia	0 (0)	3 (8)	0 (0)	0 (0)
Neutropenia	3 (8)	5 (13)	2 (5)	0 (0)
Leukopenia	0 (0)	1 (3)	0 (0)	0 (0)
Urogenital				
Chronic kidney disease	1 (3)	1 (3)	0 (0)	0 (0)
Creatinine increased	9 (23)	0 (0)	0 (0)	0 (0)
Cardiovascular				
Pericarditis	0 (0)	1 (3)	0 (0)	0 (0)
Sinus tachycardia	0 (0)	1 (3)	0 (0)	0 (0)

susceptible to early metastasis,[22] local therapies, such as surgical resection, radiofrequency ablation, or RT, are not particularly effective by themselves. Immune checkpoint blockade has been reported to be effective in neoplasms with relatively high tumor mutation burden, such as melanoma and NSCLC.[23,24] SCLC, being strongly associated with smoking, has a relatively high tumor mutation burden, suggesting it may respond to immune checkpoint blockade therapy.[25] To our knowledge, this is the first prospective trial evaluating the safety and efficacy of concurrent pembrolizumab and chemoradiation in patients with LS-SCLC. This regimen was associated with few high-grade toxicities and promising outcomes, and hence, further randomized investigation is justified.

The study population and chemoradiation regimen in our trial were comparable with those in the randomized phase 3 CONVERT trial.[10] Despite this, we observed fewer grade 4 or 5 adverse events (grade 5: 0% versus 1% CONVERT, grade 4: 8% versus >50% CONVERT) and fewer and less severe episodes of esophagitis (42.5% versus 81% CONVERT, 0% versus 18% grade $\geq$ 3), and fewer episodes of pneumonitis (15% versus 21% in the CONVERT trial). A likely contributing factor to these findings was the uniform use of intensity-modulated

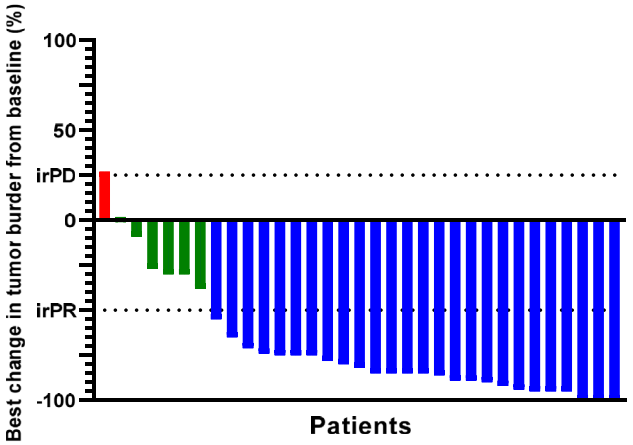

Figure 2. Waterfall plot illustrating the best responses for the 33 assessable patients. irRC, immune-related response criteria; irPD, immune-related progressive disease; irPR, immune-related partial response.

radiation therapy herein, which was given to only a few patients in the CONVERT study. Given a pneumonitis rate of 2.7% for patients on anti–PD-1 monotherapy,[26] our findings strongly corroborate that our pembrolizumab-plus-chemoradiation regimen has an appropriate safety profile, at least in the short term. Owing to the short follow-up time in this study (median 23.1 mo versus 45 mo for the CONVERT trial), at the time of this analysis, long-term toxic effects, such as pulmonary fibrosis and esophageal stricture or fistula, were incompletely assessed. The patient who experienced radiation pericarditis developed constrictive pericarditis, highlighting the need for a dose constraint to the heart during RT planning. We are cautiously optimistic regarding the risk of long-term complications given the low rates of pneumonitis and esophagitis in this study. Because the evaluation of adverse events (severity, attribution) could vary between trials, a multicenter, randomized phase 2/3 trial that compares combined pembrolizumab and chemoradiation with chemoradiation alone would provide a more accurate assessment of the safety of this regimen.

Table 3. Pattern of First Recurrence Sites

Sites	No. (%)
Local-regional	
Infield	0 (0)
Out-of-field	3 (19)
Remote	
Brain	6 (38)
Other sites	7 (44)

Although this phase 1/2 trial was limited in its ability to evaluate the effectiveness of combined pembrolizumab and chemoradiation by its small sample size and relatively short follow-up, OS and PFS times at the time of analysis were favorable compared with those in the CONVERT trial (OS: 39.5 mo versus 30 mo; PFS: 19.7 mo versus 15.4 mo). In addition, the 2-year OS rate was higher in our study (65.8% versus 56%). However, direct comparison of time to events between these trials is not possible given that survival in the CONVERT trial was calculated from time of randomization, which generally precedes the time of first treatment (as was used in our analysis). Moreover, although the method for response assessment also varied between trials (irRC versus Response Evaluation Criteria in Solid Tumors), the overall response rate (79%) in the current trial was comparable with that of the Intergroup 0096 trial (87%).[9]

Unlike its controversial use in extensive-stage SCLC,[27] PCI is recommended for patients with LS-SCLC who have response to chemotherapy and chemoradiation.[28] The PCI was associated with superior OS in this study. However, the PCI findings herein

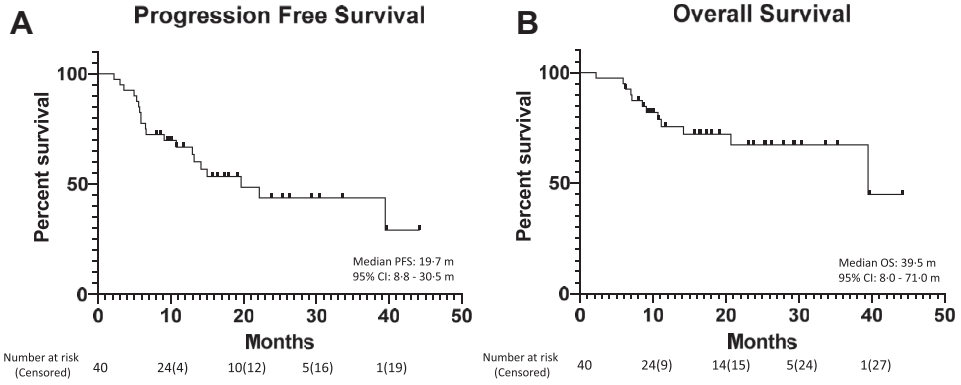

Figure 3. Kaplan-Meier estimates of (*A*) PFS and (*B*) OS for the 40 enrolled patients. CI, confidence interval; m, month; OS, overall survival; PFS, progression-free survival.

should be interpreted cautiously, as it was optional in this trial, and thus, selection bias may have contributed to the difference in OS times. In addition, PCI is often associated with numerous biases in delivery. For example, patients had to be alive and free of brain metastasis before PCI was offered, leading to immortal time bias.

In summary, concurrent pembrolizumab and chemoradiation for LS-SCLC is safe and effective, which forms the basis for a variety of trials evaluating combined-modality therapy for such patients.[29] This includes the recently activated NRG LU005 trial (NCT03811002), which will be randomly assigning patients with LS-SCLC to chemoradiation alone versus chemoradiation plus concurrent anti–PD-1 immunotherapy.

Acknowledgments

This study was supported by Merck and Cancer Center Support (core) grant P30 CA016672 from the National Cancer Institute, National Institutes of Health. We thank Christine F. Wogan for editing this manuscript.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.08.022.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7–30.
2. Johnson DH, Bass D, Einhorn LH, et al. Combination chemotherapy with or without thoracic radiotherapy in limited-stage small-cell lung cancer: a randomized trial of the Southeastern Cancer Study Group. *J Clin Oncol*. 1993;11:1223–1229.
3. Aisner J, Goutsou M, Maurer LH, et al. Intensive combination chemotherapy, concurrent chest irradiation, and warfarin for the treatment of limited-disease small-cell lung cancer: a Cancer and Leukemia Group B pilot study. *J Clin Oncol*. 1992;10:1230–1236.
4. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol*. 1992;10:890–895.
5. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med*. 1992;327:1618–1624.
6. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1993;11:336–344.
7. Perry MC, Eaton WL, Propert KJ, et al. Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. *N Engl J Med*. 1987;316:912–918.
8. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol*. 2002;20:3054–3060.
9. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340:265–271.
10. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18:1116–1125.
11. Sharma P, Wagner K, Wolchok JD, Allison JP. Novel cancer immunotherapy agents with survival benefit: recent successes and next steps. *Nat Rev Cancer*. 2011;11:805–812.
12. Restifo NP, Smyth MJ, Snyder A. Acquired resistance to immunotherapy and future challenges. *Nat Rev Cancer*. 2016;16:121–126.
13. Vanpouille-Box C, Pilones KA, Wennerberg E, Formenti SC, Demaria S. In situ vaccination by radiotherapy to improve responses to anti-CTLA-4 treatment. *Vaccine*. 2015;33:7415–7422.
14. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919–1929.
15. Jabbour SK, Berman AT, Decker RH, et al. Phase 1 trial of pembrolizumab administered concurrently with chemoradiotherapy for locally advanced non-small cell lung cancer: a nonrandomized controlled trial. *JAMA Oncol*. 2020;6:848–855.
16. Durm GA, Althouse SK, Sadiq AA, et al. Phase II trial of concurrent chemoradiation with consolidation pembrolizumab in patients with unresectable stage III non-small cell lung cancer: Hoosier Cancer Research Network LUN 14-179. *J Clin Oncol*. 2018;36(suppl 15):8500–8500.
17. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. *J Clin Oncol*. 2017;35:3823–3829.
18. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342–2350.
19. Endris V, Buchhalter I, Allgäuer M, et al. Measurement of tumor mutational burden (TMB) in routine molecular diagnostics: in silico and real-life analysis of three larger gene panels. *Int J Cancer*. 2019;144:2303–2312.
20. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15:7412–7420.
21. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. *Lancet*. 2011;378:1741–1755.

22. Nakazawa K, Kurishima K, Tamura T, et al. Specific organ metastases and survival in small cell lung cancer. *Oncol Lett*. 2012;4:617–620.
23. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372:2521–2532.
24. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
25. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med*. 2017;9:34.
26. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2016;2:1607–1616.
27. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:663–671.
28. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999;341:476–484.
29. Cushman TR, Caetano MS, Welsh JW, Verma V. Overview of ongoing clinical trials investigating combined radiotherapy and immunotherapy. *Immunotherapy*. 2018;10:851-00.