Adding Base-Excision Repair Inhibitor TRC102 to Standard Pemetrexed–Platinum–Radiation in Patients with Advanced Nonsquamous Non–Small Cell Lung Cancer: Results of a Phase I Trial

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ABSTRACT

Purpose: TRC102, a small-molecule base-excision repair inhibitor, potentiates the cytotoxicity of pemetrexed and reverses resistance by binding to chemotherapy-induced abasic sites in DNA. We conducted a phase I clinical trial combining pemetrexed and TRC102 with cisplatin–radiation in stage III nonsquamous non–small cell lung cancer (NS-NSCLC).

Patients and Methods: Fifteen patients were enrolled from 2015 to 2019. The primary objective was to determine the dose-limiting toxicity and maximum tolerated dose of TRC102 in combination with pemetrexed, cisplatin, and radiotherapy. Secondary objectives were to assess toxicity, tumor response, and progression-free survival at 6 months. Based on our preclinical experiments, pemetrexed–TRC102 was given on day 1, and cisplatin/radiotherapy was initiated on day 3. This schedule was duplicated in the second cycle. After completion, two additional cycles of pemetrexed–cisplatin were given. Toxicities were assessed using NCI CTACAE versions 4/5.

Results: The median age was 69 years (45–79) with the median follow-up of 25.7 months (range, 7.9–47.4). No dose-limiting toxicities and no grade 5 toxicity were seen. Hematologic and gastrointestinal toxicities were the most common side effects. No clinical radiation pneumonitis was seen. Of 15 evaluable patients, three had complete response (20%), and 12 had partial response (80%). The 6-month progression-free survival was 80%, and the 2-year overall survival was 83%.

Conclusions: Pemetrexed–TRC102 combined with cisplatin/radiotherapy in NS-NSCLC is safe and well tolerated. The recommended phase II dose is 200 mg TRC102 along with cisplatin–pemetrexed. No additional safety signal was seen beyond the expected CRT risks. A phase II trial, integrating post-CRT immunotherapy with this aggressive DNA-damaging regimen, is warranted.

Introduction

Lung cancer remains the leading cause of death in the United States and globally is the most common cancer in both incidence and mortality (1.35 million deaths annually; ref. 1). Non–small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers (1, 2). About 35% of patients with lung cancer present with locally advanced (inoperable or at best borderline operable) but nonmetastatic disease (1, 2). Prior to the PACIFIC trial, the 5-year overall survival (OS) remained poor at approximately 15% with median survival rates ranging from 17 to 28 months with standard concurrent chemoradiation using a platinum-based doublet regimen (1–5).

In 2017, results of the PACIFIC trial of adding consolidative durvalumab after concurrent chemoradiation established the new standard of care in patients with stage III unresectable NSCLC (6, 7). The recent 5-year result showed persistent benefit with 42.9% in favor of durvalumab versus 33.4% with placebo surviving at 60 months. About 33.1% patients remained alive and progression-free compared with 19% with placebo (8). Because durvalumab was the study drug, a platinum-based doublet was allowed with a variety of second agents, including etoposide, vinblastine, vinorelbine, taxane (paclitaxel or docetaxol), and pemetrexed, for the concurrent chemoradiation portion of the trial.

Pemetrexed is a third-generation antifolate chemotherapy agent that inhibits thymidylate synthase and several other enzymes in the nucleotide synthesis pathway (9). In addition to its efficacy with cisplatin in producing first-line responses and improved freedom from progression and survival in metastatic NSCLC, pemetrexed has also been found to be effective as a maintenance therapy (10–13). This has been achieved without negatively affecting quality of life in patients with metastatic nonsquamous NSCLC (NS-NSCLC; ref. 14). In addition, pemetrexed has been shown to be safe in elderly patients with good performance status (15). Although several phase I and II studies have shown encouraging results from combinations of pemetrexed and a platinum agent with concurrent thoracic radiotherapy in locally advanced NSCLC (16–19) and similar efficacy compared with more standard chemotherapy regimens, the phase III PROCLAIM trial failed to show improved survival with pemetrexed/cisplatin over the

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Translational Relevance

The study drug TRC102 (methoxyamine) is a small-molecule inhibitor of base-excision repair (BER), is highly water soluble, and can be administered parenterally or orally. TRC102 potentiates the cytotoxicity of alkylator and antimetabolite chemotherapy and reverses chemotherapy resistance by rapidly and covalently binding to chemotherapy-induced apurinic/apyrimidinic (AP, abasic) sites in DNA. We previously published preclinical data showing significantly better radiosensitization by pemetrexed when combined with methoxyamine (TRC102) prior to radiotherapy in both *in vitro* and *in vivo* studies. Based on our preclinical results, we conducted a phase I dose-escalation trial to determine safety, tolerability, and maximum tolerated dose of TRC102 in combination with pemetrexed–cisplatin and standard thoracic radiotherapy in advanced nonsquamous NSCLC. This is the result of the phase I trial.

standard cisplatin/etoposide regimen. However, there was significantly lower incidence of both hematologic and some nonhematologic toxicities when cisplatin was combined with pemetrexed rather than etoposide (20–21). The cisplatin/pemetrexed combination was better tolerated with fewer adverse effects and can be tested with newer strategies to enhance its efficacy given its low rate of adverse events (20, 21).

Methoxyamine (TRC102) is a small-molecule inhibitor of base-excision repair (BER) and is highly water soluble. It can be administered parenterally or orally (i.e., it is bioavailable after oral administration). Methoxyamine potentiates the cytotoxicity of alkylator and antimetabolite chemotherapy and reverses chemotherapy resistance by rapidly and covalently binding to chemotherapy-induced apurinic/apyrimidinic (AP, abasic) sites in DNA (22–26). The first phase I study in advanced solid tumors combining methoxyamine and pemetrexed (performed with the participation of our institution) showed safety of this combination with encouraging response rates in a small number of patients with NSCLC (27, 28).

We previously published preclinical data showing significantly better radiosensitization by pemetrexed when combined with methoxyamine before radiotherapy in both *in vitro* and *in vivo* studies (29). Based on our experience, we conducted a phase I dose-escalation trial to determine safety, tolerability, and maximum-tolerated dose (MTD) of TRC102 in combination with pemetrexed–cisplatin and standard thoracic radiotherapy in patients with advanced NS-NSCLC. An important objective was to assess any indication of efficacy of this regimen in the treatment of advanced NSCLC.

Patients and Methods

We performed a Cancer Therapy Evaluation Program (CTEP)–approved phase I single-institution open-label dose-escalation study, adding TRC102 to standard-of-care cisplatin–pemetrexed and thoracic radiotherapy in patients with stage III and oligometastatic stage IVA NS-NSCLC. The primary objective was safety and feasibility and to determine the MTD and recommended phase II dose of TRC102. The secondary objectives were to assess the toxicity profile, tumor response, and progression-free survival (PFS) at 6 months.

Patients aged ≥18 years with histologically confirmed adenocarcinoma of the lung with stage III or oligometastatic stage IV disease were eligible.

TRC102 was administered orally with pemetrexed on day 1 of cycle 1 and again on day 1 of cycle 2 at 3 weeks. Based on our preclinical data that suggested a strong effect of sequencing of the study drug with radiation, cisplatin, and radiation were administered on day 3 (Supplementary Fig. S1). For cycle 2, the same sequence was repeated. For the second cycle, because radiation was held until after chemotherapy on Wednesday (Supplementary Fig. S1), one additional fraction of radiation was delivered on Saturday. Following completion of chemoradiation, two additional cycles of adjuvant chemotherapy with cisplatin–pemetrexed were administered. The total radiation dose was selected to be 60 Gy, administered in 30 fractions. For dose escalation, a classic 3 + 3 design was used, and the TRC102 doses tested were 50, 100, 150, and 200 mg. Dose escalation was capped at 200 mg primarily because prior phase I data of TRC102 in combination with pemetrexed reported an estimated MTD to be 60 mg/m^2.

The study protocol was approved by the local Institutional Review Board at Case Western Reserve University. All patients provided written informed consent before study eligibility screening. The study was conducted in accordance with Good Clinical Practice Guidelines as per the International Conference on Harmonization and principles of the Declaration of Helsinki following its regulatory and ethical requirements. The trial is registered with ClinicalTrials.gov, number NCT02535325.

Study assessments

The primary endpoint of the study was to determine the MTD of TRC102 in combination with pemetrexed–cisplatinum and thoracic radiotherapy and to assess the dose-limiting toxicity. The secondary objectives were to assess the toxicity profile of this regimen and PFS at 6 months.

Adverse events were assessed at every visit and reported per the Common Terminology Criteria for Adverse Events (versions 4 and 5). Clinical activity of the experimental treatment was evaluated with serial computed tomography (CT) scans to assess the response to treatment based on Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Both baseline and posttreatment CT were performed. Subsequently, serial CT scans were performed every 3 months. A baseline positron emission tomography–computed tomography (PET-CT) scan and immediate posttreatment PET-CT scan were also obtained. Responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease. We also evaluated overall survival (OS), progression-free survival (PFS), locoregional relapse-free survival (LRRFS) and distant relapse-free survival (DRFS).

Statistical methods

The response rate (CR + PR) along with its 95% confidence interval (CI) was estimated by Wilson's method (30). The OS was measured from the onset of treatment to the date of death and censored at the date of last follow-up for survivors. The PFS was measured from the onset of treatment to the date of disease progression, as defined in RECIST 1.1, or the date of death and censored at the date of last follow-up for those still alive without disease progression. LRRFS was measured from the onset of treatment to the date of locoregional relapse and was censored at the date of last follow-up for patients without locoregional relapse. DRFS was measured from the onset of treatment to the date of distant relapse and was censored at the date of last follow-up for patients without distant relapse. Survivor distribution was estimated using the Kaplan–Meier method (31).

Table 1. Patient and treatment characteristics of 15 patients.

Factor	Median (range) or frequency (%)
Age (y)	69 (45–79)
Gender	
Female	12 (80)
Male	3 (20)
Race	
Black	4 (26.7)
White	10 (66.7)
Hispanic	1 (6.6)
Stage	
III/IIIA/IIIB	12 (80)
IVA	3 (20)
T stage	
0	1 (6.6)
1	4 (26.7)
2	4 (26.7)
3	6 (40)
N stage	
0	1 (6.6)
1	1 (6.6)
2	8 (53.4)
3	5 (33.4)
M stage	
0	12 (80)
1	3 (20)
Smoking	
No	2 (13.3)
Yes	13 (86.7)
PTV[a]	439.5 (197.9–1,088.9)
Lung V20!	30.5% (14.3–34.2)
Mean lung dose	17 Gy (10–20.3 Gy)
Lung V5!	55% (38.7–65)
Esophagus mean dose	25.5 Gy (16.5–34)
Heart mean dose	13.6 Gy (3.5–27.9)

[a]Planning target volume, ! Volume of lung receiving 20 and 5 Gy of radiation, respectively.

Results

The study was opened in 11/2015 with CTEP approval, and accrual was completed in 8/2019

Patient characteristics

A total of 15 patients were enrolled in the study and are included in the analysis. **Table 1** describes the patient and treatment details. The median follow-up was 25.7 months (range, 7.9–47.4). The median age was 69 years (range, 45–79). There were 12 female patients and three male patients. Twelve patients had stage III, and three patients had stage IVA oligometastatic disease. Of the three patients with stage IVA disease, two had solitary brain metastasis at time of diagnosis, and the third patient had biopsy-proven solitary nonregional lymph node metastasis. One patient with brain metastasis had resection followed by stereotactic radiation to the resection cavity. This patient developed leptomeningeal recurrence and died. The second patient had solitary brain metastasis and underwent stereotactic radiosurgery alone and at the time of her last follow-up was alive without recurrence. The third patient developed both local and distant recurrence and was alive with disease on his last follow-up.

Dose escalation and toxicity

The predetermined dose-escalation schedule of TRC102 was completed through doses of 50, 100, 150, and 200 mg orally with two cycles of chemotherapy during concurrent chemoradiotherapy. Up to and including the maximum tested dose, we observed no dose-limiting toxicity. The MTD of TRC 102 was determined to be 200 mg in combination with combined platinum-based chemoradiation.

TRC102 in combination with pemetrexed–cisplatin and thoracic radiotherapy was well tolerated. The most common all grade toxicities were hematologic (**Table 2**). Two patients in dose level 4 developed grade 3 anemia requiring blood transfusions. One patient in dose level 4 developed grade 4 neutropenia requiring a delay in her third cycle of chemotherapy.

Among GI toxicities, nausea and vomiting were the most common. Seven patients developed grade 2 esophagitis not needing treatment interruption. The dose to the esophagus is shown in **Table 1**. Of these seven patients with grade 2 esophagitis, two patients were at dose level I, three patients at dose level IV, and one each in dose levels II and III.

The median V20 and mean lung dose are shown in **Table 1**. Importantly, no clinical radiation pneumonitis was observed in any patient.

Response and survival

All 15 patients were evaluable for clinical response; three (20%) had CR, and 12 (80%) had PR (**Fig. 1**) as per each dose level of TRC102. The clinical response (CR + PR) rate was 100% with 95% CI (0.8–1).

The 6-month PFS was 80% (**Fig. 2**) with a 2-year OS (**Fig. 3**) of 83%. Additionally, **Fig. 4A** and **B** shows LRRFS and DRFS. Five patients developed distant relapse, and three patients developed localregional relapse. Two patients have died, one from both regional recurrence and malignant pleural effusion, and the other from leptomeningeal recurrence. She had a solitary brain metastasis at diagnosis and was enrolled in the trial in the oligometastatic disease cohort as stated above. Seven patients are without any evidence of either local or distant disease relapse at the time of their last follow-up.

Discussion

This is the first clinical trial incorporating a BER inhibitor with pemetrexed in combination with cisplatin and thoracic radiation in

Table 2. The most common toxicities and grade.

	Grade 1	Grade 2	Grade 3	Grade 4	Total ($n = 15$)
Hematologic toxicity					
Anemia	4	7	2		13
Lymphopenia		3	7	3	13
Decreased neutrophil count			6	1	7
Decreased platelet count	10	2			12
Decreased WBC	1	5	7		13
GI toxicity					
Nausea	5	6			11
Vomiting	1	3			4
Dehydration		3	2		5
Esophagitis	1	7			8
Fatigue	1	3	1		5
Anorexia	2	2	3		7
Weight loss			3		3
Pulmonary toxicity					
Pneumonitis					0
Cough	1	2			3
Skin toxicity					
Dermatitis	2	2			4

Figure 1.
The waterfall plot shows the best response for target lesions by patient, based on the maximal percentage of tumor reduction.

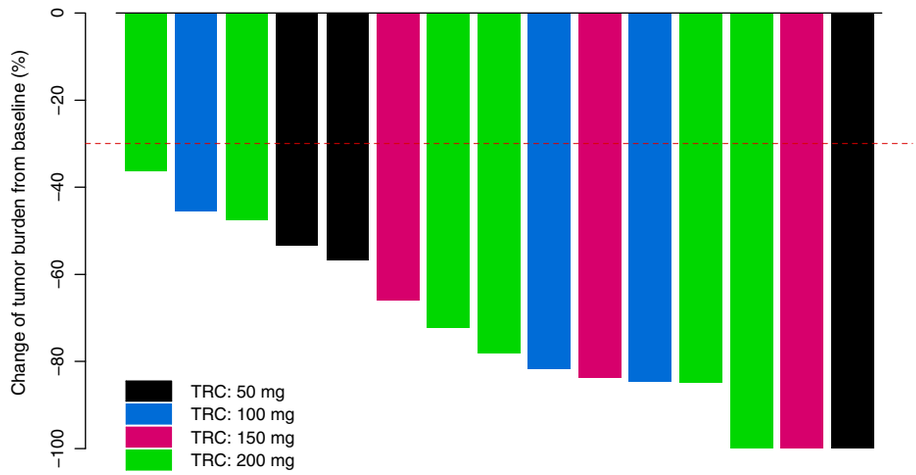


Figure 2.
Kaplan–Meier estimation of PFS with 95% CI. The probabilities of PFS at 6, 12, 24, and 36 months were 80%, 60%, 51.4%, and 51.4%, respectively.

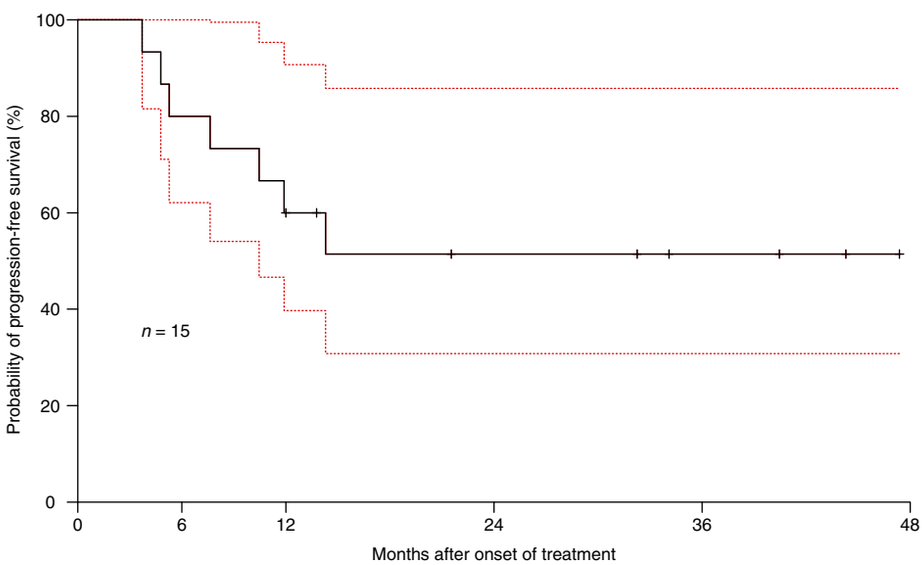
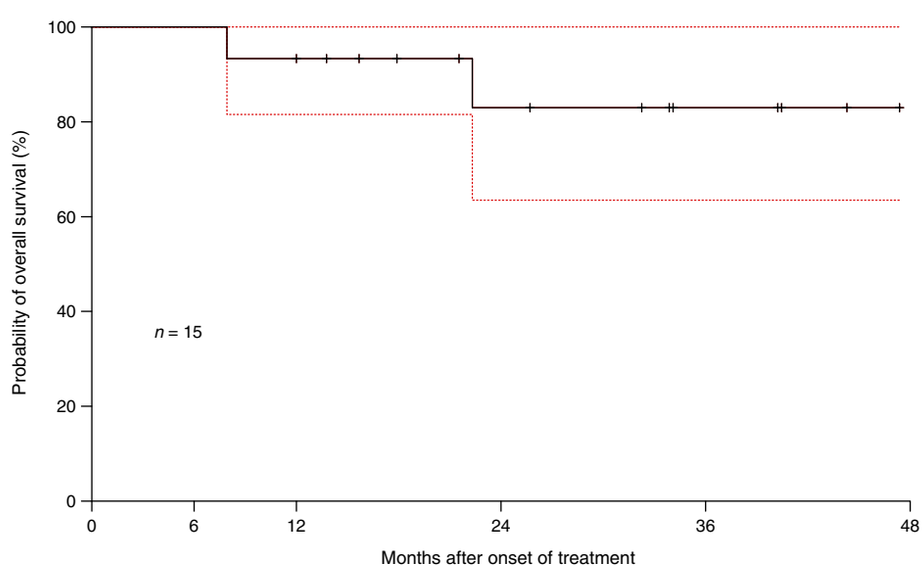


Figure 3.
Kaplan–Meier estimation of OS with 95% CI. The probabilities of OS at 6, 12, 24, and 36 months were 100%, 93.3%, 83%, and 83%, respectively.



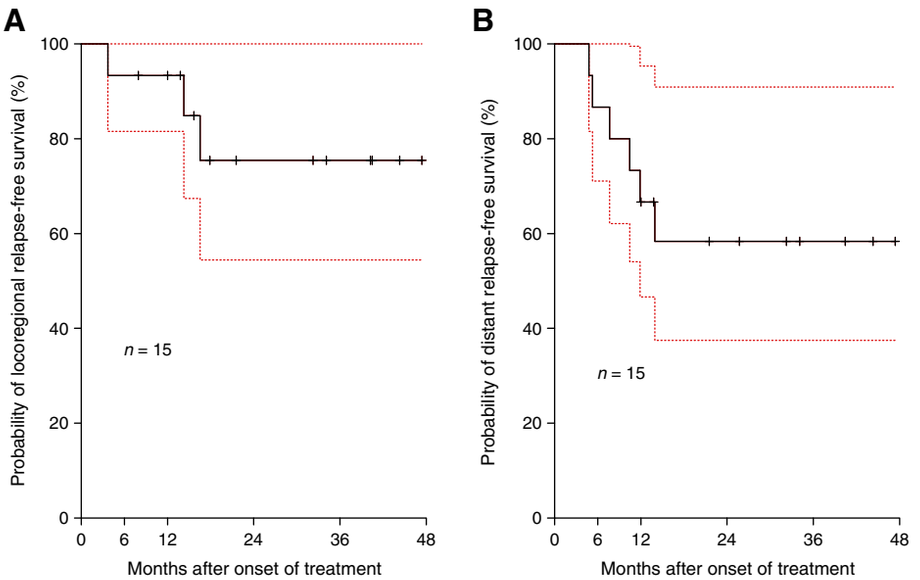


Figure 4.
(**A**) Kaplan–Meier estimation of locoregional relapse-free survival with 95% CI. The probabilities of locoregional relapse-free survival at 6, 12, 24, and 36 months were 93.3%, 93.3%, 75.4%, and 75.4%, respectively. (**B**) Kaplan–Meier estimation of DRFS with 95% CI. The probabilities of DRFS at 6, 12, 24, and 36 months were 86.7%, 66.7%, 58.3% and 58.3%, respectively.

patients with advanced NS-NSCLC. The rationale for this trial was based on robust preclinical studies both *in vitro* and *in vivo* showing enhanced radiosensitization by pemetrexed when combined with methoxyamine (TRC102) (26). In addition, the present study also established the safety of the BER inhibitor TRC102 in combination with standard-of-care pemetrexed–platinum doublet and thoracic radiotherapy for locally advanced NSCLC when the trial was initiated.

Pemetrexed is an antimetabolite that blocks several key folate-dependent enzymes in the purine and pyrimidine pathways of DNA synthesis, resulting in misincorporation of uracil in DNA. Incorporated uracil bases are recognized and excised by uracil DNA glycosylase, thereby protecting cells from mutagenesis and eventual cytotoxicity. The removal of the defective base results in the creation of an abasic site (AP site), which is a critical step in the BER pathway. BER is the most effective way of repairing a variety of single-base lesions, including those induced by chemotherapeutic agents, such as pemetrexed, thereby rendering tumor cells resistant to these drugs. TRC102 can overcome the BER-induced drug resistance by reacting chemically with the aldehyde group in the sugar moiety of the AP site, forming a TRC102-bound AP site. This modified AP site is resistant to repair by AP endonuclease 1 (22, 24, 25). In the trial, TRC102 and pemetrexed were given in a sequential fashion based on our preclinical data showing optimal radiosensitization by pemetrexed when methoxyamine was given prior to radiation.

Adenocarcinoma is now the most commonly diagnosed subtype of NSCLC. The pemetrexed–cisplatin combination is an attractive regimen with thoracic radiation, given its better tolerance allowing for the delivery of a full systemic dose of thoracic radiation for stage III NSCLC with a lower toxicity rate especially with the new standard of adding consolidative durvalumab. Our preclinical studies (29) demonstrated significant improvement in efficacy of pemetrexed when TRC102 was added, which in turn increased the radiosensitization activity of pemetrexed. This increased efficacy of pemetrexed is consistent with our scientific rationale that was validated in preclinical studies.

In the present phase I trial, the combination of pemetrexed–cisplatin and thoracic radiation with the study drug TRC102 in advanced adenocarcinoma was well tolerated with no dose-limiting toxicities seen. The recommended phase II dose was established as a 200-mg flat dose in combination with a standard dose of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) during thoracic radiotherapy. The most common adverse events seen were hematologic with decreased neutrophil and lymphocyte counts. Two patients developed grade 3 anemia requiring blood transfusion.

The most notable observation was the absence of pneumonitis of any grade. This is important, as the current standard of care in stage III NSCLC, based on the PACIFIC trial, is addition of 1 year of consolidative durvalumab (6–8). Both thoracic radiotherapy and the PDL1 inhibitor durvalumab have the potential to cause pneumonitis. The reported incidence of any grade radiation pneumonitis after chemoradiation therapy is in the range of 5% to 15% (32), although it approached 30% in a meta-analysis of patient-reported data (33).

In the PACIFIC trial, the overall rate of pneumonitis was 33.9%, although the incidence of grade 3 to 4 pneumonitis was comparable in the two arms, 3.4% with durvalumab versus 2.6% with placebo. In addition, the PACIFIC trial reported any grade radiation pneumonitis of 20.2%, with grade 3 to 4 incidence of 1.9% in the treatment arm compared with 15.8% any grade and 0.4% grade 3 to 4 radiation pneumonitis with placebo. However, recent data show that in real-world practice, grade 3 or higher pneumonitis is somewhat more frequent than this, at 6.5%, with 1.5% of patients experiencing fatal pneumonitis (34). Other reports also showed increased rates of grade 3 pneumonitis with the addition of durvalumab, 14.3% compared with 3.4% that was reported in the PACIFIC trial (35). As the use of consolidative durvalumab is now being integrated routinely in the treatment of stage III NSCLC, there is a potential for increased occurrence of radiation pneumonitis in real-world settings. Although the current study showed no incidence of radiation pneumonitis, we acknowledge that only 15 patients were involved. Nonetheless, the low incidence of pneumonitis makes it a promising combination therapy to be followed by consolidative durvalumab in a future trial.

When the trial was initiated, results of the PACIFIC trial were not available and, since then, consolidative durvalumab has become the standard of care following completion of chemoradiation. Although

the primary endpoint of this phase I trial was to determine the MTD of TRC102 in combination with chemoradiation, we did see indication of efficacy of this regimen without any increase in toxicity as shown in **Fig. 1**. Patients in the PACIFIC trial were randomized only if they did not have disease progression after chemoradiation. It will be important to improve further the response rate of the concurrent part of the treatment prior to starting durvalumab using novel approaches. Although the PACIFIC trial has improved both OS and PFS, at 5 years, only one-third of patients remained both alive and disease free.

The 6-month PFS rate was 80%. The most common type of tumor recurrence was distant, which is known to occur in one third of patients after chemoradiation (1). Taken in context with results of the PACIFIC trial, showing response rates of 2.2% CR, 48.9% PR, and 47.4% SD after standard chemoradiation, our trial demonstrated an overall response rate of 100%, highlighting the promising activity of this combination in stage III NS-NSCLC. The recent report of KEYNOTE 799, a phase II trial in stage III NSCLC that used upfront pembrolizumab in addition to chemoradiation, showed a 67% overall response rate in the carboplatin–paclitaxel–radiation group and a 56.6% overall response rate in the cisplatin–pemetrexed–radiation group (36). Addition of upfront pembrolizumab did not translate into improved response rates compared with standard chemoradiation. The 6-month PFS with upfront pembrolizumab was reported as 81%, similar to our result without the addition of an upfront immune checkpoint inhibitor. In addition, with upfront pembrolizumab, 8% grade 3 pneumonitis occurred in the carboplatin-paclitaxel group and 5.5% grade 3 pneumonitis occurred in the cisplatin–pemetrexed groups. In the carboplatin–paclitaxel cohort, with 6 months OS of 87%, four patients had grade 5 pneumonitis, which needs to be taken into consideration when choosing another agent that has the potential to increase the pneumonitis rate observed with concurrent chemoradiation.

In the current study, incorporation of TRC102 as the third agent with chemoradiation has shown encouraging efficacy and requires future trials to test this regimen along with consolidative durvalumab. Although the result of this phase I trial is promising, especially in NS-NSCLC, this trial focused primarily on tolerability in a limited number of patients. The trial also included patients with both stage III and oligometastatic stage IV disease and, therefore, may include bias in interpreting the OS result.

In conclusion, TRC102 in combination with cisplatin–pemetrexed and 60 Gy of thoracic radiation was well tolerated with no dose-limiting toxicities and produced promising disease response and 6 months PFS in patients with NS-NSCLC. Importantly, TRC102 was well tolerated in combination with standard chemoradiation. This combination has the potential to improve both PFS and OS when administered with consolidative durvalumab. A future phase II trial is under consideration with consolidative durvalumab.

Authors' Disclosures

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Authors' Contributions

T. Biswas: Conceptualization, resources, data curation, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **A. Dowlati:** Resources, supervision, funding acquisition, validation, investigation, methodology, writing–review and editing. **C.A. Kunos:** Project administration, writing–review and editing. **J.J. Pink:** Resources, supervision, writing–review and editing. **N.L. Oleinick:** Conceptualization, supervision, writing–review and editing. **S. Malik:** Supervision, project administration, writing–review and editing. **P. Fu:** Formal analysis, writing–review and editing. **S. Cao:** Formal analysis, writing–review and editing. **D.S. Bruno:** Data curation, investigation, methodology, writing–review and editing. **D.L. Bajor:** Data curation, investigation, writing–review and editing. **M. Patel:** Data curation, investigation, writing–review and editing. **S.L. Gerson:** Resources, funding acquisition, writing–review and editing. **M. Machtay:** Conceptualization, resources, data curation, supervision, investigation, methodology, writing–review and editing.

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