Review Article on Synergy in Action: Novel Approaches to Combining Radiation Therapy and Immunotherapy

The utilization of immunotherapy with radiation therapy in lung cancer: a narrative review

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Contributions: (I) Conception and design: JH Heinzerling, CB Simone 2nd; (II) Administrative support: JH Heinzerling, CB Simone 2nd, KF Mileham; (III) Provision of study materials or patients: JH Heinzerling; (IV) Collection and assembly of data: JH Heinzerling; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Despite decreasing smoking rates, lung cancer remains the leading cause of death from cancer in the United States. Radiation therapy has been established as an effective locoregional therapy for both early stage and locally advanced disease and is known to stimulate local immune response. Past treatment paradigms have established the role of combining cytotoxic chemotherapy regimens and radiation therapy to help address the local and systemic nature of lung cancer. However, these regimens have limitations in their tolerability due to toxicity. Additionally, cytotoxic chemotherapy has limited efficacy in preventing systemic spread of lung cancer. Newer systemic agents such as immune checkpoint inhibitors have shown improved survival in metastatic and locally advanced lung cancer and have the advantage of more limited toxicity profiles compared to cytotoxic chemotherapy. Furthermore, improved overall response rates and systemic tumor responses have been observed with the combination of radiation therapy and immunotherapy, leading to numerous active clinical trials evaluating the combination of immune checkpoint inhibition with radiotherapy. This comprehensive review discusses the current clinical data and ongoing studies evaluating the combination of radiation therapy and immunotherapy in both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

Keywords: Immunotherapy; immune checkpoint inhibitors; radiation therapy; lung cancer; systemic therapy

Submitted Jun 20, 2020. Accepted for publication Sep 20, 2020.
doi: 10.21037/tcr-20-2241
View this article at: http://dx.doi.org/10.21037/tcr-20-2241

Introduction

Lung cancer remains the second most common cancer in the United States and the leading cause of cancer death (1). Most cancers have a non-small cell lung cancer (NSCLC), representing approximately 87% of all lung cancers, with small cell lung cancer (SCLC) making up the remaining 13% of cases. Treatment paradigms depend on stage, with surgical resection or stereotactic body radiation therapy (SBRT) for early-stage disease, a combination of surgery and chemotherapy with or without radiation therapy or chemoradiation for locally advanced disease, and multiple systemic options for metastatic disease (2). However, traditional therapies have shown limited long-term survival, with historical 5-year survival rates of 5% for patients

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presenting with stage IV disease. Risk of systemic failure also remains high in earlier stage disease, with distant failure rates around 15–25% (3). Therefore, newer systemic agents are needed to address the risk of systemic spread in lung cancer.

Utilizing the immune system as an effective oncologic tool to fight cancer has been the subject of preclinical and clinical research for several decades (4). Immunotherapy agents allow the immune system to recognize cancer cells as foreign, prompting an immune response resulting in tumor cell death and/or inhibition of tumor growth. These newer immunotherapy agents have shown effectiveness in reducing systemic risk and extending survival in both NSCLC and SCLC. In addition, the combination of radiation therapy and immunotherapy has the ability to achieve a synergistic therapeutic effect (5-8), leading to interest in introducing immune checkpoint blockade (ICB) in combination with radiation in earlier stage disease. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2241).

Radiation therapy in lung cancer

Definitive radiation continues to be the standard of care for patients with locally advanced NSCLC and SCLC as well as those with earlier stage disease who refuse surgery or are medically inoperable due to cardiopulmonary or other comorbidities (2).

In early stage lung cancer, newer radiation technologies have allowed delivery of high dose, highly conformal hypofractionated regimens over 1–5 fractions to patients who are medically unfit for surgery (9,10). Known as SBRT or stereotactic ablative body radiation (SABR), these ablative regimens have become standard of care for early stage NSCLC and are also being utilized increasingly for patients with early stage SCLC (11,12). These regimens have been extensively studied internationally through prospective phase 2 and 3 studies with results showing local control rates of approximately 90–95%, similar to lobectomy (13-15).

In the locally advanced setting, conventionally fractionated radiation therapy remains the standard, with doses of 60 Gy in 30 fractions commonly, given concurrently with doublet chemotherapy (2,16). Conventional radiation therapy uses these lower doses of 1.8–2.0 Gy per day delivered over several weeks to spare central structures from excessive toxicities and fibrosis (17). Newer technologies such as intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT), and proton therapy are increasingly being utilized and studied to lower rates of toxicities with combined modality therapy for both NSCLC and SCLC (18-20). A meta-analysis demonstrated improved overall survival (OS) with concurrent platinum-based chemotherapy compared to sequential chemotherapy and radiation therapy (21). Toxicity is also higher with concurrent therapy, particularly esophagitis due to synergistic effects from both modalities.

Radiation therapy in the setting of metastatic lung cancer was traditionally reserved for palliative purposes such as the relief of pain, hemoptysis, or dyspnea (22,23). Newer data in NSCLC have shown that radiation therapy can improve survival in limited oligometastatic disease. Multiple randomized phase II studies have evaluated stage IV NSCLC patients without progression after first-line therapy who were then randomized to receive local consolidative therapy (radiotherapy or surgery) to limited sites of disease versus observation/maintenance therapy (24,25). In one study, those that received treatment to all residual sites of metastatic disease had a more than doubling of OS compared to maintenance therapy alone (median OS of 41.2 *vs.* 17.0 months) (24). A similar study evaluating multiple cancer subtypes including NSCLC, SABR-COMET, also randomized patients to observation/maintenance therapy versus radiation therapy to up to five metastases (26). Patients who received radiation comparably had nearly a doubling of OS. Ongoing phase III trials (NRG Oncology LU002) are attempting to confirm these promising randomized phase II results. Additionally, the use of thoracic radiation therapy in metastatic or extensive stage SCLC has shown benefit an OS benefit when utilized in the consolidative setting after chemotherapy. The CREST trial showed an improvement in two-year OS in extensive stage SCLC patients who received standard chemotherapy followed by consolidative thoracic radiotherapy and prophylactic cranial irradiation (PCI), making it one of the first trials in several years to provide a survival benefit in the treatment of extensive stage SCLC (27).

Immune checkpoint blockade

ICB agents allow increased T-cell activation by removing barriers to the systemic immunologic response to cancer cells. Several checkpoint inhibitors have been utilized amongst a spectrum of malignancies including monoclonal antibodies that inhibit cytotoxic T-lymphocyte antigen

4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed cell death protein 1 ligand (PD-L1). The PD-1 inhibitors pembrolizumab and nivolumab are approved for use in metastatic NSCLC (28-30). The PD-L1 inhibitor atezolizumab is also approved in the first-line metastatic setting (31), while durvalumab, which also targets PD-L1, is approved as consolidative therapy following definitive chemoradiation for locally advanced, unresectable NSCLC (32). Atezolizumab and durvalumab are now also approved in the first line treatment of extensive stage SCLC (33,34).

ICB has been utilized both as monotherapy and in combination with cytotoxic chemotherapy to increase OS in both locally advanced and metastatic NSCLC as well as extensive stage SCLC. While these agents have significantly improved survival in these populations, there are many patients who do not respond initially or who progress after initial response, suggesting the need for ongoing clinical trials attempting to improve response through identifying and counteracting mechanisms of resistance.

The combination of radiation therapy and immunotherapy

The combination of radiation as a local therapy and immunotherapy has shown synergistic therapeutic effects in both preclinical and clinical studies (5,6,35). Ionizing radiation can increase tumor antigen presentation (which higher levels often able to be released with SBRT), causing locoregional antigen presenting cells to increase uptake and subsequent presentation of cancer neoantigens. This augments immunomodulation by bolstering cytotoxic T-lymphocyte activity and reducing myeloid-derived suppressor cells (6,36,37). In addition, radiation activates release of proinflammatory cytokines and stimulates the type I interferon pathway, also leading to cytotoxic T-cell activation (38).

Radiation therapy, and especially SBRT, can increase homing of immune cells to tumor. In fact, SBRT may be the radiation modality most optimally combined with immunotherapy due to its stimulation of a more robust immune response than conventionally fractionated radiation (39). SBRT can induced immunogenic cell death and has been shown to induce cellular expression of major histocompatibility complex (MHC) I, inflammatory mediators, costimulatory molecules, heat shock proteins, immunomodulatory cytokines, adhesion molecules, and death receptors, all of which can enhance the antitumor immune response of checkpoint blockade (40). Such effects and potential benefit of combining radiotherapy and immunotherapy have pictorially been demonstrated by prior investigators (41,42).

There have been dramatic manifestations of radiation-induced systemic immune activation through distant tumor regression following the administration of radiation therapy, known as the abscopal effect (43-45). Such abscopal effects have been infrequently reported by our group (46) and by others (47) in lung and thoracic cancers both in patients treated with radiation therapy alone as well as with the combination of radiation therapy and immunotherapy (48). Furthermore, abscopal effects are thought to be significantly more likely when combining immunotherapy with SBRT than palliative radiotherapy (49), and optimizing the dose fractionation and synergy of radiotherapy and immunotherapy to maximize abscopal effects is a rapidly growing area of research (50).

There is also preclinical evidence of immune system counteracting the immunostimulatory effects of radiotherapy. For instance, tumor PD-L1 expression has been shown to increase after radiation therapy, reflecting enhanced resistance to T-cell mediated killing in several mouse models (36,51). However, this may not translate to the clinical PD-L1 response as shown in a study of patients with locally advanced NSCLC who were treated with neoadjuvant chemoradiation followed by surgery, where PD-L1 expression on tumor cells significantly decreased or stayed the same in the majority of patients after chemoradiation (52). The difference in findings may be related to the timing of radiation therapy and use of concurrent chemotherapy. These mixed data in markers for immune response show the challenges associated with immune systemic effects both systemically and in the tumor microenvironment from different agents in regard to combining and optimizing timing of these modalities. However, clearly there is a potential for additive effect observed both in preclinical and clinical data from utilization of radiation therapy in combination with immunotherapy. The clinical evidence supporting this combination will be highlighted below for both NSCLC and SCLC.

Radiation and immunotherapy in NSCLC

Advanced/metastatic NSCLC

The combination of radiation and immunotherapy

in NSCLC was first evaluated in the advanced or metastatic setting. Radiation therapy for metastatic NSCLC is usually for palliative purposes such as lung obstruction, hemoptysis, or pain, and it is not thought to have effect on OS. However, a secondary analysis of the phase I KEYNOTE 001 trial examined patients with metastatic NSCLC who received RT prior to their first dose of pembrolizumab (43 of 97 patients). This analysis demonstrated improved median OS (10.7 *vs.* 5.3 months) and progression-free survival (PFS) in patients who received radiotherapy prior to pembrolizumab (53). Similarly, investigators from Saitama Medical University in Japan treated 124 consecutive previously treated advanced NSCLC patients with nivolumab. Patients who received radiotherapy (53%) before starting nivolumab had a higher overall response rate than patients who did not have prior radiotherapy (36% *vs.* 19%), leading the authors to conclude that previous radiotherapy was an independent favorable prognostic marker after nivolumab administration, likely due to a synergistic effect between the modalities (54).

These data have prompted further investigation into the possible synergistic effect of this treatment combination, either with fractionated radiotherapy or SBRT. A trial involving the anti-CTLA-4 antibody ipilimumab and SBRT in patients with a variety of solid malignancies including NSCLC (55). SBRT was directed to a single site of disease in either the lung or liver and was administered either concurrently or sequentially (during cycle 2) with ipilimumab. Ten percent of patients experienced a partial response (excluding the irradiated lesion) and 23% had either a partial response or stable disease lasting ≥6 months. A similar trial performed in metastatic NSCLC also combined ipilimumab with concurrent SBRT to a single site of disease (47). The objective response rate to unirradiated disease was 18%, with 2 complete responses and 5 partial responses. Recent publications have highlighted larger randomized trials in this setting. The PEMBRO RT trial randomized 76 patients to pembrolizumab with or without SBRT given to one metastatic site prior to immunotherapy (56). Patients had to have progressed after first line chemotherapy and have at least two metastases. The primary endpoint was overall response rate excluding the irradiated lesion. Most of the patients received SBRT to an intrathoracic site (55%). Overall response rate doubled from 18% to 36% in patients receiving SBRT, but this still did not meet the prespecified endpoint of 50%. However, given the increase in response, a phase II/III study with a similar design is being proposed.

Other prospective trials have evaluated the role of radiation therapy and immunotherapy in patients with more limited or oligometastatic NSCLC. Early trials mentioned previously showed benefit to local therapy in patients with oligometastatic disease who did not have progression after first line chemotherapy (24,25). However, these earlier trials were performed prior to immunotherapy becoming a standard component of most first-line therapy, and thus newer trials have been designed to include ICB (*Table 1*). A recently reported single-arm phase II trial treated patients with local therapy (surgery or radiation therapy) to four or fewer sites of disease with the addition of pembrolizumab 4–12 weeks later (57). Fifty-one patients were enrolled, and the median PFS from the start of local therapy was 19.1 months, which was significantly improved over historical controls of 6.6 months. At the reported median follow-up of 25 months, one-year OS was 91%, which was very encouraging.

The ongoing phase III trial (NRG Oncology LU002) includes patients receiving first-line immunotherapy or chemotherapy and is randomizing patients with three or fewer sites of oligometastatic disease to continued maintenance therapy versus local therapy with radiation therapy or surgery in addition to maintenance therapy. Additional ongoing studies are evaluating the timing of radiation therapy in relation to the administration of immunotherapy. A nonrandomized parallel-assignment trial from University of California, Davis (NCT02400814) is assigning patients to one of three regimens: atezolizumab and SBRT both started on day 1 of cycle 1 (concurrent arm), atezolizumab followed by SBRT on day 1 of cycle 3 (induction arm), or SBRT followed by atezolizumab. This study should yield data on optimal timing of local therapy. Another trial, SABRseq is evaluating patients treated with either SBRT followed by pembrolizumab or pembrolizumab followed by SBRT.

Locally advanced NSCLC

Given the success of immunotherapy in advanced NSCLC, there has been great interest in utilizing immunotherapy in the locally advanced/stage III setting. The benefit of immunotherapy in the curative setting was first reported with the addition of durvalumab in the PACIFIC trial (32). This was a double-blind, randomized Phase III trial in patients with locally advanced, stage III NSCLC treated with concurrent chemoradiation. Patients were then randomized to receive the anti-PD-L1 antibody durvalumab

every 2 weeks for 12 months versus placebo. The additional of durvalumab demonstrated both improved OS as well as PFS. Three-year OS showed an increase from 43.54% with standard therapy to 66.3% with durvalumab (58). On subgroup analysis, patients who received durvalumab earlier after radiation (within 14 days) had improved OS and PFS compared to those who started after 14 days. While these findings may be due to healthier patients being able to receive consolidative immunotherapy sooner, this may also point to the importance of initiating immunotherapy more quickly after radiation therapy to maximize their synergistic effects. This trial changed the treatment paradigm for locally advanced disease and eligible patients now standardly receive consolidation immunotherapy after completion of chemoradiation.

Additional immunotherapy agents have been evaluated in the locally advanced setting in phase II trials. The Hoosier Cancer Network trial LUN14-179 phase II single arm trial administered consolidative pembrolizumab to 93 patients who had not progressed 4–8 weeks after the completion of concurrent chemoradiation. Interim results were reported at ASCO 2018. At a median follow-up of 16.4, the 18-month PFS was 49.5%, and the estimated 2-year OS was 68.7%, which are similar to the outcomes reported on the PACIFIC trial (59).

Several ongoing trials are now looking at incorporating immunotherapy earlier in the treatment of locally advanced NSCLC including concurrently with chemoradiation (*Table 1*). One of the concerns about combining radiation therapy and immunotherapy is the possibility of increased pneumonitis rates. Severe pneumonitis rates were low and similar between the two arms on the PACIFIC trial, but this trial excluded patients with unresolved grade 2 toxicities after chemoradiation. Early data utilizing immunotherapy concurrently with chemoradiation have been encouraging. The ETOP NICOLAS trial recently reported an interim safety analysis of administering nivolumab at the same time as definitive chemoradiation to patients with locally advanced, unresectable NSCLC. At three months post-RT, none of the initial 21 patients experienced grade 3 or worse pneumonitis. A total of 80 patients was enrolled, with 8 having experienced grade 3 or higher pneumonitis (60). Efficacy endpoints have not been reported. A multi-center 21-patient phase I trial of pembrolizumab delivered concurrently with chemoradiation for locally advanced NSCLC showed an encouraging 70% PFS at 12 months and generally limited toxicity profile, but 1 episode of grade 5 pneumonitis was reported (61).

Given the efficacy of immunotherapy in the locally advanced setting, additional trials are exploring whether concurrent immunotherapy may be able to replace the need for chemotherapy during radiation in stage III NSCLC. Concurrent chemotherapy with radiation therapy does increase toxicity rates compared with sequential chemoradiation or monotherapy, and many patients are ineligible for standard chemoradiation due to medical comorbidities. Because ICB tends to be well tolerated compared to chemotherapy, the combination of radiation therapy and immunotherapy alone is a potentially intriguing regimen. The NRG Oncology LU004 ARCHON-1 trial is currently enrolling patients with high (>50%) PD-L1 staining NSCLC and evaluating the efficacy of definitive thoracic radiotherapy with concurrent durvalumab. Two different radiation regimens are being evaluated, including conventional radiation therapy to 60 Gy in 30 fractions and a hypofractionated regimen to 60 Gy in 15 fractions. An additional trial, DART, will evaluate concurrent durvalumab and standard radiotherapy. This single-arm study will evaluate patients receiving concurrent durvalumab and thoracic radiation therapy to 60 Gy in 30 fractions followed by a year of consolidative durvalumab.

While most trials involving immunotherapy in the locally advanced setting have been in patients with unresectable disease, trials testing neoadjuvant strategies in resectable locally advanced NSCLC are also ongoing. A phase I trial, CASE 4516 (NCT02987998), will treat patients with stage IIIA NSCLC with neoadjuvant chemoradiation with cisplatin, etoposide and 45 Gy in 25 fractions along with pembrolizumab prior to resection. After surgery, patients will go on to receive consolidation pembrolizumab. Additionally, a phase II study (NCT03237377) will look at the effects of neoadjuvant durvalumab and radiation therapy (45 Gy in 25 fractions) with neoadjuvant tremelimumab (a CTLA-4 inhibitor) added to an expansion cohort if the initial immunotherapy and radiotherapy combination appears safe. These studies will also provide interesting data on biologic changes that happen between initial biopsy and surgical resection from the combination of these agents in the neoadjuvant setting.

Early stage NSCLC

While cure rates are higher in early stage NSCLC compared to the locally advanced or advanced settings, there are still a high percentage of patients who go on to have nodal or distant failures after primary local treatment.

Table 1 Select randomized active trials combining immunotherapy and radiation therapy in NSCLC

Trial name/NCT number	Phase	Stage/inclusion	ICB agent	Trial design	RT technique/dose	RT and ICB timing
Early stage						
SWOG/ NRG S1914 NCT04214262	3	Stage I–II	Atezolizumab	SBRT +/– ICB up to 5 months	SBRT	ICB first, then SBRT and ICB concurrent, then ICB adjuvant
PACIFIC 4 NCT03833154	3	Stage I–II	Durvalumab	SBRT +/– ICB up to 24 months	SBRT	SBRT first, ICB adjuvant
I-SABR NCT03110978	2R	Stage I–IIA	Nivolumab	SBRT +/– ICB up to 3 months	SBRT to 50 Gy/4 fx, or (if constraints cannot be met) 70 Gy/10 fx	SBRT and IO concurrent
ASTEROID NCT03446547	2R	Stage I	Durvalumab	SBRT +/– ICB up to 12 months	SBRT in 3 or 4 fractions	SBRT first, ICB adjuvant
NCT02904954	2R	Resectable stage I–IIIA	Durvalumab	Neoadjuvant IO +/– SBRT, surgery, postop maintenance IO	SBRT 24 Gy/3 fx	SBRT and IO concurrent
PembroX NCT03217071	2R	Resectable stage I–IIIA	Pembrolizumab	Neoadjuvant IO +/– SBRT, followed by surgery within 6 weeks	SBRT 12 Gy/1 fx delivered to 50% of the primary lung tumor	IO first then SBRT with IO concurrent
Locally advanced						
PACIFIC 2 NCT03519971	3	Unresectable stage III	Durvalumab	Concurrent ICB + platinum-based chemoRT, followed by adjuvant ICB	Conventional 60 Gy/30 fx	Concurrent
Metastatic/oligometastatic						
NCT02492568 PEMBRO-RT	2R	Stage IV with at least 2 lesions; progression after 1st line chemo	Pembrolizumab	IO +/– SBRT	SBRT 24 Gy/3 fx	RT first then IO
NCT02658097 CASE1516	2R	Stage IV with a minimum of 2 lesions	Pembrolizumab	IO +/– SFRT (single fraction of radiation	Single fraction 8 Gy/1 fx	Concurrent
NCT02444741	1/2R	Stage IV with a minimum of 2 lesions	Pembrolizumab	IO +/– SBRT or wide field RT (WFRT)	SBRT 50 Gy/4 fx or WFRT to 45 Gy/15 fx	Variable
NCT02239900	1/2R	Stage IV with at least one metastasis or 1° in lung, liver, or adrenal	Ipilimumab	IO +/– SBRT	SBRT to 50 Gy/4 fx or 60 Gy/10 fx	IO first then concurrent with SBRT

ICB, immune checkpoint blockade; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy; RT, radiation therapy; IO, immuno-oncology therapy.

Local treatment typically consists of either surgical resection or SBRT, with local control rates of both modalities exceeding 90%. Adjuvant chemotherapy has been shown to be beneficial in specific patients, typically limited to node positive patients or those with specific risk factors (62,63). Similarly, for patients with large lesions treated with SBRT, use of adjuvant chemotherapy may improve OS, but many of these patients may not be eligible to receive such therapy since they often have comorbidities that would preclude such therapy (64).

There are several ongoing studies that are evaluating the role of immunotherapy following SBRT and its effect on PFS and OS (*Table 1*). The largest trials include the PACIFIC-4 trial that is a randomized phase III trial in patients who undergo SBRT with or without adjuvant durvalumab for a total of 2 years. A similar trial, the I-SABR, is utilizing nivolumab both concurrently with the first fraction of SBRT followed by adjuvant therapy after completion of SBRT. Both of these trials have wide inclusion criteria to hopefully capture subsets of patients that may benefit from therapy more than others. Other trials are looking at immunotherapy both neoadjuvantly and adjuvantly to potentially maximize the synergistic effect of this combination. The SWOG/NRG Oncology intergroup S1914 phase III trial is randomizing patients to SBRT alone or induction atezolizumab and then SBRT during cycle 3 of immunotherapy. This trial also has a much shorter adjuvant treatment time, with only 8 total cycles of atezolizumab and is studying higher risk patients with tumors ≥2 cm, or SUVmax of ≥6.2, or histology moderately to poorly differentiated.

Radiation and immunotherapy in SCLC

While targeted therapies and checkpoint inhibitors have led to promising improvements in treatment of advanced NSCLC, until recently little progress had been made in improving OS in patients with SCLC. SCLC, while very responsive to first line cytotoxic chemotherapy, is frequently associated with rapid relapse with few successful second line options. This has prompted numerous trials to evaluate immunotherapy as a potential agent to overcome the limitations of chemotherapy. Biologically, response to immunotherapy is thought to correlate with high mutagenic burden due to high expression of neoantigens, leading to higher response to ICBs irrespective of PD-L1 tumor expression (65). SCLC has long been identified to have high tumor mutational burden (66,67), which has been shown to correlate with response to checkpoint inhibitors by leading to strong anti-tumor CD8+ cytotoxic T-cell response (66,68).

Multiple immunotherapy regimens have been investigated in SCLC, including single agent and multi-agent regimens. Initially utilized in the second line setting, encouraging response rates and OS were seen compared to historical single agent chemotherapy (69). This prompted multiple trials evaluating utilization of ICB in the first line setting. The Impower133 study was a double-blind, placebo-controlled phase 3 randomized trial in patients with extensive stage SCLC. Patients were randomized to carboplatin/etoposide with either atezolizumab or placebo. Maintenance atezolizumab or placebo was then given until unacceptable toxicity or progression. Median OS was improved in the atezolizumab arm to 12.3 months compared to 10.3 months in the placebo group (33). Median progression free survival was also improved. The similar CASPIAN study was a phase III randomized study in untreated extensive stage SCLC where patients received standard platinum doublet chemotherapy (carboplatin or cisplatin along with etoposide) alone or in combination with durvalumab followed by durvalumab maintenance until disease progression. Patients who received durvalumab had improved 18-month OS of 34% compared to 25% in the chemotherapy alone arm and an improved 12-month PFS of 18% compared to 5% (34).

Although these trial results are encouraging and increase OS, the gains SCLC have not been as substantial as those demonstrated in NSCLC. This may be related to the neoantigen expression seen when combining chemotherapy with ICB. Thus, radiation therapy may be an ideal additional modality to enhance tumor immunogenicity by increasing immune response both systemically and in the tumor microenvironment (70). Multiple ongoing trials are evaluating the combination of radiation with ICB agents both in the setting of extensive and limited stage disease (*Table 2*). Some of these trials are utilizing ICB in the upfront setting with standard therapy, while others are looking at novel ways to increase response in the setting line setting.

Given the newfound use of immunotherapy in the extensive stage setting, the role of traditional radiation therapy, such as PCI and thoracic consolidative radiation, has been challenged given that these immunotherapy trials did not require radiotherapy. Recent guidelines from ASTRO provide guidance on PCI and thoracic radiation therapy, recommending thoracic radiotherapy in extensive

Table 2 Key active trials combining immunotherapy and radiation therapy in SCLC

Trial name/NCT number	Phase	Stage/inclusion	ICB agent	Trial design	RT technique/dose	RT and ICB timing
Limited stage						
NRG-LU005 NCT03811002	2/3R	Limited stage	Atezolizumab	ChemoXRT +/– concurrent and adjuvant ICB for 12 months	Conventional 45 Gy/30 fractions (BID) or 66 Gy/ 33 fractions	Concurrent and adjuvant
NCT03540420	2R	Limited stage	Atezolizumab	ChemoXRT +/– adjuvant ICB for 12 months	Conventional 45 Gy/30 fractions (BID)	ChemoXRT first then ICB adjuvant
NCT02046733	2R	Limited stage	Nivolumab and ipilimumab	ChemoXRT +/– consolidation and maintenance IO	Conventional	Adjuvant
NCT02402920	1	Limited or extensive stage (see below)	Pembrolizumab	ChemoXRT + ICB concurrent + adjuvant	Conventional 45 Gy/30 fractions (BID)	Concurrent and adjuvant
Extensive stage						
NCT02402920	I	Extensive or limited stage SCLC	Pembrolizumab	Chemotherapy followed by ICB and radiation therapy	Conventional (BID)	Concurrent and adjuvant
Recurrent/relapsed						
NCT02402920	2R	Relapsed/recurrent	Tremelimumab and durvalumab	IO alone *vs.* SBRT followed by IO	SBRT in 3–5 fractions	SBRT first then IO

SCLC, small cell lung cancer; ICB, immune checkpoint blockade; IO, immuno-oncology therapy.

stage patients who respond to chemotherapy but have residual disease in the thorax (71). Ongoing studies will hopefully address this question more directly in the setting of immunotherapy use in this patient population.

Radiation and immunotherapy toxicity

As the combination of radiation therapy and immunotherapy is utilized more in both NSCLC and SCLC, incidence and severity of pulmonary toxicities associated with this combination will continue to be better characterized. As with the combination of chemoradiation (72), the main dose-limiting toxicity within the lung associated with the combination radiation and ICB is pneumonitis. Pneumonitis risk is associated with either therapy independently, and there appears to be up to an additive but not synergistic risk when the two therapies are combined either concurrently or sequentially. Recent analyses have shown this combination to be reasonably safe, will still overall low pneumonitis rates. Investigators from Emory University showed that when SBRT is utilized to treat either primary lung cancer or lung metastases, the use of immunotherapy within 30 days of lung SBRT is generally safe. However, while any-grade pneumonitis was not different between SBRT patients who did or did not receive ICB (33.9% *vs.* 27.9%, P=0.47), the risk of grade 3 pneumonitis was higher in combination cohort (10.7% *vs.* 0%, P<0.01). Factors associated with increased risk of pneumonitis included common clinical characteristics associated with radiation pneumonitis, such as treatment volume and lobes involved in SBRT, but also clinical characteristics unique to immunotherapy such as combination immunotherapy (73). Among prospectively enrolled patients, an analysis of lower dose radiation in combination with immunotherapy did not show increased pneumonitis rates compared to historic outcomes (74). In the locally advanced setting, the PACIFIC data showed

a modest increase in pneumonitis in patients receiving durvalumab, again suggesting an additive effect of this combination (75). As more clinical data are available, biomarker prediction of pneumonitis risk may have a role to better characterize risk in these patients who should be closely monitored for this common toxicity (76).

Future directions

The combination of radiation therapy and ICB has preclinical and clinical promise for both NSCLC and SCLC. Radiation therapy has long been a standard treatment modality across the spectrum of stages for both lung cancer histologies, and as ICB becomes an increasingly standard part of therapy in both early stage and advanced disease, this combination will inevitably increase in utilization to hopefully maximally benefit patients. Much remains to be learned about optimal timing and sequencing of this combination, and ongoing trials will attempt to answer these questions. In addition, questions remain regarding the ideal dose and fractionation of radiation therapy that has the highest synergistic immunostimulatory effect and the greatest ability to induce abscopal effects. Other radiation modalities such as proton and carbon therapy may also allow for improved clinical synergy, and further investigation is needed on the combination of immunotherapy and particle therapy. Similarly, much remains to be learned about if certain immune checkpoint inhibitors allow for better synergy with radiotherapy and if other types of immunotherapy can achieve optimal synergistic results with radiotherapy.

Additionally, biomarkers to predict response to immunotherapy have recently been developed and may provide insight into predicting response to the combination of immunotherapy and radiation (65,77-79). Similarly, class I and II HLA allele characterization to define tumor immunogenicity may provide additional insight into predicting response to this combination therapy (80). Lastly, while radiomic has had a rapid rise in oncology management and prediction (81), and it has an increasingly established role in predicting response and outcomes following radiation therapy for lung cancer (82), radiomics may also enable prediction of response to immunotherapy for lung cancer (83) and the combination of radiation therapy and immunotherapy.

While published data have prompted widespread use of the combination of radiation therapy and immunotherapy, clinicians eagerly await the results of ongoing trials to help provide guidance on their optimal utilization.

Acknowledgments

Funding: Supported by NIH/NCI Memorial Sloan Kettering Cancer Center Support Grant/Core Grant No. P30-CA008748, period: 1/1/19–12/31/23.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Dr. Arya Amini and Dr. Tyler Robin) for the series "Synergy in Action: Novel Approaches to Combining Radiation Therapy and Immunotherapy" published in *Translational Cancer Research*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2241

Peer Review File: Available at http://dx.doi.org/10.21037/tcr-20-2241

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2241). The series "Synergy in Action: Novel Approaches to Combining Radiation Therapy and Immunotherapy" was commissioned by the editorial office without any funding or sponsorship. Dr. JHH reports grants and personal fees from Vision RT, grants and personal fees from AstraZeneca, outside the submitted work. Dr. CBS reports other from Varian Medical Systems, outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Heinzerling JH, Mileham KF, Simone CB 2nd. The utilization of immunotherapy with radiation therapy in lung cancer: a narrative review. Transl Cancer Res 2021;10(5):2596-2608. doi: 10.21037/tcr-20-2241

