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

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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 describes 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

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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...
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 induce 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
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
current 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 NIOCLAS 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

<table>
<thead>
<tr>
<th>Trial name/NCT number</th>
<th>Phase</th>
<th>Stage/inclusion</th>
<th>ICB agent</th>
<th>Trial design</th>
<th>RT technique/dose</th>
<th>RT and ICB timing</th>
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<tbody>
<tr>
<td><strong>Early stage</strong></td>
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<tr>
<td>SWOG/ NRG S1914</td>
<td>3</td>
<td>Stage I–II</td>
<td>Atezolizumab</td>
<td>SBRT +/- ICB up to 5 months</td>
<td>SBRT</td>
<td>ICB first, then SBRT and ICB concurrent, then ICB adjuvant</td>
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<tr>
<td>NCT04214262</td>
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<tr>
<td>PACIFIC 4</td>
<td>3</td>
<td>Stage I–II</td>
<td>Durvalumab</td>
<td>SBRT +/- ICB up to 24 months</td>
<td>SBRT</td>
<td>SBRT first, ICB adjuvant</td>
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<tr>
<td>NCT03833154</td>
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<tr>
<td>I-SABR</td>
<td>2R</td>
<td>Stage I–IIIA</td>
<td>Nivolumab</td>
<td>SBRT +/- ICB up to 3 months</td>
<td>SBRT</td>
<td>SBRT and IO concurrent 70 Gy/10 fx</td>
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<tr>
<td>NCT03110978</td>
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<tr>
<td>ASTEROID</td>
<td>2R</td>
<td>Stage I</td>
<td>Durvalumab</td>
<td>SBRT +/- ICB up to 12 months</td>
<td>SBRT in 3 or 4 fractions</td>
<td>SBRT first, ICB adjuvant</td>
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<td>NCT03446547</td>
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<tr>
<td>NCT02904954</td>
<td>2R</td>
<td>Resectable stage I–IIIA</td>
<td>Durvalumab</td>
<td>Neoadjuvant IO +/- SBRT, surgery, postop maintenance IO</td>
<td>SBRT 24 Gy/3 fx</td>
<td>SBRT and IO concurrent</td>
</tr>
<tr>
<td>PembroX</td>
<td>2R</td>
<td>Resectable stage I–IIIA</td>
<td>Pembrolizumab</td>
<td>Neoadjuvant IO +/- SBRT, followed by surgery within 6 weeks</td>
<td>SBRT 12 Gy/1 fx delivered IO first then SBRT with to 50% of the primary lung IO concurrent tumor</td>
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<tr>
<td>NCT03217071</td>
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<tr>
<td><strong>Locally advanced</strong></td>
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<tr>
<td>PACIFIC 2</td>
<td>3</td>
<td>Unresectable stage III</td>
<td>Durvalumab</td>
<td>Concurrent ICB + platinum-based chemoRT, followed by adjuvant ICB</td>
<td>Conventional 60 Gy/30 fx</td>
<td>Concurrent</td>
</tr>
<tr>
<td>NCT03519971</td>
<td></td>
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<tr>
<td><strong>Metastatic/oligometastatic</strong></td>
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</tr>
<tr>
<td>NCT02492568</td>
<td>2R</td>
<td>Stage IV with at least 2 lesions; progression after 1st line chemo</td>
<td>Pembrolizumab</td>
<td>IO +/- SBRT</td>
<td>SBRT 24 Gy/3 fx</td>
<td>RT first then IO</td>
</tr>
<tr>
<td>PEMBRO-RT</td>
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<tr>
<td>NCT02658097</td>
<td>2R</td>
<td>Stage IV with a minimum of 2 lesions</td>
<td>Pembrolizumab</td>
<td>IO +/- SFRT (single fraction of radiation</td>
<td>Single fraction 8 Gy/1 fx</td>
<td>Concurrent</td>
</tr>
<tr>
<td>CASE1516</td>
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<tr>
<td>NCT02444741</td>
<td>1/2R</td>
<td>Stage IV with a minimum of 2 lesions</td>
<td>Pembrolizumab</td>
<td>IO +/- SBRT or wide field RT (WFRT)</td>
<td>SBRT 50 Gy/4 fx or WFRT Variable to 45 Gy/15 fx</td>
<td>Variable</td>
</tr>
<tr>
<td>NCT02239900</td>
<td>1/2R</td>
<td>Stage IV with at least one metastasis or 1° in lung, liver, or adrenal</td>
<td>Ipilimumab</td>
<td>IO +/- SBRT</td>
<td>SBRT to 50 Gy/4 fx or 60 Gy/10 fx</td>
<td>IO first then concurrent with SBRT</td>
</tr>
</tbody>
</table>

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...
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

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

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

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

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