The Integration of Radiotherapy with Immunotherapy for the Treatment of Non–Small Cell Lung Cancer

Eric C. Ko1, David Raben2, and Silvia C. Formenti1

Abstract

Five-year survival rates for non–small cell lung cancer (NSCLC) range from 14% to 49% for stage I to stage IIIA disease, and are $<5\%$ for stage IIIB/IV disease. Improvements have been made in the outcomes of patients with NSCLC due to advancements in radiotherapy (RT) techniques, the use of concurrent chemotherapy with RT, and the emergence of immunotherapy as first- and second-line treatment in the metastatic setting. RT remains the mainstay treatment in patients with inoperable early-stage NSCLC and is given concurrently or sequentially with chemotherapy in patients with locally advanced unresectable disease. There is emerging evidence that RT not only provides local tumor control but also may influence systemic control. Multiple preclinical studies have demonstrated that RT induces immunomodulatory effects in the local tumor microenvironment, supporting a synergistic combination approach with immunotherapy to improve systemic control. Immunotherapy options that could be combined with RT include programmed cell death-1/programmed cell death ligand-1 blockers, as well as investigational agents such as OX-40 agonists, toll-like receptor agonists, indoleamine 2,3-dioxygenase-1 inhibitors, and cytokines. Here, we describe the rationale for the integration of RT and immunotherapy in patients with NSCLC, present safety and efficacy data that support this combination strategy, review planned and ongoing studies, and highlight unanswered questions and future research needs.

Introduction

Lung cancer is the second most common cancer in the United States (1), and non–small cell lung cancer (NSCLC) comprises the majority of cases (2). Five-year survival rates range from 14% to 49% for node-negative NSCLC, and $<5\%$ for locally advanced, node-positive through metastatic disease (3). Surgical resection is often the preferred treatment approach for early-stage NSCLC (4), and radiotherapy (RT) is a mainstay of treatment for locally advanced NSCLC patients considered inoperable. Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative RT (SABR), can be safely and effectively delivered to patients with inoperable early-stage disease, including those with poor pulmonary function at baseline (5). RT may be given concurrently or sequentially with chemotherapy in patients with locally advanced disease (4). Systemic therapy with platinum-based combination chemotherapy, or an agent directed to either targetable rearrangement/mutation (such as ALK, ROS1, or EGFR) or other targets [such as programmed cell death-1 (PD-1)], is recommended as first-line treatment in patients with metastatic disease (4).

Despite therapeutic advances, there remains a significant need to improve outcomes across all stages. Although SBRT provides excellent local control rates (98% at 3 years and 87% at 5 years) in patients with early-stage NSCLC (6, 7), patients often develop distant metastases in follow-up, suggesting an ongoing need to improve systemic disease control, even in earlier stages. In the setting of unresectable stage III NSCLC, trials of induction or consolidation chemotherapy with concurrent chemoradiation have failed to show improved tumor control or survival benefits beyond standard-of-care chemoradiation (8, 9). Immunotherapy with checkpoint blockers has been a recent addition to the armamentarium of NSCLC treatment for patients with metastatic disease (10–12), and for patients with unresectable stage III disease with no evidence of disease progression after concurrent platinum-based chemoradiation (13).

There is now increasing recognition of the complex interplay between RT and the immune system, with a greater appreciation of the ability of RT to influence systemic tumor responses. This has led to significant interest in approaches that combine RT with immunotherapy, harnessing both components to expand the currently available therapeutic options. In this review, we describe the current practices in utilizing RT and immunotherapy for NSCLC, present the rationale and early results of integrating these modalities, and highlight some of the key unanswered questions in the field.

RT and Locoregional Tumor Control

For early-stage node-negative NSCLC, surgery is recommended for patients with operable disease, whereas SBRT is the recommended approach for patients considered medically inoperable (4). In retrospective studies of patients with early-stage NSCLC, SBRT has been shown to provide similar rates of local control and cancer-specific survival in inoperable patients as for patients...
undergoing surgical resection (14, 15). A pooled analysis of 58 medically operable stage I NSCLC patients from two phase III trials, STARS and ROSEL (which did not meet their accrual goals), suggested that SBRT is better tolerated and may lead to improved OS compared with surgery (16).

For patients with resectable locally advanced NSCLC, the standard treatment is surgery followed by adjuvant chemotherapy (4). Adjuvant RT is indicated in patients with mediastinal nodal involvement and/or positive resection margins, with RT offered either sequentially or concurrently with adjuvant chemotherapy (4). Neoadjuvant chemoradiation and chemotherapy prior to surgery are potential treatment options for select patients (4). In patients with locally advanced NSCLC who cannot undergo surgery, concurrent chemoradiation with conventionally fractionated RT is typically recommended (4, 17). A meta-analysis of 25 randomized clinical trials showed significantly decreased risk of death with concurrent chemoradiation versus RT alone (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.64–0.80) and versus sequential chemoradiation (HR, 0.74; 95% CI, 0.62–0.89) in patients with stage III NSCLC (17).

Failure pattern analyses have shown that not only are locally advanced NSCLC patients at a significant risk of developing distant metastases, but a notable proportion of recurrent patients also show locoregional failure (18). Thus, defining the RT dose and fractionation for optimal locoregional tumor control remains an important area of investigation. The role of RT dose escalation was addressed by RTOG 0617, a phase III study of patients with unresectable stage IIIA/B NSCLC that demonstrated that concurrent chemoradiation with high-dose RT (74 Gy) was associated with decreased overall survival (OS) and increased incidence of treatment-related deaths and severe esophagitis versus chemoradiation with standard dose RT (60 Gy; ref. 19). Consequently, based on current evidence, conventionally fractionated RT dose beyond 60 Gy should generally be avoided in the setting of concurrent chemoradiation. A meta-analysis of 10 randomized controlled trials observed that accelerated or hyperfractionated RT provided a modest OS benefit compared with conventional RT in locally advanced NSCLC (HR, 0.88; 95% CI, 0.80–0.97; P = 0.009; ref. 20). A study of adaptive RT, with treatment fields informed by 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) conducted at mid-treatment, demonstrated improved locoregional tumor control in patients with unresectable or inoperable stage II–III NSCLC who were receiving concurrent chemotherapy (21). These results have provided the background for the ongoing phase II study RTOG 1106, evaluating an individualized adaptive RT plan used after FDG-PET/CT compared with standard RT in unresectable or inoperable stage III NSCLC patients who receive concurrent chemotherapy. Multiple studies have also shown a positive local control benefit of SBRT boost after concurrent chemoradiation in patients with locally advanced NSCLC, with no additional toxicity beyond what is expected for conventional RT (22–25).

Despite improvements in clinical outcomes from current treatments (SBRT in early-stage node-negative NSCLC, and concurrent chemotherapy with conventionally fractionated RT in locally advanced NSCLC), there has been only a modest improvement in endpoints including freedom from progression, recurrence, and/or metastasis as well as OS (6, 7, 14, 15, 18). These limitations provide further rationale to support studies such as the combination of RT or chemoradiation with immunotherapy.

Rationale for Integration of RT and Immunotherapy

In addition to providing effective local treatment at the irradiated tumor site, RT can also mediate an abscopal effect, a phenomenon in which tumor regression occurs in nonirradiated lesions (26–28). Although the abscopal effect has been observed for decades, the exact mechanisms underlying this phenomenon remained elusive for much of this time (27). Demaria and colleagues were the first to link the abscopal effect of RT to an immune-mediated mechanism (29), and recent studies have provided further evidence that RT has the potential to activate a tumor-directed systemic immune response (26–28). With the advent of immunotherapy, new areas of research have emerged, with significant recent interest in combining RT with immunotherapeutic agents to potentially enhance the abscopal effect (26).

Preclinical evidence points to RT as a priming event for immunotherapy. By modulating the host’s immune system, RT can render tumor cells more susceptible to T-cell–mediated attack (30). RT promotes the release of tumor neoantigens from dying tumor cells, enhances MHC class I expression, and upregulates chemokines, cell-adhesion molecules, and other immunomodulatory cell surface molecules, thereby potentiating an antitumor immune response by triggering immunogenic cell death (Fig. 1; refs. 30, 31). The expression of programmed cell death ligand-1 (PD-L1), a checkpoint activated by tumor cells to evade the immune system, is upregulated in response to RT in preclinical models of NSCLC and other tumors (Fig. 1; refs. 31–34). RT and PD-L1 blockade in mouse models of melanoma, colorectal cancer, and breast cancer resulted in significantly delayed tumor growth, which was mediated by CD8+ T cells (32, 35). Similar synergistic antitumor activity has also been noted in mouse models of NSCLC (33, 34). Using a mouse model of colon carcinoma, Dovedi and colleagues found that concurrent but not sequential administration of RT and anti–PD-1 therapy led to tumor regression of distal nonirradiated lesions (36). In a study using a melanoma mouse model, RT given before or concurrently with CTLA-4 blockade delayed tumor growth and improved survival, compared with mice treated with anti–CTLA-4 therapy alone (37). Importantly, when RT is combined with immune checkpoint blockade, the dose per fraction of RT has been demonstrated in preclinical models to have an impact on its systemic effects. RT-induced cytoplasmic double-stranded DNA is sensed by the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway to induce IFN-1, a key mediator of dendritic cell recruitment and maturation (38–40). Vanpouille-Box and colleagues demonstrated a threshold dose per fraction of RT administered beyond which TREX1 is induced (41): as an exonuclease, TREX1 digests cytosolic double-stranded DNA, thereby removing the substrate that triggers cGAS-STING signaling. These findings have significant clinical implications in the selection of dose and fractionation when RT is combined with immunotherapy.

Immunotherapy for Systemic Tumor Control

The advent of immunotherapy for NSCLC has provided opportunities to enhance systemic tumor control by mechanisms distinct from those that underlie the use of chemotherapy or agents that target tumor-driver mutations (Fig. 2; refs. 42, 43).
Multiple agents are under active investigation in NSCLC (Fig. 3). Checkpoint molecules are regulators of T-cell activation that deliver negative or positive regulatory signals (44), and activation of inhibitory checkpoints may enable tumors to evade the immune system (45). Within the lymph node, CTLA-4 acts as an inhibitory checkpoint on T cells (42, 44). Ipilimumab and tremelimumab are anti–CTLA-4 antibodies that prevent the binding of CTLA-4 on T cells with CD80 and CD86 on antigen-presenting cells, thereby enhancing T-cell activation (46). Ipilimumab is approved for the treatment of patients with melanoma (47), whereas tremelimumab is still investigational. Within the tumor microenvironment, PD-1 is an inhibitory checkpoint that...
downregulates effector T cells (45). Nivolumab and pembrolizumab are anti–PD-1 antibodies that bind and block PD-1 receptors on activated T cells, whereas durvalumab, atezolizumab, and avelumab are anti–PD-L1 antibodies that bind and block PD-L1 on tumor cells (45). Blockade of the PD-1/PD-L1 pathway enables T cells to recognize and destroy tumor cells (45). To date, only the PD-1 blockers pembrolizumab and nivolumab and the PD-L1 blocker atezolizumab are FDA-approved for the treatment of metastatic NSCLC (10–12), with PD-L1 expression as a selection criteria for treatment with pembrolizumab (11). Durvalumab has been recently approved by the FDA for the treatment of unresectable stage III NSCLC patients whose disease has not progressed following concurrent platinum-based chemoradiation (13). Avelumab is currently being tested in clinical trials in NSCLC. Other targets for immunotherapy include OX-40 (48, 49), toll-like receptors (TLR; refs. 50, 51), IDO1 (52, 53), and cytokines (54). OX-40 agonists, TLR agonists, IDO1 inhibitors, cytokines, and cytokine blockers are currently in clinical development, and some of these agents are being tested in combination with RT.

Safety and Efficacy of RT Combined with Immunotherapy

Checkpoint blockers

The integration of RT with checkpoint inhibitors may present overlapping toxicities such as pneumonitis (10–12) and, potentially, myocarditis (55). Recent data from clinical trials and secondary or retrospective analyses include patients with locally
advanced or metastatic NSCLC. Durvalumab is the only check-
point blocker with phase III data following definitive platinum-
based concurrent chemoradiation in locally advanced, unrect-
sectable stage III NSCLC patients without evidence of disease pro-
gression (56). The phase III randomized PACIFIC study investi-
gated durvalumab versus placebo in 713 patients with unrect-
sectable stage III NSCLC who did not have disease progression after
≥2 cycles of platinum-based chemoradiation (56). The incidence of
adverse events (AE) of any cause was similar for durvalumab
versus placebo for AEs of any grade (97% vs. 95%), grade 3/4 AEs
(30% vs. 26%), and serious AEs (SAEs; 29% vs. 23%; ref. 56).

Treatment-related AEs of all grades were reported in 68% of
durvulumab-treated patients versus 53% of placebo-treated
patients, and the incidence of grade 3/4 AEs was 12% versus 4%,
respectively (56). The most frequent grade 3/4 AEs of any
cause were pneumonia (4% in each arm) and pneumonitis (3% in
each arm), which were expected after definitive chemoradiation
(56). The incidence of treatment-related grade 3/4 pneumonitis
was comparable at 1% in each arm (56). A planned interim
analysis of the PACIFIC trial showed that durvalumab signif-
ically extended both the median progression-free survival (PFS)
versus placebo (16.8 vs. 5.6 months; HR, 0.52; 95% CI, 0.42–0.65;
P < 0.001) as well as the median time to death or distant metastasis
(23.2 vs. 14.6 months; HR, 0.52; 95% CI, 0.39–0.69; P < 0.001), and
significantly increased the objective response rate (28% vs.
16%; P < 0.001; ref. 56). Based on these data, durvalumab recently
received FDA approval for the treatment of unresectable stage III
NSCLC patients achieving at least stable disease following defini-
tive chemoradiation (13).

In a secondary analysis of the phase I KEYNOTE-001 study, 24
of 97 patients with metastatic NSCLC received thoracic RT prior to
pembrolizumab. Pulmonary toxicity of any grade was observed in
63% of patients (15/24) with previous thoracic RT versus 40% of
patients (29/73) with no previous thoracic RT (P = 0.052; ref. 57).
The incidence of pembrolizumab-related pulmonary toxicity of
any grade was significantly higher in patients with previous thoracic RT (13% vs. 3/24 versus patients with no previous thoracic RT (1%; P = 0.046; ref. 57). Pembrolizumab was associated with significantly longer PFS and OS in patients who previously
received extracranial RT versus those without prior extracranial
RT (PFS, 6.3 vs. 2.0 months; P = 0.008; OS, 11.6 vs. 5.3 months;
P = 0.034; ref. 57). Early results from a phase II study of consolidation therapy with pembrolizumab following concur-
rent chemoradiation in 93 patients with unresectable stage III
NSCLC showed that 15% of patients (14/93) experienced pneu-
monitis of grade ≥ 2, 2% (6/93) had grade 3–5 pneumonitis, and
2 patients died due to pneumonitis (58).

Multiple retrospective analyses have provided additional
insight beyond recent clinical trials. In a retrospective analysis of
advanced NSCLC patients (n = 201) treated with nivolumab, 50
patients (25%) had received prior thoracic RT, among whom 34
(68%) experienced RT-related pneumonitis before nivolumab
(59). The incidence of nivolumab-related interstitial lung disease
(ILD) was higher in patients with a history of RT-related pneu-
monitis versus those without such history (27% vs. 10%; P = 0.018);
similarly, nivolumab-related ILD was higher in patients with prior thoracic RT versus those without prior thoracic RT (22% vs.
9%; P = 0.03; ref. 59). Of note, a history of RT-related pneumonitis versus no history was significantly correlated with
improved median PFS (3.6 vs. 2.3 months; P = 0.023; ref. 59).
Prior treatment with thoracic RT versus no RT did not significantly
extend median PFS (3.3 vs. 2.2 months, respectively; P = 0.635; ref.
59). In a retrospective analysis of NSCLC patients (n = 146)
treated with nivolumab after second-line systemic chemotherapy,
no difference in PFS was found between patients who received
RT 6 months before receiving nivolumab and those without
previous RT (60). In a retrospective analysis of 133 patients
with metastatic cancer (n = 71 with NSCLC) who received RT
and immunotherapy either concurrently or sequentially (anti-
PD-1 therapy, 66% anti–CTLA-4 therapy, 21% both anti–PD-1
and anti–CTLA-4 therapy, 13%), 35% of patients experienced
immune-mediated AEs (imAEs) of any grade, which were
manageable and not related to the site of RT (61). ImAEs of
any grade were more frequent in patients who received both
anti–CTLA-4 and anti–PD-1 therapies versus either immuno-
therapy alone (71% vs. 29%; P = 0.0008), and tended toward
increased frequency in patients who received RT within 14 days of
immunotherapy compared with >14 days (39% vs. 23%; P = 0.06; ref. 61). Taken together, these data suggest that combin-
ning RT with immunotherapy does not appear to produce
significantly increased toxicities beyond those associated with
each treatment independently, and that this combined treat-
ment approach may provide improved clinical benefit.

Another important rationale for the combination of RT and
immunotherapy is the potential for RT to overcome resistance
to immune checkpoint blockade. Yuan and colleagues
described a patient with PD-L1-negative metastatic squamous
NSCLC that was refractory to nivolumab (62). After palliative
RT, this patient exhibited near resolution of the irradia-
ted primary tumor and significant regression of metastases outside
the RT field, hence consistent with an abscopal effect (62).
Komatsu and colleagues reported the case of a patient with
metastatic NSCLC who experienced an increase in size of liver
metastases after treatment with nivolumab (63). The patient
was subsequently treated with RT, which led to a reduction in
size of the irradiated liver metastases as well as a reduction in
size of pulmonary metastases, which were outside the RT field,
hence also consistent with an abscopal effect (63). These case
reports point to the potential role of RT in overcoming immune
resistance mechanisms in NSCLC patients when administered
after an initial failure of immunotherapy.

Other investigational immunotherapies

Data for combinations of RT with other immunotherapeutic
agents are also available, suggesting that there is potential
clinical benefit with no significant additive toxicity when com-
bining RT with immunotherapy. The phase III study START
investigated vaccination with tecemotide as maintenance ther-
apy after chemoradiation in unresectable stage III NSCLC
patients (n = 1,513; refs. 64, 65). Treatment-related AEs of any
grade were reported in 34% of tecemotide-treated patients
versus 27% of placebo-treated patients, and imAEs were infre-
quent and not significantly different between groups (64).

Treatment-related SAEs were reported in 2% of tecemotide-
treated patients versus 1% of placebo-treated patients, and grade
3/4 treatment-related AEs occurred in 1% of each arm (64).
Among the 1,239 patients evaluable for efficacy in the START
trial, 65% of patients had prior concurrent chemoradiation and
35% had prior sequential chemoradiation (64). Although the
primary endpoint (OS across all randomized patients) was not
met, maintenance therapy with tecemotide was associated
with significantly longer median OS versus placebo (30.8 vs.

5796 Clin Cancer Res; 24(23) December 1, 2018 Clinical Cancer Research
Areas of Investigation and Future Directions

Although early evidence points to the clinical viability of combining RT and immunotherapy in NSCLC, many unanswered questions remain. For example, at what stage of NSCLC is this treatment approach most effective? In addition to the metastatic and locally advanced NSCLC settings, it is conceivable that patients with early-stage disease may also potentially benefit from these treatment combinations. Patients with early-stage NSCLC still have high rates of relapse after definitive resection or SBRT, as evidenced by 5-year survival rates of 30% to 49%; thus, there continues to be an unmet need for postresection adjuvant therapy and post-SBRT maintenance/consolidation therapy (3, 71).

The optimal sequence and timing of RT and immunotherapy remain investigational. Available data in NSCLC showed clinical benefit when immunotherapy was given after RT (± chemotherapy; refs. 56, 57, 67, 68). A subgroup analysis of the PACIFIC study found that the PFS improvement in favor of durvalumab was more pronounced among patients who had their last RT dose <14 days before randomization (HR, 0.39; 95% CI, 0.26–0.58), compared with those who had their last RT dose ≥14 days before randomization (HR, 0.63; 95% CI, 0.49–0.80; ref. 56). Although provocative, this finding needs to be interpreted with caution, because variables like tumor burden or performance status may have caused a treatment delay, enriching the proportion of patients with less favorable disease among those randomized >14 days from RT completion. To date, few studies have tested concomitant administration of immunotherapy with RT (69, 72, 73), and only a few case reports have described a treatment benefit with RT after immunotherapy (62, 63). The type of immunotherapy used in combination with RT is likely to play a role in whether a concurrent or sequential strategy is more efficacious. For example, RT may elicit more effective antitumor immunity if administered concurrently with anti–CTLA-4 therapy (as both therapies act at the early stage of the antitumor immune response), whereas in other cases, RT may be more effective if administered prior to anti–PD-1/PD-L1 therapy, as PD-1/PD-L1 signaling typically acts at a later stage of the antitumor immune response. Clinical trials that evaluate the optimal therapeutic sequence are needed, as are preclinical data to better understand the underlying mechanisms at play.

There are conflicting data on changes in PD-L1 expression after chemoradiation. A small retrospective analysis in locally advanced NSCLC (n = 15) found that neoadjuvant chemoradiation led to a decrease in PD-L1 expression (74), whereas retrospective analyses in patients with other tumor types found that neoadjuvant chemoradiation increased PD-L1 expression (75, 76). It is possible that the differential effects could be accounted for by differences in tumor types, staging, and/or treatment. Additional studies are needed to clarify this issue and its therapeutic implications.

The optimal RT dose and schedule to ensure adequate priming for immunotherapy, and the extent of tumor that should be irradiated while minimizing local toxicity, remain to be defined. Preclinical studies using breast and colon carcinoma mouse models (41, 77) and a clinical study in patients with melanoma (78) suggest that fractionated dosing is preferred to a single-dose strategy to elicit an abscopal response when paired with anti–CTLA-4 antibodies. However, among fractionated strategies, it is not clear if the dosing should be modeled after ablative...
Table 1. Ongoing studies of immunotherapy in combination with RT in NSCLC

<table>
<thead>
<tr>
<th>NCT number/trial name</th>
<th>Study phase</th>
<th>Disease stage</th>
<th>Trial design</th>
<th>RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)</th>
<th>Line of therapy</th>
<th>Status</th>
<th>Estimated primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-stage NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT0310978 I-SABR</td>
<td>2R</td>
<td>Inoperable stage I and II NSCLC (N = 140)</td>
<td>SBRT alone vs. SBRT + nivolumab given within 36 hours before or after the first SBRT fraction</td>
<td>SBRT delivered at 50 Gy in 4 fractions, or if this cannot meet normal-tissue dose-volume constraints, 70 Gy in 10 fractions over 1-2 weeks</td>
<td>Any line</td>
<td>Recruiting</td>
<td>June 2022</td>
</tr>
<tr>
<td>NCT02904954</td>
<td>2R</td>
<td>Resectable stage I NSCLC (N = 60)</td>
<td>Neoadjuvant durvalumab ± SBRT, followed by surgery, followed by postoperative monthly maintenance durvalumab</td>
<td>SBRT delivered at 24 Gy in 3 daily fractions starting concurrently with the first cycle of durvalumab</td>
<td>Neoadjuvant/adjuvant/maintenance</td>
<td>Recruiting</td>
<td>January 2020</td>
</tr>
<tr>
<td>NCT03217071 PembroX</td>
<td>2R</td>
<td>Inoperable stage I and II NSCLC (N = 40)</td>
<td>Neoadjuvant pembrolizumab ± SBRT</td>
<td>SBRT delivered at 12 Gy in 1 fraction to 50% of the primary tumor only, administered within 1 week (&lt;3 days) following the second administration of pembrolizumab</td>
<td>Neoadjuvant</td>
<td>Recruiting</td>
<td>September 2019</td>
</tr>
<tr>
<td>NCT02818920 TOP 1501</td>
<td>2R</td>
<td>Resectable stage I NSCLC (N = 32)</td>
<td>Neoadjuvant pembrolizumab, followed by surgery, followed by standard adjuvant chemotherapy ± RT, followed by adjuvant pembrolizumab</td>
<td>N/A</td>
<td>Neoadjuvant/adjuvant</td>
<td>Recruiting</td>
<td>January 2020</td>
</tr>
<tr>
<td>NCT03148327</td>
<td>2R</td>
<td>Inoperable stage I/II NSCLC (N = 105)</td>
<td>Durvalumab ± SBRT vs. SBRT alone</td>
<td>SBRT delivered at 54 Gy in 3 fractions, or at 50 Gy in 4 fractions, or at 65 Gy in 10 fractions, administered within 10 days after durvalumab first dose</td>
<td>IL</td>
<td>Recruiting</td>
<td>June 2020</td>
</tr>
<tr>
<td>NCT02581787 SABR-ATAC</td>
<td>1/2</td>
<td>Stage IA/B NSCLC under consideration for SBRT as definitive primary therapy (N = 60)</td>
<td>Fresolimumab on days 1, 15, 36 &amp; SBRT</td>
<td>SBRT delivered in 4 fractions, between days 8 and 12</td>
<td>IL</td>
<td>Recruiting</td>
<td>January 2020</td>
</tr>
<tr>
<td>NCT0350554</td>
<td>1/2</td>
<td>Inoperable stage I NSCLC (N = 56)</td>
<td>Avelumab ± SBRT</td>
<td>SBRT delivered at 48 Gy in 4 fractions, or at 50 Gy in 5 fractions (given every other day over 10–12 days)</td>
<td>Adjuvant</td>
<td>Recruiting</td>
<td>March 2020</td>
</tr>
<tr>
<td>NCT02599454</td>
<td>1</td>
<td>Inoperable stage I NSCLC (N = 33)</td>
<td>Atezolizumab + SBRT</td>
<td>SBRT delivered at 50 Gy in 4 fractions (for peripherally located tumors) or in 5 fractions (for centrally located tumors) over days 1–5 of cycle 3, administered within 24–48 hours after receiving atezolizumab</td>
<td>N/A</td>
<td>Recruiting</td>
<td>November 2017</td>
</tr>
<tr>
<td>Locally advanced stage NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02768558 RTOG 3055</td>
<td>3R</td>
<td>Inoperable or unresectable stage IIIA/B (not metastatic) immunotherapy-naive NSCLC (N = 660)</td>
<td>Chemotherapy (cisplatin/etoposide + RT), followed by nivolumab vs. placebo</td>
<td>60 Gy of thoracic RT (3D-CRT or IMRT)</td>
<td>N/A</td>
<td>Recruiting</td>
<td>October 2022</td>
</tr>
<tr>
<td>NCT02343952 HCRN LUN14-179</td>
<td>2</td>
<td>Inoperable or unresectable stage IIIA/B NSCLC (not metastatic, N = 93)</td>
<td>Chemotherapy (either cisplatin/etoposide or carboplatin/paclitaxel + RT), followed by consolidation pembrolizumab</td>
<td>RT delivered at 59.4–66.6 Gy</td>
<td>Consolidation</td>
<td>Ongoing not recruiting</td>
<td>March 2018 (SB)</td>
</tr>
<tr>
<td>NCT02434081 NICOLAS</td>
<td>2</td>
<td>Locally advanced stage IIIA/B NSCLC (not metastatic, N = 78)</td>
<td>Nivolumab + standard chemoradiation</td>
<td>N/A</td>
<td>IL</td>
<td>Ongoing not recruiting</td>
<td>August 2020</td>
</tr>
</tbody>
</table>

(Continued on the following page)
### Table 1. Ongoing studies of immunotherapy in combination with RT in NSCLC (Cont’d)

<table>
<thead>
<tr>
<th>NCT number / trial name</th>
<th>Study phase</th>
<th>Disease stage</th>
<th>Trial design</th>
<th>RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)</th>
<th>Line of therapy</th>
<th>Status</th>
<th>Estimated primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02572843 (N=68)</td>
<td>2</td>
<td>Resectable stage IIIA NSCLC</td>
<td>Neoadjuvant chemotherapy (cisplatin/docetaxel), followed by neoadjuvant durvalumab, followed by surgery, followed by adjuvant durvalumab for R0 patients or standard RT prior to adjuvant durvalumab for R1/R2 patients</td>
<td>RT delivered at 60 Gy in 30 daily fractions over 6 weeks, in conjunction with chemotherapy and immunotherapy</td>
<td>Neoadjuvant/adjuvant</td>
<td>Recruiting</td>
<td>March 2021</td>
</tr>
<tr>
<td>NCT03102242 (N=63)</td>
<td>2</td>
<td>Unresectable stage IIIA/B NSCLC, eligible for chemoradiation with curative intent</td>
<td>Neoadjuvant atezolizumab + chemoradiation (carboplatin/paclitaxel + RT), followed by adjuvant atezolizumab</td>
<td>RT delivered at 44 Gy in 22 daily fractions over 5 weeks</td>
<td>Adjuvant</td>
<td>Not yet recruiting</td>
<td>May 2021</td>
</tr>
<tr>
<td>NCT03087760 (N=41)</td>
<td>2</td>
<td>NSCLC patients who have received previous chemotherapy and concurrent intrathoracic RT with definitive intent and have a tumor recurrence in or near the prior irradiation fields (N=4)</td>
<td>Pembrolizumab monotherapy</td>
<td>RT delivered at 45 Gy in 25 daily fractions (1.8 Gy each)</td>
<td>Neoadjuvant/adjuvant</td>
<td>Recruiting</td>
<td>January 2019</td>
</tr>
<tr>
<td>NCT02S5757 (DETERRED)</td>
<td>2</td>
<td>Unresectable stage II/III NSCLC (not metastatic; N=40)</td>
<td>Standard chemoradiation (carboplatin/paclitaxel + RT)</td>
<td>RT delivered at 45 Gy in 25 daily fractions over 5 weeks</td>
<td>Adjuvant</td>
<td>Not yet recruiting</td>
<td>September 2019</td>
</tr>
<tr>
<td>NCT03S5866 (N=37)</td>
<td>2</td>
<td>Stage IIIA NSCLC (N=37)</td>
<td>Neoadjuvant chemoradiation (cisplatin/paclitaxel + RT), followed by surgery, followed by adjuvant pembrolizumab alone</td>
<td>RT delivered at 45 Gy in 25 daily fractions over 5 weeks</td>
<td>Adjuvant</td>
<td>Not yet recruiting</td>
<td>May 2021</td>
</tr>
<tr>
<td>NCT03237377 (N=32)</td>
<td>2</td>
<td>Resectable stage IIIA NSCLC</td>
<td>Pembrolizumab + tremelimumab + RT, followed by surgery</td>
<td>Thoracic RT delivered at 45 Gy in 25 daily fractions over 5 weeks</td>
<td>Neoadjuvant</td>
<td>Not yet recruiting</td>
<td>September 2019</td>
</tr>
<tr>
<td>NCT02987998 (N=20)</td>
<td>1</td>
<td>Resectable stage IIIA NSCLC</td>
<td>Neoadjuvant chemoradiation (cisplatin/etoposide + RT) + pembrolizumab, followed by consolidation pembrolizumab</td>
<td>RT delivered at 45 Gy in 25 daily fractions (1.8 Gy each)</td>
<td>Neoadjuvant/consolidation</td>
<td>Recruiting</td>
<td>January 2019</td>
</tr>
<tr>
<td>Stage IV (metastatic) NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02992912 (SABR-PD-L1)</td>
<td>2</td>
<td>Metastatic solid tumor, including NSCLC, CRC, or RCC (N=180)</td>
<td>Atezolizumab + SBRT</td>
<td>SBRT delivered at 45 Gy in 3 fractions (15 Gy each)</td>
<td>2L+ (for NSCLC)</td>
<td>Recruiting</td>
<td>November 2018</td>
</tr>
<tr>
<td>NCT02888743 (N=180)</td>
<td>2</td>
<td>Metastatic NSCLC and metastatic CRC</td>
<td>Durvalumab + tremelimumab ± RT (either high-dose or low-dose)</td>
<td>RT starts at week 2: either high-dose RT in up to 3 daily fractions over 10 days, or low-dose RT every 6 hours twice per day on weeks 2, 6, 10, and 14</td>
<td>2L+ (for NSCLC after progression to anti-PD-1/ PD-L1 therapy)</td>
<td>Recruiting</td>
<td>December 2020</td>
</tr>
<tr>
<td>NCT03044626 (FORCE)</td>
<td>2</td>
<td>Metastatic nonsquamous NSCLC (N=130)</td>
<td>Nivolumab + concurrent RT (for patients necessitating RT) or nivolumab alone (for patients without the necessity of RT)</td>
<td>RT delivered at 20 Gy in 5 fractions (4 Gy each) to 1 target lesion over 2 weeks, administered within 3 days after nivolumab first dose</td>
<td>2/3L</td>
<td>Recruiting</td>
<td>August 2019</td>
</tr>
</tbody>
</table>

(Continued on the following page)
### Table 1. Ongoing studies of immunotherapy in combination with RT in NSCLC (Cont’d)

<table>
<thead>
<tr>
<th>NCT number/trial name</th>
<th>Study phase</th>
<th>Disease stage</th>
<th>Trial design</th>
<th>RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)</th>
<th>Line of therapy</th>
<th>Status</th>
<th>Estimated primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03050060</td>
<td>2</td>
<td>Stage IV NSCLC, stage IV melanoma, or metastatic RCC (N = 120)</td>
<td>Nelﬁnav mesylate + immunotherapy (pembrolizumab or nivolumab or atezolizumab) + RT</td>
<td>Hypofractionated IGRT administered over 3-14 days, starting after course 1 and before course 3 of immunotherapy</td>
<td>Prior immunotherapy or chemotherapy allowed</td>
<td>Recruiting</td>
<td>December 2021</td>
</tr>
<tr>
<td>NCT0378173</td>
<td>2</td>
<td>Metastatic NSCLC undergoing standard immunotherapy (N = 85)</td>
<td>Immunotherapy (nivolumab or pembrolizumab or atezolizumab) + RT</td>
<td>Radical-dose IGRT administered daily for up to 10 days (within 2 weeks)</td>
<td>Patients must have been receiving anti–PD-1 or anti–PD-L1 therapy for at least 4 weeks</td>
<td>Recruiting</td>
<td>June 2020</td>
</tr>
<tr>
<td>NCT02492568</td>
<td>2R</td>
<td>Stage IV (metastatic) NSCLC (N = 74)</td>
<td>Pembrolizumab after SBRT vs nivolumab</td>
<td>SBRT delivered at 24 Gy in 3 fractions (1-2 weeks prior to start of pembrolizumab)</td>
<td>2L+</td>
<td>Recruiting</td>
<td>October 2017</td>
</tr>
<tr>
<td>NCT02823535</td>
<td>2</td>
<td>Stage IV NSCLC (N = 60)</td>
<td>GM-CSF daily from days 1 to 14 + SBRT</td>
<td>SBRT delivered at 50 Gy in 5 fractions to 1 lung lesion from days 1 to 5</td>
<td>3L+ (progression after standard 2L chemotherapy)</td>
<td>Recruiting</td>
<td>May 2019</td>
</tr>
<tr>
<td>NCT02978404</td>
<td>2</td>
<td>Stage IV NSCLC, or RCC (with brain metastases; N = 60)</td>
<td>Nivolumab + SRM</td>
<td>SRS delivered at 15–20 Gy in 1 fraction to brain metastases, administered 1-2 weeks after receiving the first dose of nivolumab</td>
<td>1-4L</td>
<td>Recruiting</td>
<td>June 2020</td>
</tr>
<tr>
<td>NCT03664183</td>
<td>2</td>
<td>Metastatic NSCLC or TNBC (N = 57)</td>
<td>In situ oncolytic virus therapy (ADV/HSV-tk on day 0 + valacyclovir from days 1 to 15) + SBRT, followed by pembrolizumab (starting on day 17)</td>
<td>SBRT delivered at 30 Gy in 5 fractions (6 Gy each) over 2 weeks from days 2 to 16</td>
<td>1L (immunotherapy and chemotherapy naive)</td>
<td>Recruiting</td>
<td>May 2022</td>
</tr>
<tr>
<td>NCT03004183</td>
<td>STOMP</td>
<td>Metastatic NSCLC or TNBC (N = 57)</td>
<td>Immunotherapy (nivolumab or pembrolizumab or atezolizumab) + concurrent RT</td>
<td>RT (SBRT or 3D-CRT) administered within 14 days of receiving the first dose of immunotherapy to 1 target lesion (non-CNS): either SBRT to achieve BED &gt; 100 Gy or 30 Gy of fractionated 3D-CRT</td>
<td>For NSCLC: 1L or relapsed</td>
<td>Recruiting</td>
<td>June 2018</td>
</tr>
<tr>
<td>NCT03313804</td>
<td>2</td>
<td>Advanced or metastatic NSCLC, or HNSCC (N = 57)</td>
<td>Standard two-drug platinum-containing chemotherapy (carboplatin or cisplatin + pemetrexed or docetaxel or paclitaxel or etoposide or gemcitabine or vinorelbine or nab-paclitaxel) alone vs. standard two-drug platinum-containing chemotherapy + SBRT</td>
<td>SBRT to primary lesions or metastatic lesions</td>
<td>N/A</td>
<td>Not yet recruiting</td>
<td>December 2019</td>
</tr>
<tr>
<td>NCT02940990</td>
<td>2R</td>
<td>Stage IV (metastatic) NSCLC with &gt;5 metastases and pan-negative for driver mutations (N = 50)</td>
<td>GM-CSF daily from days 1 to 14 + thymosin-β4 from weeks 1 to 12 + SBRT</td>
<td>SBRT delivered at 50 Gy in 4-10 fractions to 1 lung lesion from days 1 to 10</td>
<td>3L+ (after progression to standard 2L chemotherapy)</td>
<td>Recruiting</td>
<td>June 2019</td>
</tr>
<tr>
<td>NCT02978470</td>
<td>2</td>
<td>Stage IV (metastatic) NSCLC (N = 46)</td>
<td>SFRT followed by pembrolizumab vs nivolumab</td>
<td>SBRT delivered at 40-45 Gy in 5-15 fractions (starting at week 1)</td>
<td>2L+</td>
<td>Recruiting</td>
<td>December 2018</td>
</tr>
<tr>
<td>NCT02658097</td>
<td>2R</td>
<td>Stage IV (metastatic) NSCLC (N = 48)</td>
<td>SFRT followed by pembrolizumab vs nivolumab</td>
<td>SBRT delivered at 8 Gy in 1 fraction on the first day of pembrolizumab therapy</td>
<td>Thoricacic hypofractionated RT delivered at 40–45 Gy in 5-15 fractions (starting at week 1)</td>
<td>Consolidaion</td>
<td>December 2017</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 1. Ongoing studies of immunotherapy in combination with RT in NSCLC (Cont’d)

<table>
<thead>
<tr>
<th>NCT number/trial name</th>
<th>Study phase</th>
<th>Disease stage</th>
<th>Trial design</th>
<th>RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)</th>
<th>Line of therapy</th>
<th>Status</th>
<th>Estimated primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03113851</td>
<td>2</td>
<td>Stage IV (metastatic) NSCLC (N = 40)</td>
<td>GM-CSF daily from days 1 to 14, every 3 weeks + SBRT</td>
<td>SBRT delivered at 35 Gy in 10 fractions to 1 lung lesion over 2 weeks</td>
<td>Consolidation (for patients with response or SD after 1L chemotherapy) or 3L+ (for patients with disease progression after standard 2L chemotherapy)</td>
<td>Recruiting</td>
<td>August 2018</td>
</tr>
<tr>
<td>NCT02831933 ENSIGN</td>
<td>2</td>
<td>Stage IV (metastatic) NSCLC (N = 29)</td>
<td>In situ gene therapy (ADV/HSV-tk on day 0 + valacyclovir from days 1 to 15) + SBRT, followed by nivolumab (starting on day 17)</td>
<td>SBRT delivered at 30 Gy in 5 fractions (6 Gy each) over 2 weeks from days 2 to 16</td>
<td>2L+</td>
<td>Recruiting</td>
<td>December 2021</td>
</tr>
<tr>
<td>NCT02859265</td>
<td>2</td>
<td>Stage III/IV NSCLC not amenable to curative therapy (N = 29)</td>
<td>CDX-301 daily for 5 days + concomitant SBRT</td>
<td>SBRT delivered to a single lung lesion, starting on the same day of immunotherapy 34 Gy in 1 fraction (for peripheral tumors smaller than 2 cm and not adjacent to the chest wall), or 54 Gy in 3 fractions (for peripheral tumors not eligible for 34 Gy in 1 fraction), or 50 Gy in 5 fractions (for central tumors)</td>
<td>2L+ (at least one standard chemotherapy regimen or targeted therapy)</td>
<td>Recruiting</td>
<td>July 2020</td>
</tr>
<tr>
<td>NCT0239900</td>
<td>1/2R</td>
<td>Metastatic solid tumors, including patients with lung metastases (N = 120)</td>
<td>Ipilimumab + SBRT (concurrent vs. sequential)</td>
<td>SBRT delivered to 1-4 lung lesion(s) at either 50 Gy in 4 fractions or 60 Gy in 10 fractions</td>
<td>N/A</td>
<td>Recruiting</td>
<td>August 2019 (73)</td>
</tr>
<tr>
<td>NCT02444741</td>
<td>1/2R</td>
<td>All stages NSCLC for phase I; stage IV (metastatic) NSCLC for phase II (N = 104)</td>
<td>Pembrolizumab + RT (SBRT vs. WFRT)</td>
<td>SBRT delivered at 45 Gy in 15 daily fractions</td>
<td>N/A</td>
<td>Recruiting</td>
<td>September 2020</td>
</tr>
<tr>
<td>NCT05159738 QUILT-3D44</td>
<td>1/2</td>
<td>NSCLC (N = 85)</td>
<td>Nant NSCLC vaccine consisting of immunotherapy combination therapy with avilamab, bevacizumab, capcitabine, cisplatin, cyclophosphamide, 5-fluorouracil, fulvestrant, leucovorin, nab-paclitaxel, nivolumab, tivozan, oxaliplatin, RT, ALT-803, ETBX-011, ETBX-021, ETBX-051, ETBX-061, GI-4000, GI-6207, GI-6301, and hank</td>
<td>SBRT</td>
<td>Not yet recruiting</td>
<td>January 2019</td>
<td></td>
</tr>
<tr>
<td>NCT02696993</td>
<td>1/2</td>
<td>Stage IV (metastatic) NSCLC with brain metastasis (N = 80)</td>
<td>Nivolumab + ipilimumab + RT (SBRT or WBRT)</td>
<td>SBRT or WBRT administered the day after the first administration of immunotherapy or within the first 2 weeks SBRT delivered in 1 fraction (dose determined by treating physician) WBRT delivered at 30 Gy in 10 daily fractions</td>
<td>N/A</td>
<td>Recruiting</td>
<td>December 2020</td>
</tr>
</tbody>
</table>

(Continued on the following page)
<table>
<thead>
<tr>
<th>NCT number / trial name</th>
<th>Study phase</th>
<th>Disease stage</th>
<th>Trial design</th>
<th>RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)</th>
<th>Line of therapy</th>
<th>Status</th>
<th>Estimated primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0240717I</td>
<td>1/2</td>
<td>Metastatic NSCLC (anti–PD-L1 therapy-naive patients) or metastatic melanoma (after progression to anti–PD-L1 therapy; N = 50)</td>
<td>Pembrolizumab + RT (starting at day 1), followed by pembrolizumab monotherapy until PD, then SBRT</td>
<td>Starting dose: 30 Gy in 5 fractions to 1 target lesion. Other dose cohorts: 30 Gy in 3 fractions to 1 target lesion; 10 Gy in 1 fraction to 1 target lesion</td>
<td>For NSCLC: anti–PD-L1 therapy naive</td>
<td>Recruiting</td>
<td>December 2018</td>
</tr>
<tr>
<td>NCT03168464</td>
<td>1/2</td>
<td>Metastatic NSCLC (N = 45)</td>
<td>Ipilimumab + RT (both starting at day 1), followed by addition of nivolumab (on day 22)</td>
<td>Nonablative RT delivered at 30 Gy in 5 fractions to 1 lesion</td>
<td>2L+</td>
<td>Recruiting</td>
<td>December 2021</td>
</tr>
<tr>
<td>NCT03168464</td>
<td>1/2</td>
<td>Metastatic NSCLC, HNSCC, or esophageal cancer (N = 40)</td>
<td>Durvalumab + tremelimumab + concurrent RT</td>
<td>SBRT administered at day 15 of cycle 1</td>
<td>2L+</td>
<td>Recruiting</td>
<td>February 2018</td>
</tr>
<tr>
<td>NCT03212469</td>
<td>1/2</td>
<td>Metastatic NSCLC, HNSCC, or esophageal cancer (N = 40)</td>
<td>Pembrolizumab + RT</td>
<td>Hypofractionated RT to an isolated lesion</td>
<td>2L+</td>
<td>Recruiting</td>
<td>February 2017</td>
</tr>
<tr>
<td>NCT02303990</td>
<td>1/2</td>
<td>Advanced and metastatic cancers including NSCLC, melanoma (who have failed anti–PD-L1 therapy), breast cancer, pancreatic cancer, and other cancers (who have progressed after at least one prior systemic therapy; N = 70)</td>
<td>Pembrolizumab + RT + palliative RT</td>
<td>Low-dose or high-dose RT</td>
<td>N/A</td>
<td>Recruiting</td>
<td>June 2018</td>
</tr>
<tr>
<td>NCT02587455</td>
<td>1/2</td>
<td>Thoracic tumors including NSCLC (immunotherapy naive; N = 48)</td>
<td>Pembrolizumab + RT</td>
<td>Pembrolizumab (starting on day 1 of cycle 1), followed by SBRT (starting on day 1 of cycle 3)</td>
<td>SBRT delivered in 5 fractions, 2-3 times per week over 1.5-2 weeks</td>
<td>2L+</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT0231877I</td>
<td>1/2</td>
<td>Recurrent/metastatic lung cancer, HNSCC, RCC, or melanoma (N = 40)</td>
<td>Pembrolizumab + SRS</td>
<td>SRS delivered at 30 Gy in 5 fractions (6-Gy each), or at 27 Gy in 3 fractions (9-Gy each) between days 2 and 15 of cycle 1, or at 18-21 Gy in 1 fraction between days 2 and 3 of cycle 1</td>
<td>1L+</td>
<td>Recruiting</td>
<td>October 2019</td>
</tr>
</tbody>
</table>

(Continued on the following page)
<table>
<thead>
<tr>
<th>NCT number/ trial name</th>
<th>Study phase</th>
<th>Disease stage</th>
<th>Trial design</th>
<th>RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)</th>
<th>Line of therapy</th>
<th>Status</th>
<th>Estimated primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02608385</td>
<td>1</td>
<td>Advanced metastatic solid tumors including NSCLC (N = 35)</td>
<td>Pembrolizumab + SBRT</td>
<td>SBRT delivered in 3–5 fractions</td>
<td>N/A</td>
<td>Ongoing</td>
<td>December 2017</td>
</tr>
<tr>
<td>NCT03035890</td>
<td>N/A</td>
<td>Stage IV (metastatic) NSCLC (N = 35)</td>
<td>Immunotherapy (nivolumab or pembrolizumab or atezolizumab) + concurrent RT</td>
<td>Response-adapted hypofractionated RT delivered at either 24–45 Gy in 3 fractions (8–15 Gy each), or 30–50 Gy in 5 fractions (6–10 Gy each) over 3–10 days</td>
<td>2L+ (prior chemotherapy ± RT)</td>
<td>Recruiting</td>
<td>December 2017</td>
</tr>
<tr>
<td>NCT03307759 SABRseq</td>
<td>1 Metastatic PD-L1+ NSCLC (N = 32)</td>
<td>RT followed by pembrolizumab or pembro lizumab followed by RT after cycle 1</td>
<td>Hypofractionated RT delivered at 24 Gy in 3 fractions (8 Gy each), or 17 Gy in 1 fraction over 1–3 days during the first week of therapy</td>
<td></td>
<td>N/A</td>
<td>Recruiting</td>
<td>December 2018</td>
</tr>
<tr>
<td>NCT03224871</td>
<td>(pilot)</td>
<td>Metastatic NSCLC after failure to anti-PD-1/PD-L1 therapy (N = 30)</td>
<td>Checkpoint inhibition (nivolumab or pembrolizumab) + concurrent RT + interlesional IL2 (starting 1–3 days after the completion of RT and to be completed by day 21)</td>
<td></td>
<td>N/A</td>
<td>Recruiting</td>
<td>July 2020</td>
</tr>
<tr>
<td>NCT02615981</td>
<td>1 Inoperable stage II, IIIA/B NSCLC (N = 30)</td>
<td>Pembrolizumab + SBRT (from weeks 1 to 6) + pembrolizumab (from weeks 5 to 6)</td>
<td>3D-CRT or IMRT once daily 5 days a week for 6 weeks</td>
<td></td>
<td>1L+</td>
<td>Ongoing</td>
<td>September 2018</td>
</tr>
<tr>
<td>NCT02639026</td>
<td>1 Metastatic NSCLC, melanoma, breast cancer, or pancreatic adenocarcinoma (N = 30)</td>
<td>Durvalumab + tremelimumab + RT</td>
<td>Hypofractionated RT delivered at 24 Gy in 3 fractions (8 Gy each), or 17 Gy in 1 fraction over every other day during the first week of therapy</td>
<td></td>
<td>2L+</td>
<td>Recruiting</td>
<td>December 2018</td>
</tr>
<tr>
<td>NCT03158883</td>
<td>(pilot)</td>
<td>Stage IV NSCLC after failure to anti-PD-1 therapy (N = 26)</td>
<td>Avelumab + RT</td>
<td>SBRT delivered at 50 Gy in 5 fractions (10 Gy each) every other day over 1.5–2 weeks</td>
<td>2L+</td>
<td>Recruiting</td>
<td>June 2020</td>
</tr>
<tr>
<td>NCT0324977</td>
<td>1 Unresectable stage III NSCLC patients not suitable for concurrent chemoradiation; stage IV NSCLC patients with low burden of metastatic disease who may benefit from thoracic RT (N = 25)</td>
<td>Pembrolizumab + concurrent RT</td>
<td>Thoracic RT delivered at 60–66 Gy in 30–33 daily fractions (2 Gy each) over 40–45 days, administered 14 days after the first dose of pembrolizumab</td>
<td></td>
<td>1L+</td>
<td>Not yet recruiting</td>
<td>August 2018</td>
</tr>
<tr>
<td>NCT03275597</td>
<td>Immunotherapy-naive stage IV, EGFR or ALK wt, NSCLC (N = 21)</td>
<td>RT followed by durvalumab + tremelimumab (starting 7 days after RT)</td>
<td>SBRT delivered at 30–50 Gy in 5 fractions to all sites of disease, administered over 2 weeks</td>
<td></td>
<td>1L+</td>
<td>Not yet recruiting</td>
<td>October 2020</td>
</tr>
<tr>
<td>NCT02463994</td>
<td>(pilot)</td>
<td>Stage IIIb IV (metastatic) or recurrent NSCLC (N = 12)</td>
<td>Atezolizumab + IGRRT</td>
<td>Hypofractionated IGRRT</td>
<td>2L+ (for stage IV patients requiring palliative radiation for symptomatic lesion)</td>
<td>Ongoing</td>
<td>July 2020</td>
</tr>
</tbody>
</table>

**NOTE:** The boldface words indicate the immunotherapeutic agents utilized in the respective trials.

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; ADV/HSV-tk, adenovirus-mediated expression of herpes simplex virus thymidine kinase; ALK, anaplastic lymphoma kinase; BED, biological equivalent dose; CNS, central nervous system; CRC, colorectal cancer; Gy, Gray; HNC, head and neck cancer; HNSCC, squamous cell carcinoma of the head and neck; IGRRT, image-guided radiotherapy; IMRT, intensity-modulated radiation therapy; L, line(s); N/A, not available information; PD, progressive disease; PD-L1, programmed death-ligand 1; PT, prospective trial; R0, no microscopic residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor; RCC, renal cell cancer; SD, stable disease; SFRT, single fraction radiation therapy; SRS, stereotactic radiosurgery; TNBC, triple-negative breast cancer; WBRT, whole brain radiation therapy; WFRT, wide-field radiation therapy; wt, wild type.
(SABR/SBRT) or subablative RT strategies (41). In addition, in cases where high doses of RT are warranted, the use of novel technologies that cause less damage to healthy tissues, such as proton beam RT (4), should be taken into consideration as potential combination partners for immunotherapy.

The optimal RT field size also remains undefined. For example, if RT is utilized in combination with immunotherapy in settings where the malignancy is not confined to just one region, it is not clear if all gross disease or only a specific site (e.g., the primary tumor) should be irradiated, as large-field irradiation may have a negative impact on circulating immune cells and may also increase the risk of toxicity (79).

As more clinical research on the integration of RT with immunotherapy evolves, it will be important to establish and validate predictive biomarkers to identify which patients would benefit the most from RT and immunotherapy.

Conclusions
Currently available data, though limited, suggest that the pairing of RT with immunotherapy may be a safe and viable treatment approach in patients with NSCLC. Ongoing clinical trials will add to the growing evidence on this promising combination.

Disclosure of Potential Conflicts of Interest
D. Raben reports receiving consulting fees from AstraZeneca, EMD Serono, Genentech, Merck, Nanobiotix, and Suvica, and is a consultant/advisory board member for AstraZeneca and Genentech. S.C. Formenti reports receiving commercial research grants from Bristol-Myers Squibb, Eisai, Janssen, Merck, Regeneron, and Varian, and honoraria from AstraZeneca, Bristol-Myers Squibb, Dynavax, Eisai, Elekta, GlaxoSmithKline, Janssen, Merck, Regeneron, and Varian. No potential conflicts of interest were disclosed by the other author.

Acknowledgments
Medical writing support was provided by Robert Schupp, PharmD, CMPP, and Francesca Balordi, PhD, of The Lockwood Group, in accordance with Good Publication Practice (GPP3) guidelines, and funded by AstraZeneca.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received February 13, 2018; revised April 5, 2018; accepted June 22, 2018; published first June 26, 2018.

References
Radiotherapy and Immunotherapy in Non–Small Cell Lung Cancer


The Integration of Radiotherapy with Immunotherapy for the Treatment of Non–Small Cell Lung Cancer

Eric C. Ko, David Raben and Silvia C. Formenti


Updated version Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-17-3620

Cited articles This article cites 68 articles, 13 of which you can access for free at: http://clincancerres.aacrjournals.org/content/24/23/5792.full#ref-list-1

Citing articles This article has been cited by 2 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/24/23/5792.full#related-urls

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/24/23/5792. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.