Review

Clinical Cancer Research

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

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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. *Clin Cancer Res; 24(23); 5792–806.* ©2018 AACR.

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 early-stage 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

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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 ^{18}F-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-I, 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).

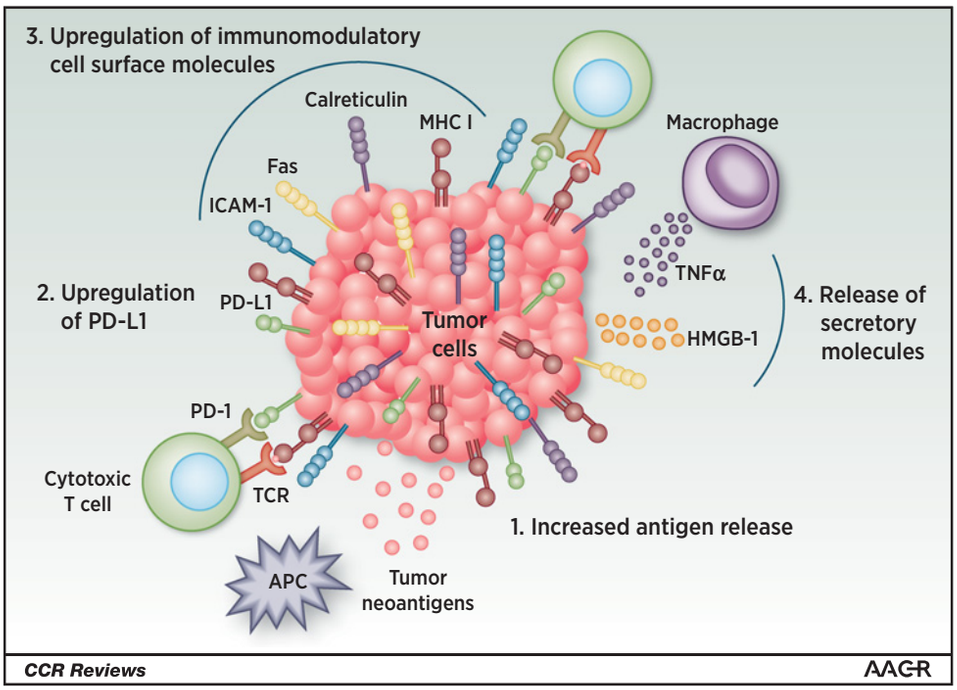

Figure 1.
Radiation-induced immunomodulatory mechanisms. APC, antigen-presenting cell; HMGB-1, high-mobility group protein B1; ICAM-1, intercellular adhesion molecule-1; TCR, T-cell receptor. Adapted from Daly and colleagues (2015, ref. 31), Copyright 2018, with permission from Elsevier.

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

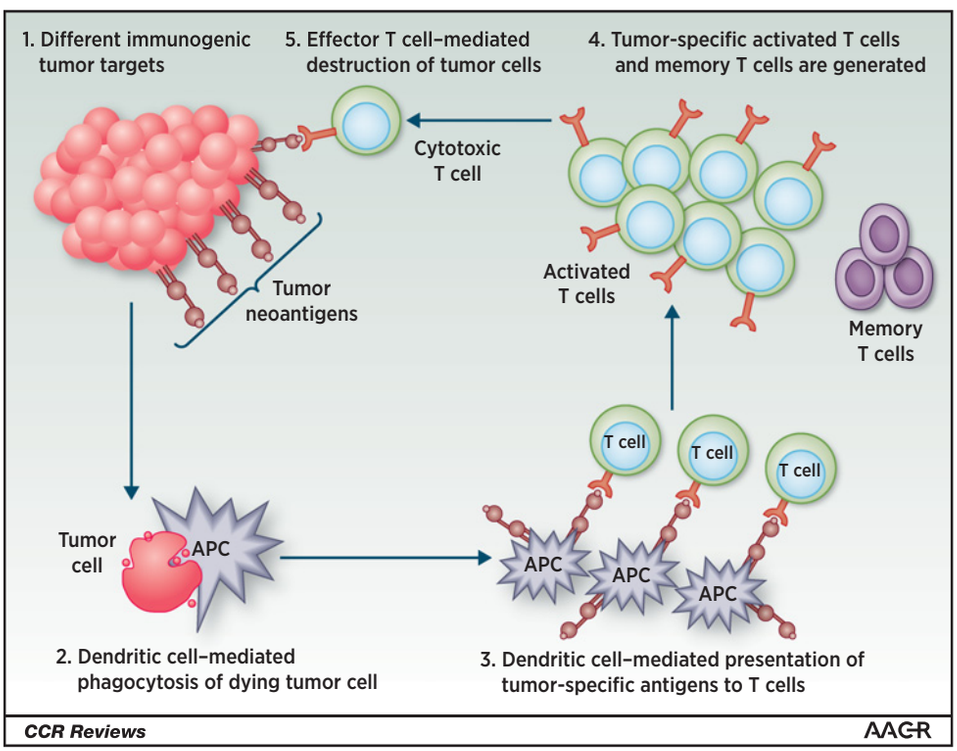

Figure 2.
Generation of an antitumor immune response. APC, antigen-presenting cell. Adapted from Chen and Mellman (2013, ref. 42), Copyright 2018, with permission from Elsevier.

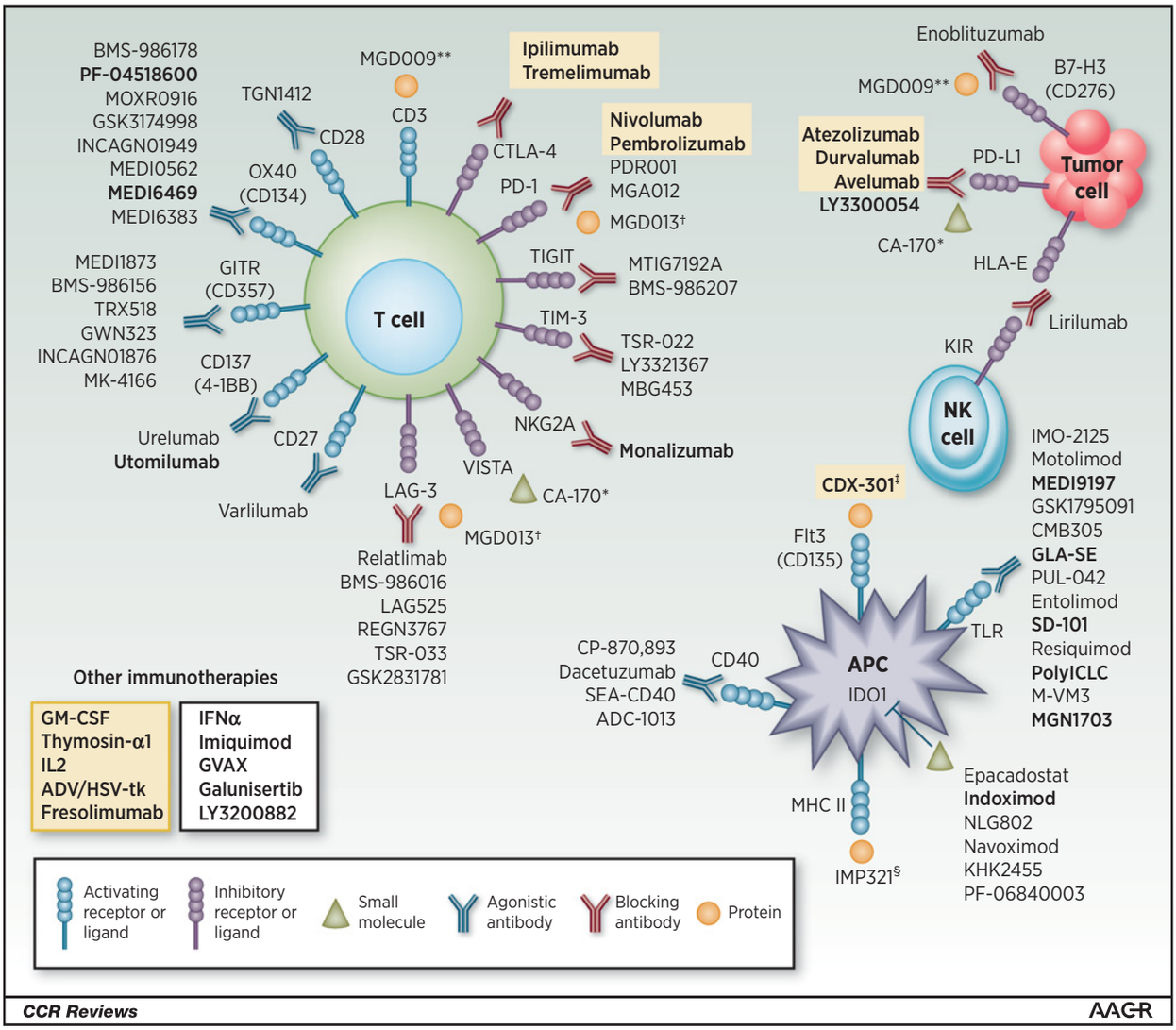

Figure 3.

Positive and negative immune regulators and therapeutic agents in clinical development. Bold: agents investigated in combination with RT in clinical trials. Yellow highlighting: agents investigated in combination with RT in NSCLC in clinical trials. *, PD-L1/PD-L2/VISTA antagonist small molecule. †, Bispecific anti–PD-1 and anti–LAG-3 DART protein. §, Soluble form of LAG-3. ‡, Soluble form of Flt3L. **, DART molecule that recognizes both B7-H3 and CD3. APC, antigen-presenting cell; NK, natural killer. Adapted from Mellman and colleagues (2011, ref. 44), copyright 2018, by permission from Macmillan Publishers Ltd.

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 checkpoint blocker with phase III data following definitive platinum-based concurrent chemoradiation in locally advanced, unresectable stage III NSCLC patients without evidence of disease progression (56). The phase III randomized PACIFIC study investigated durvalumab versus placebo in 713 patients with unresectable 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 durvalumab-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 significantly 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 definitive 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%; 3/24) versus patients with no previous thoracic RT (1%; 1/73; $P = 0.046$; 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 concurrent chemoradiation in 93 patients with unresectable stage III NSCLC showed that 15% of patients (14/93) experienced pneumonitis of grade ≥ 2, 7% (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 pneumonitis 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 immunotherapy alone (71% vs. 29%; $P = 0.0008$), and trended 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 combining RT with immunotherapy does not appear to produce significantly increased toxicities beyond those associated with each treatment independently, and that this combined treatment 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 irradiated 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 combining RT with immunotherapy. The phase III study START investigated vaccination with tecemotide as maintenance therapy 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 infrequent 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.

20.6 months; HR, 0.78; 95% CI, 0.64–0.95; $P = 0.016$) among the 806 patients who had received prior concurrent chemoradiation (64). The phase III STOP study investigated vaccination with belagenpumatucel-L as maintenance therapy after platinum-based frontline chemotherapy with or without RT in stage III/IV NSCLC patients ($n = 532$; ref. 66). In this trial, 5 treatment-related SAEs were reported, 3 in the belagenpumatucel-L arm and 2 in the placebo arm (66). Although this trial did not meet its primary endpoint of OS in all randomized patients, maintenance therapy with belagenpumatucel-L was associated with significantly longer median OS than placebo (28.4 vs. 16.0 months; HR, 0.61; 95% CI, 0.38–0.96; $P = 0.032$) among the 161 patients who had received prior chemoradiation (66).

In a phase III study of adjuvant chemotherapy or RT followed by lymphokine-activated killer (LAK) cell adoptive immunotherapy in NSCLC patients ($n = 170$; 63% with stage III; 69 curative cases and 101 noncurative cases), there were no serious side effects other than fever and rigors associated with LAK cell administration (67). In this study, RT followed by LAK immunotherapy resulted in improved 9-year survival versus no adjuvant therapy, or adjuvant chemotherapy or RT alone (52% vs. 24%; $P < 0.001$; ref. 67).

In a phase II study investigating telomerase peptide vaccination with GV1001 after chemoradiation in inoperable stage III NSCLC patients ($n = 23$), no treatment-related SAEs were observed (68). Vaccination with GV1001 after chemoradiation led to specific immune responses in 16 of 20 (80%) evaluable patients, with a trend toward longer median PFS in responders when compared with nonresponders (12.2 vs. 6.0 months; $P = 0.20$; ref. 68). In a phase II study testing granulocyte-macrophage colony-stimulating factor (GM-CSF) with concurrent chemoradiation in 41 patients with metastatic solid tumors ($n = 18$ with NSCLC), grade 3/4 AEs of fatigue and hematologic findings were the most common AEs observed in 6 and 10 patients, respectively (69). One patient experienced a grade 4 SAE of pulmonary embolism that emerged during GM-CSF administration; however, no patient discontinued treatment due to toxicity (69). GM-CSF combined with concurrent chemoradiation resulted in abscopal responses in 4 of 18 NSCLC patients (69). Finally, in a phase Ib dose-escalation study investigating RT followed by the immunocytokine NHS-IL2 in metastatic NSCLC patients ($n = 13$) attaining disease control (at least stable disease) after first-line platinum-based chemotherapy, there were only 3 grade 3 AEs related to NHS-IL2 (70). Although no objective responses were observed in this study, long-term survival occurred in 2 of 13 patients with good performance status 4 years after the start of first-line chemotherapy, including 1 patient with long-term tumor control (70).

Ongoing Trials

Planned or ongoing clinical trials investigating RT combined with immunotherapy (including concurrent and sequential approaches) in patients with NSCLC are presented in Table 1. The majority of these trials are phase I or phase II studies investigating RT combined with checkpoint blockers. The only phase III study (RTOG 3505), which is currently recruiting patients, is investigating the use of nivolumab versus placebo after concurrent chemoradiation in patients with stage III unresectable NSCLC.

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

NCT number/ trial name	Study phase	Disease stage	Trial design	RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)	Line of therapy	Status	Estimated primary completion date
Early-stage NSCLC							
NCT03110978 I-SABR	2R	Inoperable stage I and IIA immunotherapy-naïve NSCLC ($N = 140$)	SBRT alone vs. SBRT + **nivolumab** given within 36 hours before or after the first SBRT fraction	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	Any line	Recruiting	June 2022
NCT02904954	2R	Resectable stage I–IIIA NSCLC ($N = 60$)	Neoadjuvant **durvalumab** ± SBRT, followed by surgery, followed by postoperative monthly maintenance **durvalumab**	SBRT delivered at 24 Gy in 3 daily fractions starting concurrently with the first cycle of durvalumab	Neoadjuvant/adjuvant/ maintenance	Recruiting	January 2020
NCT03217071 PembroX	2R	Resectable stage I–IIIA NSCLC ($N = 40$)	Neoadjuvant **pembrolizumab** ± SBRT	SBRT delivered at 12 Gy in 1 fraction to 50% of the primary tumor only, administered within 1 week (±3 days) following the second administration of pembrolizumab	Neoadjuvant	Recruiting	September 2019
NCT02818920 TOP 1501	2	Resectable stage IB, IIA/B, IIIA NSCLC ($N = 32$)	Neoadjuvant **pembrolizumab**, followed by surgery, followed by standard adjuvant chemotherapy ± RT, followed by adjuvant **pembrolizumab**	N/A	Neoadjuvant/adjuvant	Recruiting	January 2020
NCT03148327	1/2R	Inoperable stage I/IIA NSCLC ($N = 105$)	**Durvalumab** + SBRT vs. SBRT alone	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	1L	Recruiting	June 2020
NCT02581787 SABR-ATAC	1/2	Stage IA/B NSCLC under consideration for SBRT as definitive primary therapy ($N = 60$)	**Fresolimumab** on days 1, 15, 36 + SBRT	SBRT delivered in 4 fractions, between days 8 and 12	1L	Recruiting	January 2020
NCT03050554	1/2	Inoperable stage I NSCLC ($N = 56$)	**Avelumab** ± SBRT	SBRT delivered at 48 Gy in 4 fractions, or at 50 Gy in 5 fractions (given every other day over 10–12 days)	Adjuvant	Recruiting	March 2020
NCT02599454	1	Inoperable stage I NSCLC ($N = 33$)	**Atezolizumab** + SBRT	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	N/A	Recruiting	November 2017
Locally advanced stage NSCLC							
NCT02768558 RTOG 3505	3R	Inoperable or unresectable stage IIIA/B (not metastatic) immunotherapy-naïve NSCLC ($N = 660$)	Chemoradiation (cisplatin/etoposide + RT), followed by **nivolumab** vs. placebo	60 Gy of thoracic RT (3D-CRT or IMRT)	N/A	Recruiting	October 2022
NCT02343952 HCRN LUN14-179	2	Inoperable or unresectable stage IIIA/B NSCLC (not metastatic; $N = 93$)	Chemoradiation (either cisplatin/ etoposide or carboplatin/paclitaxel + RT), followed by consolidation **pembrolizumab**	RT delivered at 59.4–66.6 Gy	Consolidation	Ongoing not recruiting	March 2018 (58)
NCT02434081 NICOLAS	2	Locally advanced stage IIIA/B NSCLC (not metastatic; $N = 78$)	**Nivolumab** + standard chemoradiation	N/A	1L	Ongoing not recruiting	August 2020

(Continued on the following page)

Table 1. Ongoing studies of immunotherapy in combination with RT in NSCLC (Cont'd)

NCT number/ trial name	Study phase	Disease stage	Trial design	RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)	Line of therapy	Status	Estimated primary completion date
NCT02572843	2	Resectable stage IIIA NSCLC ($N = 68$)	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	N/A	Neoadjuvant/adjuvant	Recruiting	March 2021
NCT03102242	2	Unresectable stage IIIA/B NSCLC, eligible for chemoradiation with curative intent ($N = 63$)	Neoadjuvant **atezolizumab** + chemoradiation (carboplatin/paclitaxel + RT), followed by adjuvant **atezolizumab**	RT delivered at 60 Gy in 30 daily fractions over 6 weeks, in conjunction with chemotherapy and immunotherapy	Neoadjuvant/adjuvant	Not yet recruiting	March 2020
NCT03087760	2	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 ($N = 41$)	**Pembrolizumab** monotherapy	No more than 74 Gy in 37 daily fractions (2 Gy each) of prior RT	Consolidation	Recruiting	July 2019
NCT02525757 DETERRED	2	Unresectable stage II/III NSCLC (not metastatic; $N = 40$)	Standard chemoradiation (carboplatin/paclitaxel + RT) ± **atezolizumab** for 6–7 weeks, followed by a 3–4-week rest period (no chemoradiation) ± **atezolizumab**, followed by consolidation therapy with **atezolizumab** + chemotherapy for 2 cycles, followed by maintenance therapy with **atezolizumab** alone	60–66 Gy delivered in 30–33 daily fractions over 6–7 weeks	1L	Recruiting	January 2020
NCT03053856	2	Stage IIIA NSCLC ($N = 37$)	Neoadjuvant chemoradiation (cisplatin/paclitaxel + RT), followed by surgery, followed by adjuvant **pembrolizumab**	RT delivered at 44 Gy in 22 daily fractions over 5 weeks	Adjuvant	Not yet recruiting	May 2021
NCT03237377	2	Resectable stage IIIA NSCLC ($N = 32$)	Neoadjuvant **durvalumab** ± **tremelimumab** + RT, followed by surgery	Thoracic RT delivered at 45 Gy in 25 daily fractions over 5 weeks	Neoadjuvant	Not yet recruiting	September 2019
NCT02987998 CASE4516	1	Resectable stage IIIA NSCLC ($N = 20$)	Neoadjuvant chemoradiation (cisplatin/etoposide + RT) + **pembrolizumab**, followed by consolidation **pembrolizumab**	RT delivered at 45 Gy in 25 daily fractions (1.8 Gy each)	Neoadjuvant/consolidation	Recruiting	January 2019
Stage IV (metastatic) NSCLC							
NCT02992912 SABR-PD-L1	2	Metastatic solid tumor, including NSCLC, CRC, or RCC ($N = 180$)	**Atezolizumab** + SBRT	SBRT delivered at 45 Gy in 3 fractions (15 Gy each)	2L+ (for NSCLC)	Recruiting	November 2018
NCT02888743	2R	Metastatic NSCLC and metastatic CRC ($N = 180$)	**Durvalumab** + **tremelimumab** ± RT (either high-dose or low-dose)	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	2L+ (for NSCLC: after progression to anti–PD-1/PD-L1 therapy)	Recruiting	December 2020
NCT03044626 FORCE	2	Metastatic nonsquamous NSCLC ($N = 130$)	**Nivolumab** + concurrent RT (for patients necessitating RT) or **nivolumab** alone (for patients without the necessity of RT)	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	2/3L	Recruiting	August 2019

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Table 1. Ongoing studies of immunotherapy in combination with RT in NSCLC (Cont'd)

NCT number/ trial name	Study phase	Disease stage	Trial design	RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)	Line of therapy	Status	Estimated primary completion date
NCT03050060	2	Stage IV NSCLC, stage IV melanoma, or metastatic RCC ($N = 120$)	Nelfinavir mesylate + immunotherapy (**pembrolizumab** or **nivolumab** or **atezolizumab**) + RT	Hypofractionated IGRT administered over 3–14 days, starting after course 1 and before course 3 of immunotherapy	Prior immunotherapy or chemotherapy allowed	Recruiting	December 2021
NCT03176173	2	Metastatic NSCLC undergoing standard immunotherapy ($N = 85$)	Immunotherapy (**nivolumab** or **pembrolizumab** or **atezolizumab**) ± concurrent IGRT	Radical-dose IGRT administered daily for up to 10 days (within 2 weeks)	Patients must have been receiving anti–PD-1 or anti–PD-L1 therapy for at least 4 weeks	Recruiting	June 2020
NCT02492568 PEMBRO-RT	2R	Stage IV (metastatic) NSCLC ($N = 74$)	**Pembrolizumab** after SBRT vs. **pembrolizumab** alone	SBRT delivered at 24 Gy in 3 fractions (1–2 weeks prior to start of pembrolizumab)	2L+	Recruiting	October 2017
NCT02623595	2	Stage IV NSCLC ($N = 60$)	**GM-CSF** daily from days 1 to 14 + SBRT	SBRT delivered at 50 Gy in 5 fractions to 1 lung lesion from days 1 to 5	3L+ (progression after standard 2L chemotherapy)	Recruiting	May 2019
NCT02978404	2	Stage IV NSCLC, or RCC (with brain metastases; $N = 60$)	**Nivolumab** + SRS	SRS delivered at 15–20 Gy in 1 fraction to brain metastases, administered 1–2 weeks after receiving the first dose of nivolumab	1-4L	Recruiting	June 2020
NCT03004183 STOMP	2	Metastatic NSCLC or TNBC ($N = 57$) For NSCLC: EGFR or ALK wt or with EGFR or ALK aberrations after failure to targeted therapy	*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)	SBRT delivered at 30 Gy in 5 fractions (6 Gy each) over 2 weeks from days 2 to 16	1L (immunotherapy and chemotherapy naïve) 2L (1 prior regimen of platinum-containing chemotherapy or, if carrying EGFR or ALK aberrations after failure to targeted therapy)	Recruiting	May 2022
NCT03313804	2	Advanced or metastatic NSCLC, or HNSCC ($N = 57$)	Immunotherapy (**nivolumab** or **pembrolizumab** or **atezolizumab**) + concurrent RT	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 > 100 Gy or 30 Gy of fractionated 3D-CRT	For NSCLC: 1L or relapsed	Recruiting	June 2018
NCT02940990	2R	Stage IV (metastatic) NSCLC with >5 metastases and pan-negative for driver mutations ($N = 50$)	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 + **GM-CSF**	SBRT to primary lesions or metastatic lesions	N/A	Not yet recruiting	December 2019
NCT02976740	2	Stage IV (metastatic) NSCLC ($N = 48$)	**GM-CSF** daily from days 1 to 14 + **thymosin-α1** from weeks 1 to 12 + SBRT	SBRT delivered at 50 Gy in 4–10 fractions to 1 lung lesion from days 1 to 10	3L+ (after progression to standard 2L chemotherapy)	Recruiting	June 2019
NCT02658097 CASE1516	2R	Stage IV (metastatic) NSCLC ($N = 48$)	SFRT followed by **pembrolizumab** vs. **pembrolizumab** alone	SFRT delivered at 8 Gy in 1 fraction on the first day of pembrolizumab therapy	2L+	Recruiting	December 2018
NCT02787447	2	Metastatic NSCLC with EGFR mutations with SD after 3 months of targeted therapy ($N = 46$)	Gefitinib or erlotinib or icotinib + RT + **thymosin-α1** (starting at week 2)	Thoracic hypofractionated RT delivered at 40–45 Gy in 5–15 fractions (starting at week 1)	Consolidation	Recruiting	December 2017

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Table 1. Ongoing studies of immunotherapy in combination with RT in NSCLC (Cont'd)

NCT number/ trial name	Study phase	Disease stage	Trial design	RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)	Line of therapy	Status	Estimated primary completion date
NCT03113851	2	Stage IV (metastatic) NSCLC ($N = 40$)	**GM-CSF** daily from days 1 to 14, every 3 weeks + SBRT	SBRT delivered at 35 Gy in 10 fractions to 1 lung lesion over 2 weeks	Consolidation (for patients with response or SD after 1L chemotherapy) or 3L+ (for patients with disease progression after standard 2L chemotherapy)	Recruiting	August 2018
NCT02831933 ENSIGN	2	Stage IV (metastatic) NSCLC ($N = 29$)	*In situ* gene therapy (**ADV/HSV-tk** on day 0 + **valacyclovir** from days 1 to 15) + SBRT, followed by **nivolumab** (starting on day 17)	SBRT delivered at 30 Gy in 5 fractions (6 Gy each) over 2 weeks from days 2 to 16	2/3L+	Recruiting	December 2021
NCT02839265	2	Stage III/IV NSCLC not amenable to curative therapy ($N = 29$)	**CDX-301** daily for 5 days + concomitant SBRT	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)	2L+ (at least one standard chemotherapy regimen or targeted therapy)	Recruiting	July 2020
NCT02239900	1/2R	Metastatic solid tumors, including patients with lung metastases ($N = 120$)	**Ipilimumab** + SBRT (concurrent vs. sequential)	SBRT delivered to 1–4 lung lesion(s) at either 50 Gy in 4 fractions or 60 Gy in 10 fractions	2L+	Recruiting	August 2019 (73)
NCT02444741	1/2R	All stages NSCLC for phase I; stage IV (metastatic) NSCLC for phase II ($N = 104$)	**Pembrolizumab** + RT (SBRT vs. WFRT)	SBRT delivered at 50 Gy in 4 daily fractions WFRT delivered at 45 Gy in 15 daily fractions	N/A	Recruiting	September 2020
NCT03169738 QUILT-3.044	1/2	NSCLC ($N = 85$)	Nant NSCLC vaccine consisting of immunotherapy combination therapy with: **avelumab**, bevacizumab, capecitabine, cisplatin, cyclophosphamide, 5-fluorouracil, fulvestrant, leucovorin, nab-paclitaxel, **nivolumab**, lovaza, oxaliplatin, RT, ALT-803, ETBX-011, ETBX-021, ETBX-051, ETBX-061, GI-4000, GI-6207, GI-6301, and hank Induction phase, followed by a maintenance phase for patients with complete response	SBRT	2L+ (after progression to anti–PD-1/PD-L1 therapy)	Not yet recruiting	January 2019
NCT02696993	1/2	Stage IV (metastatic) NSCLC with brain metastasis ($N = 80$)	**Nivolumab** ± **ipilimumab** + RT (SBRT or WBRT)	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	N/A	Recruiting	December 2020

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Table 1. Ongoing studies of immunotherapy in combination with RT in NSCLC (Cont'd)

NCT number/ trial name	Study phase	Disease stage	Trial design	RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)	Line of therapy	Status	Estimated primary completion date
NCT02407171	1/2	Metastatic NSCLC (anti–PD-1/PD-L1 therapy–naïve patients) or metastatic melanoma (after progression to anti–PD-1 therapy; $N = 60$)	For anti–PD-1/PD-L1 therapy–naïve NSCLC patients: **pembrolizumab** monotherapy until PD, then SBRT, followed by **pembrolizumab** monotherapy	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	For NSCLC: anti–PD-1/PD-L1 therapy naïve	Recruiting	December 2018
NCT03168464	1/2	Metastatic NSCLC ($N = 45$)	**Ipilimumab** + RT (both starting at day 1), followed by addition of **nivolumab** (on day 22)	Nonablative RT delivered at 30 Gy in 5 fractions to 1 lesion	2L+	Recruiting	December 2021
NCT03212469 ABBIMUNE	1/2	Metastatic NSCLC, HNSCC, or esophageal cancer ($N = 40$)	**Durvalumab** ± **tremelimumab** + concurrent RT	SBRT administered at day 15 of cycle 1	2L+	Recruiting	February 2018
NCT03223155	1R	Stage IV NSCLC ($N = 80$)	SBRT, followed by **nivolumab** + **ipilimumab** between 1 and 7 days after completion of SBRT vs. **nivolumab** + **ipilimumab** + concurrent SBRT to be completed within 2 weeks (prior to second dose of nivolumab)	SBRT delivered in 3–5 fractions to 2–4 sites	1L	Recruiting	December 2020
NCT02303990 RADVAX	1	Advanced and metastatic cancers including NSCLC, melanoma (who have failed anti–PD-1 therapy), breast cancer, pancreatic cancer, and other cancers (who have progressed after at least one prior systemic therapy; $N = 70$)	**Pembrolizumab** + RT	Hypofractionated RT to an isolated lesion	2L+	Recruiting	February 2017
NCT02587455 PEAR	1	Thoracic tumors including NSCLC (immunotherapy naïve; $N = 48$)	**Pembrolizumab** + palliative RT	Low-dose or high-dose RT	N/A	Recruiting	June 2018
NCT02400814	1	Stage IV (metastatic) or recurrent NSCLC ($N = 45$)	**Atezolizumab** + SBRT (both starting on day 1 of cycle 1) or **atezolizuma**b (starting on day 1 of cycle 1), followed by SBRT (starting on day 1 of cycle 3) or SBRT (starting on day 1 of cycle 1), followed by **atezolizumab** (starting on day 1 of cycle 2)	SBRT delivered in 5 fractions, 2–3 times per week over 1.5–2 weeks	2L+	Recruiting	December 2017
NCT02858869	1	Stage IV NSCLC, or melanoma (with brain metastases; $N = 43$)	**Pembrolizumab** + SRS	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	1L+	Recruiting	October 2019
NCT02318771	1	Recurrent/metastatic lung cancer, HNSCC, RCC, or melanoma ($N = 40$)	RT followed by **pembrolizumab** (3–16 days later) or **pembrolizumab** + concomitant RT or **pembrolizumab** + concomitant RT, followed by **pembrolizumab**	8 Gy in 1 fraction (day 1) or 20 Gy in 5 fractions of 4 Gy each (days 1–5)	N/A	Recruiting	January 2020

(Continued on the following page)

Table 1. Ongoing studies of immunotherapy in combination with RT in NSCLC (Cont'd)

NCT number/ trial name	Study phase	Disease stage	Trial design	RT details (dose, fractionation, number of lesions to be treated, timing relative to immunotherapy)	Line of therapy	Status	Estimated primary completion date
NCT02608385	1	Advanced metastatic solid tumors including NSCLC ($N = 35$)	**Pembrolizumab** + SBRT	SBRT delivered in 3–5 fractions	N/A	Ongoing not recruiting	December 2017
NCT03035890	N/A	Stage IV (metastatic) NSCLC ($N = 33$)	Immunotherapy (**nivolumab** or **pembrolizumab** or **atezolizumab**) + concurrent RT	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	2L+ (prior chemotherapy ± RT)	Recruiting	December 2017
NCT03307759 SABRseq	1	Metastatic PD-L1^{+} NSCLC ($N = 32$)	RT followed by **pembrolizumab** or **pembrolizumab** followed by RT after cycle 1	SBRT	1L+	Not yet recruiting	November 2021
NCT03224871	1 (pilot)	Metastatic NSCLC after failure to anti–PD-1/PD-L1 therapy ($N = 30$)	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)	Hypofractionated RT delivered at 24 Gy in 3 fractions (8 Gy each) daily or every other day during the first week of therapy	N/A	Recruiting	July 2020
NCT02621398	1	Inoperable stage II, IIIA/B NSCLC ($N = 30$)	Chemoradiation (carboplatin/paclitaxel + RT from weeks 1 to 6) + **pembrolizumab** (from weeks 5 to 6)	3D-CRT or IMRT once daily 5 days a week for 6 weeks	1L	Ongoing not recruiting	September 2018
NCT02639026	1	Metastatic NSCLC, melanoma, breast cancer, or pancreatic adenocarcinoma ($N = 30$)	**Durvalumab** + **tremelimumab** + RT	Hypofractionated RT delivered at 24 Gy in 3 fractions (8 Gy each), or 17 Gy in 1 fraction	2L+ for NSCLC (immunotherapy naïve)	Recruiting	December 2018
NCT03158883	1 (pilot)	Stage IV NSCLC after failure to anti–PD-1 therapy ($N = 26$)	**Avelumab** + RT	SBRT delivered at 50 Gy in 5 fractions (10 Gy each) every other day over 1.5–2 weeks	2L+	Recruiting	June 2020
NCT03245177 PARIS	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 ($N = 25$)	**Pembrolizumab** + concurrent RT	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	1L+	Not yet recruiting	August 2018
NCT03275597	1	Immunotherapy-naïve stage IV, EGFR or ALK wt, NSCLC ($N = 21$)	RT followed by **durvalumab** + **tremelimumab** (starting 7 days after RT)	SBRT delivered at 30–50 Gy in 5 fractions to all sites of disease, administered over 2 weeks	1L+	Not yet recruiting	October 2020
NCT02463994	1 (pilot)	Stage IIIB/IV (metastatic) or recurrent NSCLC ($N = 12$)	**Atezolizumab** + IGRT	Hypofractionated IGRT	2L+ 1L (for stage IV patients requiring palliative radiation for symptomatic lesion)	Ongoing not recruiting	July 2020

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; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiation therapy; L, line(s); N/A, not available information; PD, progressive disease; 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.

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References

1. National Cancer Institute. SEER cancer stat facts: lung and bronchus cancer [cited 13 Jan 2018]. Available from: https://seer.cancer.gov/statfacts/html/lungb.html.
2. American Cancer Society. What is non-small cell lung cancer? [cited 13 Jan 2018]. Available from: https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html.
3. Cancer.net, Lung cancer - non-small cell: statistics [cited 13 Jan 2018]. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics.
4. NCCN.org. NCCN clinical practice guidelines in oncology (NCCN Guidelines®) for non-small cell lung cancer V.3.2018. © National Comprehensive Cancer Network, Inc.; 2018.
5. Stanic S, Paulus R, Timmerman RD, Michalski JM, Barriger RB, Bezjak A, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early-stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. Int J Radiat Oncol Biol Phys 2014;88:1092–9.
6. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352–8.
7. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070–6.
8. Ahn JS, Ahn YC, Kim JH, Lee CG, Cho EK, Lee KC, et al. Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. J Clin Oncol 2015;33:2660–6.
9. Hanna N, Neubauer M, Yiannoutsos C, McGarry R, Arseneau J, Ansari R, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 2008;26:5755–60.
10. OPDIVO (nivolumab) injection [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2018.
11. KEYTRUDA (pembrolizumab) for injection [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; 2017.
12. TECENTRIQ (atezolizumab) injection [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2017.
13. IMFINZI (durvalumab) injection [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.
14. Crabtree TD, Denlinger CE, Meyers BF, El Naqa I, Zoole J, Krupnick AS, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010;140:377–86.
15. Grills IS, Mangona VS, Welsh R, Chmielewski G, McInerney E, Martin S, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928–35.
16. Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 2015;16:630–7.
17. O'Rourke N, Roqué IFM, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev 2010:CD002140.
18. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181–90.
19. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187–99.
20. Mauguen A, Le Péchoux C, Saunders MI, Schild SE, Turrisi AT, Baumann M, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. J Clin Oncol 2012;30:2788–97.
21. Kong FM, Ten Haken RK, Schipper M, Frey KA, Hayman J, Gross M, et al. Effect of midtreatment PET/CT-adapted radiation therapy with concurrent chemotherapy in patients with locally advanced non-small-cell lung cancer: a phase 2 clinical trial. JAMA Oncol 2017;3:1358–65.
22. Feddock J, Arnold SM, Shelton BJ, Sinha P, Conrad G, Chen L, et al. Stereotactic body radiation therapy can be used safely to boost residual disease in locally advanced non-small cell lung cancer: a prospective study. Int J Radiat Oncol Biol Phys 2013;85:1325–31.
23. Hepel JT, Leonard KL, Safran H, Ng T, Taber A, Khurshid H, et al. Stereotactic body radiation therapy boost after concurrent chemoradiation for locally advanced non-small cell lung cancer: a phase 1 dose escalation study. Int J Radiat Oncol Biol Phys 2016;96:1021–7.
24. Higgins KA, Pillai RN, Chen Z, Tian S, Zhang C, Patel P, et al. Concomitant chemotherapy and radiotherapy with SBRT boost for unresectable, stage III non-small cell lung cancer: a phase I study. J Thorac Oncol 2017;12:1687–95.

25. Kumar S, Feddock J, Li X, Hall L, Shelton BJ, Arnold S, et al. An update of a prospective study of SBRT for postchemoradiation residual disease in stage II/III nonsmall cell lung cancer. Radiat Oncol 2017;99:652–9.
26. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. Curr Probl Cancer 2016;40:25–37.
27. Grass GD, Krishna N, Kim S. The immune mechanisms of abscopal effect in radiation therapy. Curr Probl Cancer 2016;40:10–24.
28. Ng J, Dai T. Radiation therapy and the abscopal effect: a concept comes of age. Ann Transl Med 2016;4:118.
29. Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys 2004;58:862–70.
30. Hodge JW, Guha C, Neefjes J, Gulley JL. Synergizing radiation therapy and immunotherapy for curing incurable cancers. Opportunities and challenges. Oncology (Williston Park) 2008;22:1064–70; discussion 1075, 1080–1, 1084.
31. Daly ME, Monjazeb AM, Kelly K. Clinical trials integrating immunotherapy and radiation for non-small-cell lung cancer. J Thorac Oncol 2015;10:1685–93.
32. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 2014;124:687–95.
33. Gong X, Li X, Jiang T, Xie H, Zhu Z, Zhou F, et al. Combined radiotherapy and anti-PD-L1 antibody synergistically enhances antitumor effect in non-small cell lung cancer. J Thorac Oncol 2017;12:1085–97.
34. Herter-Sprie GS, Koyama S, Korideck H, Hai J, Deng J, Li YY, et al. Synergy of radiotherapy and PD-1 blockade in Kras-mutant lung cancer. JCI Insight 2016;1:e87415.
35. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 2014;74:5458–68.
36. Dovedi SJ, Cheadle EJ, Popple AL, Poon E, Morrow M, Stewart R, et al. Fractionated radiation therapy stimulates antitumor immunity mediated by both resident and infiltrating polyclonal T-cell populations when combined with PD-1 blockade. Clin Cancer Res 2017;23:5514–26.
37. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 2015;520:373–7.
38. Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, et al. STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. Immunity 2014;41:843–52.
39. Harding SM, Benci JL, Irianto J, Discher DE, Minn AJ, Greenberg RA. Mitotic progression following DNA damage enables pattern recognition within micronuclei. Nature 2017;548:466–70.
40. Mackenzie KJ, Carroll P, Martin CA, Murina O, Fluteau A, Simpson D, et al. cGAS surveillance of micronuclei links genome instability to innate immunity. Nature 2017;548:461–5.
41. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun 2017;8:15618.
42. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1–10.
43. Shekarian T, Valsesia-Wittmann S, Caux C, Marabelle A. Paradigm shift in oncology: targeting the immune system rather than cancer cells. Mutagenesis 2015;30:205–11.
44. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480–9.
45. Anagnostou VK, Brahmer JR. Cancer immunotherapy: a future paradigm shift in the treatment of non-small cell lung cancer. Clin Cancer Res 2015;21:976–84.
46. ADIS R&D Profile. Tremelimumab. Drugs R D 2010;10:123–32.
47. YERVOY (ipilimumab) injection [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
48. Aspeslagh S, Postel-Vinay S, Rusakiewicz S, Soria JC, Zitvogel L, Marabelle A. Rationale for anti-OX40 cancer immunotherapy. Eur J Cancer 2016;52:50–66.
49. Linch SN, McNamara MJ, Redmond WL. OX40 agonists and combination immunotherapy: putting the pedal to the metal. Front Oncol 2015;5:34.
50. Wang K, Wang J, Wei F, Yang F, Ren X. Expression of TLR4 in non-small cell lung cancer is associated with PD-L1 and poor prognosis in patients receiving pulmonectomy. Front Immunol 2017;8:456.
51. Kaczanowska S, Joseph AM, Davila E. TLR agonists: our best frenemy in cancer immunotherapy. J Leukoc Biol 2013;93:847–63.
52. Maleki Vareki S, Chen D, Di Cresce C, Ferguson PJ, Figueredo R, Pampillo M, et al. IDO downregulation induces sensitivity to pemetrexed, gemcitabine, FK866, and methoxyamine in human cancer cells. PLoS One 2015;10:e0143435.
53. Yue EW, Sparks R, Polam P, Modi D, Douty B, Wayland B, et al. INCB24360 (Epacadostat), a highly potent and selective indoleamine-2,3-dioxygenase 1 (IDO1) inhibitor for immuno-oncology. ACS Med Chem Lett 2017;8:486–91.
54. Kang J, Demaria S, Formenti S. Current clinical trials testing the combination of immunotherapy with radiotherapy. J Immunother Cancer 2016;4:51.
55. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016;375:1749–55.
56. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919–29.
57. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 2017;18:895–903.
58. Durm GA, Johnson C, Jalal SI, Sadiq AA, Jabbour SS, Zon R, et al. Safety and feasibility of consolidation pembrolizumab following concurrent chemoradiation for unresectable stage III non-small cell lung cancer: Hoosier Cancer Research Network LUN14-179. J Clin Oncol 2017;35(suppl):abstr 8523.
59. Tamiya A, Tamiya M, Nakahama K, Taniguchi Y, Shiroyama T, Isa SI, et al. Correlation of radiation pneumonitis history before nivolumab with onset of interstitial lung disease and progression-free survival of patients with pre-treated advanced non-small cell lung cancer. Anticancer Res 2017;37:5199–205.
60. Kataoka Y, Ebi N, Fujimoto D, Hara S, Hirano K, Narabayashi T, et al. Prior radiotherapy does not predict nivolumab response in non-small-cell lung cancer: a retrospective cohort study. Ann Oncol 2017;28:1402.
61. Bang A, Wilhite TJ, Pike LRG, Cagney DN, Aizer AA, Taylor A, et al. Multicenter evaluation of the tolerability of combined treatment with PD-1 and CTLA-4 immune checkpoint inhibitors and palliative radiation therapy. Int J Radiat Oncol Biol Phys 2017;98:344–51.
62. Yuan Z, Fromm A, Ahmed KA, Grass GD, Yang GQ, Oliver DE, et al. Radiotherapy rescue of a nivolumab-refractory immune response in a patient with PD-L1-negative metastatic squamous cell carcinoma of the lung. J Thorac Oncol 2017;12:e135–6.
63. Komatsu T, Nakamura K, Kawase A. Abscopal effect of nivolumab in a patient with primary lung cancer. J Thorac Oncol 2017;12:e143–4.
64. Butts C, Socinski MA, Mitchell PL, Thatcher N, Havel L, Krzakowski M, et al. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. Lancet Oncol 2014;15:59–68.
65. Mitchell P, Thatcher N, Socinski MA, Wasilewska-Tesluk E, Horwood K, Szczesna A, et al. Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: updated overall survival and biomarker analyses. Ann Oncol 2015;26:1134–42.
66. Giaccone G, Bazhenova LA, Nemunaitis J, Tan M, Juhász E, Ramlau R, et al. A phase III study of belagenpumatucel-L, an allogeneic tumour cell vaccine, as maintenance therapy for non-small cell lung cancer. Eur J Cancer 2015;51:2321–9.
67. Kimura H, Yamaguchi Y. A phase III randomized study of interleukin-2 lymphokine-activated killer cell immunotherapy combined with chemotherapy or radiotherapy after curative or noncurative resection of primary lung carcinoma. Cancer 1997;80:42–9.
68. Brunsvig PF, Kyte JA, Kersten C, Sundstrøm S, Møller M, Nyakas M, et al. Telomerase peptide vaccination in NSCLC: a phase II trial in stage III patients vaccinated after chemoradiotherapy and an 8-year update on a phase I/II trial. Clin Cancer Res 2011;17:6847–57.

69. Golden EB, Chhabra A, Chachoua A, Adams S, Donach M, Fenton-Kerimian M, et al. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. Lancet Oncol 2015;16:795–803.
70. van den Heuvel MM, Verheij M, Boshuizen R, Belderbos J, Dingemans AM, De Ruysscher D, et al. NHS-IL2 combined with radiotherapy: preclinical rationale and phase Ib trial results in metastatic non-small cell lung cancer following first-line chemotherapy. J Transl Med 2015;13:32.
71. Taunk NK, Rimner A, Culligan M, Friedberg JS, Brahmer J, Chaft J. Immunotherapy and radiation therapy for operable early stage and locally advanced non-small cell lung cancer. Transl Lung Cancer Res 2017;6:178–85.
72. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res 2013;1:365–72.
73. Tang C, Welsh JW, de Groot P, Massarelli E, Chang JY, Hess KR, et al. Ipilimumab with stereotactic ablative radiation therapy: phase I results and immunologic correlates fromperipheral T cells. Clin Cancer Res 2017;23:1388–96.
74. Fujimoto D, Uehara K, Sato Y, Sakanoue I, Ito M, Teraoka S, et al. Alteration of PD-L1 expression and its prognostic impact after concurrent chemoradiation therapy in non-small cell lung cancer patients. Sci Rep 2017;7:11373.
75. Hecht M, Buttner-Herold M, Erlenbach-Wunsch K, Haderlein M, Croner R, Grützmann R, et al. PD-L1 is upregulated by radiochemotherapy in rectal adenocarcinoma patients and associated with a favourable prognosis. Eur J Cancer 2016;65:52–60.
76. Lim SH, Hong M, Ahn S, Choi YL, Kim KM, Oh D, et al. Changes in tumour expression of programmed death-ligand 1 after neoadjuvant concurrent chemoradiotherapy in patients with squamous oesophageal cancer. Eur J Cancer 2016;52:1–9.
77. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res 2009;15:5379–88
78. Chandra RA, Wilhite TJ, Balboni TA, Alexander BM, Spektor A, Ott PA, et al. A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab. Oncoimmunology 2015;4:e1046028.
79. Schoenhals JE, Seyedin SN, Anderson C, Brooks ED, Li YR, Younes AI, et al. Uncovering the immune tumor microenvironment in non-small cell lung cancer to understand response rates to checkpoint blockade and radiation. Transl Lung Cancer Res 2017;6:148–58.