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Clinical Trials Integrating Immunotherapy and Radiation for Non–Small-Cell Lung Cancer

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Abstract: Methods of harnessing the immune system to treat cancer have been investigated for decades, but yielded little clinical progress. However, in recent years, novel drugs that allow immune recognition and destruction of tumor cells are emerging as potent cancer therapies. Building upon previous immunotherapy strategies that included therapeutic vaccines, recombinant cytokines, and other immunostimulatory agents, newer immunotherapy agents targeting immune checkpoints including programmed cell death 1, programmed cell death ligand-1, and cytotoxic T-lymphocyte-associated protein 4, among others, have garnered substantial enthusiasm after demonstrating clinical activity in a broad spectrum of tumor types. Trials evaluating immune checkpoint inhibitors in metastatic non–small-cell lung cancer (NSCLC) demonstrate robust and durable responses in a subset of patients. However, with overall response rates less than 20%, combinatorial strategies that extend the benefit of these agents to more patients are desirable. The integration of radiotherapy with immunotherapy is a conceptually promising strategy, as radiotherapy has potent immunomodulatory effects and may contribute not only to local control but may also augment systemic antitumor immune response. Preclinical data and case reports suggest the potential for robust clinical responses in metastatic NSCLC patients using this strategy, but prospective clinical trials evaluating the integration of radiation and immunotherapy are limited. The use of immunotherapy in nonmetastatic settings is also intriguing but understudied. We review the potential clinical settings of interest for the partnering of immunotherapy and radiation in NSCLC, including early stage, locally advanced, and metastatic disease, and review completed, accruing, and developing clinical trials.

Key Words: Non–small-cell lung cancer, Immunotherapy, Radiotherapy.

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Lung cancer has traditionally been characterized as insensitive to immune strategies. The first randomized trials to evaluate immunotherapy date back to the 1970s with the instillation of adjuvant intrapleural BCG.[1,2] Although BCG was ineffective, the pursuit of an immune agent to treat lung cancer continued. Phase III trials evaluating interferon and a variety of vaccines, however, were unsuccessful.[3,4] Meanwhile, dramatic advances in our understanding of the molecular mechanisms of tumor immunology, now known as the cancer-immunity cycle, have allowed for the development of new drugs and improved vaccines and cellular therapies, reigniting enthusiasm for immunotherapy of lung cancer.[5] Most exciting is the new class of agents called immune checkpoint inhibitors. Checkpoint inhibitors targeting programmed cell death 1 (PD-1), programmed cell death ligand-1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and others have demonstrated clinical efficacy in a broad spectrum of tumor types, with pronounced and durable remissions in a subset of patients. In lung cancer, PD-1 and PD-L1 inhibitors as monotherapy for metastatic non–small-cell lung cancer (NSCLC) have shown response rates of 15% to 20%, with typically dramatic and durable results in both nonsquamous and squamous histologies.[6–8] A recently published phase III trial comparing the anti-PD-1 monoclonal antibody nivolumab to docetaxel as second-line treatment for advanced squamous NSCLC demonstrated superior median survival of 9.2 months (95% confidence interval [CI]: 7.3–13.3) with nivolumab as compared with 6.0 months (95% CI: 5.1–7.3) with docetaxel,[9] and a parallel study identified superior median survival of 12.2 months (95% CI: 9.7, 15.0) for nivolumab versus 9.4 months (95% CI: 8.0, 10.7) with docetaxel for nonsquamous histology (hazard ratio = 0.73; 96% CI: 0.59, 0.89; $p = 0.00155$).[10] Nivolumab was recently FDA approved for the second-line treatment of advanced stage patients with squamous histology.[11]

There is substantial interest in extending the benefit of immune checkpoint inhibitors to a greater proportion to patients. Efforts are underway to develop combined modality strategies, including dual immunotherapies, integration of chemotherapy and targeted therapies, and combination with radiotherapy. Radiotherapy is a particularly appealing partner therapy, offering the benefit of a generally nonoverlapping toxicity profile, with both preclinical and early clinical data suggesting potential potent immunostimulatory effects. Radiotherapy induces multiple immunomodulatory changes that can potentially influence the effectiveness of immunotherapy including tumor vasculature normalization,[12] improved T-cell extravasation and

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homing to tumors,[12] destruction of immunosuppressive stromal cells,[13] induction of immunogenic tumor cell death via high mobility group protein B1 release,[14] or exposure of calreticulin on the cell surface,[15] among others (Table 1, Fig. 1). Clinical support for an interaction between radiotherapy and the immune response is demonstrated by the abscopal (*ab-scopus*, away from the target) effect, in which a systemic tumor response is observed after local radiation.[24] Although once thought to be an infrequent event, increasing reports of an abscopal effect with the combination of immune checkpoint inhibitors and radiation have renewed our interest in this phenomenon and justify the evaluation of immunoradiotherapy strategies.[25]

Clinical studies evaluating immunotherapy and radiation for NSCLC have focused on metastatic disease. However, other settings, including early stage and locally advanced disease, are also intriguing. The effects of immunotherapy may be best suited to eradication of micrometastases, suggesting neoadjuvant, concurrent, or adjuvant immunotherapy strategies in the localized setting should be further explored. We review a representative sample of completed, ongoing, and developing clinical trials evaluating the combination of radiotherapy and immunotherapy for NSCLC, and suggest areas for future investigation.

TABLE 1. Mechanisms of Radiation-Induced Immune Modulation

Tumor debulking and releasing tumor antigens	
Not systemically immunosuppressive	
Up-regulation of immunogenic cell surface markers	
ICAM-1	Chakraborty et al.[16]
MHC-1	Formenti et al.[17]
Fas	Chakraborty et al.[16]
Secretion of danger signals and cytokines	
IFN-g	Lugade et al.[18]
TNFa	Formenti et al.[17]
IL-1b	Formenti et al.[17]
Induction of immunogenic cell death	
Calreticulin	Obeid et al.[19]
HMGB1	Apetoh et al.[14]
Increased homing of immune cells to tumors	
Normalization of tumor vasculature	Ganss et al.[20]
Secretion of chemo-attractants (cxcl16)	Matsumura et al.[21]
Endothelial expression of VCAM-1	Lugade et al.[18]
Improved T-cell homing to tumors	Klug et al.[12]
Improved antigen presentation by APC's	
Irradiated tumors prime dendritic cells	Strome et al.[22]
Improved antigen presentation via TLR-4	Apetoh et al.[14]
Depletion of immunosuppressive cells	Wu et al.[13]
Shifting TAM polarization to M1	Klug et al.[12]
Up-regulation of cell surface PD-L1	Dovedi et al.[23]

MHC-1, major histocompatibility complex 1; HMGB-1, high mobility group protein B1; VCAM, Vascular Cell Adhesion Protein-1; APC, Antigen-presenting cell; TLR-4, toll-like receptor; TAM, tumor-associated macrophage; PD-L1, programmed cell death ligand-1.

IMMUNOTHERAPY AND RADIATION IN METASTATIC NSCLC

Rationale

Early combinatorial strategies for radiotherapy and immunotherapy in NSCLC have logically focused on patients with metastatic disease, a patient population with a dismal median survival of 10 to 12 months and few efficacious treatment strategies beyond first-line chemotherapy.[26] Important questions include not only the efficacy of radiation–immunotherapy combinations, patient selection, and choice of immunotherapy agent(s), but also the optimal sequencing, radiotherapy dose/fractionation, disease burden at treatment, and impact of potentially immunosuppressive prior therapies. Relatively few studies have been completed, but substantial enthusiasm for these agents has led to a number of accruing and developing clinical trials. Many currently accruing trials combine immunotherapy agents with stereotactic body radiotherapy (SBRT), a precise technique that allows delivery of high radiation doses over one to five fractions. The optimal dose and fractionation to best augment the antitumor immune response, however, is unclear. A study combining a toll-like receptor 7 agonist and local radiation in a murine lymphoma model found that 2 Gy ×5 fractions resulted in greater tumor response than the toll-like receptor 7 agonist and a single 10 Gy fraction.[27] Similarly, a study using a breast cancer murine model found that anti-CTLA-4 therapy combined with fractionated radiation (8 Gy ×3 or 6 Gy ×5) resulted in abscopal tumor responses while the same immunotherapy combined with 20 Gy ×1 did not generate a systemic response.[28] By contrast, a study using a murine melanoma model found that a single dose of 20 Gy better promotes priming of antigen-specific cells than 4 Gy ×5, and that 12 Gy ×2 combined with intratumoral injections of a T cell therapy resulted in prolonged survival and prevented metastases.[29] Other work in murine melanoma models suggests a moderate, hypofractionated regimen using 7.5 Gy fractions may optimize tumor control, antitumor immunity, and minimize the contribution of regulatory T cells.[30] Similar studies specific to lung cancer models are lacking.

Completed and Currently Accruing Clinical Studies in Metastatic Disease

Trials combining immune checkpoint inhibitors with radiotherapy are ongoing or planned as shown in Table 2. After noting a durable complete systemic response in a NSCLC patient treated with ipilimumab plus SBRT to a liver lesion, investigators at New York University have activated a phase I/II study evaluating ipilimumab delivered at 3 mg/kg IV combined with SBRT to 30 Gy over five fractions to a single metastasis for stage IV NSCLC[31,32] (NCT02221739). SBRT and ipilimumab begin within a 24-hour interval, and ipilimumab is repeated every 21 days for up to four cycles. The primary outcome measure is tumor response by the immune-related response evaluation criteria in solid tumors[33] outside the radiation field.

A second accruing study evaluates radiotherapy and ipilimumab for metastatic solid tumors, including NSCLC. Investigators at the MD Anderson Cancer Center have activated a phase I/II trial enrolling patients with metastatic solid

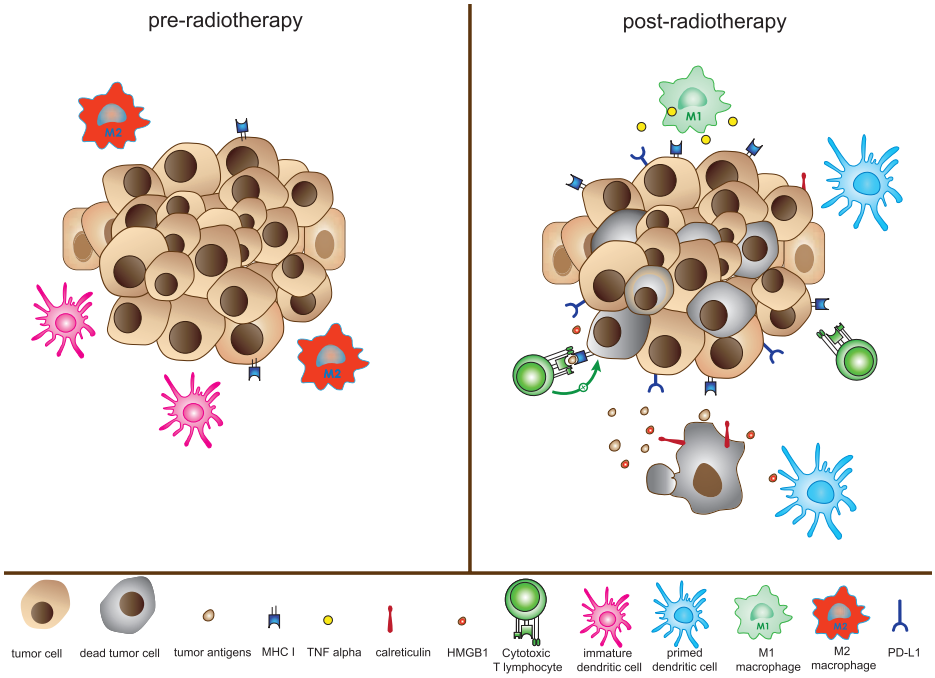

FIGURE 1. Radiotherapy induces multiple immunomodulatory changes that can potentially influence the effectiveness of immunotherapy. Shown above from left to right and in Table 1: radiation may lead to direct tumor cell killing; upregulation of immunogenic cell surface markers, such as MHC-1; secretion of danger signals and cytokines, such as TNF-alpha; induction of immunogenic cell death via calreticulin and HMGB-1, among others; improved homing of immune cells, such as cytotoxic T lymphocytes to tumor; improved antigen presentation by mechanism including priming of dendritic cells; a shift in TAM from the M2 to M1 phenotype; and upregulation of cell surface PD-L1, among others. MHC-1, major histocompatibility complex 1; HMGB-1, high mobility group protein B1; TAM, tumor-associated macrophage; PD-L1, programmed cell death ligand-1.

tumors evaluating ipilimumab (3 mg/kg every 21 days) and SBRT to either a liver, lung, or adrenal lesion with a starting SBRT dose of 50 Gy in four fractions or 60 Gy in 10 fractions[34] (NCT02239900). The investigators include separate arms to evaluate concurrent or sequential SBRT delivery. The safety, efficacy, toxicity profile, and the maximally tolerated dose for SBRT are the primary outcome measures, with immune-related response evaluation criteria in solid tumors response a secondary measure.

A currently accruing study designed to explore the immunomodulatory effects of radiotherapy with checkpoint blockade at Thomas Jefferson University combines the PD-1 inhibitor pembrolizumab with single or multi-fraction radiotherapy to a metastatic site for patients with metastatic NSCLC, melanoma, head and neck cancer, or renal cell carcinoma[35] (NCT02318771). Radiotherapy is 8 Gy in one fraction or 20 Gy over five fractions, and patients are stratified into concurrent (radiation and pembrolizumab initiated on the same day) or sequential (radiation delivered first, with a post-radiation biopsy, followed by pembrolizumab 10 days later). Pembrolizumab is continued over 21 day cycles until disease progression or unacceptable toxicity. Change in PD-L1 expression is the primary outcome measure, with secondary measures of response rate, toxicity, progression-free survival, and biomarker expression.

A registered trial currently pending activation at the University of Pennsylvania will evaluate hypofractionated radiotherapy with the PD-1 inhibitor pembrolizumab in melanoma and NSCLC patients who previously failed anti-PD-1 or PD-L1 monotherapy, or other metastatic solid tumors who failed at least first-line systemic therapy[36] (NCT02303990). Details on timing of therapy and radiation fractionation are not yet available. However, the choice to include a cohort of NSCLC patients previously refractory to anti-PD-1 or PD-L1 therapy highlights the largely unexplored potential for radiotherapy to induce responses in tumors initially unresponsive to checkpoint inhibition. Retrospective clinical series evaluating melanoma patients suggest that following disease progression on ipilimumab, local radiotherapy generates an abscopal effect.[37] The use of radiotherapy specifically to generate or regenerate a response following failure of checkpoint inhibition in NSCLC is essentially unexplored, and this trial should provide valuable information on the viability of this strategy.

Our group is preparing to activate a study exploring the impact of timing of SBRT in relation to immunotherapy. We will enroll patients with metastatic NSCLC who have progressed on at least one line of prior systemic therapy to receive the PD-L1 inhibitor MPDL3280A until tumor progression or intolerable toxicity and SBRT to a single metastatic site. The trial has three arms exploring different timing approaches: sequential (SBRT followed by MPDL3280A), concurrent treatment, or priming (two cycles of MPDL3280A then delivery of SBRT with cycle 3).[38] Unpublished preclinical data from our institution suggests that the sequencing of immunotherapy and SBRT can markedly affect response rates. This finding has recently been corroborated by other groups.[16] We expect the results of this trial to provide valuable insight into the optimal sequencing strategy for future studies.

A small prospective trial testing the combination of a unique immunocytokine plus radiation for metastatic NSCLC was recently reported. Van Den Huevel et al. completed a Phase Ib study enrolling 13 metastatic and nonprogressing NSCLC patients following first-line chemotherapy. Local radiation was delivered to a single pulmonary nodule to 20 Gy in five fractions delivered day 7 to day 3. Starting day 1, patients received a human antibody specific for necrotic DNA fused to a genetically modified human interleukin 2 (IL-2; NHS-ILS) that selectively activates the high-affinity IL-2 receptor.

TABLE 2. Clinical Trials Combining Immunotherapy and Radiation for Metastatic NSCLC

Institution/Group	Phase	Eligibility	Radiotherapy	Immunotherapy
Completed				
Netherlands Cancer Institute	Ib	Metastatic NSCLC; disease control with first-line palliative chemotherapy	5 Gy ×4	Dose-escalated NHS-IL2 on three consecutive days q3 week
Accruing				
Thomas Jefferson University	I	Metastatic or recurrent solid tumor (NSCLC, H&N, RCC, skin, melanoma)	8 Gy ×1 or 4 Gy ×5	MK-3475 IV Q 21 days until PD or unacceptable toxicity
University of Pennsylvania NCT02303990	I	Metastatic melanoma or NSCLC that failed anti PD-1 therapy	Not stated	Pembrolizumab (schedule not stated)
MD Anderson	I/II	Metastatic solid tumor with ≥1 prior therapy; lung, liver, or adrenal lesion amenable to SBRT	12.5 Gy ×4 or 6 Gy ×10	Dose-escalated ipilimumab × four cycles Q3W (starting dose 3 mg/kg IV)
New York University	II	Metastatic NSCLC with ≥1 prior therapy; ≥2 measurable disease sites	6 Gy ×5	Ipilimumab 3 mg/kg IV ×4 cycles (Q3W)

NSCLC, non–small-cell lung cancer; Gy, Gray; NHS-IL2, human antibody specific for necrotic DNA fused to a genetically modified human interleukin-2.

Patients received escalating doses of 0.15, 0.30, or 0.45 mg/kg daily by IV infusion for three consecutive days every 21 days until disease progression or intolerable side effects. The maximally tolerated dose was not reached; two of 13 patients had long-term disease control. Side effects were mild, including fatigue, anorexia, rash, and thyroid dysfunction.[39] No other completed, prospective trials have been published.

Future Directions in Metastatic NSCLC

While currently accruing trials exploring radiation–immunotherapy combinations should provide preliminary evidence for the efficacy of this approach, key details addressing the radiation component are not defined, including timing, fractionation, selection of a radiation target, and impact of disease burden. Crucial questions in patient selection also include baseline patient immune function and the impact of short- or long-term of potentially immunosuppressive medications, such as corticosteroids. Biomarkers to predict response are also urgently needed.

Two subsets of patients with metastatic disease deserve special mention (1) those with limited burden or oligometastatic disease and (2) patients with brain metastasis. The potential to eradicate limited burden macroscopic disease via SBRT with concurrent or sequential immunotherapy targeting micrometastatic disease is mechanistically promising but unexplored. NSCLC patients with brain metastases are known to have a poorer prognosis, with a median survival of approximately 7 months with standard therapies including whole brain radiotherapy or stereotactic radiosurgery.[40] Treatment options for radiotherapy failures are dismal. Systemic therapy, including immune checkpoint inhibitors, has been reported to temporarily shrink brain metastases.[41] A small study of 10 patients with untreated or progressing brain metastasis after radiation received pembrolizumab. Four of nine evaluable patients had an objective response in the brain, and no grade three to four adverse CNS events were observed.[42] In the setting of melanoma brain metastases, ipilimumab has demonstrated a 16% intracranial response rate.[43] Interestingly, extracranial responses have been described in patients previously refractory to ipilimumab treated with radiotherapy for brain metastases. Grimaldi et al. report 21 patients with metastatic melanoma who progressed through treatment with ipilimumab and subsequently required palliative radiotherapy at a median of 5 months (range: 3.4–8.0 months) after initiation of ipilimumab, including 13 patients with brain metastases. Abscopal responses outside the radiation field were noted in 11 patients (52%), including seven of 13 (54%) treated for brain metastases (four with whole brain radiation and three with stereotactic radiosurgery).[37] These observations suggest that radiotherapy–immunotherapy strategies should be investigated for the treatment of brain metastases, and there is an ongoing clinical trial examining combining radiotherapy and ipilimumab for the treatment of brain metastases.[44]

Use of dual checkpoint blockade with radiotherapy is also promising in preclinical models, and may overcome resistance to single-agent combinatorial strategies. Researchers at the University of Pennsylvania report data combining CTLA-4 blockade, PD-L1 blockade, and radiotherapy in a murine melanoma model. The addition of PD-L1 blockade to tumors previously resistant to CTLA-4 blockade and radiotherapy improved responses, and for treatment-naïve tumors complete responses to triple therapy were an impressive 80%. Mechanistic correlates demonstrated complementary mechanisms of immune modulation, including decreased T regulator cells secondary to CTLA-4 blockade, reinvigoration of exhausted CD8 tumor infiltrating lymphocytes via PD-L1 blockade, and diversification of the T cell receptor repitoire of the tumor infiltrating lymphocytes induced by radiotherapy.[45] However, dual blockade with radiotherapy has not yet been reported in human clinical trials nor in lung cancer preclinical models.

In aggregate, future clinical trials evaluating radiotherapy–immunotherapy combinations should further clarify the optimal selection and sequencing of treatment, choice of the radiotherapy target(s) and dose schema, and illuminate the utility of more aggressive eradication of oligometastatic deposits.

IMMUNOTHERAPY AND RADIATION IN LOCALLY ADVANCED NSCLC

Rationale

Concurrent chemoradiation (CRT) has remained the mainstay of therapy for locally advanced, unresectable NSCLC for more than two decades. Early trials demonstrated a survival benefit with the addition of sequential chemotherapy to radiotherapy,[46,47] and subsequent studies confirmed a benefit to concurrent as opposed to sequential therapy for good performance patients.[48–51] Further efforts to improve outcomes via radiation dose escalation,[52] use of induction[53,54] or consolidation chemotherapy,[55] or via the integration of molecular targeted agents[56] have been disappointing, and 5-year survival remains less than 30%, with distant failure the predominant relapse pattern.[57,58] Innovative strategies to improve outcomes for patients with locally advanced NSCLC are desperately needed. Immunotherapy is a logical therapeutic addition for locally advanced NSCLC, as thoracic radiotherapy should eradicate macrometastatic disease and promote antitumor immunogenicity. However, the optimal approach to integrate immunotherapy agents into combined modality treatment is unclear.

Completed and Currently Accruing Clinical Trials

Relatively few completed prospective studies have combined immunotherapy and radiotherapy for locally advanced NSCLC (Table 3). A phase III trial published in 1997 enrolled patients with resected NSCLC and included a subset of patients treated with both radiotherapy and immunotherapy. Patients were stratified based on "curative" (complete) or noncurative (residual nodes, metastatic disease, or positive margin) resection. Patients with noncurative resection were randomized to either standard adjuvant therapy alone, including mediastinal radiotherapy for incomplete resections, or standard adjuvant therapy with the addition of IL-2 and lymphokine activated killer (LAK) cell adoptive immunotherapy. Patients with "curative" resections were randomized to no additional therapy versus chemoimmunotherapy with cisplatin, vindesine, mitomycin C, and IL-2/lymphokine activated killer. Patients receiving radiotherapy were not analyzed separately, but both the "curative" and "noncurative" populations resulted in improved 5- and 9-year survival with the addition of immunotherapy.[59]

The most extensively studied immunotherapy agent for locally advanced NSCLC is the liposomal vaccine L-BLP25 (tecemotide), a synthetic lipopeptide designed to induce a T cell response to the mucin 1 (MUC1) glycoprotein which is overexpressed and abnormally glycosylated in NSCLC and other solid tumors and is involved in pathways promoting growth, proliferation, and survival of cancer cells.[60] After an initial phase I trial in stage IIIB/IV NSLCL patients that demonstrated safety and tolerability (including patients with prior thoracic radiation),[61] Butts et al.[62,63] enrolled 171 patients with stage IIIB/IV NSCLC and stable disease or clinical response to standard therapy (chemotherapy for stage IV or thoracic CRT for stage IIIB) to a randomized phase IIB comparison of L-BLP25 versus best supportive care. A 3-week washout period was followed by enrollment and randomization to best supportive care or 8 weekly doses of L-BLP25 with a single low dose of cyclophosphamide 3 days before cycle 1. At investigator discretion, maintenance L-BLP25 was delivered at 6-week intervals. Although the investigators did not explicitly evaluate radiotherapy/immunotherapy combinations, they included a subset of patients treated with radiotherapy. An updated analysis identified a significant survival advantage in the immunotherapy arm for the entire population, with 3-year overall survival of 31% versus 17% ($p = 0.035$). Among the small subset of patients with stage IIIB NSCLC treated with CRT, the 3-year OS was 49% versus 27% favoring the addition of L-BLP25 ($p = 0.07$) with a median survival improvement of 17.3 months. The authors speculate that use of radiotherapy in 85% of stage IIIB patients may have augmented antitumor effects of L-BLP25.

This phase II trial was followed by an international, double-blind phase III randomized trial, stimulating targeted antigenic response to NSCLC (START), enrolling locally advanced NSCLC patients. 1513 eligible patients completed concurrent or sequential CRT for stage IIIA/B NSCLC with confirmed stable disease or objective response, and were randomized 2:1 in a double blind fashion to maintenance L-BLP25 versus placebo. In the planned analysis for all eligible patients, no significant difference in median survival was identified (25.6 versus 22.3 months; $p = 0.12$). In an unplanned subgroup analysis stratifying by use of concurrent versus sequential CRT, a statistically significant survival benefit was identified for patients treated with concurrent CRT (30.8 versus 20.6 months; $p = 0.016$) but not for sequential CRT (19.4 versus 24.6 months; $p = 0.38$).[64] A trial in Japan similarly accrued patients with unresectable stage III NSCLC without progression following concurrent or sequential CRT to an integrating phase I/randomized phase II study comparing L-BLP25 with placebo.[65] A planned analysis identified no benefit in overall survival or any secondary endpoint, and as a result the development of L-BLP25 was discontinued prematurely, closing the INSPIRE and START2 trials for NSCLC patients treated with concurrent CRT.[66–68] However, an ongoing Eastern Cooperative Oncology Group trial is evaluating the combination of L-BLP25 and bevacizumab after concurrent CRT and consolidative chemotherapy (NCT00828009).[69]

There is substantial interest in incorporating newer immunotherapy agents, particularly immune checkpoint inhibitors, into treatment algorithms for locally advanced disease. The currently accruing Phase III double-blind PACIFIC trial randomizes patients with unresectable stage IIII NSCLC without progression following definitive concurrent CRT 2:1 to maintenance therapy with the PD-L1 inhibitor MEDI4736 versus placebo for a maximum of 12 months or until progression[70] (NCT02125461). Similarly, a developing trial within the radiation therapy oncology group foundation proposes the addition of nivolumab after concurrent CRT.

One trial has evaluated the use of immunotherapy with node positive, resectable NSCLC. Radiation therapy oncology

TABLE 3. Clinical Trials Combining Immunotherapy and Radiation for Locally Advanced NSCLC

Institution/Group	Phase	Eligibility	Radiotherapy	Immunotherapy
Completed				
Chiba Cancer Center	III	Clinical stage II–IIIA NSCLC s/p resection (complete or incomplete)	40–60 Gy if residual disease of the chest wall, diaphragm, pericardium, nodes, or bronchial stump	IL-2/LAK cell adoptive immunotherapy after two courses of cisplatin/vindesine (control arm chemo alone
Cross Cancer Institute, University of Alberta	I	Stage IIIB or IV NSCLC	Not specified (delivered to 7/17 pts)	L-BLP25 20 mcg or 200 mcg (randomly assigned) × 4 doses (weeks 0, 2, 5, and 9)
Cross Cancer Institute, University of Alberta	IIB	Stage IIIB or IV NSCLC	Not specified (stage IIIB only)	Adjuvant L-BLP25 weekly 1000 μg Sub-Q × 8 (Q 6 week maintenance allowed starting week 13) vs. best supportive care
The Cancer Institute Hospital of JFCR	I/II	Unresectable stage IIIA/B NSCLC s/p concurrent or sequential CRT	Thoracic RT ≥50	Adjuvant L-BLP25 sub-Q 1000 μg QW × 8 → 1000 μg Q 6 weeks maintenance until disease progression
Multi-institution (START)	III	Unresectable stage IIIA/B NSCLC s/p concurrent or sequential CRT	Thoracic RT ≥50	Adjuvant L-BLP25 sub-Q 806 μg Qweek × 8→ 806 μg Q 6 weeks maintenance until disease progression
Accruing				
Multi-Institution (PACIFIC)	III	Unresectable stage IIIA/B NSCLC s/p concurrent CRT	Thoracic RT, dose unspecified	Adjuvant MEDI4736 × 12 months (dosing not available)
Eastern Cooperative Oncology Group (ECOG E6508)	II	Unresectable stage IIIA/B NSCLC	Thoracic RT 66 Gy in 33 fractions with concurrent carboplatin/ paclitaxel	Adjuvant bevacizumab 15 mg/kg day 1 and L-BLP25 806 mcg SQ days 1, 8, and 15 of cycles 1 and 2, and day 1 of cycles 4, 6, 8
Terminated				
Multi-Institution (START2)	III	Unresectable stage IIIA/B NSCLC s/p concurrent CRT	Thoracic RT ≥60 Gy in ≥1.8 Gy fractions	Adjuvant L-BLP25 sub-Q 806 μg QW × 8→ 806 μg Q 6 weeks maintenance until disease progression
Multi-Institution (INSPIRE)	III	Asian pts with stage IIIA/B unresectable NSCLC with SD or OR following concurrent CRT	Thoracic RT ≥50	Adjuvant L-BLP25 sub-Q 918 μg QW × 8→ 918 μg Q 6 weeks maintenance until disease progression
Radiation Therapy Oncology Group (RTOG 9909)	II	Completely resected stage II/IIIA NSCLC	Thoracic RT 50.4–61.2 Gy in 1.8 Gy fractions	Concurrent 11D10 and 3H1 anti-idiotype vaccines Sub-Q weekly × 3 weeks → monthly × 2 years

NSCLC, non–small-cell lung cancer; Gy, Gray; RT, radiotherapy; IL-2/LAK, interleukin-2/lymphokine activated killer cell; Sub-Q, sub-cutaneous; QW, weekly.

group 9909 evaluated concurrent and adjuvant delivery of two novel anti-idiotype cancer vaccines designed to generate an immune response against two common tumor antigens: carcinoembryonic antigen and human milk fat globule antigen after surgical resection of stage II/IIIA NSCLC. Vaccines were delivered in combination with postoperative radiotherapy, without chemotherapy. However, the trial was close prematurely following enrollment of 22 patients and results have not been reported.[71] No further trials have attempted integration of immunotherapy and radiation in the trimodality or postoperative setting for locally advanced disease.

Future Directions

While results from ongoing and developing trials should help clarify the role of immune checkpoint inhibitors for locally advanced, unresectable NSCLC, many questions remain. No studies have explored integration of immunotherapy as concurrent or neoadjuvant therapy for locally advanced disease, and such approaches will be complicated by the delivery of chemotherapy. Systemic chemotherapy used for locally advanced disease is often immunosuppressive and may hinder tumor-directed immune activation, although certain chemotherapies may induce immunogenic cell death in preclinical models,[14] potentially augmenting immune response and synergizing with radiation–immunotherapy combinations. It is also unclear whether the conventionally fractionated, larger-field radiotherapy used for locally advanced disease will have the immunostimulatory effects of more localized, high dose SBRT, or may result in immunosuppression via incidental irradiation of adjacent bone marrow and circulating blood volume. Timing and patient selection will likely be crucial to realizing a benefit in this setting. For patients unable to tolerate systemic chemotherapy, concurrent or sequential immunotherapy with radiation should also be explored. Checkpoint inhibitors should also be systematically tested as part of the treatment algorithm for node positive, resectable disease.

IMMUNOTHERAPY AND RADIATION IN EARLY STAGE NSCLC

Rationale

Surgical resection remains the standard therapy for early stage (stage I/II) NSCLC, with systemic chemotherapy added for high risk or node positive patients. Radiotherapy

is typically added only for positive resection margins or unexpected upstaging with occult mediastinal involvement. However, SBRT has emerged as the standard of care for medically inoperable early stage NSCLC, with local control similar to historical surgical results using sublobar resection.[65,66] The predominant pattern-of-failure for early stage NSCLC, whether managed surgically or nonsurgically, remains distant.[67] The adjuvant chemotherapy used after surgical resection of high-risk early stage NSCLC is rarely used after SBRT as the risk factors that preclude surgery frequently preclude chemotherapy. With distant failure exceeding 30% at 5 years, novel strategies to improve distant control are desperately needed.[68] Immunotherapy is an appealing partner given the modest and nonoverlapping toxicity profile and the potential for SBRT to augment the systemic antitumor effects.

Developing Trials and Future Directions

No completed or currently accruing prospective studies have evaluated radiotherapy–immunotherapy combinations for early stage NSCLC. Our group will soon activate a phase I dose escalation trial evaluating the PDL-1 inhibitor MPDL3280A in combination with SBRT (50 Gy over four to five fractions) for high risk, early stage, medically inoperable NSCLC. Based on our preclinical data (unpublished), we postulate that the optimal approach involves priming the immune system with two cycles of MPDL3280A followed by concurrent administration of MPDL3280A with SAR followed by three cycles of adjuvant MPDL3280A. A standard phase one, 3 + 3 design will be used, with three dose levels of MPDL3280A (3 mg/kg, 10 mg/kg, and 1200 mg [equivalent to 15 mg/kg]) with a 15 patient expansion cohort at the maximum tolerated dose.

CONCLUSIONS

The impressive efficacy results from recent trials evaluating new immunotherapy agents in heavily pretreated, metastatic NSCLC have garnered substantial enthusiasm for expanding their evaluation to a greater proportion of lung cancer patients, including the potential to increase cure rates among patients with localized disease. Preclinical data suggest rationale combinatorial strategies with radiotherapy and immunotherapy may enhance antitumor effects and improve clinical response rates. Hence, multiple clinical trials testing immunotherapy–radiotherapy combinations in both metastatic and localized disease are ongoing or in development. Their success will require rationale integration of these two modalities based on sound preclinical data, and will need to address sequencing, radiation dose fractionation, target organ, choice of immunotherapy agent, and patient selection.

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