

Novel radiotherapy approaches for lung cancer: combining radiation therapy with targeted and immunotherapies

Charles B. Simone II¹, Stuart H. Burri², John H. Heinzerling²

¹Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; ²Department of Radiation Oncology, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

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

Correspondence to: John H. Heinzerling, MD. Department of Radiation Oncology, Levine Cancer Institute, Carolinas Healthcare System, 1021 Morehead Medical Drive, Charlotte, NC 28204, USA. Email: John.Heinzerling@carolinashealthcare.org.

Abstract: Targeted therapies and immunotherapies have quickly become fixtures in the treatment armamentarium for metastatic non-small cell lung cancer (NSCLC). Targeted therapies directed against epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) translocations, and ROS-1 rearrangements have demonstrated improved progression free survival (PFS) and, in selected populations, improved overall survival (OS) compared with cytotoxic chemotherapy. Immunotherapies, including checkpoint inhibitor monoclonal antibodies against programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1), have now also demonstrated improved survival compared with chemotherapy. The use of these novel systemic agents in non-metastatic patient populations and in combination with radiation therapy is not well defined. As radiation therapy has become more effective and more conformal with fewer toxicities, it has increasingly been used in the oligometastatic or oligoprogression setting. This has allowed improvement in PFS and potentially OS, and in the oligoprogressive setting may overcome acquired drug resistance of a specific lesion(s) to allow patients to remain on their targeted therapies. Molecularly targeted therapies and immunotherapies for patients with metastatic NSCLC have demonstrated much success. Advances in radiation therapy and stereotactic body radiotherapy, radiation therapy have led to combination strategies with targeted therapies among patients with lung cancer. Radiation therapy has also been combined with immunotherapies predominantly in the metastatic setting. In the metastatic population, radiation therapy has the ability to provide durable local control and also augment the immune response of systemic agents, which may lead to an abscopal effect of immune-mediated tumor response in disease sites outside of the radiation field in select patients.

Keywords: Abscopal effect; immunotherapy; lung cancer; radiation therapy; targeted therapy

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Role of radiation in early stage and locally advanced non-small cell lung cancer (NSCLC)

Definitive radiation therapy has been part of the standard of care for patients with locally advanced NSCLC for almost 5 decades. Combined modality therapy with chemoradiation became the preferred treatment of these patients based on multiple clinical trials showing improved survival (1,2).

Conventionally fractionated radiation therapy remains the standard, and attempts at dose escalation have failed to show a benefit in this patient population (3). Newer technologies such as intensity modulated radiation (4), image guided radiation therapy, and proton therapy (5-7) are increasingly being utilized or studied to lower rates of toxicity with combined modality therapy.

Table 1 Classes of targeted therapies in clinical use in metastatic non-small cell lung cancer

Target	Currently available targeted therapies
EGFR	Erlotinib
	Afatinib
	Gefitinib
	Cetuximab
ALK	Crizotinib
	Ceritinib
ROS1	Crizotinib
MET	Crizotinib
VEGF	Bevacizumab
	Ramucirumab

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1; VEGF, vascular endothelial growth factor.

Surgical resection has been the standard of care for patients with stage I NSCLC with 5 years survival rates of approximately 60-70% (8,9). While patients determined to be medically inoperable have been treated in the past with standard fractionated radiotherapy, newer technologies within radiation therapy have led to the standardization of high dose, ablative hypofractionated therapy termed stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) (10). SBRT has allowed for improved dose conformity, improved local tumor control, and superior overall survival (OS) when compared to conventionally fractionated radiotherapy (11,12). Based on the improved outcomes with SBRT and the increased utilization of this technology, interest in its use for medically operable patients has emerged. A recently published pooled analysis of two randomized trials comparing surgery and SBRT for stage I NSCLC demonstrated that SBRT was highly effective and had a limited toxicity profile, and that there was equipoise between the two treatment options (13).

SBRT has also begun to be used more frequently in patients with oligometastatic disease, including lung, liver, and bone metastases. Recent data has shown excellent control rates with encouraging progression free survival (PFS) in patients with oligometastatic NSCLC (14,15). Conventionally fractionated radiotherapy, in combination with chemotherapy, can also be considered in patients with oligometastatic disease not amenable to treatment with SBRT and may improve survival in a select subset of patients with minimal extrathoracic disease (16).

Targeted therapy for advanced NSCLC

With the discovery of molecular pathways that correspond with tumor progression and growth, numerous potential targets have been identified and explored for potential therapeutics for advanced NSCLC (*Table 1*).

Epidermal growth factor receptor (EGFR) is an essential part of the oncogenic growth pathway and is expressed at higher levels in some lung cancers. EGFR as a molecular target has shown promising results in advanced lung cancer. Monoclonal antibodies, such as cetuximab and panitumumab, and tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, and afatinib, are available. Initial trials evaluating patients treated with cytotoxic chemotherapy either in combination or followed by EGFR pathway inhibitors without prior molecular mutation analyses demonstrated mixed results, although trials have generally demonstrated at least a benefit to PFS (17-23). Further subset analysis of many of these trials showed clear correlation between the presence of EGFR driver mutations and clinical benefit of these agents. This has led to the standardization of the use of EGFR TKIs in the first line setting for patients with EGFR mutations (24-30).

Vascular endothelial growth factor (VEGF) plays an essential part in tumor angiogenesis and is often expressed at higher rates in NSCLC, thus creating another molecular pathway target for therapy. The most well studied VEGF inhibitor in NSCLC, bevacizumab, has shown increased PFS and OS in patients with non-squamous NSCLC when added to standard cytotoxic chemotherapy (31-33). Ongoing trials are evaluating bevacizumab with other platinum combinations (NCT00150657, NCT00753909), as well as with other targeted agents such as erlotinib and ramucirumab (NCT01532089, NCT00257608, NCT00553800).

One of the most promising recent areas of new drug development in treatment of NSCLC has been anaplastic lymphoma kinase (ALK) inhibitors. These are targeted agents directed at the novel fusion oncogene echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase (EML4-ALK). The first available drug was crizotinib, an oral small-molecule inhibitor of ALK and c-Met tyrosine kinases. Crizotinib has shown favorable outcomes both in the second line setting, as well as in the primary treatment setting for patients that are positive for this rearrangement (34,35). Second generation TKI inhibitors of ALK include ceritinib and alectinib are undergoing investigation in national trials in ALK positive patients that have progressed, as well as the primary setting with pending

Table 2 Checkpoint inhibitors in clinical use or under development for advanced or metastatic non-small cell lung cancer

Monoclonal antibody	Target	FDA approved
Ipilimumab	CTLA-4 on T cells	Melanoma
Nivolumab	PD-1 on T cells	Lung cancer, melanoma
Pembrolizumab	PD-1 on T cells	Melanoma
BMS-936559	PD-L1 on tumor cells	No
MEDI4736	PD-L1 on tumor cells	No
MPDL3280A	PD-L1 on tumor cells	No
Lirilumab	Killer-cell immunoglobulin-like receptor (KIR) on NK cells	No
BMS-986016	Lymphocyte-activation gene 3 (LAG3) on tumor infiltrating lymphocytes	No

FDA, Food and Drug Administration; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death receptor 1; PD-L1, programmed death ligand 1; NK, natural killer.

results (NCT02292550, NCT02393625, NCT02075840, NCT02271139). ALK inhibitors have also demonstrated efficacy in patients with chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase, which occurs in 1-2% of patients with NSCLC (36).

Immunotherapy for advanced NSCLC

Utilizing the immune system as an effective oncologic tool to fight cancer has been the subject of preclinical and clinical research for several decades (37). Immunotherapy agents allow the immune system to recognize a patient's cancer cells as foreign, prompting an immune response resulting in tumor cell death and/or inhibition of tumor growth. Newer immunotherapy agents have been developed based on improved knowledge of the molecular process of the immune response, leading to a resurgence in investigative use of these agents for patients with NSCLC. Such checkpoint inhibitors include monoclonal antibodies to cytotoxic T-lymphocyte antigen 4 (CTLA-4) such as ipilimumab, as well as antibodies to programmed death receptor 1 (PD-1), such as nivolumab and pembrolizumab (Table 2).

CTLA-4 is responsible for regulation of early T cell activity. It becomes upregulated after antigen exposure and competes for binding with CD28, preventing the stimulatory signal needed for T cell activation. Thus, inhibition of this receptor allows T cell activation after tumor antigen presentation. PD-1 is also upregulated on T cells, but it is thought to play a role further down the immune response pathway within the tumor microenvironment. Binding of PD-1 to programmed death ligand 1 (PD-L1) leads to T cell inactivation, and antibodies

to PD-1 allow activation to proceed at the site of direct anti-tumor immune response.

The majority of data for use of these newer immunotherapy agents in NSCLC have been studied in advanced, stage IV patients. Ipilimumab was developed as an IgG1 CTLA-4 monoclonal antibody and was originally investigated in metastatic melanoma. A phase II randomized trial combining ipilimumab with standard first line chemotherapy in patients with stage IIIB-IV NSCLC showed improvement of PFS with the addition of ipilimumab (38). Subset analysis showed that patients with squamous cell histology benefitted primarily from the addition of ipilimumab, prompting an ongoing phase III trial that is comparing standard first line chemotherapy with carboplatin and paclitaxel with or without the addition of ipilimumab in patients with advanced squamous cell NSCLC. Additional trials are evaluating its effectiveness in combination with other targeted or immunotherapy agents (39).

Anti PD-1 antibody agents have been more commonly studied in patients with progressive metastatic NSCLC and showed promising results with prolonged tumor responses (40). Based on the recently published data from the CheckMate 017 and 063 trials in 2014, nivolumab has now received Food and Drug Administration (FDA) approval for treatment of advanced squamous cell NSCLC. Checkmate 063 was a single arm phase II trial in patients that had progressed after at least two prior systemic treatments. Nivolumab achieved an encouraging 1 year survival rate of 41% in these heavily pretreated patients (41). The follow up phase III trial, CheckMate 017, randomized patients with metastatic squamous cell NSCLC who had progressed after doublet chemotherapy to nivolumab or and docetaxel. The trial was stopped early due to superior OS in the nivolumab arm with a median survival of 9.2 *vs.* 6 months

in the docetaxel arm ($P=0.00025$). Nivolumab also showed a more favorable toxicity profile compared with docetaxel (42). Additional phase III trials are currently evaluating pembrolizumab monotherapy in both the first line and second line setting for advanced and metastatic NSCLC (NCT02220894, NCT02142738) (38).

Targeted therapy with radiation therapy for localized NSCLC

Many targeted therapies have been integrated into the treatment of localized NSCLC. While the data are much more limited than for the metastatic setting, targeted therapies have been used in combination with or concurrently with radiation therapy. The majority of this data are in conjunction with radiation therapy in the setting of locally advanced NSCLC classically treated with concurrent chemotherapy and radiation.

Preclinical data have shown biologic rationale for combining EGFR inhibitors and radiation therapy. Cetuximab has been combined with chemotherapy and radiation in treatment of locally advanced NSCLC in both phase II and phase III trials (3,43,44). In two sequential Radiation Therapy Oncology Group (RTOG) trials, cetuximab was combined with carboplatin/paclitaxel and radiation therapy for stage IIIA/IIIB lung cancer. While the median survival (22.7 months) and 24-month OS (49.3%) achieved in the phase II study (RTOG 0324) of cetuximab and concurrent chemoradiation were longer than any previously reported by the RTOG (43), the randomized phase III trial RTOG 0617 failed to show a benefit to the addition of cetuximab to chemoradiation in an unselected population (3). Among all patients, median OS in patients randomized to cetuximab was 25.0 *vs.* 24.0 months among those not receiving cetuximab ($P=0.29$). However, in a planned analysis of the association of EGFR expression and outcome, among patients with an EGFR H score of 200 or higher, cetuximab use was associated with improved OS (42.0 *vs.* 21.2 months, $P=0.032$) (3).

Gefitinib and erlotinib have also been integrated into both the concurrent chemoradiation setting, as well as a maintenance therapy after chemoradiation for locally advanced NSCLC (45-47). Again, phase III trials have failed to show a benefit to these agents in all subsets of patients, but they have shown improved outcomes in patients who had evidence of EGFR amplification or EGFR mutation, suggesting that in selected patients, these drugs may prolong PFS or OS in combination with chemotherapy

and radiation therapy for non-metastatic patients. Newer studies are evaluating the use of these agents in patients with confirmed mutations (NCT01391260, NCT01822496, NCT02277457) (38).

Another area of clinical interest combining radiation and targeted therapy has been in the limited or oligometastatic setting. While the definition of oligometastatic has varied in the clinical literature, there has been increased use of local therapies for patients with limited sites of metastatic disease, especially as the ability to deliver effective local therapies with less morbidity has improved. Given the encouraging local control and limited toxicity profile of SBRT in both the lung and other organs commonly afflicted with metastasis from lung cancer, this remains an active area of research in treating patients with limited oligometastatic disease in combination with targeted agents. One recent published phase II trial showed encouraging results for PFS in advanced NSCLC patients with six or fewer sites of metastatic disease when they were treated with local SBRT to these sites in combination with second line erlotinib (7). Other active studies are similarly looking at this patient population in combination with other targeted as well as immunotherapeutic agents (NCT02450591, NCT0208672, NCT02444741).

As in the oligometastatic setting, the use of radiation therapy can be considered in the oligoprogression setting among patients being treated with TKIs for metastatic NSCLC. While patients with stage IV NSCLC and EGFR mutation or ALK rearrangement have achieved excellent PFS with targeted therapy, disease progression often occurs within a year of therapy initiation. While initial progression of EGFR- or ALK-directed therapy can be diffuse, many patients can have oligoprogression, or limited sites of progression, potentially due to acquired resistance from evolutionary selection on molecularly diverse tumors in which tumor clones in some sites of metastasis but not others develop resistance. Systemic options for such patients include increasing the dose of the targeted therapy they are progressing on, switching to another next-line targeted therapy, switching to cytotoxic chemotherapy, or adding chemotherapy to the targeted therapy (48). However, several groups have recently demonstrated that radiation therapy or other local therapies to sites of oligoprogression can also be considered and can achieve durable local control of the sites of progression and also allow for patients to be maintained on their existing TKI, thus saving alternative or next-line systemic therapy options for subsequent disease progression (49,50).

Anti-angiogenesis agents typically targeting VEGF have become standard treatment components of therapy for advanced NSCLC. Bevacizumab has been studied in combination with radiation therapy, but this combination has shown a high incidence of tracheoesophageal fistula formation when given concurrently, especially among patients with squamous cell carcinoma and centrally located tumors being irradiated (51).

Given the favorable results in advanced lung cancer, integration of ALK inhibitors into the setting of locally advanced NSCLC has already entered ongoing randomized phase II trials, including NRG/RTOG 1306/NCT01822496, which is evaluating erlotinib and crizotinib as induction therapy followed by standard chemoradiation in patients with confirmed EGFR mutation or EML4-ALK fusion rearrangement, respectively (39).

Immunotherapy with radiation therapy for NSCLC

Although there is limited data to date combining radiation therapy and immunotherapy, this combination has the ability to achieve a synergistic therapeutic effect (52,53). As ionizing radiation can increase the production and presentation of tumor antigens, it can serve to augment the antitumor immune responses achieved by checkpoint inhibitors (54). Radiation therapy can augment immunomodulation by bolstering cytotoxic T-lymphocyte activity (53) and reduce myeloid-derived suppressor cells (55), allowing for synergism with checkpoint inhibitors.

SBRT may be the radiotherapy modality most optimally combined with immunotherapy since it can achieve a more robust immune response than conventionally fractionated radiotherapy. SBRT has been shown to induce cellular expression of major histocompatibility complex (MHC) I, inflammatory mediators, costimulatory molecules, heat shock proteins, immunomodulatory cytokines, adhesion molecules, and death receptors, all of which can enhance antitumor immune responses of systemic therapy (56).

There have been a number of reports in which a distant tumor mass regresses following the administration of radiation therapy before or after treatment with immunotherapy, known as the abscopal effect (57-59). In addition to the abscopal effect, radiation therapy may also allow for immune activation that leads to a more complete or accelerated clearance of the irradiated tumor, or sterilization of microscopic metastasis that were not clinically apparent at the time of irradiation. Aside from case reports, a number

of prospective clinical trials have been completed that have combined anti-CTLA-4 therapy and radiotherapy for melanoma (60) and prostate cancer (61) with promising results. A phase I/II study in metastatic castration resistant prostate cancer combining ipilimumab in combination with radiation therapy showed 50% of patients having a decline in prostate-specific antigen (PSA) with one complete response (60). A phase I trial combining ipilimumab and radiation in melanoma showed a response rate of 18% and PFS of 3.8 months prompting further investigation into this combination in the clinical setting (62). To date, no prospective study combining radiation therapy with anti-CTLA-4, anti-PD-1, or anti-PD-L1 therapy has been completed for lung cancer.

Future directions

Targeted therapy and immunotherapy have become pillars of lung cancer treatment. As we gain a greater understanding of the molecular basis of lung cancer, additional targeted agents will become part of standard practice to expand the role beyond the currently limited proportion of lung cancer patients with a known targetable mutation or translocation. Additionally, with increasing knowledge of acquired mutations, second- and third-line targeted agents will become standard options over salvage cytotoxic chemotherapy offering the promise of greater effectiveness and less toxicity. Cooperative group studies combining targeted agents and radiotherapy for non-metastatic patients are ongoing (NCT01822496).

Similarly, immunotherapies will become more entrenched as standard therapy for second-line NSCLC and will be investigated in the first line setting. Combination therapies will increasingly be the subject of investigation, including the inhibition of both CTLA-4 and PD-1, or the use of an immunotherapy agent with a targeted therapy or with a cytotoxic chemotherapy. Toxicities to such combinations, however, may prove prohibitive.

While there is much excitement around the phenomenon of a radiotherapy-induced anticancer immune response and combining radiation therapy with immunotherapy, numerous questions remain before this combination can be exported to routine clinical practice. Additional research is needed to determine if conventionally fractionated irradiation, multi-fraction SBRT, or single fraction SBRT is most effectively combined with immunotherapy, and how radiotherapy and immunotherapy should be sequenced. Like with combination systemic therapies, combining

radiotherapy with such novel immunotherapies and systemic therapies may result in overlapping toxicities of radiation therapy and immunotherapy. In addition to the immune modulators and checkpoint inhibitors discussed in this manuscript, additional ways to provide tumor-associated antigen to the immune system that can be combined with radiotherapy are currently being investigated, including recombinant vaccines, tumor lysates, and synthetic peptides. While early results are promising, studies combining radiation therapy with immunotherapy warrant careful consideration of toxicity and safety.

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Footnote

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