



# Combination of immunotherapy and radiotherapy in the treatment of brain metastases from non-small cell lung cancer

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**Abstract:** It was commonly assumed in the past that blood-brain barrier could efficiently prohibit penetration of large peptide molecules, such as monoclonal antibodies, including programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors. This belief has been recently revised by studies that demonstrate the presence of functional lymphatic vessels lining the dural sinuses. Furthermore, the activated circulating T cells have been shown to cross the blood-brain barrier. Such observations created strong rationale for attempts of immunotherapy for patients with brain metastases, used either alone or in combination with radiotherapy. The expected benefit from immunotherapy particularly refers to patients without targetable “driver” mutations who are not considered as candidates for novel targeted therapies. Current inference on efficacy and safety of combination of immunotherapy and radiotherapy in the treatment of brain metastases from non-small cell lung cancer (NSCLC) origins, in most, from the retrospective studies. The existing data suggest that use of immune checkpoint inhibitors (ICIs) with brain radiotherapy improves patients outcome, compared to brain radiotherapy alone. The available data also suggest that concurrent use of ICI and stereotactic radiation therapy (SRT) for brain metastases from NSCLC is tolerable and appears more effective than sequential combination of radiotherapy and ICI. Use of steroids appeared detrimental. Since a dependence between the risk of adverse events and type of ICI therapy as well as tumor pathology was found, further studies are required to establish optimal dosage, selection of drugs and sequence of ICI and brain radiotherapy in patients with brain metastases from NSCLC.

**Keywords:** Non-small cell lung cancer (NSCLC); brain metastases; radiotherapy; immune checkpoint inhibitor (ICI); review

Submitted Aug 06, 2020. Accepted for publication Sep 29, 2020.

doi: 10.21037/jtd-2019-rbmlc-08

**View this article at:** <http://dx.doi.org/10.21037/jtd-2019-rbmlc-08>

## Introduction

From the historical perspective, development of brain metastases was considered as one of the most grim and devastating events in natural course and therapy of patients with non-small cell lung cancer (NSCLC). Despite use of surgery, whole brain radiotherapy (WBRT) and best supportive care median overall survival ranged between 2 and 7 months, depending on the prognostic class of the patient (1). Recent advances in imaging, molecular biology, surgery, radiation treatment and systemic therapy considerably expanded therapeutic options available for such patients and, in most of the cases, favorably altered the

prognosis. Among recent developments in systemic therapy introduction of immunotherapy for NSCLC influenced standard approach to patients with advanced disease, including those with brain metastases (2,3). Combination of immunotherapy and radiotherapy (RT) became intensively explored considering the potentially beneficial interaction of these modalities. Here we provide a concise review of recent research progress on this subject.

## Current place of immunotherapy for NSCLC

The first clinical approvals of immunotherapy in locally

advanced or metastatic NSCLC referred to previously treated patients who progressed on chemotherapy (4-6).

### *Nivolumab*

Nivolumab is a programmed death-1 (PD-1) inhibitor proven to increase overall survival (OS) over docetaxel in both squamous (4) and nonsquamous (5) NSCLC. For nonsquamous cancer the outcomes had improved with increase in programmed death-ligand 1 (PD-L1) expression, while in squamous cancer the PD-L1 expression was neither prognostic nor predictive of benefit. Two-year overall survival rates with nivolumab versus docetaxel were 23% versus 8% in squamous NSCLC and 29% versus 16% in nonsquamous NSCLC (7). In both trials (4,5) patients with brain metastases were included, providing they underwent brain irradiation, had no neurological deficits and did not require high doses of steroids.

### *Atezolizumab*

Atezolizumab the anti-PD-L1 antibody, has been approved as second-line treatment for patients with previously treated non-small-cell lung cancer based on the results of a phase II trial that demonstrated its improved efficacy compared to docetaxel (8). Patients with active or untreated CNS metastases were excluded in this trial.

Recently, major changes in systemic therapy for NSCLC have been influenced by introduction of immunotherapy to first line treatment for locally advanced or metastatic NSCLC.

### *Durvalumab*

Durvalumab, the anti PD-L1 antibody, significantly prolonged overall survival among patients with stage III, unresectable NSCLC who did not have disease progression after concurrent chemoradiotherapy. Inclusion criteria for the pivotal PACIFIC trial (9,10) precluded recruitment of patients with brain metastases.

### *Pembrolizumab*

Pembrolizumab, PD-L1 inhibitor, was initially investigated in NSCLC PD-L1 positive patients (expression on at least 1% of tumor cells) who had two or more cycles of platinum-doublet chemotherapy (6). Those with an EGFR-sensitising mutation or ALK gene rearrangement were

eligible, providing they progressed on appropriate tyrosine kinase inhibitor therapy. Patients with known active brain metastases were excluded. Further studies of pembrolizumab referred to first line of treatment for patients with metastatic NSCLC. It was approved as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 (Tumor Proportion Score TPS  $\geq 50\%$ ) (11). Recently, based on results of the KEYNOTE-042 trial (12), its use in monotherapy has been expanded to include the first-line treatment of patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation and for patients with metastatic NSCLC with no EGFR or ALK genomic aberrations and TPS  $\geq 1\%$ . Pembrolizumab has been also shown to significantly improve overall survival in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations (13). Another pivotal trial shown improved survival for pembrolizumab in combination with carboplatin and paclitaxel as first-line treatment of patients with metastatic squamous cell lung cancer (14).

In general, patients with untreated brain metastases were not included in trials that investigated the safety and activity of pembrolizumab in first line treatment for patients with metastatic NSCLC, nevertheless, patients after brain RT or surgery could be included. For example, 11.7% of the patients from KEYNOTE-024 trial on pembrolizumab as a single agent for the first-line treatment of patients with metastatic NSCLC had brain metastases (11). Subgroup analysis from this trial suggest that the benefit, in terms of progression-free survival, from pembrolizumab was comparable in patients with brain metastases and no brain metastases with hazard ratios of 0.50 and 0.55 respectively.

## **Radiotherapy and brain metastases from NSCLC**

When assessing the efficacy and tolerance of combined RT and immunotherapy for brain metastases it is necessary to consider the diversity of radiation treatment techniques and dose fractionation prescription practices that are employed in such treatment. Historically, the management of brain metastases with RT was performed using WBRT. The advances in tumor imaging and in conformal delivery of radiation shifted clinical interest toward stereotactic radiation therapy (SRT), particularly in patients with small number of brain metastases. Initial trials suggested clinical benefit from combining WBRT and SRT, mostly

in terms of reduction of recurrences in the brain (15,16). A concern appeared, however, regarding higher incidence of neurocognitive functional deficits in WBRT + SBRT, compared to SRT alone (17). Therefore, despite trials showing lower rates of intracranial failures with WBRT + SRT, compared to SRT alone, an increase in neurocognitive deficits, lack of survival improvement as well as new clinical data on effectiveness and tolerance of treatment prevail in favor of SRT alone, whenever such treatment is feasible (18). The quality of life is considered, thus, equally, or even more important than control rate in the brain. Regardless of preferences one has to recognize the abovementioned differences in treatment tolerance and effectiveness according to RT technique and fractionation when assessing the tolerance of combined ICI and RT.

### Targeted therapy vs. immunotherapy for brain metastases from NSCLC

When deciding upon treatment selection for patients with brain metastases from NSCLC it is necessary to appreciate recent advances in treatment for tumors with targetable “driver” mutations. High effectiveness of new generation epidermal growth factor (EGFR) receptor tyrosine kinase inhibitors, such as osimertinib, in patients with EGFR mutation and brain metastases (19) or alectinib in ALK (anaplastic lymphoma kinase) mutation-positive NSCLC patients with brain metastases (20) advocate in favor of targeted therapy as first line treatment for tumors with such genetic alterations. Importantly, thus, most of the trials on immunotherapy for patients with NSCLC excluded the patients with targetable “driver” mutations, including those with brain metastases.

### Immunotherapy alone for brain metastases from NSCLC

It was commonly assumed in the past that blood-brain barrier could efficiently prohibit penetration of large peptide molecules, such as monoclonal antibodies, including PD-1/PD-L1 inhibitors. Furthermore, it was believed that central nervous system had no classical lymphatic drainage. This belief has been recently revised by studies that demonstrate the presence of functional lymphatic vessels lining the dural sinuses (21). Instead of an immune privileged location, the brain is currently considered as actively regulated site of immune surveillance (22). It is, however, also recognized that endothelial, epithelial and glial brain barriers establish

compartments that differ considerably with regard to their accessibility to immune-cell subsets (23).

While CNS penetration of PD-1/PD-L1 inhibitors has not been extensively studied, the activated circulating T cells have been shown to cross the blood-brain barrier (23). This created strong rationale to study the effect of immunotherapy in patients with untreated brain metastases. Goldberg *et al.* (24) prospectively assessed 36 patients (18 with melanoma and 18 with NSCLC) with untreated or progressive brain metastases. Four of 18 patients with melanoma (22%) and 6 of 18 patients with NSCLC (33%) responded to treatment. This included four durable responses among patients with NSCLC that lasted over 6 months. The safety profile was considered acceptable. This study demonstrated, thus, activity of pembrolizumab in untreated or progressive brain metastases in patients with NSCLC and melanoma. Similar results were obtained in the studies investigating the activity of nivolumab in patients with untreated or progressing brain metastases (25), including both patients with squamous (26) and non-squamous (27) lung cancer. Median overall survival reported in these studies (26,27) was 5.8 and 8.6 months for squamous and non-squamous cancer respectively.

The exploratory analysis of the phase III OAK study that compared atezolizumab and docetaxel in patients with previously treated non-small-cell lung cancer focused on patients with asymptomatic, treated brain metastases (28). Median overall survival in this subset of the patients tended to be longer with atezolizumab compared to docetaxel (16.0 *vs.* 11.9 months), although the difference was not statistically significant (HR 0.74; 95% CI: 0.49–1.13).

In general, thus, the studies presented here, while demonstrating the activity of immunotherapy alone for brain metastases suggest, also, the necessity to combine this treatment with other active therapies to improve still relatively poor prognosis.

### Sequencing of immunotherapy and radiotherapy in the treatment of brain metastases from NSCLC

Several recent studies document synergy between extracranial radiation therapy and immune checkpoint inhibitors (ICIs). Durvalumab, approved as consolidation therapy after concurrent chemoradiation, is among the most spectacular examples (9,10). A secondary analysis of KEYNOTE-001 trial of phase I pembrolizumab in advanced NSCLC also suggested synergy between

**Table 1** The original studies containing the data on brain radiotherapy combined with immune checkpoint inhibitors (ICI) in non-small cell lung cancer patients with brain metastases

Study	ICI	No of patients	Sequence of ICI and RT
Patruni <i>et al.</i> (30)	Diverse	545	N/A
Hendriks <i>et al.</i> (31)	PD-1/PD-L1 inhibitors	173/1,025*	sequential: RT before ICI
Chen <i>et al.</i> (32)	PD-1 inhibitors	157/260*	sequential vs. concurrent
Kotecha <i>et al.</i> (33)	PD-1/PD-L1 inhibitors	99/150*	sequential vs. concurrent
Koenig <i>et al.</i> (34)	PD-1/PD-L1 inhibitors	45/97*	sequential vs. concurrent
Singh <i>et al.</i> (35)	PD-1 inhibitors	39/85*	concurrent
Schapira <i>et al.</i> (36)	PD-1/PD-L1 inhibitors	37	sequential vs. concurrent
Ahmed <i>et al.</i> (37)	PD-1/PD-L1 inhibitors	17	sequential vs. concurrent
Lin <i>et al.</i> (38)	Atezolizumab	1	concurrent

\*, the proportion of patients with brain metastases from non-small cell lung cancer (NSCLC) among all patients included in the study.

extracranial RT and immunotherapy; previous treatment with RT in patients with advanced NSCLC resulted in longer progression-free survival and overall survival with pembrolizumab than that observed in patients who did not have previous RT (29).

Following encouraging reports on successful and safe combination of ICIs and extracranial RT one may identify new studies focused on safety and effectiveness combination of ICIs and WBRT or SRT for brain metastases from NSCLC (30-38). *Table 1* summarizes these reports and directs to the respective references.

The study based on the largest number of patients, published, however, only in abstract (30), compares the outcomes in patients with brain metastases from NSCLC receiving intracranial RT with or without immunotherapy. The survival data of 545 patients who received immunotherapy and of 13,998 patients who did not receive immunotherapy were extracted from the National Cancer Database. Unfortunately, no detail information on immunotherapy used or sequencing of RT and immunotherapy was provided. Use of immunotherapy significantly improved survival (median 13.1 *vs.* 9.7 months), and the significance was maintained in propensity score matched comparison. While this analysis is prompt to biases typical for the retrospective studies it provides strong support for efficacy of immunotherapy combined with intracranial RT in patients with brain metastases from NSCLC.

Hendriks *et al.* (31) compared the outcome of patients with NSCLC and brain metastases or no brain metastases

treated with ICI. Out of 1,025 patients included in the study 173 were treated with brain RT before ICI (72 with WBRT, 99 with SRT and 2 with WBRT+SBRT). The response rates of patients with brain metastases or without brain metastases were similar (20.6% *vs.* 22.7%), median OS was 8.6 *vs.* 11.4 months respectively. When adjusted for confounding factors the presence of brain metastases appeared not associated with poorer survival. Corticosteroids use appeared to negatively influence survival.

Seven, out of 9 studies presented in *Table 1* were focused on sequencing of brain RT and ICI (31-34,36,37). Chen *et al.* (32) compared the outcome of NSCLC patients with brain metastases treated with SRT alone (SRT, n=181), sequential SRT and ICI (n=51) and concurrent SRT and ICI (n=28). Median overall survival was 12.9, 14.5 and 24.7 months, respectively, and the differences were statistically significant, in favor of concurrent SRT + ICI, also when adjusted for confounding factors. Importantly, no significant differences in acute neurologic toxicity were found. Also, no significant differences with respect to immune related adverse events were detected among the patients who received sequential *vs.* concurrent SRT+ICI.

Kotecha *et al.* (33) reported on impact of sequencing of PD-1/PD-L1 inhibitors and SRT for patients with brain metastases from tumors at various primary sites. Out of 150 patients included in the study 99 (66%) had brain metastases from NSCLC. Concurrent use of SRT and ICI was associated with improved response rate and duration of response in this study. Use of steroids appeared detrimental.

The detrimental effect of steroids in combined brain

radiotherapy and immunotherapy can be explained by well-known immunosuppressant effect of these drugs. Clearly, use of steroids may diminish the beneficial immunostimulant effect of ICI. Furthermore, patients with neurological symptoms from brain metastases (and hence with worse prognosis) may more often be treated with steroids, which further enhance the observed detriment from steroids in non-randomized studies. Replacement of steroids by antioedematous drugs such as mannitol or hypertonic saline may be considered in combined brain radiotherapy and immunotherapy, whenever clinically feasible. Steroids, nevertheless, have well-established and dominant role in control of the inflammatory immune-related adverse events.

Koenig *et al.* (34) analyzed disease control and adverse effects of SRT and ICI in 97 patients with brain metastases from various primary sites, including 45 patients (46%) with NSCLC. Concurrent use of SRT and ICI improved overall survival and intracranial disease control compared to sequential use of SRT and ICI. Concurrent SRT-ICI was considered tolerable, although the incidence of radiation adverse events was higher in concurrent SRT-ICI, compared to sequential treatment (8% *vs.* 2%). Two other studies compared sequential *vs.* concurrent SRT + ICI in patients with brain metastases from NSCLC, both demonstrating favorable outcome of patients treated concurrently (36,37).

Singh *et al.* (35) reported on concurrent use of SRT and ICI in 39 PD-L1 positive patients with NSCLC. Concurrent SRT+ICI resulted in a faster and better volumetric response in large lesions, compared to chemotherapy with SRT.

While no randomized studies comparing concurrent *vs.* sequential SRT and ICI in patients with brain metastases from NSCLC were identified, the above evidence from the retrospective studies strongly advocates in favor of concurrent treatment.

An interesting case report (38) demonstrated extracranial abscopal effect induced by brain radiotherapy in patient treated with lung adenocarcinoma who had received atezolizumab, that was later combined with brain radiation for brain metastasis. Abscopal effects are relatively frequently in patients with malignant melanoma treated with combined radiotherapy and immunotherapy. A report by Lin *et al.* is, however, perhaps the first to demonstrate the ability of radiotherapy for brain metastases to induce tumor response at sites that are far beyond the irradiated volume.

In addition to the original studies on combination of

radiotherapy and immunotherapy in patients with brain metastases from NSCLC a valuable insight one may find in recent review papers that focus on this subject (2,3,39). Some additional information one may also find in meta-analysis of individual patient data that focused on SRT plus ICI treatment of brain metastases from various primary sites (40), with NSCLC representing only minority of the included studies. Also, a review paper on combination of radiotherapy and immunotherapy in patients with brain metastases from various primary includes some relevant data on patients with NSCLC (41).

### Safety of concurrent SRT and immunotherapy

Concurrent use of two treatment modalities should always raise cautiousness about possible additive or supra-additive toxicity of such approach. Hubbeling *et al.* (42) reported on 163 patients with brain metastases from NSCLC treated with SRT (n=94), WBRT (n=101) and partial brain RT (n=28). Fifty patients received ICI in combination with RT. Treatment with an ICI and cranial RT was not associated with a significant increase in RT-related adverse events. Furthermore, the sequence and timing of PD-1 pathway inhibitor administration with respect to RT did not affect RT-related toxicity in this study. This findings are in good accordance with outcomes of studies by Chen *et al.* (32) and Ahmed *et al.* (37) who did not find increase in toxicity among diverse sequencing of treatment.

By contrast, Martin *et al.* (43) found symptomatic necrosis in 23/ 115 (20.0%) *vs.* 25/365 (6.8%) of patients with brain metastases from various primary sites, who did or did not receive immunotherapy, respectively. Risk of necrosis was, however, strongly associated with use of ipilimumab for melanoma. Considering clear dependence of adverse events on ICI type and tumor pathology the applicability of these data to patients with NSCLC is limited. Such censure also refers to the study by Koenig *et al.* (34) who found that the incidence of radiation adverse events was higher in concurrent SRT-ICI, compared to sequential treatment (8% *vs.* 2%). Notably, however, this study recruited the patients with various primary sites, including 46% with melanoma.

While the existing retrospective studies support concurrent use of ICI and SRT for patients with brain metastases from NSCLC the ongoing prospective trials, that are reviewed by other authors (3) will more precisely address this important issue.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editor (Lucyna Kepka) for the series “Radiotherapy for Brain Metastases from Lung Cancer” published in *Journal of Thoracic Disease*. The article has undergone external peer review.

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form, available at <http://dx.doi.org/10.21037/jtd-2019-rbmlc-08>. The series “Radiotherapy for Brain Metastases from Lung Cancer” was commissioned by the editorial office without any funding or sponsorship. The author reports grants and other from Bristol-Myers-Squibb, grants and other from Merck Sharp & Dohme, grants and other from Astellas Pharma, outside the submitted work.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Cite this article as:** Suwinski R. Combination of immunotherapy and radiotherapy in the treatment of brain metastases from non-small cell lung cancer. *J Thorac Dis* 2021;13(5):3315-3322. doi: 10.21037/jtd-2019-rbmlc-08