PD-1/PD-L1 Blockers in NSCLC Brain Metastases: Challenging Paradigms and Clinical Practice

Iñaki Eguren-Santamaria[1,2], Miguel F. Sanmamed[1,2,3,4], Sarah B. Goldberg[5], Harriet M. Kluger[5], Miguel A. Idoate[6], Benjamin Y. Lu[5], Jesús Corral[1], Kurt A. Schalper[7], Roy S. Herbst[5], and Ignacio Gil-Bazo[1,3,4,8]

ABSTRACT

Immune checkpoint inhibitors (ICI) have revolutionized the management of advanced non–small cell lung cancer (NSCLC). However, most pivotal phase III trials systematically excluded patients with active brain metastases, precluding the generalization of the results. Although theoretically restricted from crossing the blood–brain barrier, the novel pharmacokinetic/pharmacodynamic profiles of anti-PD-1/PD-L1 drugs have prompted studies to evaluate their activity in patients with NSCLC with active central nervous system (CNS) involvement. Encouraging results have suggested that ICI could be active in the CNS in selected patients with driver-negative advanced NSCLC with high PD-L1 expression and low CNS disease burden. Single-agent CNS response rates around 30% have been reported. Beyond this particular setting, anti-PD-1/PD-L1 antibodies have been evaluated in patients receiving local therapy for brain metastases (BM), addressing concerns about potential neurologic toxicity risks associated with radiotherapy, more specifically, radionecrosis (RN). Accordingly, a variety of clinical and imaging strategies are being appropriately developed to evaluate tumor response and to rule out pseudoprogression or radionecrosis. Our purpose is to critically summarize the advances regarding the role of systemic anti-PD-1/PD-L1 antibodies for the treatment of NSCLC BM. Data were collected from the PubMed database, reference lists, and abstracts from the latest scientific meetings. Recent reports suggest anti-PD-1/PD-L1 agents are active in a subset of patients with NSCLC with BM showing acceptable toxicity. These advances are expected to change soon the management of these patients but additional research is required to address concerns regarding radionecrosis and the appropriate sequencing of local and systemic therapy combinations.

Introduction

Brain metastases (BM) occur in 20% to 32% of patients diagnosed with non–small cell lung cancer (NSCLC) (1). In some particular settings, such as previously treated *ALK*-driven NSCLC, however, BM prevalence can reach 59% (2).

Patients with untreated BM have traditionally been excluded from clinical trials due to concerns that the particular pharmacokinetic/pharmacodynamic (PK/PD) profile of the investigational agent in the CNS could preclude the correct interpretation of the results (3). The exclusion of patients with active BM was supported by the fact that initial attempts to use systemic drugs against BM were discouraging (see Background on Systemic Treatment of Brain Metastases). However, in recent years, the development of new-generation highly penetrant kinase inhibitors has shown that appropriately designed drugs are active in the CNS (4, 5). Beyond oncogene-driven NSCLC, immunotherapeutic agents have recently shown promising activity in the CNS in patients with NSCLC BM. The results from the latest clinical trials are challenging traditional dogmas that claimed that monoclonal antibodies (mAbs) were not meaningfully active in the CNS. These findings are expected to change the clinical management of patients with NSCLC BM in the near future and warrant a review of the literature. In this review, we provide an overview of the recent results of mAb-based immunotherapy to treat BM, and how these results are challenging previous paradigms and current clinical practice.

Methods

Studies were identified from the PubMed database with the search strategy (PD-1[Title/Abstract]) OR PD-L1[Title/Abstract]) OR immunotherapy[Title/Abstract]) AND brain metastases[Title/Abstract]. The last date the search was performed was on the July 17, 2019. Abstracts from the 2019 American Society of Clinical Oncology (ASCO), American Association for Cancer Research (AACR), European Society for Medical Oncology (ESMO), International Association for the Study of Lung Cancer (IASLC) World Congress on Lung Cancer (WCLC) annual meetings were reviewed and considered for inclusion. Reference lists of reviewed articles were also considered for potential inclusion. Studies in the English language were reviewed. Studies were included regardless of date of publication but studies that included only patients with leptomeningeal disease were excluded. Reports that included patients with melanoma and clear cell renal cell carcinoma (ccRCC) BM were considered relevant if exclusively systemic therapeutic approaches were assessed. 408

[1]Department of Oncology, Clínica Universidad de Navarra, Pamplona, Spain. [2]University of Navarra, Center for Applied Medical Research, Program of Immunology and Immunotherapy, Pamplona, Spain. [3]IdiSNA, Navarra Institute for Health Research, Pamplona, Spain. [4]Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain. [5] Yale University School of Medicine and Yale Cancer Center, New Haven, Connecticut. [6] Department of Pathology, Clínica Universidad de Navarra, Pamplona, Spain. [7]Department of Pathology, Yale University School of Medicine, New Haven, Connecticut. [8]University of Navarra, Center for Applied Medical Research, Program of Solid Tumors, Pamplona, Spain.

I. Eguren-Santamaria and M.F. Sanmamed contributed equally as the co-first authors of this article.

R.S. Herbst and I. Gil-Bazo contributed equally as the co-senior authors of this article.

Corresponding Author: Ignacio Gil-Bazo, Clínica Universidad de Navarra, Pamplona 31008, Spain. Phone: 34-948-255-400; Fax 34-948-255-500; E-mail: igbazo@unav.es

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references were initially identified. After title/abstract assessment, 93 references were selected for full-text evaluation. After assessing reference lists and previously mentioned additional sources, a total of 90 publications were included.

Background on Systemic Treatment of Brain Metastases

Clinical observations that chemotherapy was less active in BM have been mainly attributed to poor passage across the blood–brain barrier (BBB). This CNS-specific anatomic structure composed of endothelial cells (with tight junctions between them), pericytes, and astrocytes, is intended to protect the brain from inflammation and other circulating noxa. However, it is believed that the BBB also limits the access of drugs to the brain parenchyma (6).

Drug access to the brain parenchyma is regulated by Starling's forces, binding to serum proteins, liposolubility, molecular weight, and local molecular biology (7). Traditionally, it has been thought that molecular size and solubility are critical for antitumor activity in the CNS (8, 9). In tumors, neovessels are thought to disrupt the physiologic characteristics of the BBB (the basis of contrast enhancement in MRI) and, presumably, increase the access of large molecules to the damaged brain parenchyma. However, the fact that CNS disease progression is common in patients under treatment with first-generation *EGFR* and *ALK* tyrosine kinase inhibitors (TKI; ref. 10), but patients can be rescued by next-generation highly penetrant inhibitors such as osimertinib (4) or alectinib (5), underscores that pharmacokinetics/pharmacodynamics (PK/PD) are still critical for the activity of drugs in the CNS.

Initial attempts to effectively treat BM from solid tumors tested small conventional cytostatic drugs, such as temozolomide, that had previously shown activity against glioblastoma. Results were discouraging: the response rate (RR) was 7% in melanoma BM and median progression-free survival (PFS) was 1.2 months (11). Slightly better results have been obtained in NSCLC BM with pemetrexed, which is estimated to reach a distribution that is up to 10% of that in plasma (12, 13). When pemetrexed is combined with carboplatin, brain RR can reach 40% (14). Other platinum-based combinations have obtained similar results (15), but response is generally short-lasting.

With the development of *EGFR* and *ALK* TKI, the role of systemic treatment for patients with oncogene-driven NSCLC with BM was significantly reinforced. Currently, with the development of third-generation oral TKI such as osimertinib and alectinib, which have shown meaningful activity in the CNS (16, 17), radiotherapy-sparing management has become a common practice in this patient population.

mAbs have traditionally been excluded when systemic treatment of BM was attempted due to their high molecular weight and low penetration through the BBB. Only a few clinical PK/PD studies have evaluated the penetration of mAbs into cerebrospinal fluid (CSF), a commonly accepted surrogate of drug distribution into the brain interstitium. Rituximab levels in the CSF, for instance, are between 0.1 and 0.7% of those in plasma (18, 19). In solid tumors, trastuzumab CSF levels show a CSF:plasma ratio of 1:420 (20). Interestingly, the ratio increased to 1:76 after brain radiotherapy. Considering clinical evidence, a prospective randomized clinical trial that compared the addition of trastuzumab or lapatinib to a taxane therapy observed that, despite PFS being significantly shorter for the lapatinib arm, CNS was the first site of progressive disease (PD) slightly more frequently in the trastuzumab group (21). This suggests that the anatomical peculiarities of the CNS probably influence the local activity of conventional tumor cell–targeted mAbs.

The novel class of mAbs, the immune checkpoint inhibitors (ICI), have revolutionized oncology practice in recent years, progressively permeating the therapeutic algorithms of many malignancies with high epidemiologic impact. Their novel mechanism of action, distinct from other tumor cell–targeted agents, has prompted research to evaluate anti-PD-1/anti-PD-L1 agents' activity in patients with NSCLC with CNS involvement. The mechanism of action theoretically relates to modified immune cell activity rather than direct action of these agents in the brain. Indeed recently, nivolumab CSF levels have also been measured in 5 patients with suspected leptomeningeal metastases from a variety of solid tumors. CSF:plasma ratios ranged from 1:52 to 1:299 (22), suggesting that local access of anti-PD-1 agents to the brain is not significantly different from that of other mAbs. Among them, the approval of anti-PD-1/anti-PD-L1 mAbs for advanced NSCLC is making an unprecedented difference on long-term survival for a significant proportion of patients (23–26). Their novel mechanism of action, distinct from other tumor cell–targeted agents, has prompted research to evaluate anti-PD-(L)1 agents' activity in patients with NSCLC with CNS involvement.

Rationale For the Use of ICI Against NSCLC BM

There are many critical biological features that distinguish the brain from other tissues; the composition of the extracellular matrix is distinctive, there are unique tissue-resident cells including microglia, astrocytes, and neurons, and it is physically protected from inflammation and drug delivery by the BBB (6). Therefore, the inflammatory tumor microenvironment of BM exhibits several unique factors compared with that of extracranial lesions. However, there is robust evidence to support that these factors do not exclude the brain parenchyma from active immune surveillance.

Unlike extracranial tumors, in which macrophages are among the most abundant nonmalignant cells in the infiltrate (27), ontogenetically different cells are represented within the infiltrate in tumors in the CNS; both conventional macrophages of myeloid origin and resident microglial cells (which diverge ontogenetically from the former prenatally) are present. According to a recent publication, monocyte-derived macrophages are more abundant than microglia in the NSCLC BM microenvironment (28). Myeloid macrophages can be recruited from peripheral blood under certain inflammatory conditions (29), while tissue resident microglia are thought to be capable of local self-renewal. Human microglia are represented by highly heterogeneous cell populations, with little transcriptomic similarities to peripheral M1/M2 phenotypes and only a subset expressing major histocompatibility complex (MHC) class II or costimulatory molecules CD80 or CD86 (30).

T-cell infiltration is widely accepted as a key component of adaptive cancer immune surveillance. Certainly, almost all relevant therapeutic advances in the field of immunotherapy have been achieved in so-called "hot" (inflamed) tumors, which are naturally infiltrated by tumor-infiltrating lymphocytes (TIL).

In normal brain parenchyma, low densities of lymphocytes (around 1 to 2 per mm^2) have been identified mainly in the perivascular Virchow–Robin spaces (31). However, under particular pathologic conditions, such as cancer, antigen-specific lymphocytes can extensively infiltrate the CNS. It is established that mediators of innate immunity such as TNFα, IL1, and IL6 can bind to brain microvascular endothelial cells and weaken the BBB (32). $CD4^+$ cells additionally

contribute to brain infiltration by other lymphocytes via local IFNγ production (32). In a series including 116 BM specimens from a variety of primary cancers (with lung cancer representing 53% of cases), high densities of $CD3^+$, $CD8^+$, and $CD45RO^+$ cells were associated with improved OS (33). However, it has been recently reported that T-cell densities were significantly lower in NSCLC BM compared to paired primary tumor specimens (28, 34). Comparable results indicating lower adaptive immune responses in brain metastases relative to primary human NSCLCs have been reported by our group using multiplexed immunofluorescence analysis for PD-L1 and major B- and T-cell populations (35). Representative histology preparations and multiplexed immunofluorescence images from a primary lung adenocarcinoma and the corresponding brain metastasis are shown in **Fig. 1**.

Although imperfectly, PD-L1 expression by immunohistochemistry (IHC) predicts clinical benefit from ICI. In advanced NSCLC, a tumor PD-L1 expression of ≥50% robustly favors first-line pembrolizumab over chemotherapy (26). Clinical trials evaluating anti-PD-L1 drugs confirm a dose–response relationship between PD-L1 tumor expression and clinical benefit from ICI, although the latter is not restricted to the PD-L1–positive (≥1%) population (23, 36). PD-L1 expression has been evaluated in NSCLC BM surgical resection specimens, showing that PD-L1 tumor expression (≥5%) is present in 22% to 33% of the samples (37–39). This proportion is similar to the 31% PD-L1 positivity (≥5%) reported in extracranial NSCLC metastases (36). To date, the largest series in which PD-L1 expression between BM and primary NSCLC was evaluated (73 patients) show a qualitative concordance in the level of PD-L1 expression between BM and primary tumors that is above 80% (39, 40). However, lower concordance rates have been reported in smaller heterogeneous cohorts, with a trend toward lower PD-L1 expression in the CNS than in primary tumors (41, 42).

The mechanism of action of ICI, which is not specifically dependent on close contact with all tumor cell foci, could lead to immune recognition in more accessible extracranial metastatic lesions and secondarily, immune cell trafficking could be responsible for producing an antitumor response in the CNS, as suggested by others (43). This would confirm preclinical findings suggesting T-cell priming in the extracranial compartment is essential for an effective immune response in the CNS (44). Moreover, recent discoveries of the presence of lymphatic vessels in the dura mater, which are potentially capable of allowing CNS antigen presentation in the peripheral lymph nodes (45), are altering our understanding of immune privilege in the CNS. In addition, activated $CD4^+$ T cells in the brain can loosen the BBB to

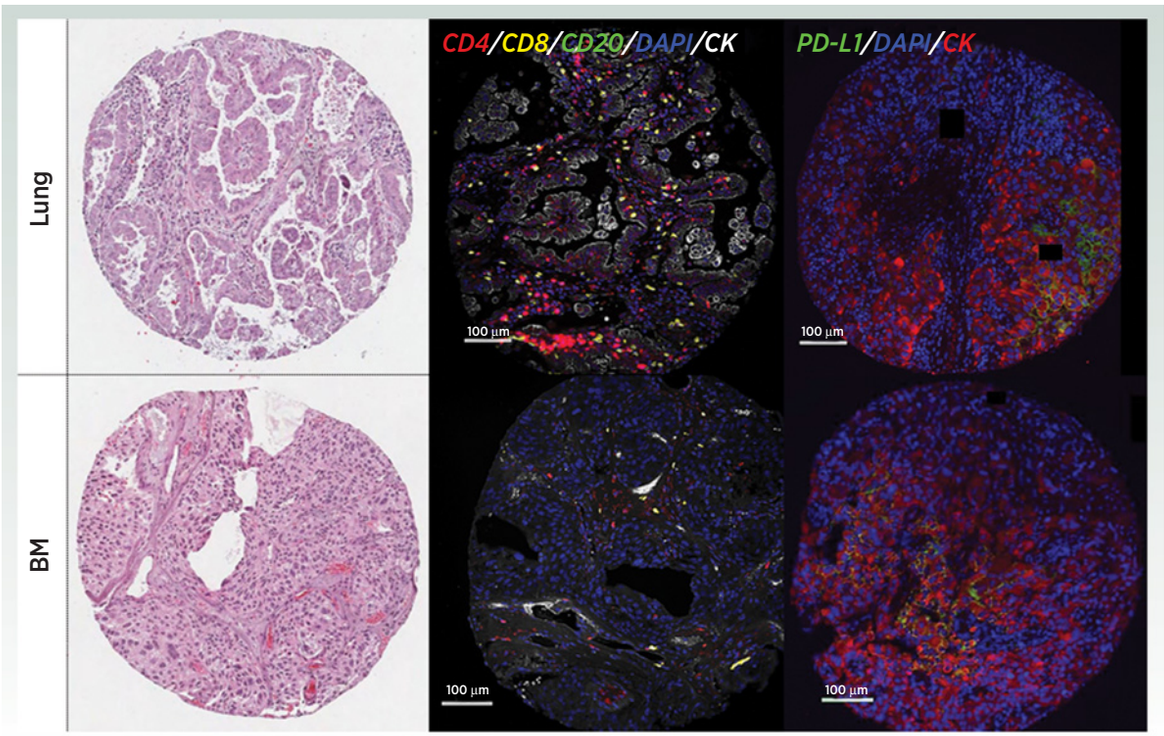

Figure 1.

Detection of TILs and PD-L1 expression in a primary lung tumor (Lung, top) and corresponding brain metastasis (BM, bottom). Representative microphotographs from tissue microarrays showing the histology features of hematoxylin & eosin–stained preparations (left) and levels/distribution of major B- and T-cell populations and PD-L1 protein using multiplexed immunofluorescence (center and right). The color code for each target in the fluorescence analysis is indicated within the panels. The histology aspect reveal reduced tumor differentiation of the brain lesion characterized by increased nuclear pleomorphism, reduction of acinar/glandular structures and a more solid architectural pattern. The stromal compartment shows marked reduction of immune cells and enhanced vascular structures. The immunofluorescence analysis shows prominent reduction of both $CD4^+$ helper and $CD8^+$ cytotoxic T cells in the metastatic lesion; and virtual absence of B cells. PD-L1 immunoreactivity was also lower in the secondary lesion and was localized predominantly in cytokeratin (CK)-positive tumor cells with membranous/cytoplasmic staining pattern. Left, H-E; middle, representative fluorescence pictures showing DAPI (blue), cytokeratin (CK, white), CD4 (red), CD8 (yellow), and CD20 (green) staining. Right, representative fluorescence pictures showing DAPI (blue), cytokeratin (CK, red), PD-L1 (green). Scale bar = 100 μm.

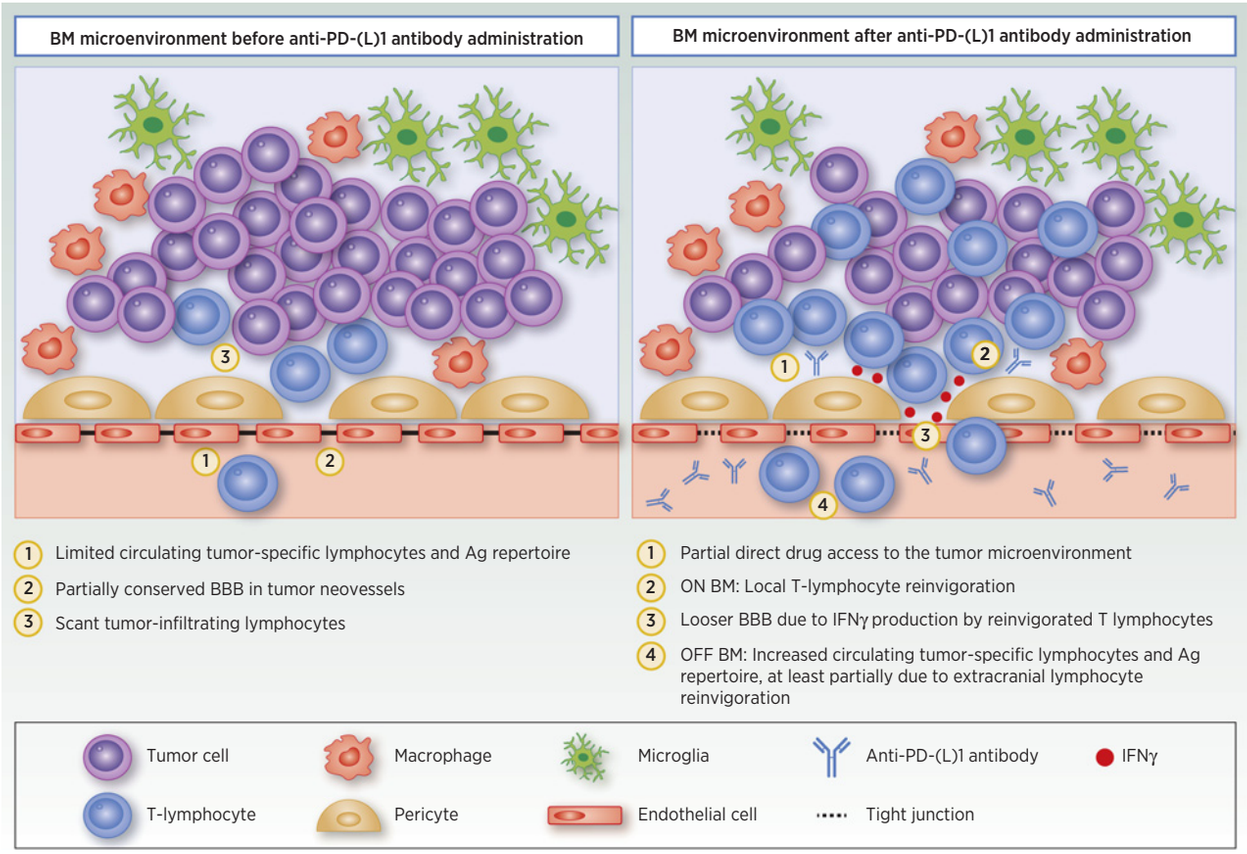

Figure 2.

Potentially relevant mechanisms of action of immune checkpoint inhibitors in the central nervous system (CNS). Lymphatic vessels in the dura mater are potentially capable of allowing CNS antigen presentation in the peripheral lymph nodes. In addition, activated $CD4^+$ T cells in the brain can loosen the BBB to circulating antibodies through local IFNγ production, a mechanism anti-PD-1/PD-L1 therapy could potentially enhance.

circulating antibodies through local IFNγ production (32), a mechanism anti-PD-1/PD-L1 therapy could potentially enhance. These potentially relevant mechanisms of action are summarized in **Fig. 2**.

The fact that immune surveillance in BM shares some similarities with that in extracranial tumors supports research to evaluate the role of ICI for the treatment of solid tumor BM. The active research that is being conducted in the field is reviewed here. Solid data regarding the activity of immune checkpoint inhibitors in patients with leptomeningeal involvement are lacking because clinical trials systematically exclude patients in this particular CNS involvement situation and only some retrospective studies and case reports have partially addressed this issue. Therefore, the current review focusses mainly on brain metastasis.

ICI for the treatment of active NSCLC BM

Proof-of-concept that ICI could be active against NSCLC BM was obtained from heterogeneous clinical studies that were conducted in patients with previously untreated BM or in patients with brain involvement that have progressed after previous local therapy. These two scenarios have been included under the "active" BM definition herein.

In 2016, Dudnik and colleagues reported a retrospective analysis of patients with NSCLC BM who remained asymptomatic and corticosteroid-free before nivolumab initiation (46). Five patients were included. Two intracranial responses were observed, which were maintained for up to 24 and 28 weeks. Notably, intracranial and systemic responses were largely concordant, except for one patient in whom stable CNS disease was associated with rapid systemic progression. No severe adverse events (AE) were attributed to treatment.

To date, the most robust evidence on the activity of ICI for the treatment of NSCLC BM comes from a phase II trial (NCT02085070) that included patients with melanoma and NSCLC (47). The published report included the first 18 patients with NSCLC and the first 18 patients with melanoma. BM had to be between 5 and 20 mm in diameter and patients had to be steroid-free and neurologically asymptomatic. In the NSCLC arm, inclusion was restricted to patients with PD-L1 positive (≥1%) tumors. PD-L1 expression was evaluated in tumor tissue from any site. Eight of the first 18 patients with NSCLC had received no prior local therapy for BM. Six of 18 patients (33%) achieved intracranial response. Systemic RR was 33%, with only 1 patient who progressed in the CNS while responding systemically. All other responses were concordant. Neurologic AEs in the NSCLC cohort were all grade ≤2. A recent update included data from 34 patients with PD-L1–positive tumors and 5 patients with PD-L1–negative disease. CNS RR was 10 of 34 (29.4%) in PD-L1–positive patients, with a median duration of response of 10.7 months. Discordance was observed between intracranial and systemic responses in 7 patients. Among these, four individuals experienced PD in the brain

and partial response (PR) systemically while the remaining 3 patients exhibited the opposite findings. Interestingly, no intracranial responses were observed among patients with PD-L1–negative tumors. Treatment was well tolerated, with no grade ≥2 treatment-related neurologic AEs reported (48). However, no patients with BM greater than 20 mm were included, and potentially worrying lesions were prophylactically treated with local therapy prior to trial entry (49).

After anti-PD-L1 mAbs were approved for the second-line treatment of advanced NSCLC, evidence from real-world data have been published, confirming that ICI show variable activity against untreated or previously treated progressing BM (50–54). Unfortunately, the majority of real-world experiences have been published as abstracts, and limited information is available making thorough analysis difficult.

A recently published pooled analysis of patients from seven European centers included patients with NSCLC treated with ICI in a variety of settings including daily standard practice (55). Among patients with active BM that were evaluable in the CNS ($n = 73$), the intracranial RR was 27.3%. Among the 23 patients with active BM and available PD-L1 expression status, positive PD-L1 expression (≥1%) was associated with a higher intracranial RR: 35.7% versus 11.1% in PD-L1–negative patients (55). In a multivariate analysis, BM was not significantly associated with PFS or OS. However, the presence of active BM was significantly associated with poorer survival within the BM subgroup (55).

The potential activity of exclusively ICI-based systemic treatment against BM has been confirmed in similarly designed clinical trials conducted in patients with melanoma (56–59). Nivolumab has also been evaluated in patients with ccRCC with active BM (60), with an activity that seems more modest than in melanoma.

Overall, preliminary data from patients with NSCLC and ccRCC, and more mature data from melanoma trials, suggest that intracranial response is more dependent on the immunogenicity of tumor cells than on the location of metastatic disease or BBB penetration (**Table 1**). There is considerable evidence to claim that in the subset of patients with metastatic NSCLC or melanoma who obtain clinical benefit from ICI's anticancer activity, clinical benefit extends to the intracranial compartment. Although there might be a perception showing that patients with CNS involvement from melanoma may obtain a significantly larger benefit from immunotherapy (**Table 1**), different clinical trials design and the more frequent combination regimens employed may perfectly explain that observation. In addition, also higher systemic response rates have been reported among patients with melanoma compared with NSCLC individuals.

Although data are still immature, it is expected that in highly selected patients with NSCLC, anti-PD-L1 agents can reach an activity that is sufficient to shift BM management algorithms toward progressively systemic-based approaches. If clinical and biological characteristics suggest ICI can be active in the CNS, patients with an increasing number of BM could be considered for stereotactic radiotherapy (SRT) instead of whole-brain radiotherapy (WBRT) and even radiotherapy-sparing strategies could be evaluated in carefully selected patients with a very favorable predictive profile. A therapeutic approach is proposed in **Fig. 3**, which integrates the currently available predictors of intracranial activity of anti-PD-(L)1 agents in NSCLC BM. However, until more robust clinical trials are conducted, patients with NSCLC with BM should be individually evaluated by multidisciplinary tumor boards in highly experienced centers.

ICI for stable NSCLC BM

In spite of the encouraging results reviewed above that challenge traditional notions of how anticancer drugs perform in the brain, the majority of patients will be affected by CNS disease progression. Because of the particular anatomic configuration of the CNS, in which tumor growth can be more detrimental than in any other anatomic region, combining local therapy (mainly radiotherapy) and systemic therapy should be carefully considered to increase the probability of obtaining local disease control and to avoid burdensome neurologic symptoms and clinical deterioration (61), particularly if systemic regimens have a low RR. The safety and activity of ICI in the subgroup of patients with previously irradiated and controlled BM have been reported in a number of pivotal advanced NSCLC clinical trials.

A pooled analysis included data from five clinical trials with advanced NSCLC patients that were treated with atezolizumab. In the safety cohort ($n = 1{,}452$), serious neurologic AE incidence was higher in patients with BM compared with those without BM (6 vs. 3%), but none reached grade 4 (62). An efficacy subgroup analysis of patients with BM included in the OAK trial (23) confirmed that atezolizumab was superior to docetaxel in terms of delaying the appearance of new symptomatic BM [HR, 0.38; 95% confidence interval (CI): 0.16–0.91; ref. 63].

Real-world data from a nivolumab expanded access program have been reported in recent years including patients with squamous and nonsquamous NSCLC. A total of 38 patients with squamous NSCLC and asymptomatic and controlled BM were included. With a median follow-up of 4.5 months, 1 patient obtained complete response (CR), 6 reached partial response (PR), and 11 stable disease (SD; ref. 64). The authors did not specify whether responses were intracranial or systemic. Only one patient discontinued treatment due to AEs. Among the patients with nonsquamous NSCLC ($n = 409$), the authors compared overall response and survival outcomes between patients with BM and all patients included in the program ($n = 1{,}588$). Overall RR was 17% in patients with BM and 18% in the entire cohort. Median PFS and OS was 3 and 8.6 months, respectively, in patients with BM, and 3 and 11.3 months, respectively, in the entire cohort. No relevant safety differences were reported between both groups. Previously mentioned reports have included an advanced NSCLC population that predominantly included patients with controlled BM, but their relevance is limited due to their retrospective design, limited sample sizes, and patient heterogeneity (50, 51, 54, 65). Some reports, however, suggest that brain RR in the real-world setting might be lower than in the more selective clinical trial population (41).

The innovative combination of platinum-based chemotherapy and pembrolizumab has also been evaluated in NSCLC patients with BM. The pivotal phase III trial KEYNOTE-189 included patients with previously treated stable and untreated asymptomatic BM (with no lesions larger than 1.5 cm; ref. 66). It has been recently reported that the benefit of the combination in terms of PFS and OS was confirmed in the subgroup of patients with BM: HR (95% CI) of 0.42 (0.27–0.67) and 0.41 (0.24–0.67), respectively. Notably, the magnitude of benefit attributable to the addition of pembrolizumab was higher in patients with BM than in those without CNS involvement (67). A real-world retrospective cohort experience with the same combination of drugs reported similar results (68).

Cranial irradiation therapy and PD-1/PD-L1 inhibition

The preliminary reports on the activity of ICI in the CNS are encouraging, and suggest that when patients are given systemic immunotherapy, the brain should not be considered a fully protected biological sanctuary. However, even in the most favorable scenarios

Table 1. Clinical studies evaluating anti-PD1 and/or anti-CTLA-4 therapy in progressing brain metastases.

Reference	Study type	Tumor	Patients	Drug	N	CNS RR	Extracranial RR	Concordance	CNS worse to better ratio*
Dudnik 2016 (46)	Retrospective real-world data	NSCLC 3/5 ADC	CNS-asymptomatic Steroid-free Minimum BM diameter: 5 mm 3/5 previous CNS RT	Nivolumab	5	2/5	2/5	4/5[a]	0:1
Gauvain 2018 (50)	Retrospective real-world data	NSCLC	NR	Nivolumab	16	2/16	NR	NR	NR
Henon 2017 (51)	Retrospective real-world data	NSCLC	NR	Not specified	15[b]	4/15	NR	NR	NR
Geier 2018(52)	Retrospective real-world data	NSCLC	NR	Nivolumab	29	3/29	NR	NR	NR
Ashinuma 2017 (53)	Retrospective real-world data	NSCLC	NR	Not specified	4	1/4	NR	NR	NR
Watanabe 2017 (54)	Retrospective real-world data	NSCLC	NR	Nivolumab	4	0/4 (1/4 SD)	NR	NR	NR
Afzal 2018 (68)	Retrospective real-world data	Non-squamous NSCLC	NR	Pembrolizumab + Carboplatin + Pemetrexed	3	NR	1/3	NR	NR
Hendriks 2019 (55)	Pooled mainly-observational data	NSCLC All[c] NSCLC (PD-L1<1%) NSCLC (PD-L1≥1%)	Active BM	Anti-PD-(L)1 ± anti-CTLA-4	73[c] 9 14	20/73 1/9 5/14	NR	NR	NR
Goldberg 2016 (47)	Phase II	NSCLC (PD-L1≥1%) 78% ADC	CNS-asymptomatic Steroid-free BM 5-20 mm 72% ≥1 previous systemic therapy 56% previous local CNS therapy	Pembrolizumab	18	6/18	6/18[d]	8/9 systemic responders	1:0
		Melanoma	CNS-asymptomatic Steroid-free BM 5–20 mm		18	4/18	4/18		
Goldberg 2018 (48)	Phase II (update)	NSCLC (PD-L1≥1%) NSCLC (PD-L1<1%)	(see above) 69% ≥1 previous systemic therapy	Pembrolizumab	34 5	10/34 0/5	NR	27/34 NR	4:3 NR
Kluger 2018 (57)	Phase II (update)	Melanoma	(see Goldberg 2016 above) 69% ≥1 prior systemic therapy 57% prior ipilimumab 78% prior local CNS treatment	Pembrolizumab	23	6/23	7/23	14/15 patients evaluable in the CNS[e]	1:0[d]
Margolin 2012 (56)	Phase II	Melanoma	CNS-asymptomatic Steroid-free Previous CNS RT: 41%	Ipilimumab	51	7/51	7/51	NR	NR
			CNS symptoms Stable steroids Previous CNS RT: 48%		21	1/21	1/21		
Long 2018 (58)	Phase II	Melanoma BM 5–40 mm	CNS-asymptomatic Steroid-free	Nivolumab + Ipilimumab	35	16/35	24/53[f]	37/42[g]	5:0
			No previous local therapy	Nivolumab	25	5/25			
			CNS symptoms, Leptomeningeal disease OR failed previous local therapy	Nivolumab	16	1/16	NR	NR	NR

(Continued on the following page)

Table 1. Clinical studies evaluating anti-PD1 and/or anti-CTLA-4 therapy in progressing brain metastases. (Cont'd)

Reference	Study type	Tumor	Patients	Drug	N	CNS RR	Extracranial RR	Concordance	CNS worse to better ratio*
Tawbi 2018 (59)	Phase II	Melanoma	CNS-asymtomatic Steroid-free	Nivolumab + Ipilimumab	94[h]	52/94	47/94	12/33 of patients with PD as BOR	17:4 patients with PD as BOR
		PD-L1<1%	BM 5–30 mm		34	17/34			
		PD-L1 1-5%	No previous RT to target BM		16	6/16			
		PD-L1≥5%	91% No previous CNS SRT		25	18/25			
Flippot 2019 (60)	Phase II	ccRCC	CNS-asymptomatic Steroid-free	Nivolumab	39	4/34[i]	7/33[g]	25/31[g]	4:2
		PD after anti-VEGFR therapy	Median sum of target BM diameters: 11 mm						
		76% ≥1 IMDC score	Minimum BM diameter: 5 mm						

Note: *Ratio was calculated between discordant patients with worse BOR in the CNS than extracranially to discordant patients with the opposite scenario.
Abbreviations: ADC, adenocarcinoma; BOR, best overall response; ccRCC, clear cell renal cell carcinoma; NR, not reported; PD, progressive disease; RR, response rate.
[a]In the one discordant patient, CNS stable disease was associated with extracranial disease progression.
[b]Only 15/36 patients with CNS involvement were evaluable. According to the publication, a nonspecified number of patients might have received CNS RT the month before immunotherapy initiation.
[c]PD-L1 expression was available only in 23 of 73 patients.
[d]One unconfirmed partial responder.
[e]The discordant patient showed PD in the brain and mixed response in extracerebral sites with unequivocal progression of non-target lesions.
[f]7/60 patients had CNS-exclusive metastatic disease.
[g]Among the 42 patients with both CNS and extracranial metastases who were evaluable from week 12. CR/PR in one anatomical region and PD in the other defined discordance in this study.
[h]PD-L1 was evaluated in 75/94 patients.
[i]Only 34/39 and 33/39 patients could be evaluated in the brain and in the extracranial compartment, respectively. Overall, 31/39 patients were evaluable in both compartments.

such as first-line pembrolizumab for patients with PD-L1 expression ≥50% or its combination with platinum-based chemotherapy, RR lie below 50% (26, 66). In both settings, however, (first-line pembrolizumab monotherapy or first-line pembrolizumab combined with chemotherapy), immunotherapy has shown to be active against CNS involvement, as discussed previously. Nevertheless, until more active immunotherapeutic agents are developed, the brain continues to be an extremely fragile organ in which the best of anticancer treatment modality combinations are often required to avoid symptomatic local PD. Currently, this means combining radiotherapy and systemic treatment for the vast majority of patients with NSCLC BM and no target mutations. In this scenario, the approval of anti-PD-1/PD-L1 mAbs for advanced NSCLC raises questions about the optimal radiation modality and timing relative to ICI administration that should be offered to patients with NSCLC BM.

There is a strong rationale behind the combination of radiotherapy and ICI, both preclinical and clinical. Before the era of clinical cancer immunotherapy, the abscopal effect reported anecdotally suggested that the response of tumors distant from the irradiation field could be immune-mediated (69). This hypothesis was supported by loss- and gain-of-function experiments using T-cell–deficient athymic nude mice and dendritic cell enhancers, respectively (70). Some preliminary reports suggest that immune enhancers can significantly contribute to abscopal responses in patients with a variety of solid cancers (71), but results from confirmatory trials combining modern ICI and radiotherapy in BM patients are awaited. Moreover, additional complexity is conferred to trial design by the fact that preclinical and clinical data suggest that appropriate timing and dosing of irradiation might be critical for the induction of an effective antitumor immune response (72, 73).

Synergism or additivity with ICI and radiation can be assessed in the CNS. Increased PD-L1 expression in surgically resected BM specimens after radiation, for instance, supports this potential interplay (37). Interestingly, a variety of retrospective analyses from observational studies have suggested that the combination of radiotherapy and ICI could have a positive impact on patient survival over exclusively systemic treatment (74–76).

Data regarding the best brain radiotherapy modality and timing relative to ICI administration remain scarce. Initial case reports supported the rationale behind the concern that the peculiar PK/PD of ICI, which are highly dependent on the immune infiltration by cytotoxic T lymphocytes (CTLs), and the anatomic configuration of CNS could lead to neurologic toxicity (77).

Multiple reports suggest that treatment with anti-PD-1 mAbs could exacerbate symptomatic RN (57, 78, 79). Pathologic examination of surgical samples reveals extensive necrosis with residual tumor cells surrounded by an area with signs of active vasculitis (predominantly infiltrated by CD3+ and CD68+ cells), blood vessel hyalinization and astrocytosis (78). Findings are often hardly distinguishable from previously reported radiation-induced vasculitic leukoencephalopathy associated with radiosurgery alone (80). An immune infiltration analysis from a surgically removed BM of a patient who developed RN during treatment with pembrolizumab is provided in **Fig. 4**. Although clear vasculitis was not described in this case, the observed dense immune infiltration consisting predominantly of T lymphocytes, which is consistent with previous reports (78), suggests ICI could potentially exacerbate RN.

The largest series of NSCLC patients treated with a variety of radiation modalities and timings relative to ICI was recently published. Safety data were reported from patients with NSCLC BM who received brain irradiation therapy and anti-PD-1/PD-L1 antibodies at any time

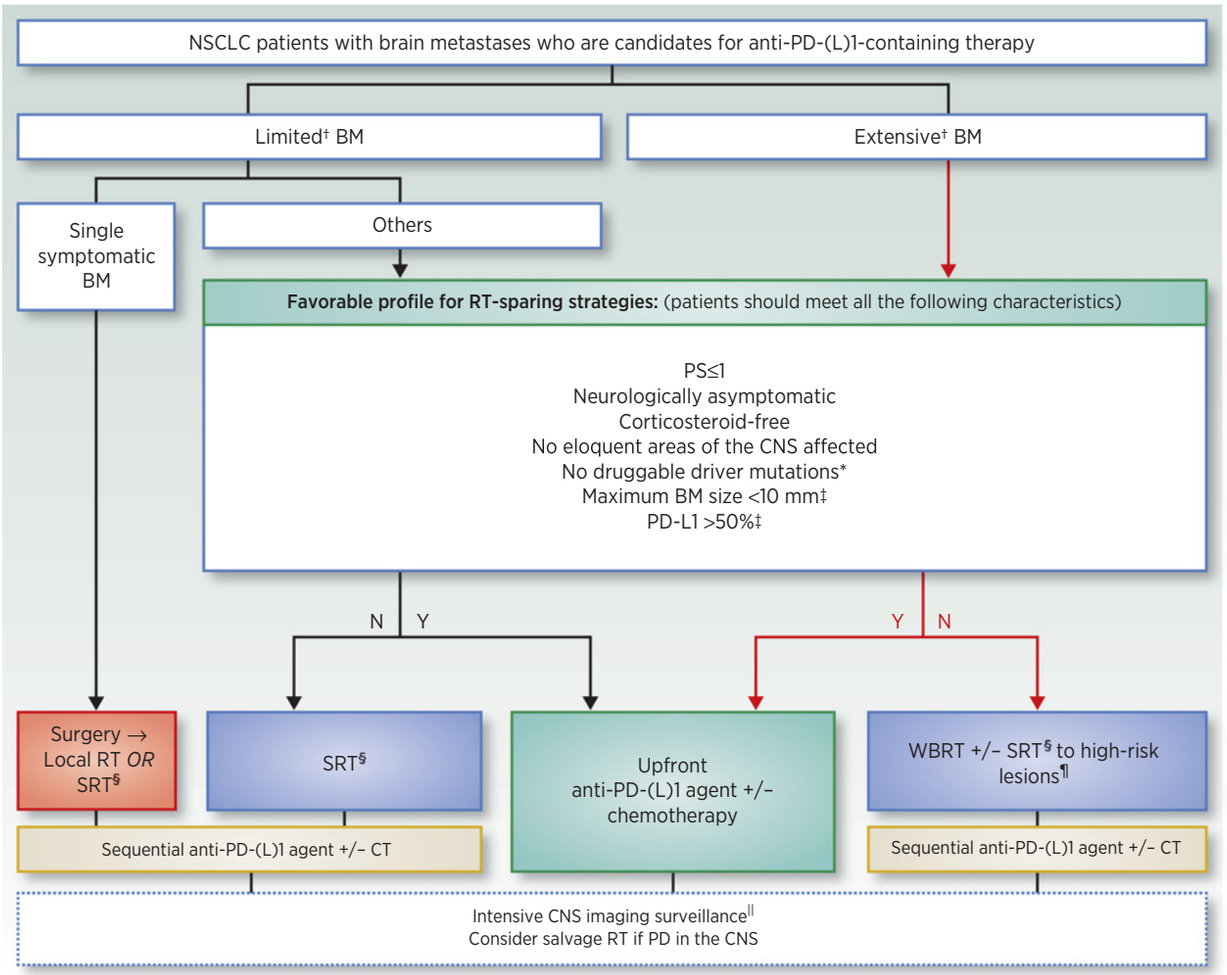

Figure 3.

A proposal for the management of patients with NSCLC with BM who are candidates for anti-PD-(L)1–containing systemic therapy. This algorithm considers patients who are candidates for an anti-PD-(L)1–containing systemic therapy after the standard tumor specimen evaluation (*EGFR, ALK, ROS1*, and *BRAF* V600E status evaluation and PD-L1 IHC expression; standard algorithm not reproduced here) regardless of treatment line and origin of the tumor sample. *With the exception of *BRAF* mutations. Although further validation is needed, if emerging negative genomic predictors of benefit from anti-PD-(L)1 agents (e.g., *STK11* and/or *KEAP1*) are found, therapeutic strategies that include local BM treatment are encouraged; †, Limited/extensive terms are used to classify patients according to the number of BM following the National Comprehensive Cancer Network (NCCN) Guidelines. However, we suggest than the threshold between limited and extensive CNS involvement should be considered indicative. Patients with a higher number of BM could be treated with SRT strategies in centers with appropriate experience; ‡, The values are considered indicative. The final therapeutic decision should be made by a multidisciplinary thoracic tumor board. §, We suggest that hypofractionated SRT rather than single-fraction SRS should be considered to decrease the risk of radionecrosis (RN). ¶, High-risk BM are defined by any of the following characteristics: symptomatic, >20 mm or location in an eloquent area. ‖, We recommend MRI 2 months after treatment initiation, preferably with perfusion sequences. CT, chemotherapy; PS, performance status.

and compared to similar patients who were anti-PD-1/PD-L1-naïve (81). In this retrospective single-center analysis, subgroups were designated by radiotherapy modality (SRS, partial brain irradiation, or WBRT) and timing according to systemic anti-PD-1/PD-L1 antibody administration (previous, concurrent, and subsequent). In addition to common AEs, a category was recorded to specifically evaluate the occurrence of symptomatic image worsening that resolved with no significant changes in treatment or was confirmed malignancy-free on histopathologic evaluation. No statistically significant differences were observed between patients who received ICI and those who did not according to radiation modalities or timing (81). Another retrospective report from a small series has supported that the neurologic toxicity of combining ICI and brain radiotherapy is manageable, with no patients undergoing surgical resection for symptomatic radionecrosis among 17 patients who received SRT and nivolumab or durvalumab (82). However, a recently published retrospective evaluation comparing the incidence of symptomatic radionecrosis in patients ($n = 480$) treated with brain SRT for metastatic NSCLC ($n = 294$), melanoma, or RCC who received ICI (including ipilimumab; $n = 115$) and in those who did not (ICI-naïve), treatment with ICI was significantly associated with an increased risk of symptomatic radionecrosis regardless of tumor histology. Notably, a tendency toward increased symptomatic radionecrosis remained, but statistical significance was not reached when patients who received ipilimumab were excluded from the

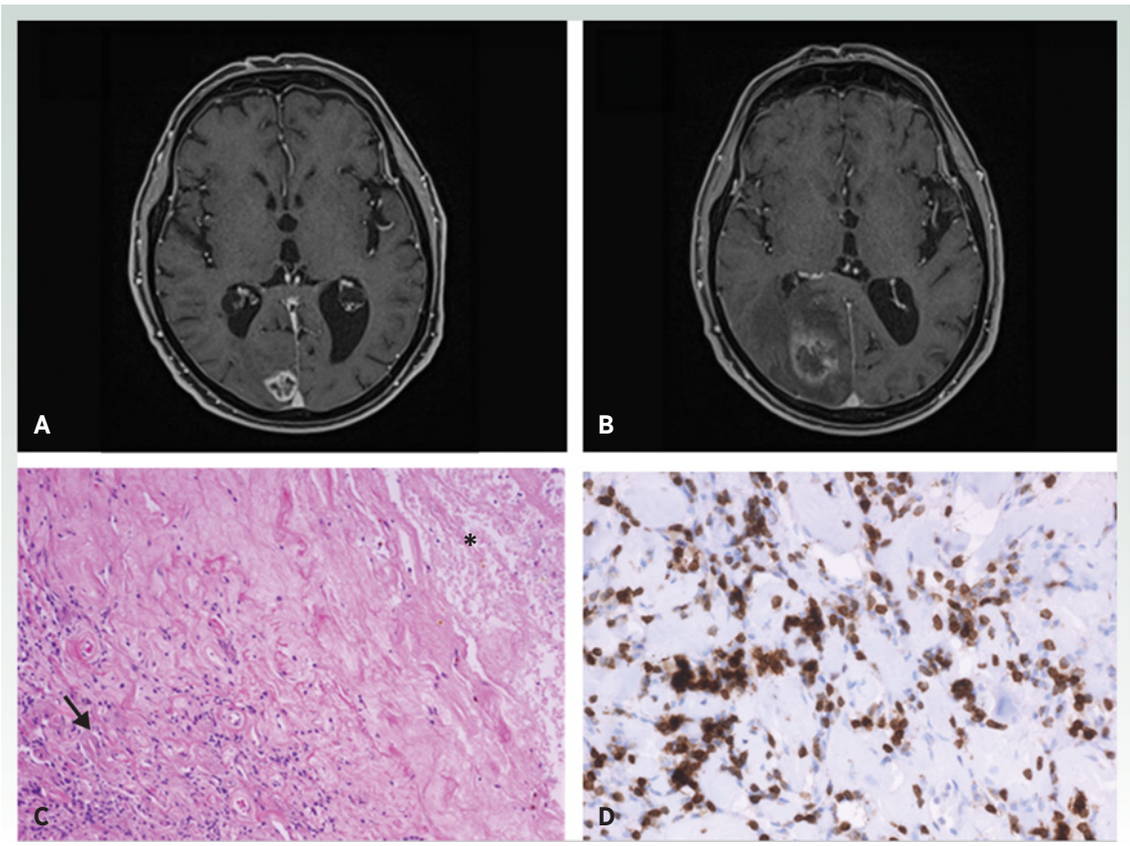

Figure 4.

Predominantly perivascular T-cell infiltration of a surgically resected radionecrosis (RN) lesion. A 75-year-old man was diagnosed with an *ALK*-driven cT2N2M1b lung adenocarcinoma. Metastatic involvement at initial diagnosis was limited to four BM. He received SRS (18 Gy, single fraction) on two of them and IMRT (42 Gy in 12 fractions) on the remaining two (including the right occipital metastasis). Anti-*ALK* therapy was initiated but permanent discontinuation was required due to hepatitis. At that point, a brain MRI showed SD in the CNS (**A**). Due to intolerance to two *ALK* inhibitors and high PD-L1 expression in a mediastinal node sample (>50%), pembrolizumab was started. After two cycles, the patient presented worsening of functional status and mild episodes of disorientation. Physical examination revealed left homonymous hemianopsia. CT revealed SD in the thorax but brain MRI revealed a significant increase of the right occipital BM (**B**). The remaining three BM were stable. A surgical resection was performed. The pathological examination revealed coagulative necrosis [**C**, (*)], thickened blood vessels surrounded by $CD3^+$ lymphocytes [**C** (arrow), **D**], and areas with foamy macrophages and necrotic cytokeratin AE1/AE3-positive tumor cells. Intense GFAP-positive gliosis was described. Findings were compatible with radionecrosis. Three months later, he developed brain PD (elsewhere in the brain). Alectinib was initiated. Tolerance was good: only grade-1 transaminase elevation. He has obtained SD in the thorax and PR in the brain. The patient remains progression-free 19 months later. Histologic images were obtained with ×200 magnification.

analysis (83). Of note, the median time of radionecrosis occurrence after SRT in patients treated with immunotherapy has consistently been reported to be above 10 months (57, 79). Therefore, the prolonged survival experienced by patients treated with ICI could have biased the increased radionecrosis incidence reported in these patients compared with other systemic treatment modalities. An innovative clinical trial (NCT02681549) that is currently recruiting patients with melanoma and NSCLC BM will evaluate whether bevacizumab in combination with pembrolizumab is capable of reducing brain edema and radionecrosis incidence while potentially synergizing with immune cell trafficking (57).

Radionecrosis can affect up to 30% of patients who have received ICIs (57), with incidences between 7% and 20% when symptomatic radionecrosis is specifically reported (83, 84). This phenomenon challenges treating physicians to establish a correct diagnosis between treatment-related changes (both pseudoprogression and radionecrosis) and true PD. Some recently published brain response evaluation criteria have incorporated the clinical status of the patient and corticosteroid use into decision algorithms to differentiate pseudoprogression from PD (49, 85). In addition, because tumor growth due to pseudoprogression is expected to be transient, several cooperative groups have suggested repeated imaging after initial radiologic PD to enhance the identification of patients who will ultimately benefit from ICI (86). The immune Response Evaluation Criteria in Solid Tumors (iRECIST) and the immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria have stressed the importance of repeated imaging, preferably at least 4 weeks or 3 months after first image evaluation that met radiologic PD criteria, respectively, to discriminate between true PD or pseudoprogression (85). The third diagnostic possibility, radionecrosis, has also been described as a transient image worsening that is followed by regression or stability (79, 87), suggesting that active imaging surveillance strategies might also be appropriate when radionecrosis is suspected. Complementarily,

imaging techniques such as positron emission tomography and magnetic resonance spectroscopy and perfusion imaging have been evaluated to differentiate PD from radionecrosis, but noninvasive diagnosis remains uncertain (88). Tumor response evaluation criteria that require PD confirmation are encouraged in both clinical trials and daily practice. From a therapeutic perspective, clinical trials are strongly encouraged to develop novel therapeutic strategies for radionecrosis (e.g., bevacizumab) that could contribute to limiting the immunosuppressive effects associated with first-line corticosteroids (89). Interestingly enough, some previous evidence has shown that bevacizumab may actually have the potential to prevent brain metastases in patients with nonsquamous NSCLC (90). Complementarily, some authors have suggested that the minimum diameter of a BM to be considered measurable should be lowered to 5 mm (using high-resolution MRI with a slice thickness of ≤2 mm for a reliable response assessment) to allow trial inclusion of patients with small BM in which ICI have shown promising activity (49).

Conclusions

The unique PK/PD of ICI are challenging the traditional idea that mAbs are marginally active against BM. There is encouraging preliminary evidence to support the development of clinical trials in which this treatment modality is evaluated alone or combined with radiotherapy. On the basis of the currently available evidence, anti-PD-1/PD-L1 agents play a relevant role when long-term disease control is attempted in the CNS of patients with advanced NSCLC. However, predictive selection criteria are required to identify individuals with the greatest probability of response to anti-PD-(L)1 agents. In these carefully selected patients, SRT can be favored over WBRT or radiotherapy-sparing strategies can be considered, although these approaches require confirmation in more robust clinical trials.

Despite the encouraging activity of ICI in the CNS, regimens with greater activity than anti-PD-1/PD-L1 monotherapy are urgently needed, and prospective trials in patients with NSCLC BM are warranted. Improved imaging modalities are needed to differentiate between radionecrosis, pseudoprogression, and tumor regrowth in previously irradiated lesions to identify patients who will ultimately obtain clinical benefit from the systemic delivery of ICI.

Disclosure of Potential Conflicts of Interest

S.B. Goldberg is a paid consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Bristol-Myers Squibb, Genentech, Amgen, and Spectrum, and reports receiving commercial research grants from AstraZeneca and Boehringer Ingelheim. H.M. Kluger reports receiving commercial research grants from Apexigen, Bristol-Myers Squibb, and Merck, is an unpaid consultant/advisory board member for Nektar, Biodesix, Roche-Genentech, Iovance, Immunocore, Celldex, Array Biopharma, Merck, and Elevate Bio, and reports receiving other remuneration from Pfizer. J. Corral reports receiving speakers bureau honoraria from Pfizer, Bristol-Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Roche, MSD, and AstraZeneca, and is an unpaid consultant/advisory board member for AstraZeneca, Pfizer, Bristol-Myers Squibb, Roche, Eli-Lilly, MSD, and Boehringer-Ingelheim. K.A. Schalper is a paid consultant for AstraZeneca, Clinica Alemana de Santiago, Dynamo Therapeutics, EMD Serono, Merck, Moderna, Pierre Fabre, Shattuck Labs, Takeda, Torque Therapeutics, Ono Pharmaceuticals, Agenus, Abbvie, and Celgene, reports receiving commercial research grants from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, Moderna, Navigate Biopharma, Pierre Fabre, Surface Oncology, Takeda, and Tesaro, and reports receiving speakers bureau honoraria from Bristol Myers Squibb, Merck, Fluidigm, and PeerView. R.S. Herbst is a paid consultant for Abbvie Pharmaceuticals, ARMO Biosciences, AstraZeneca, Biodesix, Bolt Biotherapeutics, Bristol-Myers Squibb, Eli Lilly and Company, EMD Serono, Genentech/Roche, Genmab, Halozyme, Heat Biologics, IMAB Biopharma, Immunocore, Infinity Pharmaceuticals, Loxo Oncology, Merck and Company, Midas Health Analytics, Mirati Therapeutics, Nektar, Neon Therapeutics, NextCure, Novartis, Pfizer, Sanofi, Seattle Genetics, Shire PLC, Symphogen, Takeda, Tesaro, Tocagen, Spectrum Pharmaceuticals, and Junshi Pharmaceuticals, and reports receiving commercial research grants from AstraZeneca, Eli Lilly and Company, Genentech/Roche, and Merck and Company. I. Gil-Bazo reports receiving speakers bureau honoraria from AstraZeneca, Bristol-Myers Squibb, Roche, Guardant Health, MSD, Boehringer Ingelheim, and Eli Lilly. No potential conflicts of interest were disclosed by the other authors.

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References

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the metropolitan detroit cancer surveillance system. J Clin Oncol 2004;22:2865–72.
2. Shaw AT, Kim TM, Crinò L, Gridelli C, Kiura K, Liu G, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2017;18:874–86.
3. Abrey LE. Inclusion of patients with brain metastases in clinical trials. Editor Clin Invest 2011;1:1065–8.
4. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum–pemetrexed in *EGFR* T790M–positive lung cancer. N Engl J Med 2017;376:629–40.
5. Novello S, Mazières J, Oh I-J, de Castro J, Migliorino MR, Helland Å, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann Oncol 2018;29:1409–16.
6. Quail DF, Joyce JA. The microenvironmental landscape of brain tumors. Cancer Cell 2017;31:326–41.
7. Dewhirst MW, Secomb TW. Transport of drugs from blood vessels to tumour tissue. Nat Rev Cancer 2017;17:738–50.
8. Pardridge WM. Drug Transport across the Blood–Brain Barrier. J Cereb Blood Flow Metab 2012;32:1959–72.
9. Ballard P, Yates JWT, Yang Z, Kim D-W, Yang JC-H, Cantarini M, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clin Cancer Res 2016;22:5130–40.
10. Costa DB, Shaw AT, Ou S-HI, Solomon BJ, Riely GJ, Ahn M-J, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. J Clin Oncol 2015;33:1881–8.
11. Agarwala SS, Kirkwood JM, Gore M, Dreno B, Thatcher N, Czarnetski B, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. J Clin Oncol 2004;22:2101–7.
12. Dai H, Chen Y, Elmquist WF. Distribution of the novel antifolate pemetrexed to the brain. J Pharmacol Exp Ther 2005;315:222–9.
13. Bearz A, Garassino I, Tiseo M, Caffo O, Soto-Parra H, Boccalon M, et al. Activity of pemetrexed on brain metastases from non-small cell lung cancer. Lung Cancer 2010;68:264–8.

14. Bailon O, Chouahnia K, Augier A, Bouillet T, Billot S, Coman I, et al. Upfront association of carboplatin plus pemetrexed in patients with brain metastases of lung adenocarcinoma. Neuro Oncol 2012;14:491–5.
15. Cortes J, Rodriguez J, Aramendia JM, Salgado E, Gurpide A, Garcia-Foncillas J, et al. Front-line paclitaxel/cisplatin-based chemotherapy in brain metastases from non-small-cell lung cancer. Oncology 2003;64:28–35.
16. Soria J-C, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated *EGFR*-mutated advanced non–small-cell lung cancer. N Engl J Med 2018;378:113–25.
17. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W, et al. Alectinib versus crizotinib in untreated *ALK*-positive non–small-cell lung cancer. N Engl J Med 2017;377:829–38.
18. Rubenstein JL, Combs D, Rosenberg J, Levy A, McDermott M, Damon L, et al. Rituximab therapy for CNS lymphomas: targeting the leptomeningeal compartment. Blood 2003;101:466–8.
19. Larouche J-F, Bergeron M, Hampson G, Illidge T, Delage R. Rituximab cerebrospinal fluid levels in patients with primary central nervous system lymphoma treated with intravenous high dose rituximab. Blood 2011;118:1644.
20. Stemmler H-J, Schmitt M, Willems A, Bernhard H, Harbeck N, Heinemann V. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood–brain barrier. Anticancer Drugs 2007;18:23–8.
21. Gelmon KA, Boyle FM, Kaufman B, Huntsman DG, Manikhas A, Di Leo A, et al. Lapatinib or trastuzumab plus taxane therapy for human epidermal growth factor receptor 2-positive advanced breast cancer: final results of NCIC CTG MA.31. J Clin Oncol 2015;33:1574–83.
22. Pluim D, Ros W, van Bussel MTJ, Brandsma D, Beijnen JH, Schellens JHM. Enzyme linked immunosorbent assay for the quantification of nivolumab and pembrolizumab in human serum and cerebrospinal fluid. J Pharm Biomed Anal 2019;164:128–34.
23. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, Von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255–65.
24. Vokes EE, Ready N, Felip E, Horn L, Burgio MA, Antonia SJ, et al. Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. Ann Oncol 2018;29:959–65.
25. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540–50.
26. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016;375:1823–33.
27. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity 2014;41:49–61.
28. Kudo Y, Haymaker C, Zhang J, Reuben A, Duose DY, Fujimoto J, et al. Suppressed immune microenvironment and repertoire in brain metastases from patients with resected non-small cell lung cancer. Ann Oncol 2019;30:1521–30.
29. Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. Nat Rev Immunol 2011;11:762–74.
30. Wolf SA, Boddeke HWGM, Kettenmann H. Microglia in physiology and disease. Annu Rev Physiol 2017;79:619–62.
31. Smolders J, Heutinck KM, Fransen NL, Remmerswaal EBM, Hombrink P, ten Berge IJM, et al. Tissue-resident memory T cells populate the human brain. Nat Commun 2018;9:4593.
32. Iwasaki A. Immune regulation of antibody access to neuronal tissues. Trends Mol Med 2017;23:227–45.
33. Berghoff AS, Fuchs E, Ricken G, Mlecnik B, Bindea G, Spanberger T, et al. Density of tumor-infiltrating lymphocytes correlates with extent of brain edema and overall survival time in patients with brain metastases. 2015;5: e1057388.
34. Mansfield AS, Ren H, Sutor S, Sarangi V, Nair A, Davila J, et al. Contraction of T cell richness in lung cancer brain metastases. Sci Rep 2018;8:2171.
35. Lu BY, Gupta R, Wyatt H, Ribeiro M, Stewart T, Chiang V, et al. Quantitative evaluation of tumor-infiltrating lymphocyte subsets and PD-L1 expression in lung cancer brain metastases. 2018 SITC Annu Meet 2018;Poster P84. November 7–11; Walter E. Washington Convention Center; Washington, D.C.
36. Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, et al. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). J Clin Oncol 2017;35:3924–33.
37. Takamori S, Toyokawa G, Okamoto I, Takada K, Kinoshita F, Kozuma Y, et al. Clinical significance of PD-L1 expression in brain metastases from non-small cell lung cancer. Anticancer Res 2018;38:553–7.
38. Berghoff AS, Inan C, Ricken G, Widhalm G, Dieckmann K, Birner P, et al. Tumor-infiltrating lymphocytes (TILS) and PD-L1 expression in non-small cell lung cancer brain metastases (BM) and matched primary tumors (PT). Ann Oncol 2014;25(suppl_4):iv465–6.
39. Mansfield AS, Aubry MC, Moser JC, Harrington SM, Dronca RS, Park SS, et al. Temporal and spatial discordance of programmed cell death-ligand 1 expression and lymphocyte tumor infiltration between paired primary lesions and brain metastases in lung cancer. Ann Oncol 2016;27: 1953–8.
40. Kündig A, Fung C, Scherz A, Ochsenbein A, Herrmann E, Ermis E, et al. PD-L1 expression (SP263) in lung cancer and paired brain metastases – a single center study in 211 patients. J Thorac Oncol 2019;14:S440.
41. Kim R, Keam B, Kim S, Kim M, Kim SH, Kim JW, et al. Differences in tumor microenvironments between primary lung tumors and brain metastases in lung cancer patients: therapeutic implications for immune checkpoint inhibitors. BMC Cancer 2019;19:19.
42. Wang H, Agulnik J, Kasymjanova G, Fiset PO, Camilleri-Broet S, Redpath M, et al. The metastatic site does not influence PD-L1 expression in advanced non-small cell lung carcinoma. Lung Cancer 2019;132:36–8.
43. Crinò L, Bronte G, Bidoli P, Cravero P, Minenza E, Cortesi E, et al. Nivolumab and brain metastases in patients with advanced non-squamous non-small cell lung cancer. Lung Cancer 2019;129:35–40.
44. Taggart D, Andreou T, Scott KJ, Williams J, Rippaus N, Brownlie RJ, et al. Anti–PD-1/anti–CTLA-4 efficacy in melanoma brain metastases depends on extracranial disease and augmentation of CD8+ T cell trafficking. Proc Natl Acad Sci 2018;115:E1540–9.
45. Engelhardt B, Vajkoczy P, Weller RO. The movers and shapers in immune privilege of the CNS. Nat Immunol 2017;18:123–31.
46. Dudnik E, Yust-Katz S, Nechushtan H, Goldstein DA, Zer A, Flex D, et al. Intracranial response to nivolumab in NSCLC patients with untreated or progressing CNS metastases. Lung Cancer 2016;98:114–7.
47. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol 2016;17:976–83.
48. Goldberg SB, Gettinger SN, Mahajan A, Herbst RS, Chiang AC, Lilenbaum R, et al. Durability of brain metastasis response and overall survival in patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab. J Clin Oncol 2018;36(15_suppl):2009–2009.
49. Qian JM, Mahajan A, Yu JB, Tsiouris AJ, Goldberg SB, Kluger HM, et al. Comparing available criteria for measuring brain metastasis response to immunotherapy. J Neurooncol 2017;132:479–85.
50. Gauvain C, Vauléon E, Chouaid C, Le Rhun E, Jabot L, Scherpereel A, et al. Intracerebral efficacy and tolerance of nivolumab in non–small-cell lung cancer patients with brain metastases. Lung Cancer 2018;116:62–6.
51. Henon C, Mezquita L, Auclin E, Ammari S, Caramella C, Le Pechoux C, et al. Impact of baseline leptomeningeal and brain metastases on immunotherapy outcomes in advanced non-small cell lung cancer (NSCLC) patients. J Thorac Oncol 2017;12:S2417.
52. Geier M, Descourt R, Corre R, Léveiller G, Lamy R, Goarant E, et al. Real-life intracerebral efficacy of nivolumab in non-small cell lung cancer patients with brain metastases. J Thorac Oncol 2018;13:S384–5.
53. Ashinuma H, Shingyoji M, Iuchi T, Yoshida Y, Setoguchi T, Hasegawa Y, et al. Immune checkpoint inhibitors for brain metastases of non-small-cell lung cancer. J Thorac Oncol 2017;12:S2420.
54. Watanabe H, Kubo T, Ninomiya T, Ohashi K, Ichihara E, Sato A, et al. The effect of nivolumab treatment for central nervous system metastases in non-small cell lung cancer. J Clin Oncol 2017;35(15_suppl):e20601.
55. Hendriks LEL, Henon C, Auclin E, Mezquita L, Ferrara R, Audigier-Valette C, et al. Outcome of patients with non-small cell lung cancer and brain metastases treated with checkpoint inhibitors. J Thorac Oncol 2019; 14:1244–54.
56. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012;13:459–65.

57. Kluger HM, Chiang V, Mahajan A, Zito CR, Sznol M, Tran T, et al. Long-term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. J Clin Oncol 2018;37:52–60.
58. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol 2018;19: 672–81.
59. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018;379:722–30.
60. Flippot R, Dalban C, Laguerre B, Borchiellini D, Gravis G, Négrier S, et al. Safety and efficacy of nivolumab in brain metastases from renal cell carcinoma: results of the GETUG-AFU 26 NIVOREN multicenter phase II study. J Clin Oncol 2019; 37:2088–16.
61. Fenske DC, Price GL, Hess LM, John WJ, Kim ES. Systematic review of brain metastases in patients with non–small-cell lung cancer in the United States, European Union, and Japan. Clin Lung Cancer 2017;18:607–14.
62. Lukas RV, Gandhi M, O'Hear C, Hu S, Lai C, Patel JD. 81OSafety and efficacy analyses of atezolizumab in advanced non-small cell lung cancer (NSCLC) patients with or without baseline brain metastases. Ann Oncol 2017;28(suppl_2): ii28–ii51. doi:10.1093/annonc/mdx091.
63. Gadgeel SM, Lukas RV, Goldschmidt J, Conkling P, Park K, Cortinovis D, et al. Atezolizumab in patients with advanced non-small cell lung cancer and history of asymptomatic, treated brain metastases: exploratory analyses of the phase III OAK study. Lung Cancer 2019;128:105–12.
64. Bidoli P, Chiari R, Catino A, Grossi F, Noberasco C, Gelsomino F, et al. Efficacy and safety data from patients with advanced squamous NSCLC and brain metastases participating in the nivolumab Expanded Access Programme (EAP) in Italy. Ann Oncol 2016;27(suppl_6): vi416–vi54. doi:10.1093/annonc/mdw383.28.
65. Molinier O, Audigier-Valette C, Cadranel J, Monnet I, Hureaux J, Hilgers W, et al. CLINIVO: Real-Life experience with nivolumab in 600 patients (Pts) with Advanced Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol 2017;12: S1793.
66. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med 2018;378:2078–92.
67. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, De Angelis F, et al. CT043 - Outcomes among patients (pts) with metastatic nonsquamous NSCLC with liver metastases or brain metastases treated with pembrolizumab (pembro) plus pemetrexed-platinum: Results from the KEYNOTE-189 study. Cancer Res 2019;79(13 Suppl):CT043. DOI: 10.1158/1538-7445. AM2019-CT043.
68. Afzal MZ, Dragnev K, Shirai K. A tertiary care cancer center experience with carboplatin and pemetrexed in combination with pembrolizumab in comparison with carboplatin and pemetrexed alone in non-squamous non-small cell lung cancer. J Thorac Dis 2018;10:3575–84.
69. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. Curr Probl Cancer 2016 Jan;40:25–37.
70. 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 2004;58:862–70.
71. 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.
72. 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.
73. Minniti G, Anzellini D, Reverberi C, Cappellini GCA, Marchetti L, Bianciardi F, et al. Stereotactic radiosurgery combined with nivolumab or Ipilimumab for patients with melanoma brain metastases: evaluation of brain control and toxicity. J Immunother Cancer 2019;7:102.
74. 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.
75. Karivedu V, Jandarov R, Wise-Draper TM. Brain metastases treated with immune checkpoint inhibitors: a single center experience. J Clin Oncol 2018; 36(15_suppl):e14012.
76. Chen L, Douglass J, Kleinberg L, Ye X, Marciscano AE, Forde PM, et al. Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. Int J Radiat Oncol 2018;100:916–25.
77. Kanai O, Fujita K, Okamura M, Nakatani K, Mio T. Severe exacerbation or manifestation of primary disease related to nivolumab in non-small-cell lung cancer patients with poor performance status or brain metastases: Table 1. Ann Oncol 2016l;27:1354–6.
78. Alomari AK, Cohen J, Vortmeyer AO, Chiang A, Gettinger S, Goldberg S, et al. Possible interaction of anti-PD-1 therapy with the effects of radiosurgery on brain metastases. Cancer Immunol Res 2016;4:481–7.
79. Colaco R, Martin P, Kluger H, Yu J, Chiang V. Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases? J Neurosurg 2016;125:17–23.
80. Rauch PJ, Park HS, Knisely JPS, Chiang VL, Vortmeyer AO. Delayed radiation-induced vasculitic leukoencephalopathy. Int J Radiat Oncol 2012;83:369–75.
81. Hubbeling HG, Schapira EF, Horick NK, Goodwin KEH, Lin JJ, Oh KS, et al. Safety of combined PD-1 pathway inhibition and intracranial radiation therapy in non–small cell lung cancer. J Thorac Oncol 2018;13:550–8.
82. Ahmed KA, Kim S, Arrington J, Naghavi AO, Dilling TJ, Creelan BC, et al. Outcomes targeting the PD-1/PD-L1 axis in conjunction with stereotactic radiation for patients with non-small cell lung cancer brain metastases. J Neurooncol 2017;133:331–8.
83. Martin AM, Cagney DN, Catalano PJ, Alexander BM, Redig AJ, Schoenfeld JD, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. JAMA Oncol 2018;4:1123.
84. Weingarten N, Kruser TJ, Bloch O. Symptomatic radiation necrosis in brain metastasis patients treated with stereotactic radiosurgery and immunotherapy. Clin Neurol Neurosurg 2019;179:14–8.
85. Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol 2015;16:e534–42.
86. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.
87. Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, Bozzao A, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. Radiat Oncol 2011;6:48.
88. Chao ST, Ahluwalia MS, Barnett GH, Stevens GHJ, Murphy ES, Stockham AL, et al. Challenges with the diagnosis and treatment of cerebral radiation necrosis. Int J Radiat Oncol 2013;87:449–57.
89. Vellayappan B, Tan CL, Yong C, Khor LK, Koh WY, Yeo TT, et al. Diagnosis and management of radiation necrosis in patients with brain metastases. Front Oncol 2018;8:395.
90. Ilhan-Mutlu A, Osswald M, Liao Y, Gömmel M, Reck M, Miles D, et al. Bevacizumab prevents brain metastases formation in lung adenocarcinoma. Mol Cancer Ther 2016;15:702–10.