Review Article

Integration of stereotactic radiosurgery or whole brain radiation therapy with immunotherapy for treatment of brain metastases

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Abstract

The prognosis of brain metastases (BM) is traditionally poor. BM are mainly treated by local radiotherapy, including stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT). Recently, immunotherapy (i.e., immune checkpoint inhibitors, ICI) has demonstrated a survival advantage in multiple malignancies commonly associated with BM. Individually, radiotherapy and ICI both treat BM efficiently; hence, their combination seems logical. In this review, we summarize the existing preclinical and clinical evidence that supports the applicability of radiotherapy as a sensitizer of ICI for BM. Further, we discuss the optimal timing at which radiotherapy and ICI should be administered and review the safety of the combination therapy. Data from a few clinical studies suggest that combining SRS or WBRT with ICI simultaneously rather than consecutively potentially enhances brain abscopal-like responses and survival. However, there is a lack of conclusion about the definition of "simultaneous"; the cumulative toxic effect of the combined therapies also requires further study. Thus, ongoing and planned prospective trials are needed to further explore and validate the effect, safety, and optimal timing of the combination of immunotherapy with radiotherapy for patients with BM.

Keywords: Immunotherapy; radiotherapy; immune checkpoint inhibitors; brain metastases; review

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Introduction

As a medical challenge affecting approximately 1 in 5 adult patients with systemic tumors, brain metastases (BM) have their highest incidence in breast cancer, melanoma, and lung cancer (1-3). To date, BM are typically treated by the combination of radiotherapy (RT), chemotherapy, and surgical resection (4). The outcomes and prognosis in patients have remained poor despite contemporary progress in BM treatment (5).

Immunotherapy has been very useful in many cancer types. Findings of clinical studies, such as the EORTC 18071 (6), KEYNOTE-001 (7), and CheckMate 057 (8), have proven that immune checkpoint inhibitors (ICIs) based on programmed cell death protein 1 (PD-1) (such as pembrolizumab or nivolumab) or ipilimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) can improve patient survival. However, the above clinical trials have routinely excluded patients with active or untreated BM. In most instances, BM management requires supportive approaches, such as corticosteroids, to relieve intracranial pressure (9). Therefore, evidence regarding the use of ICIs in treating patients with BM is limited, and many questions remain unresolved. In some clinical studies, findings have suggested that ICIs are effective in enhancing the OS of patients with BM (10,11). However, the results have not been confirmed by a large prospective phase III clinical study.

Immunotherapy is known to provide lasting results for the responders. However, only about one-third of patients are responsive. Therefore, strategies to increase the response rate are being investigated (5). RT is an effective therapy for BM. The immune system's interaction with irradiation has been characterized (12-14). Enhanced susceptibility of BM to immunotherapy following their increased immunogenicity caused by RT has been increasingly demonstrated by consecutive studies (15,16). These findings have attracted much attention, and many preclinical and clinical studies are underway.

In this review, we summarize the existing clinical and preclinical research findings supporting RT as an immunotherapy sensitizer for BM. Further, we discussed the optimal scheduling of immunotherapy and RT administration with respect to each therapy, and appraised the safety of combination therapy. The scope of current review is mainly focused on combination of immunotherapy and RT for BM in solid tumor including melanoma, renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC).

Evidence of immunotherapy for patients with BM

ICIs have gained revolutionary progress in anti-cancer therapy (17). Ipilimumab is the first ICI to be granted Food and Drug Administration (FDA) approval in 2011. Not long after, nivolumab and pembrolizumab were also approved (18).

As an organ once considered to be shielded from broad bodily immune surveillance, the brain was believed to be immune-privileged (18-21). A lack of lymphatic vessels directing antigen presenting cells (APC) to lymph nodes combined with the presence of the blood-cerebrospinal fluid barrier (BCB) or blood-brain-barrier (BBB) (4) may have contributed to this view. However, independent groups have published evidence showing that the brain and indeed the central nervous system (CNS) are accessible to the rest of the immune system, thus contradicting prevailing opinion on the brain's immune privilege. The CNS was demonstrated to have a resident lymphatic system in 2015, which sequesters CNS antigens from the cerebrospinal fluid (22). Additionally, in brain tumors, increased permeability of BBB, associated with the expression of vascular endothelial growth factor (VEGF), and clinically deformed microvessels were observed. Activated circulating $CD4^+$ T cells have been shown to cross the BBB, inducing local T cell activation (23). Furthermore, the CNS has the capacity to play important immunological roles, such as cytotoxicity through abundant resident microglial cells that are responsible for mediating innate immune functions within the CNS (22). These findings demonstrate that ICIs, which are the immune targets for tumor cell escape, can activate T-cells trafficking across BBB to play a role in BM, as shown in several preclinical studies (24,25).

Multiple case series and retrospective studies have investigated patients prescribed ICIs for BM (26). Among them, the largest study was conducted by Iorgulescu *et al*. They conducted analysis on data, from the National Cancer Database, of 220,439 patients diagnosed with melanoma from 2010 to 2015, and found that in comparison to OS of 5.2 months for patients not treated with ICIs, immunotherapy lengthened OS to 12.4 months (10). In contrast, the number of prospective clinical trials in this field is small. CheckMate-017 (NCT01642004), CheckMate-057 (NCT01673867), Keynote-189 (NCT02578680), and OAK (NCT02008227) were the original reports on large prospective ICI trials investigating immunotherapy for BM that included patients with asymptomatic BM (27,28).

Margolin *et al.* undertook a phase II trial, which was among the earliest published trials focused on investigating BM treatment with immunotherapy (29). In that trial, ipilimumab's effects on BM and melanoma patients were investigated (NCT00623766). Patients with both asymptomatic and symptomatic BM were included in the study. The symptomatic and asymptomatic group disease control rates were 5% (1/11) and 18% (9/51), respectively. NCT02085070 is a phase II study to evaluate the efficacy of pembrolizumab in BM of both NSCLC and melanoma (30). Interim study data analysis revealed that 22% (4 out of 18) and 33% (6 out of 18) of melanoma and NSCLC patients, respectively, achieved a BM response (30). The final results and long-term follow-up for the full melanoma cohort in this study were reported in 2019 (31). Overall, 26% of patients had a BM response, and the respective median OS and progression-free survival durations were 17 and 2 months, respectively. Two-year survival was similar to that in patients treated with anti-PD-1 agents, but without BM, suggesting that melanoma BMs could be treated using pembrolizumab with acceptable toxicity and durable responses. A recently published study from the Yale Cancer Center has revealed that pembrolizumab was effective in BM from NSCLC with PD-L1 expression at

least 1%, indicating that PD-L1 expression is an important factor for ICI treatment (32).

A combination of two ICIs for BM has also been reported in some phase I/II clinical trials. CheckMate-204 (NCT02320058) is a phase II study, which combined nivolumab and ipilimumab to treat melanoma patients with non-irradiated BM (33). The results showed that the combined treatment had clinically meaningful intracranial efficacy, with a clinical benefit rate of 57%, concordant with extracranial activity. A similar result was found in a phase II study in Australia (NCT02374242) (34). This study, combining ipilimumab and nivolumab, is one of the patient cohorts with asymptomatic untreated BM, that achieved 46% of brain response rate.

The trials mentioned above were all early clinical studies with small sample sizes. Therefore, confirmation of these initial findings will require comprehensive studies with more patients. On the other hand, treatment with ICIs combined with other therapies has been attempted for BM. RT [stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT)], has attracted much attention for possible combination with immunotherapy to increase intracranial responses. This combination approach has been examined in multiple studies (35,36).

Role of SRS and WBRT in BM

Standard RT for nonresectable BM patients is currently SRS, as clinical practice progressed from historical use of WBRT as gold standard. By convention, only patients with good performance status (PS) or few BM are given SRS, while those with bad prognosis, poor PS or numerous BM are assigned WBRT (37).

Most commonly, WBRT is given in 10 fractions during a 2-week period, to doses totaling 30 Gy (38). WBRT has been shown to increase OS to 3–7 months, up from 1 month in the absence of therapy with 64%–83% of patients reporting symptom improvements following single-agent treatment with WBRT (39,40). However, neurocognition and quality of life can be harmed by WBRT. As shown in a randomized controlled trial (C000000412), WBRT can reduce neurocognitive capacity in as many as 49% of cases (41). Brown *et al.* also generated concordant results from their phase III trial (NCCTG N0574) (42).

Highly efficient selectivity in targeting large doses to tumor tissues while avoiding normal surrounding brain cells makes SRS an advantageous RT method (43). SRS, usually provided in a single session, is commonly used to treat tiny intracranial lesions in a discreet, productive and reliable manner. Nevertheless, it may be challenging to achieve an optimal tumor control equilibrium for broad lesions or those in near proximity to vital tissues, thus minimizing disruption to normal tissues by utilizing single-fraction SRS. Treatment of a lesion in 2–5 fractions of SRS (known as "hypofractionated SRS") may have the opportunity to treat a lesion with a total radiation dose that provides sufficient tumor control and appropriate toxicity as well (44). WBRT doses ≥30 Gy are invariably associated with improved intracranial tumor control and survival in BM patients (45). The Japan Clinical Oncology Group carried out a randomized phase III trial and their results suggested that the efficacy of SRS is noninferior to that of WBRT, for the treatment of patients with 1–4 BM (46). Moreover, SRS has fewer neurocognitive side effects compared with WBRT; thus, SRS has been increasingly used for treating BM (47). The study conducted by Chang *et al.* (NCT00548756) assessed 58 patients who were assigned to either SRS + WBRT or SRS alone to treat 1–3 recently discovered BM (48). While 20% of patients who received SRS suffered cognitive decline after 4 months, but the proportion was 64% in patients treated with WBRT + SRS. The OS after one year in the SRS group was 63% compared to 21% for combination therapy (48). Brown *et al.* randomized 213 patients to be given either WBRT + SRS or SRS alone to treat 1–3 BM in a multi-center phase III trial published (NCT00377156) (49). Three months following treatment, the results from this study showed less decline in cognition with SRS alone than when combined with WBRT; despite this, a survival advantage could not be proven, and local control was similar in both groups. From the study results, prescribing SRS alone may therefore be an optimal therapeutic regimen for patients designated to receive radiosurgery while having 1–3 BM (49).

Potential mechanisms of synergy between RT and ICIs

Over the past 10–15 years, multiple studies have shown the association between tumor control using RT and the immune system (3,50). Moreover, irradiation at one location leading to metastatic cancer regression at a separate, remote site, which is referred to as an "abscopal effect", is further proof of the contribution of RT to tumor control (18,51).

The following various candidate mechanisms have been postulated to explain RT effects on the immune system

(*Figure 1*). Firstly, tumor-associated antigens (TAAs), which are released upon RT-mediated tumor cell death (52-55), could activate APCs and then prime cytotoxic T cells to kill cells in remote locations (56,57). RT has also been shown to stimulate tumor cell major histocompatibility complex (MHC) I expression (58). Secondly, RT is a potent inducer of immunogenic cell death (ICD) as it stimulates all three arms of ICD (52). ICD is typified by the migration of calreticulin (CRT) to the cell surface, release of adenosine triphosphate (ATP) and secretion of high motility group box 1 (HMGB1) protein out of the cell (53). The induction of ICD is linked to the exposure of damage-associated molecular patterns (DAMP), which induces the recruitment and affects the functions of immune cells (4). Moreover, DNA damage caused by RT can increase mutational burden (59), which may be transcribed into new antigens detected by the immune system (60). The stimulator of interferon genes (STING) is activated by DNA leaking into the cytosol following DNA damage induced by RT, which incidentally also leads to adaptive and innate immune response activation (61). Finally, RT has been reported to change the tumor environment and induce cancer cell secretion of proinflammatory chemotactic factors (such as interferons,

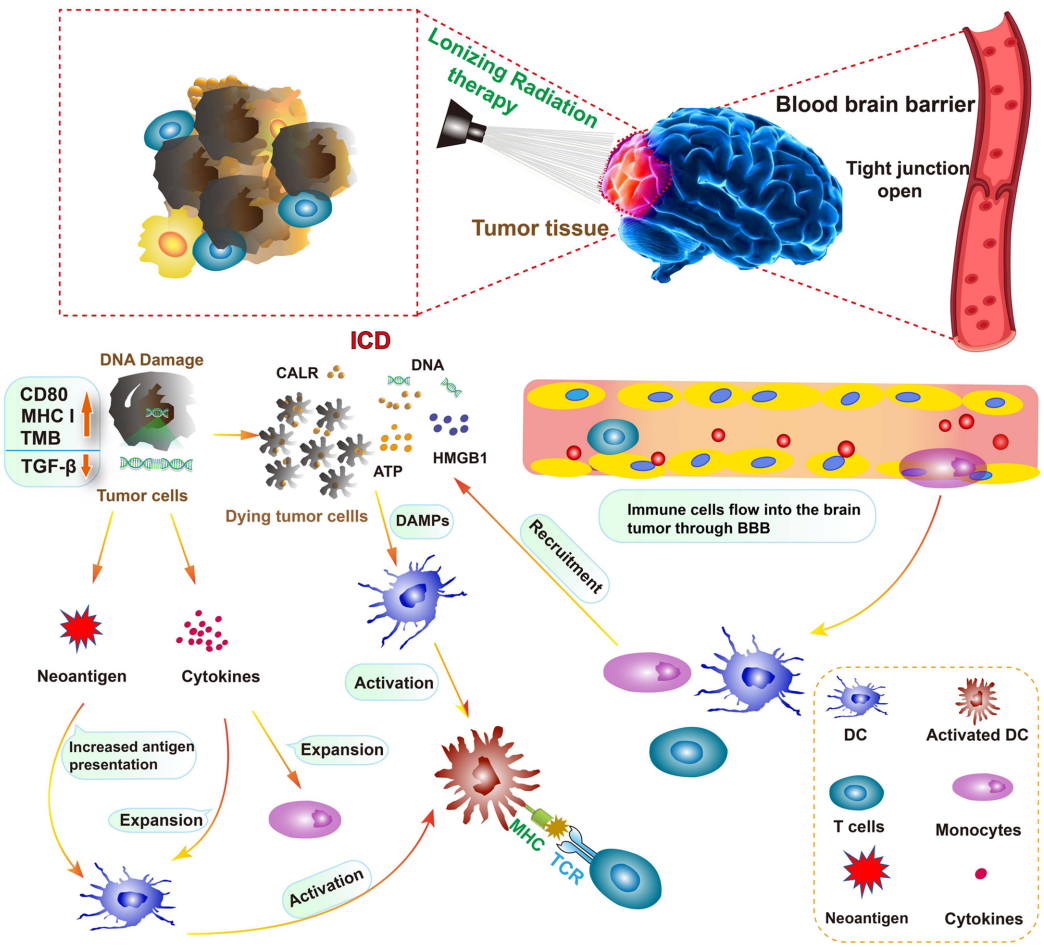

Figure 1 Immune modulatory effects of RT. First, it has been shown that RT causes all three kinds of ICD. ICD activation is related to the presence of DAMPs on cell surfaces, which causes immune cell mobilization and influences their function. Second, RT may enhance the identification of tumor antigens by triggering the appearance of neo-antigens and upregulating large molecules of MHC I. RT will also cause an intensified invasion of immune cells into brain tumors to produce cytotoxic T lymphocytes unique to the tumor. RT, radiotherapy; ICD, immunogenic cell death; DAMPs, hazard-associated molecular patterns; MHC, major histocompatibility complex; BBB, blood-brain-barrier; CD80, cluster of differentiation 80; TMB, tumor mutation burden; TGF-β, transforming growth factor-β; ATP, adenosine triphosphate; HMGB1, high motility group box 1; CALR, calreticulin; TCR, T-cell receptor; DC, dendritic cell.

tumor necrosis factor α, and interleukin 1) with strong immunostimulatory effects (62,63). These factors facilitate dendritic cell maturation, increase T-cell infiltration (64-67), and even increase tumor cell PD-L1 expression (68), thus enhancing anti-PD-L1 antibody effects on tumors (69).

Under physiological conditions the presence of BCB and BBB blocks the entry of various immune cells along with macromolecule exchange across the brain parenchyma (70). Furthermore, brain tumor microenvironments are characterized by a small proportion of $CD8^+$ effector T cells and abundant myeloid cells (4). Due to these facts, brain tumors show higher systemic tolerance than tumors at extracranial sites (71). Importantly, systemic tolerance was shown to potentially be reversed by RT. RT can stimulate immune cell migration into brain tumors (72) to generate tumor-specific cytotoxic T lymphocytes (73-75). Like the effect of RT on extracranial tumors, RT impacts cytokine secretion which attracts various immune cells, such as macrophages and dendritic cells for brain tumors. Furthermore, RT can modify important effector functions, including cytotoxicity, antigen presentation and phagocytosis, thus altering immune cell activation states which contributes to the triggering of immune responses stimulated by RT (4). Since competent T cells are crucial for effective immunotherapy, the role of RT in activating immune cells gives an opinion that immunotherapy can be sensitized by RT, thereby enabling it to treat BM.

This opinion has been backed by evidence from many preclinical trials. Smilowitz *et al.* developed an intracerebral B16 mouse model and observed that mice treated with RT alone had a shorter median survival period than those treated with immunotherapy combined with RT (76). Xia *et al.* investigated the impact of integrating RT with anti-PD-1 therapy on mouse models against metastatic osteosarcoma in the brain. They proposed that combining anti-PD-1 immunotherapy with RT could boost remote as well as local control through induction of abscopal responses, with the benefit of combination therapy being greater than anti-PD-1 alone (77). A similar finding was observed in the study conducted by Pfannenstiel *et al.* (78).

Clinical evidence of combined RT and immunotherapy to treat BM

Numerous clinical trials have explored approaches to incorporate immunotherapy with SRS or WBRT to improve BM response. *Table 1* presents 28 studies conducted in the context of BM on the combination of RT and ICI. Of these, 26 reports involved melanoma patients (35,36,79-101), 4 enrolled NSCLC patients (89,102-104), and 1 enrolled RCC patient (89). Nearly all the 28 studies were retrospective, except for one prospective study (35).

Ipilimumab was the most commonly used ICI in these trials and SRS was the most frequently used approach of RT. A total of 23 out of 28 studies have assessed a mixture of ipilimumab with SRS. Initial retrospective evidence included data emerging from a study published in 2015 by Kiess *et al.* This study evaluated the results of 46 patients treated with SRS and ipilimumab for BM. The report indicated that simultaneous therapy with SRS and ipilimumab correlated with better locoregionally regulation and longer survival (1-year OS 40%–65%; 1-year regional recurrence 64%–92%), and the combination appeared to be well tolerated (91). Cohen-Inbar *et al.* performed a related study that involved 46 patients treated with SRS and ipilimumab. The findings suggest enhanced response when prescribing ipilimumab at the same time as SRS (93). Ninety-nine metastatic melanoma patients treated with ipilimumab who were then prescribed SRS for emergent BM were retrospectively reviewed by An *et al*. In the patient cohort that received SRS for new BM within 5.5 months of ipilimumab treatment (83), increased intracranial regulation was confirmed. The rapid growth of BM is often accompanied by peritumoral edema (105). Diao *et al.* conducted a retrospective study that included 72 patients with BM and found that the application of SRS and ipilimumab strengthened tumor responses and reduced the amount of edema (11). However, not all studies had good outcomes. The retrospective study undertaken by Mathew *et al.* (81) and Patel *et al.* (95) found that it was possible to use ipilimumab and SRS safely, but this joint therapeutic approach was inconsistent with better performance.

In a randomized clinical trial for metastatic melanoma, pembrolizumab therapy led to reduced toxicity and better OS relative to ipilimumab, resulting in broad prescription of anti-PD-1 agents for metastatic melanoma (NCT01866319) (106). However, proof of efficacy of using a mixture of RT and anti-PD-1 agents for treating BM is less convincing than that of an ipilimumab and RT combination. Anderson *et al*. reported 21 patients undergoing concomitant pembrolizumab and RT for BM. The findings showed that combined SRS with pembrolizumab appeared effective and safe in substantially reducing BM size (82). Acharya *et al.* demonstrated that SRS with ICI (i.e., anti-PD-1 agent or ipilimumab) is

Table 1 Selected studies combining RT with ICI in BM

Authors	Tumor type	N	Study design	ICI target	Type of RT	Arms	Median survival (months)	Intracranial control
Williams *et al.* (35)	Melanoma	16	Prospective	CTLA-4	SRS/WBRT	RT (WBRT) + ICI	10.6	40% at 6 months
						RT (SRS) + ICI		18% at 6 months
Skrepnik *et al*. (36)	Melanoma	25	Retrospective	CTLA-4	SRS	RT→ICI	35.8	94.8%
						RT=ICI		
						ICI→RT		
Murphy *et al.* (79)	Melanoma	26	Retrospective	CTLA-4/PD-1	SRS	RT=ICI (±30 days)	26.1	NR
						RT≠ICI		
Acharya *et al.* (80)	Melanoma	56	Retrospective	CTLA-4 and/or PD-1	SRS	RT + ICI	58% OS at 1 year	85% at 1 year
						RT	31% OS at 1 year	66% at 1 year
Mathew *et al*. (81)	Melanoma	58	Retrospective	CTLA-4	SRS	RT + ICI	56% OS at 6 months	63% at 6 months
						RT	45% OS at 6 months	65% at 6 months
Anderson *et al*. (82)	Melanoma	21	Retrospective	PD-1	SRS/WBRT	NR	NR	SRS=ICI 32%
								SRS≠ICI 22%
An *et al.* (83)	Melanoma	99	Retrospective	CTLA-4	SRS	ICI→RT (early SRS)	13.4	51% at 1 year
						ICI→RT (late SRS)	11.5	25% at 1 year
Qian *et al.* (84)	Melanoma	75	Retrospective	CTLA-4/PD-1	SRS	RT=ICI (±4 weeks)	19.1	NR
						RT≠ICI	9.0	
Liniker *et al.* (85)	Melanoma	53	Retrospective	PD-1	Extracranial RT and / or SRS, WBRT	NR	NR	NR
Ahmed *et al.* (86)	Melanoma	55	Retrospective	CTLA-4/PD-1	SRS	RT+ICI (anti-PD-1)	48% OS at 12 months	NR
						RT+ICI (anti-CTLA-4)	41% OS at 12 months	
Gerber *et al*. (87)	Melanoma	13	Retrospective	CTLA-4	WBRT	RT=ICI (±30 days)	4	56% by irRC criteria
Silk *et al*. (88)	Melanoma	70	Retrospective	CTLA-4	SRS /WBRT	RT + ICI	18.3	NR
						RT	5.3	
Chen *et al.* (89)	NSCLC, Melanoma, RCC	260	Retrospective	CTLA-4/PD-1	SRS	RT	12.9	NR
						RT≠ICI	14.5	NR
						RT=ICI (±2 weeks)	24.7	88.0% at 1 year
Yusuf *et al.* (90)	Melanoma	51	Retrospective	CTLA-4/PD-1	SRS	RT	7.1	NR
						RT=ICI (±4 weeks)	7.4	
						RT≠ICI		
Kiess *et al.* (91)	Melanoma	46	Retrospective	CTLA-4	SRS	RT=ICI	56% OS at 1 year	100% at 1 year

Table 1 (*continued*)

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Authors	Tumor type	N	Study design	ICI target	Type of RT	Arms	Median survival (months)	Intracranial control
						RT→ICI	65% OS at 1 year	87% at 1 year
						ICI→RT	50% OS at 1 year	89% at 1 year
Choong *et al.* (92)	Melanoma	39	Retrospective	CTLA-4 /PD-1	SRS	NR	54.9% OS at 1 year	NR
Cohen-Inbar *et al.* (93)	Melanoma	46	Retrospective	CTLA-4	SRS	RT→ICI, RT=ICI	59% OS at 1 year	54.4% at 1 year
						ICI→RT	33% OS at 1 year	16.5% at 1 year
Amaral *et al.* (94)	Melanoma	290	Retrospective	CTLA-4 and PD-1	SRS/WBRT	NR	24.0	NR
Patel *et al.* (95)	Melanoma	54	Retrospective	CTLA-4	SRS	RT	38.5% OS at 1 year	71.4% at 1year
						RT + ICI (±4 months)	37.1% OS at 1 year	92.3% at 1 year
Rahman *et al.* (96)	Melanoma	74	Retrospective	CTLA-4/PD-1	SRS	RT=ICI (±30 days)	13.9	23.1% at 1 year
						RT≠ICI		18.8% at 1 year
Schmidberger *et al.* (97)	Melanoma	41	Retrospective	CTLA-4	SRS/WBRT	RT→ICI	11.0	NR
						ICI→RT	3.0	
Diao *et al.* (98)	Melanoma	72	Retrospective	CTLA-4	SRS	RT	NR	NR
						RT=ICI		
						RT≠ICI		
Fang *et al.* (99)	Melanoma	137	Retrospective	CTLA-4/PD-1	SRS	NR	16.9	NR
Kaidar-Person *et al.* (100)	Melanoma	58	Retrospective	CTLA-4/PD-1	SRS	RT+ICI	15.0	NR
						RT	5.5	
Martins *et al.* (101)	Melanoma	84	Retrospective	CTLA-4/PD-1	SRS	NR	12.0	NR
Singh *et al.* (102)	NSCLC	39	Retrospective	PD-1	SRS	RT + ICI	10.0	NR
Hubbeling *et al.* (103)	NSCLC	50	Retrospective	PD-1	WBRT/SR/partial brain irradiation	RT→ICI (>4 Weeks)	NR	NR
						RT=ICI (±4 weeks)		
						ICI→RT (>4 weeks)		
Lanier *et al.* (104)	NSCLC, Melanoma	271	Retrospective	CTLA-4 and/or PD-1	SRS	RT + ICI	15.9	NR
						RT	6.1	

RT, radiotherapy; ICI, immune checkpoint inhibitor; BM, brain metastases; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; irRC, immune-related response criteria. ICI→RT indicates ICI was administered prior to RT; RT=ICI indicates that ICI was administered concurrently with RT; RT→ICI indicates that ICI was administered after RT; RT≠ICI indicates that RT was not administered concurrently with SRS; RT+ICI indicates ICI was administered with RT but the relative timing of each treatment was not provided. NR indicates that the results were not reported.

associated with reduced local and distant brain tumor resistance relative to SRS alone in BM patients (80). Nonetheless, no further work has been conducted on which form of ICI has a better treatment result when paired with SRS for BM. Choong *et al.* (92) retrospectively analyzed 108 melanoma patients with BM who were treated with

SRS and systemic treatment (including inhibitors of BRAF or agents targeting PD-1 and/or CTLA4). For patients treated with SRS and anti-PD-1 agent, the mean OS was far higher than for those who received SRS and an anti-CTLA4 agent (27.4 months *vs.* 7.5 months). A study by Martins *et al.* revealed a similar finding (101). Nonetheless, there were some drawbacks to the study results. Therefore, in the future, head-to-head analysis of anti-PD-1 agents plus RT *vs*. ipilimumab plus RT for BM will be required.

Most of the reports discussed in this study used SRS to treat BM instead of WBRT. Some reports, however, were already concentrating on integrating WBRT and ICIs. Gerber *et al*., for example, performed a retrospective analysis of 13 BM patients treated with WBRT within 30 days of ipilimumab administration; their findings revealed that ipilimumab and WBRT combination provided encouraging efficacy (87).

The Thomas Jefferson University (35) performed the first prospective phase I analysis pairing RT with ipilimumab (NCT01703507). In that investigation, 16 patients were enrolled to receive WBRT plus ipilimumab or SRS plus ipilimumab. SRS was applied to patients with postoperative cavity (all less than 4 cm) or fewer than 5 BM, while WBRT was used to treat patients with any postoperative cavity/lesion larger than 4 cm in diameter or ≥5 BM. From this report, concomitant WBRT or SRS with ipilimumab was safe and well tolerated. For the 16 patients who were admitted, 14 of them showed progressive disease with some also dying during follow-up. In the end, due to slow accrual, the WBRT arm was closed prematurely, and the effectiveness was not as anticipated. As it was a phase I study, the primary endpoint was safety rather than effectiveness. Lack of appropriate patients to assess effectiveness may have led to the unexpected results.

The above listed studies were all retrospective studies except for NCT01703507; hence, the validity of these data is limited. Many prospective trials are scheduled or currently being conducted to confirm the use of ICIs in conjunction with RT in BM therapy. Details on these trials are summed up in *Table 2*. After evaluating these trials, we find that they are all phase 1 and 2 trials, suggesting that the combination of ICIs and RT remains at an exploratory level.

Establishing the best performing sequence and schedule of integrated RT and immunotherapy for BM treatment

From the data shown in *Table 1*, the combination of ICIs and RT can be performed in three different ways: patients receive RT during ICIs (concurrent RT and ICIs), patients receive RT before ICIs, and patients receive RT after ICIs. However, the optimal timing of ICIs when combined with RT remains controversial.

Kiess *et al.* (91) observed that patients with BM who received SRS before or during ipilimumab treatment had fewer regional recurring tumors and greater OS than those who received SRS after ipilimumab. "SRS during ipilimumab" means <1 month (4 weeks) following the final ipilimumab dose or between doses of ipilimumab. "SRS after ipilimumab" refers to patients who received SRS following the last dose of ipilimumab. Different effects were observed in a later retrospective analysis at the University of Virginia (93). A group of 32 patients undergoing SRS either before or during ipilimumab treatments (including patients treated with SRS up to a month following the final dose of ipilimumab) showed a significantly longer local recurrence-free duration compared to 14 patients receiving ipilimumab prior to SRS. This research reinforced previous findings that SRS might be more suitably received during the initiation of ICIs (concurrent treatment).

Chen *et al.* (89) retrospectively reported the results of melanoma, RCC and metastatic NSCLC patients with BM who had been treated with SRS. They observed that combined use of SRS and ICI correlated to better OS compared to non-concomitant ICI and SRS. In this study, patients were classified as having combined ICI and SRS if they were administered a dose of ICI within two weeks before or after SRS. In comparison to conceptualization of concurrent ICIs and SRS conducted by Chen *et al*., in Qian's study, SRS treatment and immunotherapy of any particular lesion were deemed concurrent if SRS was performed inside four weeks of immunotherapy cessation or initiation; all other patients were classified as non-concurrent (84). In fact, OS was significantly shorter in the non-concurrent treatment group at just 8 months compared to 19.1 months for the concurrent therapy cohort (84). Many trials, including those done by Diao *et al.* (98), Anderson *et al.* (82) and Yusuf *et al.* (88), have also used "4 weeks or 1 month" as the threshold value to describe "concurrent therapy". In these trials, patients treated with combined ICIs and SRS experienced better results than those diagnosed with non-concurrent therapy (79,82,90,98). In the study carried out by An *et al.*, they suggested that "5.5 months" could also be used to describe "concurrent therapy" as a threshold value (83). In Acharya's

Table 2 Ongoing clinical trials of immunotherapy and RT in the treatment of BM

Trial number	Phase	Tumor type	Country	Status	N (planned)	Arm(s)	Primary outcomes
NCT01449279	I	Melanoma	USA	Active, not recruiting	20	Ipilimumab + palliative radiation Pembrolizumab + SRS (30 Gy/5f)	Safety
NCT02858869	I	Melanoma/NSCLC	USA	Recruiting	30	Pembrolizumab + SRS (27 Gy/3f) Pembrolizumab + SRS (18–21 Gy/1f)	Safety
NCT02716948	I	Melanoma	USA	Recruiting	90	Nivolumab + SRS Nivolumab + SRS Nivolumab + WBRT	Safety
NCT02696993	I/II	NSCLC	USA	Recruiting	88	Nivolumab + ipilimumab + SRS Nivolumab + ipilimumab + WBRT	Recommended phase 2 dose; 4-month intracranial Progression-free survival Overall survival rate
NCT02107755	II	Melanoma	USA	Active, not recruiting	NR	Ipilimumab + SRS	Progression-free survival
NCT02097732	II	Melanoma	USA	Active, not recruiting	40	(a) SRS→ipilimumab (b) Ipilimumab→SRS	Local control rate
NCT02886585	II	Any solid tumor	USA	Recruiting	102	(a) Previously untreated BM (b) Progressive BM (c) Neoplastic meningitis (d) 1–4 BM from melanoma	Objective response rate; Overall survival rate; Extracranial overall Response rate
NCT02978404	II	NSCLC/RCC	Canada	Recruiting	60	Nivolumab + SRS	Intracranial progression-free survival
NCT03340129	II	Melanoma	Australia	Recruiting	218	Nivolumab + ipilimumab Nivolumab + ipilimumab + SRS	Neurological specific cause of death

RT, radiotherapy; BM, brain metastases; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy. Clinical trials were search on the database https://clinicaltrials.gov/. Clinical trials which are active or recruiting BM patients treated with immunotherapy and RT irrespective of the tumor types were included in *Table 2*.

study, concurrent therapy was described as the administration of SRS within 3 months of ICIs or targeted therapy (80). In addition, Skrepnik *et al.* in their retrospective study detected a group of 25 ICI-treated (pembrolizumab and ipilimumab) BM patients and SRS; the optimum period for ICI administration was stated to be 15–30 d after SRS treatment. However, their analysis did not include evidence to justify parallel use of SRS and ICIs (107).

Various postulations may theoretically clarify the difference between these trial findings. Firstly, the optimum timing will depend on the half-life of ICIs. Ipilimumab has a half-life of 14.9 d (108), and pembrolizumab and nivolumab have a half-life of 25 d and 25.2 d, respectively. Patel *et al.* (95) observed no better results when ipilimumab was given to BM patients within 4 months of SRS compared to those who received SRS alone. They further analyzed the evidence and found that patients who received ipilimumab and SRS within 14 d could derive an OS advantage due to ipilimumab's half-life. Consequently, ICI's half-life may give us a hint to select the best timing of combined therapy.

The levels of some biomarkers may change during the RT course, which would give us information on when to combine ICIs and RT. Radiation-induced mannose-6-phosphate receptor expression, a receptor essential to

radiation-enhanced ipilimumab effectiveness, was shown to peak within 3 d of irradiation and normalize over 7–14 d (109), indicating that ipilimumab administration can be more efficient during that process. Research by Dovedi *et al.*documented anergy in tumor-reactive T-cells 7 d following the previous fractionated RT dose and reduced expression of PD-L1 in mouse models (110), suggesting that PD-1 inhibitor therapy would be best suited to that direction. Such findings also illustrate the need for studies investigating inherent pathways and optimum scheduling of ICI and RT administration based on tumor cell molecular expression.

In conclusion, patients treated with concurrent ICIs and RT might have better outcomes than those treated with non-concurrent treatment. Nevertheless, the concept of "concurrent" remains ambiguous, with some reports stating "concurrent" to be provision of ICIs as early as 2 weeks before or after SRS, and some extending this time to 4 weeks or 1 month, or as long as 5.5 months. Most studies typically used 4 weeks/1 month as the threshold value. Indeed, studies supporting the simultaneous use of ICIs and RT showed a better synergistic effect, but the cumulative toxic effect of the two kinds of therapy also merits attention.

Safety of combined immunotherapy and RT

One specific issue is the potential increased and unforeseen toxicity when mixing RT and immunotherapy. By their own definition, immunotherapies stimulate the immune response, which induces inflammatory side effects sometimes referred to as immune-related adverse events (irAEs) (111). irAEs most commonly affect organs such as liver, skin, endocrine glands, and CNS (112,113). In patients treated with CTLA-4 inhibitory therapy, hypophysitis and colitis are typical irAEs, while thyroiditis and pneumonitis are more generally seen in patients undergoing treatment with PD-1 inhibitors (114-116). Clinical trials evaluating the efficacy and safety of ipilimumab or anti-PD-1 antibodies as monotherapy recorded irAEs of any grade in 13%–65% of patients, with third to fourth grade irAEs registered in 1%–27% of patients (17,117-122). Among them, neurological AE caused by ICIs occur in about 1% of patients and numerous autoimmune neurological side effects have been recorded, including encephalomyelitis, demyelinating polyneuropathy, encephalitis and hypophysitis (18).

For patients with BM, the association between addition of brain RT to ICIs and the incidence of irAEs seems weak. In a phase I trial by Williams, patients with BM showed no rise in neurotoxicity compared to RT alone (14 patients with neurotoxic effects in grade 1–2). Total grade 3 toxicity was just seen in 10 patients, including anemia, panhypopituitarism, pleural effusion, lymphopenia and gastrointestinal (35). A newly published retrospective study analyzed 260 patients undergoing immunotherapy and multifaction or single SRS, no elevation in acute toxicity with successive or concurrent SRS and immunotherapy administration was observed. irAE rates among patients who received simultaneous SRS and ICI or not were not significantly different (89). The occurrence of irAEs in patients treated with extracranial RT/intracranial SRS and anti-PD-1 therapy was retrospectively evaluated by Liniker *et al.* (85); only four patients reported grade 3 or 4 irAE, consistent with existing historical anti-PD-1 therapy evidence (123). Based on the above results, we cannot tell whether adding ICI to RT could increase irAE risk. The safety of the combination of ICIs with WBRT/SRS has been demonstrated by many other studies, but they did not provide details regarding the irAE incidence rate (79,82,124). Further studies are required to assess this issue.

Unlike the irAEs, the risk of RT-related AEs caused by combination therapy has been investigated by more studies. From the above literature, the possible RT-related toxicity of combined ICIs and RT involves intratumoral hemorrhage, neurocognitive impairment and radiation necrosis (RN), but most of these investigations concentrated on SRS rather than WBRT (13,82,85,87). Among them, RN is the most ubiquitous side effect rising with dual treatment.

RN is the development of irreversible tissue injury in previously irradiated brain tissue that occurs more than 12 weeks after irradiation. It is the result of an inflammatory response (125) and is frequently symptomatic on clinical appearance, including focal neurological defects, impaired emotional state or hallucinations. It is a typical side effect of SRS that occurs in about 5%–25% of patients (126,127). Many variables have been proposed to influence RN levels including previous radiation, treated length and RT dosage (127,128). Previously multiple case series established a possible correlation between RN and immunotherapy after SRS (129,130). Du *et al*. identified 7 ipilimumab and SRS-treated patients, all of whom developed RN during follow-up (130). In a separate study involving 27 BM patients treated with ipilimumab and SRS, 41% of the patients developed RN (37). Fang *et al.* (99) evaluated the outcomes

of 137 BM patients receiving SRS, together with ipilimumab and/or pembrolizumab. The median follow-up was 9.8 months from SRS, and the RN rate was 27%, for an average 6-month RN period. For this sample, the RN incidence for nearly one quarter of the patients was close to that found in the other two studies (36,131).

Various studies have measured the dangers of RN after SRS either with or without ICI (132). However, the cumulative data available on the efficacy of combined intracranial RT and ICI are contradictory, with some reports suggesting a higher risk of RN with combination therapy than with SRS monotherapy, and others finding no such effect. Kaidar-Person *et al.* observed that 13.8% (8 out of 58) of patients with RN all came from the immunotherapy plus RT group, while 29 patients who only got RT did not have RN during follow-up (100). Martin *et al.* (131) examined the results of 480 newly diagnosed patients with BM secondary to melanoma, RCC, and NSCLC who were treated with or without ICIs. They observed a correlation between immunotherapy receipt and symptomatic RN in patients receiving SRS. The findings revealed that symptomatic necrosis occurred in 6.85% and 20.0%, respectively, of patients who did not compare with those undergoing immunotherapy (131). Fifty-four patients with BM received SRS either in conjunction with (n=20) or without (n=24) ipilimumab in another retrospective study performed by Patel *et al* (95). The SRS plus ipilimumab cohort had a one-year trend towards developing higher RN rates compared to the SRS cohort alone, at rates of 20.92% *vs.* 30%, respectively (95).

The studies investigating safety of combined RT and ICI in BM are summarized in *Table 3*. Such findings pose a big warning that combined ICI and SRS could increase the risk of RN; however, evidence from subsequent studies did not indicate the same effect. Indeed, neither Silk nor Mathew reported increased rates of RN in patients treated with the combination of RT and ipilimumab (81,88). Possible reasons for these divergent outcomes include insufficient cohort sizes of multiple studies and variations in the prescribed doses of SRS, fraction numbers and isodose lines (17). For patients with BM, prospective trials which will mitigate all influencing variables that are required to better define the risks and benefits of integrating brain-directed stereotactic radiation with immunotherapy.

Conclusions and future direction

The introduction of ICIs has opened a new range of alternative treatment solutions for BM patients. Although much remains unclear about the impact of immunotherapy on BM, as well as its relationship with RT, evidence from a limited number of clinical trials has indicated that the combination of ICIs and RT can improve survival and abscopal responses within the brain, which can be enhanced if administered concurrently rather than sequentially. The goal of combining the two kinds of therapy is to make the treatment more effective with minimal toxicity. For this reason, we also discuss the optimal time or time window for combination therapy in this review. But most studies that we have discussed were retrospective with small sample sizes. Thus, there were some limitations in reaching a firm conclusion. In order to further investigate and verify the efficacy and optimum timing of RT and immunotherapy combination for patients with BM, current and scheduled specific prospective studies of a broader scale or more data are required. Additionally, there is lack of studies documented on the RT and immunotherapy combination for patients with BM for other tumors besides melanoma. The RT and immunotherapy combination for patients with BM need to be explored for other tumors to broden its therapeutic avenue. Furthermore, there are many factors affecting immunotherapy, corticosteroid is one of the important factors (133). Patients with symptomatic BM are often treated with corticosteroid to reduce symptoms (133). A recent published study showed that immunotherapy with nivolumab plus ipilimumab, particularly in combination with RT could improves OS in both asymptomatic and symptomatic melanoma BM (94). But there is lack of studies documented on the optimum timing of RT and immunotherapy separately according to the presence or absence of cranial symptoms. Further studies on this field are really needed.

In the advanced stage, immunotherapy can successfully extend the ultimate survival of patients in various tumors. Nevertheless, only a portion of people reports objective responses from such treatments which illustrate large differences in efficacy as well as adverse drug reactions (134). Loss of function as a result of heterozygosity in intrinsic resistance mechanisms previously reported include PD-1, human leukocyte antigen (HLA), beta-2 microglobulin (B2M), phosphatase and tensin homolog (PTEN), Janus-associated kinase (JAK)1, JAK2, or transporter associated with antigen processing 1 (*TAP1*) genes. Different cases in which the resistance catalyst is undisclosed have been identified, demonstrating the difficulty of resistance in the sense of immunotherapy, and

Table 3 Selected studies investigating safety of combined RT and ICI in BM

Authors	Study characteristics	Explore	RT-related toxicities
Williams *et al.* (35)	Phase I study involving 16 patients with BM from melanoma	WBRT *vs*. SRS + ipilimumab	21 grade 1–2 neurotoxicities; no grade 4–5 toxicity or RN
Mathew *et al.* (81)	Retrospective study involving 58 patients with BM from melanoma	SRS ± ipilimumab	Intratumoral hemorrhage in 28.0% of patients receiving SRS + ipilimumab *vs.* 30.3% of patients receiving SRS.
Silk *et al*. (88)	Retrospective study involving 70 patients with BM from melanoma	RT (WBRT/SRS) ± ipilimumab	Intratumoral hemorrhage in 12.5% of patients receiving RT *vs*. 3.9% of patients receiving RT + ipilimumab; RN in 9.38% of patients receiving RT *vs*. none of patients receiving RT + ipilimumab
Chen *et al.* (89)	Retrospective study involving 260 patients with BM from melanoma, NSCLC, or RCC	SRS ± ICI	RN occurred in 3% of patients, this was not significantly different among patients who received SRS alone, SRS and non-concurrent ICI, and concurrent SRS and ICI.
Patel *et al.* (95)	Retrospective study involving 54 patients with BM from melanoma	SRS ± ipilimumab	RN in 21% of patients receiving SRS *vs*. 30% of patients receiving SRT + ipilimumab (P=0.078); intratumoral hemorrhage in 14.7% of patients receiving SRS *vs.* 15.0% of patients receiving SRT + ipilimumab (P=1.00)
Diao *et al*. (98)	Retrospective study involving 72 patients with BM from melanoma	SRS ± ipilimumab (concurrent: 59 lesions; nonconcurrent: 160 lesions; none: 91 lesions	RN in 3% of patients receiving concurrent therapy and 2% in those receiving nonconcurrent therapy; TRIC in 8% of patients receiving concurrent therapy and in 6% of those receiving nonconcurrent therapy; no patients receiving SRS alone had RN or symptomatic TRIC; the overall incidence of any lesion hemorrhage was 18%, nonconcurrent ipilimumab was associated with lower risk of lesion hemorrhage compared with concurrent ipilimumab
Fang *et al.* (99)	Retrospective study involving 137 patients with BM from melanoma	SRS + CT and/or ICI	RN in 27% of patients, including in 12.5% of patients receiving ipilimumab and 7.4% of patients receiving pembrolizumab.
Kaidar-Person *et al.* (100)	Retrospective study involving 58 patients with BM from melanoma	SRS ± ICI	RN in 28% of patients receiving SRS + ICI *vs.* none of patients receiving SRS alone.
Hubbeling *et al*. (102)	Retrospective study involving 163 patients with BM from NSCLC	RT (WBRT/SRS/PBI) *vs*. RT + ICI	RN occurred in only one patient (grade 4, RT cohort); the incidence of grade ≥3 AEs was 8%–13% across treatment groups, and did not differ significantly between RT + ICI and RT cohorts.
Skrepnik *et al.* (107)	Retrospective study involving 25 patients with BM from melanoma	SRS + ipilimumab	RN in 21% of patients
Martin *et al*. (131)	Retrospective study involving 480 patients with BM from melanoma, NSCLC, or RCC	SRS/SRT *vs*. SRS/SRT + ICI	Symptomatic RN in 7% of patients receiving SRS/SRT *vs*. 20% in patients receiving SRS/SRT + ICI
Colaco *et al*. (132)	Retrospective study involving 180 patients with BM from various tumor types	RT + ICI, CT, and/or TT	RN in 21.7% of patients including 16.9% in patients receiving RT + CT, 25.0% in patients receiving RT + TT, and 37.5% in patients receiving RT + ICI

RT, radiotherapy; ICI, immune checkpoint inhibitor; BM, brain metastases; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; PBI, partial brain irradiation; RN, radiation necrosis; SRT, stereotactic radiotherapy; CT, chemotherapy; TT, target therapy; AE, adverse event; TRIC, treatment-related imaging change.

further rigorous attempts to combine analysis of such unusual cases to uncover mechanistic insight are needed (135-139). Therapeutically, by analyzing the alters status of these resistance-related genes, which may also be known as

biomarkers, it would be beneficial to assess the weak responders and the chance of relapse. Thus, we could also used these biomarkers to select suitable BM patients for the treatment of RT and immunotherapy combination.

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Footnote

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References

1. Kumar Shah B, Pak I, Budhathoki N, et al. Targeted therapy for leptomeningeal metastases in non-small cell lung cancer - Changing treatment paradigms. Chin J Cancer Res 2017;29:535-42.
2. Kamath SD, Kumthekar PU. Immune checkpoint inhibitors for the treatment of central nervous system (CNS) metastatic disease. Front Oncol 2018;8:414.
3. Hartgerink D, van der Heijden B, De Ruysscher D, et al. Stereotactic radiosurgery in the management of patients with brain metastases of non-small cell lung cancer: Indications, decision tools and future directions. Front Oncol 2018;8:154.
4. Sevenich L. Turning "Cold" into "Hot" tumors-opportunities and challenges for radio-immunotherapy against primary and metastatic brain cancers. Front Oncol 2019;9:163.
5. Protopapa M, Kouloulias V, Nikoloudi S, et al. From Whole-brain radiotherapy to immunotherapy: A multidisciplinary approach for patients with brain metastases from NSCLC. J Oncol 2019;2019: 3267409.
6. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:522-30.
7. Leighl NB, Hellmann MD, Hui R, et al. Pembrolizumab in patients with advanced non-small-cell lung cancer (KEYNOTE-001): 3-year results from an open-label, phase 1 study. Lancet Respir Med 2019;7:347-57.
8. Horn L, Spigel DR, Vokes EE, 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.
9. Rossi S, Finocchiaro G, Marchetti S, et al. Checkpoint inhibitors: 'raising the bar' also in brain metastases from non-small-cell lung cancer? Immunotherapy 2018;10:403-10.
10. Iorgulescu JB, Harary M, Zogg CK, et al. Improved risk-adjusted survival for melanoma brain metastases in the era of checkpoint blockade immunotherapies: results from a national cohort. Cancer Immunol Res 2018;6:1039-45.
11. Di Giacomo AM, Ascierto PA, Queirolo P, et al. Three-year follow-up of advanced melanoma patients who received ipilimumab plus fotemustine in the Italian Network for Tumor Biotherapy (NIBIT)-M1 phase II study. Ann Oncol 2015;26: 798-803.
12. Schaue D. A century of radiation therapy and adaptive immunity. Front Immunol 2017;8:431.
13. Baskar R, Dai J, Wenlong N, et al. Biological response of cancer cells to radiation treatment. Front Mol Biosci 2014;1:24.
14. Eriksson D, Stigbrand T. Radiation-induced cell death mechanisms. Tumour Biol 2010;31:363-72.
15. Sahebjam S, Sharabi A, Lim M, et al. Immunotherapy and radiation in glioblastoma. J Neurooncol 2017;134:531-9.
16. Margolin K. Ipilimumab in a phase II trial of melanoma patients with brain metastases. Oncoimmunology 2012;1:1197-9.
17. Bai R, Li W, Du N, et al. Challenges of evaluating immunotherapy efficacy in solid tumors. Chin J Cancer Res 2019;31:853-61.
18. Lauko A, Thapa B, Venur VA, et al. Management of brain metastases in the new era of checkpoint inhibition. Curr Neurol Neurosci Rep 2018;18:70.
19. Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway. Nat Rev Immunol

2018;18:153-67.
20. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: Mechanisms of action, efficacy, and limitations. Front Oncol 2018;8:86.
21. Galea I, Bechmann I, Perry VH. What is immune privilege (not)? Trends Immunol 2007;28:12-8.
22. Preusser M, Lim M, Hafler DA, et al. Prospects of immune checkpoint modulators in the treatment of glioblastoma. Nat Rev Neurol 2015;11:504-14.
23. Engelhardt B, Vajkoczy P, Weller RO. The movers and shapers in immune privilege of the CNS. Nat Immunol 2017;18:123-31.
24. El Rassy E, Farhat F, Kattan J. The forgotten role of adjuvant immune checkpoint inhibitors in preventing melanoma brain metastasis. Immunotherapy 2018;10:1289-91.
25. Koelzer VH, Rothschild SI, Zihler D, et al. Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors-an autopsy study. J Immunother Cancer 2016;4:13.
26. Parakh S, Park JJ, Mendis S, et al. Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases. Br J Cancer 2017;116:1558-63.
27. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078-92.
28. Gadgeel SM, Lukas RV, Goldschmidt J, 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.
29. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012;13:459-65.
30. Goldberg SB, Gettinger SN, Mahajan A, 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.
31. Kluger HM, Chiang V, Mahajan A, et al. Long-term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. J Clin Oncol 2019;37:52-60.
32. Goldberg SB, Schalper KA, Gettinger SN, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. Lancet Oncol 2020;21:655-63.
33. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018;379:722-30.
34. Long GV, Atkinson V, Lo S, 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.
35. Williams NL, Wuthrick EJ, Kim H, et al. Phase 1 study of ipilimumab combined with whole brain radiation therapy or radiosurgery for melanoma patients with brain metastases. Int J Radiat Oncol Biol Phys 2017;99:22-30.
36. Skrepnik T, Sundararajan S, Cui H, et al. Improved time to disease progression in the brain in patients with melanoma brain metastases treated with concurrent delivery of radiosurgery and ipilimumab. Oncoimmunology 2017;6:e1283461.
37. Franceschini D, Franzese C, Navarria P, et al. Radiotherapy and immunotherapy: Can this combination change the prognosis of patients with melanoma brain metastases? Cancer Treat Rev 2016;50:1-8.
38. Lehrer E, Mcgee H, Peterson J, et al. Stereotactic radiosurgery and immune checkpoint inhibitors in the management of brain metastases. Int J Mol Sci 2018;19:3054.
39. Mctyre E, Scott J, Chinnaiyan P. Whole brain radiotherapy for brain metastasis. Surg Neurol Int 2013;4:S236-44.
40. Tarek M, Michael S, Robert S. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. Curr Oncol Rep 2011;13:255-8.
41. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy *vs*. stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. JAMA 2006;295:2483-91.

42. Kim H, Rajagopalan MS, Beriwal S, et al. Cost-effectiveness analysis of stereotactic radiosurgery alone versus stereotactic radiosurgery with upfront whole brain radiation therapy for brain metastases. Clin Oncol (R Coll Radiol) 2017;29:e157-e164.
43. Sun X, Deng L, Lu Y. Challenges and opportunities of using stereotactic body radiotherapy with anti-angiogenesis agents in tumor therapy. Chin J Cancer Res 2018;30:147-56.
44. Kirkpatrick JP, Soltys SG, Lo SS, et al. The radiosurgery fractionation quandary: single fraction or hypofractionation? Neuro Oncol 2017;19(suppl 2):ii38-ii49.
45. Li Z, Shen D, Zhang J, et al. Relationship between WBRT total dose, intracranial tumor control, and overall survival in NSCLC patients with brain metastases - a single-center retrospective analysis. BMC Cancer 2019;19:1104.
46. Priya V. SRS is non-inferior to WBRT for brain metastases. Lancet Oncol 2018;19:e386.
47. Ajithkumar T, Parkinson C, Fife K, et al. Evolving treatment options for melanoma brain metastases. Lancet Oncol 2015;16:e486-e497.
48. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009;10:1037-44.
49. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: A randomized clinical trial. JAMA 2016;316:401-9.
50. Kondziolka D, Shin SM, Brunswick A, et al. The biology of radiosurgery and its clinical applications for brain tumors. Neuro Oncol 2015;17:29-44.
51. Reynders K, Illidge T, Siva S, et al. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. Cancer Treat Rev 2015;41:503-10.
52. Hellevik T, Martinez-Zubiaurre I. Radiotherapy and the tumor stroma: the importance of dose and fractionation. Front Oncol 2014;4:1.
53. Kepp O, Senovilla L, Vitale I, et al. Consensus guidelines for the detection of immunogenic cell death. Oncoimmunology 2014;3:e955691.
54. Golden EB, Pellicciotta I, Demaria S, et al. The convergence of radiation and immunogenic cell death signaling pathways. Front Oncol 2012;2:88.
55. Ngwa W, Irabor OC, Schoenfeld JD, et al. Using immunotherapy to boost the abscopal effect. Nat Rev Cancer 2018;18:313-22.
56. Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 2009;114:589-95.
57. Grass GD, Krishna N, Kim S. The immune mechanisms of abscopal effect in radiation therapy. Curr Probl Cancer 2016;40:10-24.
58. Reits EA, Hodge JW, Herberts CA, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med 2006;203:1259-71.
59. Behjati S, Gundem G, Wedge DC, et al. Mutational signatures of ionizing radiation in second malignancies. Nat Commun 2016;7:12605.
60. Lauss M, Donia M, Harbst K, et al. Mutational and putative neoantigen load predict clinical benefit of adoptive T cell therapy in melanoma. Nat Commun 2017;8:1738.
61. Barber GN. STING: infection, inflammation and cancer. Nat Rev Immunol 2015;15:760-70.
62. Satoko M, Baomei W, Noriko K, et al. Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells. J Immunol 2008;181:3099-107.
63. Schaue D, Kachikwu EL, McBride WH. Cytokines in radiobiological responses: a review. Radiat Res 2012;178:505-23.
64. Liu C, Lin J, Zhao L, et al. Gamma-ray irradiation impairs dendritic cell migration to CCL19 by down-regulation of CCR7 and induction of cell apoptosis. Int J Biol Sci 2011;7:168-79.
65. Spiotto M, Fu YX, Weichselbaum RR. The intersection of radiotherapy and immunotherapy: mechanisms and clinical implications. Sci Immunol 2016;1::EAAG1266.
66. Van Limbergen EJ, De Ruysscher DK, Olivo Pimentel V, et al. Combining radiotherapy with immunotherapy: the past, the present and the future. Br J Radiol 2017;90:20170157.
67. Weichselbaum RR, Liang H, Deng L, et al.

Radiotherapy and immunotherapy: a beneficial liaison? Nat Rev Clin Oncol 2017;14:365-79.
68. Sato H, Niimi A, Yasuhara T, et al. DNA double-strand break repair pathway regulates PD-L1 expression in cancer cells. Nat Commun 2017;8: 1751.
69. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515: 563-7.
70. Forrester JV, McMenamin PG, Dando SJ. CNS infection and immune privilege. Nat Rev Neurosci 2018;19:655-71.
71. Jackson CM, Kochel CM, Nirschl CJ, et al. Systemic tolerance mediated by melanoma brain tumors is reversible by radiotherapy and vaccination. Clin Cancer Res 2016;22:1161-72.
72. Corso CD, Ali AN, Diaz R. Radiation-induced tumor neoantigens: imaging and therapeutic implications. Am J Cancer Res 2011;1:390-412.
73. Takeshima T, Chamoto K, Wakita D, et al. Local radiation therapy inhibits tumor growth through the generation of tumor-specific CTL: its potentiation by combination with Th1 cell therapy. Cancer Res 2010;70:2697-706.
74. Ahn GO, Tseng D, Liao CH, et al. Inhibition of Mac-1 (CD11b/CD18) enhances tumor response to radiation by reducing myeloid cell recruitment. Proc Natl Acad Sci U S A 2010;107:8363-68.
75. Russell JS, Brown JM. The irradiated tumor microenvironment: role of tumor-associated macrophages in vascular recovery. Front Physiol 2013; 4:157.
76. Smilowitz HM, Sasso D, Lee EW, et al. Therapy model for advanced intracerebral B16 mouse melanoma using radiation therapy combined with immunotherapy. Cancer Immunol Immunother 2013;62:1187-97.
77. Xia L, Wu H, Qian W. Irradiation enhanced the effects of PD-1 blockade in brain metastatic osteosarcoma. J Bone Oncol 2018;12:61-4.
78. Pfannenstiel LW, McNeilly C, Xiang C, et al. Combination PD-1 blockade and irradiation of brain metastasis induces an effective abscopal effect in melanoma. Oncoimmunology 2019;8:e1507669.
79. Murphy B, Walker J, Bassale S, et al. Concurrent radiosurgery and immune checkpoint inhibition: improving regional intracranial control for patients with metastatic melanoma. Am J Clin Oncol 2019;42: 253-7.
80. Acharya S, Mahmood M, Mullen D, et al. Distant intracranial failure in melanoma brain metastases treated with stereotactic radiosurgery in the era of immunotherapy and targeted agents. Adv Radiat Oncol 2017;2:572-80.
81. Mathew M, Tam M, Ott PA, et al. Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. Melanoma Res 2013;23: 191-5.
82. Anderson ES, Postow MA, Wolchok JD, et al. Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression;efficacy and safety of combined treatment. J Immunother Cancer 2017;5:76.
83. An Y, Jiang W, Kim BYS, et al. Stereotactic radiosurgery of early melanoma brain metastases after initiation of anti-CTLA-4 treatment is associated with improved intracranial control. Radiother Oncol 2017;125:80-8.
84. Qian JM, Yu JB, Kluger HM, et al. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. Cancer 2016;122: 3051-8.
85. Liniker E, Menzies AM, Kong BY, et al. Activity and safety of radiotherapy with anti-PD-1 drug therapy in patients with metastatic melanoma. Oncoimmunology 2016;5:e1214788.
86. Ahmed KA, Abuodeh YA, Echevarria MI, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. Ann Oncol 2016;27:2288-94.
87. Gerber NK, Young RJ, Barker CA, et al. Ipilimumab and whole brain radiation therapy for melanoma brain metastases. J Neurooncol 2015;121:159-65.
88. Silk AW, Bassetti MF, West BT, et al. Ipilimumab and radiation therapy for melanoma brain metastases. Cancer Med 2013;2:899-906.
89. Chen L, Douglass J, Kleinberg L, 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 Biol Phys 2018;100:916-25.
90. Yusuf MB, Amsbaugh MJ, Burton E, et al. Peri-SRS administration of immune checkpoint therapy for melanoma metastatic to the brain: investigating efficacy and the effects of relative treatment timing on lesion response. World Neurosurg 2017;100: 632-40.
91. Kiess AP, Wolchok JD, Barker CA, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. Int J Radiat Oncol Biol Phys 2015;92:368-75.
92. Choong ES, Lo S, Drummond M, et al. Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies. Eur J Cancer 2017;75:169-78.
93. Cohen-Inbar O, Shih HH, Xu Z, et al. The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab. J Neurosurg 2017;127:1007-14.
94. Amaral T, Kiecker F, Schaefer S, et al. Combined immunotherapy with nivolumab and ipilimumab with and without local therapy in patients with melanoma brain metastasis: a DeCOG* study in 380 patients. J Immunother Cancer 2020;8:e000333.
95. Patel KR, Shoukat S, Oliver DE, et al. Ipilimumab and stereotactic radiosurgery versus stereotactic radiosurgery alone for newly diagnosed melanoma brain metastases. Am J Clin Oncol 2017;40:444-50.
96. Rahman R, Cortes A, Niemierko A, et al. The impact of timing of immunotherapy with cranial irradiation in melanoma patients with brain metastases: intracranial progression, survival and toxicity. J Neurooncol 2018;138:299-306.
97. Schmidberger H, Rapp M, Ebersberger A, et al. Long-term survival of patients after ipilimumab and hypofractionated brain radiotherapy for brain metastases of malignant melanoma: sequence matters. Strahlenther Onkol 2018;194:1144-51.
98. Diao K, Bian SX, Routman DM, et al. Combination ipilimumab and radiosurgery for brain metastases: tumor, edema, and adverse radiation effects. J Neurosurg 2018;129:1397-406.
99. Fang P, Jiang W, Allen P, et al. Radiation necrosis with stereotactic radiosurgery combined with CTLA-4 blockade and PD-1 inhibition for treatment of intracranial disease in metastatic melanoma. J Neurooncol 2017;133:595-602.
100. Kaidar-Person O, Zagar TM, Deal A, et al. The incidence of radiation necrosis following stereotactic radiotherapy for melanoma brain metastases: the potential impact of immunotherapy. Anticancer Drugs 2017;28:669-75.
101. Martins F, Schiappacasse L, Levivier M, et al. The combination of stereotactic radiosurgery with immune checkpoint inhibition or targeted therapy in melanoma patients with brain metastases: a retrospective study. J Neurooncol 2020;146:181-93.
102. Singh C, Qian JM, Yu JB, et al. Local tumor response and survival outcomes after combined stereotactic radiosurgery and immunotherapy in non-small cell lung cancer with brain metastases. J Neurosurg 2019;132:512-7.
103. Hubbeling HG, Schapira EF, Horick NK, 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.
104. Lanier CM, Hughes R, Ahmed T, et al. Immunotherapy is associated with improved survival and decreased neurologic death after SRS for brain metastases from lung and melanoma primaries. Neurooncol Pract 2019;6:402-9.
105. Wang D, Wang ML, Li YH. Quantitative MRI study of the permeability of peritumoral brain edema in lung cancer patients with brain metastases. Brain Res 2017;1669:126-30.
106. Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017;390:1853-62.
107. Skrepnik T, Brookshier A, Romagnolo A, et al. Increased control of melanoma brain metastases after stereotactic radiosurgery as a function of timing of immunotherapy infusion. Int J Radiat Oncol Biol Phys 2016;96(suppl 2):S179-S179.
108. Weber JS, O'Day S, Urba W, et al. Phase I/II study of ipilimumab for patients with metastatic melanoma. J Clin Oncol 2008;26:5950-6.
109. Kim S, Ramakrishnan R, Lavillaalonso S, et al.

Radiation-induced autophagy potentiates immunotherapy of cancer via up-regulation of mannose 6-phosphate receptor on tumor cells in mice. Cancer Immunol Immunother 2014;63:1009-21.
110. Dovedi SJ, Adlard AL, Grazyna LB, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 2014;74:5458-68.
111. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378: 158-68.
112. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 2017;35:785-92.
113. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. N Engl J Med 2016;375:1767-78.
114. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of endocrine complications in cancer patients treated with immune check point inhibitors: a meta-analysis. Future Oncol 2016;12:413-25.
115. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol 2017;35:709-17.
116. Osorio JC, Ni A, Chaft JE, et al. Antibody-mediated thyroid dysfunction during t-cell checkpoint blockade in patients with non-small cell lung cancer. Ann Oncol 2017;28:583-9.
117. Di Giacomo AM, Ascierto PA, Pilla L, et al. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. Lancet Oncol 2012;13: 879-86.
118. Nieder C. Ipilimumab in patients with melanoma and brain metastases. Lancet Oncol 2012;13:e277-8.
119. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010;11: 155-64.
120. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014;32:1020-30.
121. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014;384:1109-17.
122. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015;16:908-18.
123. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521-32.
124. Arscott WT, Zhu S, Plastaras JP, et al. Acute neurologic toxicity of palliative radiotherapy for brain metastases in patients receiving immune checkpoint blockade. Neurooncol Pract 2019;6: 297-304.
125. Szeifert GT, Atteberry DS, Kondziolka D, et al. Cerebral metastases pathology after radiosurgery: a multicenter study. Cancer 2006;106:2672-81.
126. Lesueur P, Lequesne J, Barraux V, et al. Radiosurgery or hypofractionated stereotactic radiotherapy for brain metastases from radioresistant primaries (melanoma and renal cancer). Radiat Oncol 2018;13:138.
127. Kohutek ZA, Yoshiya Y, Chan TA, et al. Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases. J Neurooncol 2015;125:149-56.
128. Verma N, Cowperthwaite MC, Burnett MG, et al. Differentiating tumor recurrence from treatment necrosis: a review of neuro-oncologic imaging strategies. Neuro Oncol 2013;15:515-34.
129. Schoenfeld JD, Mahadevan A, Floyd SR, et al. Ipilmumab and cranial radiation in metastatic melanoma patients: a case series and review. J Immunother Cancer 2015;3:50.
130. Du Four S, Hong A, Chan M, et al. Symptomatic histologically proven necrosis of brain following stereotactic radiation and ipilimumab in six lesions in four melanoma patients. Case Rep Oncol Med 2014; 2014:417913.
131. Martin AM, Cagney DN, Catalano PJ, et al. Immunotherapy and symptomatic radiation necrosis

in patients with brain metastases treated with stereotactic radiation. JAMA Oncol 2018;4:1123-4.
132. Colaco RJ, Martin P, Kluger HM, et al. Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases? J Neurosurg 2016;125:17-23.
133. Suh JH, Kotecha R, Chao ST, et al. Current approaches to the management of brain metastases. Nat Rev Clin Oncol 2020;17:279-99.
134. Song M, Chen X, Wang L, et al. Future of anti-PD-1/PD-L1 applications: Combinations with other therapeutic regimens. Chin J Cancer Res 2018; 30:157-72.
135. Ascierto ML, Makohon-Moore A, Lipson EJ, et al. Transcriptional mechanisms of resistance to anti-PD-1 therapy. Clin Cancer Res 2017;23:3168-80.
136. Zaretsky JM, Garcia-Diaz A, Shin DS, et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med 2016;375: 819-29.
137. Gettinger S, Choi J, Hastings K, et al. Impaired HLA class I antigen processing and presentation as a mechanism of acquired resistance to immune checkpoint inhibitors in lung cancer. Cancer Discov 2017;7:1420-35.
138. Janjigian YY, Sanchez-Vega F, Jonsson P, et al. Genetic predictors of response to systemic therapy in esophagogastric cancer. Cancer Discov 2018;8: 49-58.
139. Li Y, Sun R. Tumor immunotherapy: New aspects of natural killer cells. Chin J Cancer Res 2018;30: 173-96.

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