

## REVIEW

# Combined irradiation and targeted therapy or immune checkpoint blockade in brain metastases: toxicities and efficacy

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**Background:** Targeted therapies (TT) and immune checkpoint inhibitors (ICI) are currently modifying the landscape of metastatic cancer management and are increasingly used over the course of many cancers treatment. They allow long-term survival with controlled extra-cerebral disease, contributing to the increasing incidence of brain metastases (BMs). Radiation therapy remains the cornerstone of BMs treatment (either whole brain irradiation or stereotactic radiosurgery), and investigating the safety profile of radiation therapy combined with TT or ICI is of high interest. Discontinuing an efficient systemic therapy, when BMs irradiation is considered, might allow systemic disease progression and, on the other hand, the mechanisms of action of these two therapeutic modalities might lead to unexpected toxicities and/or greater efficacy, when combined.

**Patients and methods:** We carried out a systematic literature review focusing on the safety profile and the efficacy of BMs radiation therapy combined with targeted agents or ICI, emphasizing on the role (if any) of the sequence of combination scheme (drug given before, during, and/or after radiation therapy).

**Results:** Whereas no relevant toxicity has been noticed with most of these drugs, the concomitant use of some other drugs with brain irradiation requires caution.

**Conclusion:** Most of available studies appear to advocate for TT or ICI combination with radiation therapy, without altering the clinical safety profiles, allowing the maintenance of systemic treatments when stereotactic radiation therapy is considered. Cognitive functions, health-related quality of life and radiation necrosis risk remain to be assessed. The results of prospective studies are awaited in order to complete and validate the above discussed retrospective data.

**Key words:** cerebral, radiation therapy, immunotherapy, combination, toxicity, radiosurgery

## Introduction

Brain metastases (BMs) management has evolved from whole-brain radiotherapy (WBRT) as a ‘one-size-fits-all’ policy to tailored treatments, in the context of new systemic agents, participating in brain control. Treatment options include surgery, stereotactic radiosurgery (SRS), WBRT, and systemic agents, alone or combined. Due to WBRT-induced neurotoxicity, stereotactic radiosurgery is increasingly considered in BMs management, even in multiple BMs setting, provided the disease burden is limited [1]. WBRT still remains the gold standard in patients with a large

burden of symptomatic disease. When asymptomatic and not functional-threatening, multiple BMs might be treated with systemic agents active on primary disease, postponing SRS or WBRT.

Tumor cells response to ionizing radiations involves the activation of various cellular signal transduction pathways, altering DNA-repair and cell-growth genes expression, some of them paradoxically promoting pro-oncogenes. Targeting the RT-activated signaling pathways promoting cell-proliferation, and thus radio-resistance, might enhance RT efficacy.

Moreover, RT has long been recognized as an immune-modulator, more recently known to promote cancer cell phenotype

changes, potentially making them better targets for immune cells reactivity [2]. The limited rate of solid tumor patients responding to immune checkpoint inhibitors (ICI) prompts for new investigations, especially for the use of combined therapies such as RT, in an attempt to enhance ICI efficacy.

We herein propose to overview the combination of RT and targeted therapies (TT) or ICI in patients with BM, focusing on its safety and efficacy. The sequence of treatment delivery will also be part of the discussion. Importantly, it must be noticed that the cumulative rate of RT adverse events, including radiation necrosis (RN) is directly linked to the median follow-up of surviving patients, rising with time with no plateau [3].

### Literature review search

We carried out a literature review search, using Medline PubMed and Web of sciences databases from 2000 to 2017 (March), focusing on studies investigating the safety and efficacy of TT or ICI associated with brain RT for BM. We identified and reviewed relevant clinical trials report in the international literature, and the reference list from these sources was manually searched for additional relevant trials. Review articles were not included. Data extracted from these studies included: number of patients evaluated in the combined treatment arm of the study, type of RT, administration sequence, mutation status if any, duration of the follow-up, disease control rate, median survival, overall survival (OS), and toxicities. RT was considered administered 'concurrently' with systemic therapy when administered in a period less than five half-lives of the drug (Table 1). Data extracted from text, tables and figures of the articles were then tabulated.

### Radiotherapy and targeted therapy

#### BRAF inhibitors

The mitogen-activated protein kinase (MAPK) pathway, activated after ionizing radiation exposure, leads to cell proliferation, survival, and differentiation. Reversing this paradoxical ionizing radiation-effect, through MAPK signaling pathway inhibition, was successfully tested in pre-clinical models, leading to tumor cells radio-sensitivity enhancement [4, 5].

Some case reports suggested unexpected toxicities in the portal field area, when combining RT and BRAF inhibitors (BRAF-I) [6–13].

**WBRT and BRAF-I.** In six out of eight studies or case reports [7–9, 11, 13–16] examining the tolerance of WBRT combined with BRAF-I, patients were given BRAF-I *before and during* WBRT [7–9, 11, 13, 16]. Four case reports warned against severe skin side-effects, despite partial response or stable disease [7, 9, 11, 13]. Severe skin-toxicity was mainly limited to the irradiated area, and resembled cutis vercitis gyrate. It occurred a few weeks after WBRT completion, and in most cases ceased up under symptomatic therapeutic, Vemurafenib being maintained without toxicity recurrence. One study retrospectively compared 123 metastatic melanoma patients treated with WBRT with ( $n = 32$ ) or without ( $n = 91$ ) concomitant BRAF-I [8]. Grade  $\geq 2$  radiodermatitis was more frequent in

**Table 1. Drugs half-lives (approximate values, from transparency commissions)**

Drug	Median half-life (h)
Vemurafenib	51.6 (29.8–119.5)
Dabrafenib	8 (when orally administered)
Trametinib	127
Erlotinib	36.2
Gefitinib	41
Sunitinib	95
Bevacizumab	480
Trastuzumab	456
Lapatinib	24
Trastuzumab-emtansine	96
Ipilimumab	370
Pembrolizumab	600
Nivolumab	578

patients receiving combined treatment (44% versus 8%). BRAF-I dose-reduction did not reduce the skin toxicity rate. Vemurafenib was most likely to enhance skin toxicity than Dabrafenib, follicular cystic proliferation only appeared in patients taking Vemurafenib. Nonetheless, no severe late skin-related toxicity was reported. Conversely, no increased skin toxicity and no other severe adverse event was observed with SRS combined with BRAF-I therapy (Table 2).

A case report related a radiation recall in a patient treated with Vemurafenib initiated *after* WBRT completion, while complete response was observed at 3 months [14].

In Narayana et al.'s retrospective study, more than half of the 12 patients were previously treated with ipilimumab (Ipi). The toxicity was not analyzed according to the sequence of Vemurafenib administration, and was reported as low with no intra-tumor hemorrhage (Table 2). In this small series, response rate (RR) appeared improved (complete response: 48%) [15].

In summary, it is not recommended to continue Vemurafenib administration during WBRT; minimally, patients should be closely monitored with early supportive care intervention.

**SRS and BRAF-I.** Reported toxicities were increased risk of intra-tumor hemorrhage [17] and RN [10, 15, 18, 19] which was not found in all studies; however the follow-up period was too short to actually assess RN risk.

Seven studies or case reports analyzed the safety profile of BRAF-I combined with SRS, with treatment sequencing detailed [10, 16–21]. Five authors reported on 1–24 patients treated with Vemurafenib or Dabrafenib, given *before and during* SRS [10, 16, 17, 20, 21]. Local control (LC) showed mixed results and brain control appeared not improved. Only one case report noticed a severe RN in a melanoma BM patient treated with SRS while on Vemurafenib first line, started 3 months before [10]. Patel et al. [19] analyzed 87 melanoma patients with BM, among whom only 15 were treated with SRS while on BRAF-I. They found significantly increased RN rate in patients submitted to the combined treatment, without improved brain control. Two authors reported on 1, and 17 patients, respectively, treated with *combined BRAF-I and SRS, with a washout period* [21, 22]. Ly et al. noticed

Table 2. RT and BRAF inhibitors

Study	Primary	n	RT	Drug	Brain control	Median Survival	Toxicity/type	Median follow-up (months)
Peuvrel et al. [10]	Melanoma	1	SRS	Vemurafenib Before-during SRSa	Brain PD	9 mo	Severe RN	9
Reigneau et al. [11]	BRAFV600-mutated melanoma	1	WBRT	Vemurafenib Before-during WBRTa	NR	NR	Radiation recall (grade 3 skin toxicity)	7
Harding et al. [7]	Melanoma	2	WBRT	Vemurafenib Before-during WBRTa	NA	NA	Cutis verrucosus gyrate-like skin thickening	4
Schulze et al. [13]	Melanoma	2	WBRT	Vemurafenib Before-during WBRTa	NR	NA	Skin toxicity: multiple cystic lesions	3
Lang et al. [9]	BRAFV600-mutated melanoma	1	WBRT	Vemurafenib Before-during WBRTa	NA	NA	Cutis verrucosus gyrate-like skin thickening	5
Hecht et al. [8]	Melanoma	32	WBRT	Vemurafenib Dabrafenib Before-during WBRTa	NR	NR	Increased acute radio-dermatitis (grade 2: 44% versus 8% without BRAF)	6.6
Rompoti et al. [16]	Melanoma	5	SRS (2) WBRT (3)	Vemurafenib Dabrafenib Before-during RTa	NR	NR	Grade 2 skin toxicity in WBRT group	3
Forschner et al. [14]	BRAFV600-mutated Melanoma	1	WBRT	Vemurafenib After WBRT	CR	NR	Radiation recall (grade 3 skin toxicity)	3
Narayana et al. [15]	BRAFV600-mutated Melanoma	12	WBRT, PBRT, and/or SRS	Vemurafenib before/after RT	Brain 57%	(OS 6mo) 92%	1 RN (with SRS) 2 intracranial edema	12.2
Ahmed et al. [17]	BRAF V600E-mutated Melanoma	24	SRS	Vemurafenib Hold for 2–3 days before and after SRS	(1-y) 23%	7.2 mo	No increased toxicity	5.1
Patel et al. [19]	Melanoma	15	SRS	Vemurafenib Dabrafenib concurrently	(1-y) 36.1% (not > SRS alone)	(1-y OS) 64.3% (not > SRS alone)	RN rate increased (1-y rate: 28% versus 11% without BRAFi)	6.5
Liebner et al. [18]	BRAFV600E-mutated melanoma	2	SRS SRT	Vemurafenib After SRT	NA	NA	RN	4
Gaudy-Marquestre et al. [20]	Melanoma	30	SRS	Vemurafenib 26 Dabrafenib 4 Before-during (24) After (6)	(6mo) 25%	5.2 mo	No relevant toxicity	6

Continued

Table 2. Continued

Study	Primary	n	RT	Drug	Brain control	Median Survival	Toxicity/type	Median follow-up (months)
Xu et al. [21]	Melanoma (BRAFV600E-mutated or not)	17	SRS +/- WBRT	Vemurafenib: 12 During SRS: 2 After SRS: 10 Dabrafenib: 5 Washout 8d: 1 After SRS: 4	NR	92% (higher than SRS without BRAF-I)	No increased toxicity	3
Ly et al. [22]	BRAFV600-mutated melanoma	17	SRS	Vemurafenib Dabrafenib before/after SRS, not concurrently	Not improved	(1-y) 85% (versus 51.5% WT)	ITH rate increased	10.5
Wolf et al. [23]	BRAFV600E-mutated melanoma	31	SRS	Dabrafenib: 15 Vemurafenib: 9 Dabrafenib/ Trametinib: 7 Before SRS: 1 During SRS: 18 After SRS: 12		92.5% (not > WT)	No significantly increased ITH (17.9% versus 10.3% WT)	12

<sup>a</sup>BRAF-I were considered administered during radiation therapy when they were administered less than 5 half-lives before or after radiation therapy.

RT, radiation therapy; SRS, stereotactic radiosurgery; SRT, fractionated stereotactic RT; OS, overall survival; WBRT, whole brain radiation therapy; PBRT, partial brain radiation therapy; WT, wild type; RN, radiation necrosis; ITH, intra-tumor hemorrhage; BRAFi, BRAF inhibitor; PD, progressive disease; CR, complete response; NR, not reported; NS, not significant; NA, not applicable.

in BRAF-I-treated patients, significantly higher intra-tumor hemorrhage rate and higher LC than in patients treated with SRS without inhibitor [22]. Three authors reported on 2–14 patients treated with BRAF-I *after* SRS [18, 20, 21]. Two of them found no relevant toxicity, and improved LC [20, 21], whereas the other reported a RN in a patient previously treated with SRS twice before the initiation of Vemurafenib [18].

Four studies compared patients treated with SRS with or without BRAF-I [19, 21–23]. Two of them reported significantly increased brain-toxicity in the combined treatment arm [19, 22], the two other found no significant difference in intra-tumor hemorrhage rate [21, 23]. Analysis of patients outcomes in these four studies also provided mixed results: LC was not altered by the use of concomitant BRAF-I in two studies [19, 23], and seemed improved in two other studies [18, 21, 22]; BRAF-I had no impact on distant brain control; OS was not altered by the use of concomitant BRAF-I in two studies [19, 22], and was improved in the two other studies [21, 23].

BRAF-I interruption before gamma-knife procedure did not have any impact on toxicity rate [22] and a good safety profile of SRS combined with Dabrafenib and Trametinib (MEK-inhibitor) was reported in a small series of six melanoma patients with BM [24].

In summary, an ongoing BRAF-I treatment can be maintained during SRS, since it would not enhance the toxicity risk. The combination of BRAF-I and SRS, assessed in small and heterogeneous series, showed mixed results relative to both LC and tolerance. Toxicity seemed to be independent of BRAF-I administration sequence. The combination of BRAF-I and SRS, as well as its optimal sequencing, both remain to be assessed.

### Tyrosine kinase inhibitors/anti-epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR) signal transduction pathway activation elicits intracellular signals promoting tumor cells proliferation, differentiation, and survival. There are three main reasons to combine EGFR-inhibitors and RT: (i) EGFR signaling pathway has been identified to induce tumor cells radio-resistance, by several mechanisms, including accelerated tumor clonogen repopulation, reduction of radiation-induced apoptosis [25–27], in tumors with high level of EGFR; (ii) RT has been shown to enhance EGFR signaling pathway [25, 26]; and (iii) many solid tumors show EGFR overexpression, known as prognostic of worse clinical outcome. Thus, the use of EGFR-inhibitors might circumvent the radio-resistance of EGFR-enriched tumors. Pre-clinical studies have suggested a synergistic effect of tyrosine kinase inhibitors (TKIs) and RT combination.

However, clinical studies of combined TKIs and RT are conflicting, relative to efficacy and toxicity, both in retrospective and prospective studies [28–43] (Table 3).

**Erlotinib/gefitinib.** Four randomized trials compared molecularly unselected non-small-cell lung cancer (NSCLC) patients with BM treated with WBRT (+/– SRS) and TKIs or WBRT (+/– SRS) alone or combined with chemotherapy [32, 37–39]. RR or brain control, as well as OS seemed not improved by TKI delivery, only one study reported improved median survival (13.3 versus 12.7 months,  $P < 0.05$ ) [39]. The RTOG 0320 trial found

significantly increased grade 3–5 toxicity rate, whereas the other studies reported a good safety profile.

Four prospective trials found no increased neuro-toxicity when combining TKIs and WBRT [33, 40, 42, 43], two of them reporting improved LC and OS in patients treated with erlotinib and WBRT [40, 43]. Another trial reported significantly higher RR in patients with EGFR-mutant disease (83.33% versus 11.11% in patients with EGFR wild-type disease) [42].

Among six retrospective trials assessing the concomitant use of TKIs and WBRT for NSCLC patients with BM [28, 31, 34–36, 41] only one small retrospective study, including eight patients, reported unexpected systemic toxic effects in half the patients treated with erlotinib combined with WBRT [36]. The authors hypothesized that these toxicities (myelosuppression, mental status changes, respiratory failure) might originate from drug–drug interaction, particularly with steroid and anti-fungal medication. In a case report, Huang et al. [30] described a severe *skin reaction* in the radiation field and bilateral subdural hemorrhage occurring 11 days after WBRT completion in a patient treated with Gefitinib switched for erlotinib without gap during WBRT, with erlotinib maintenance. In a retrospective study, the concomitant use of EGFR-TKI and WBRT was shown to be an independent risk-factor for grade 2 leukoencephalopathy [44].

RR (ranging from 25% to 81%) *were not improved compared with RT alone in none of these studies*; conversely, OS was increased compared with WBRT alone in three of them, although a comparative arm was not always present [28, 34, 41].

**Icotinib.** The concomitant use of Icotinib and WBRT was found efficient and safe in 20 molecularly unselected NSCLC patients [29], and in a phase I dose-escalating study [45].

Two recent meta-analyses assessed the efficacy and safety of TKIs plus radiotherapy (WBRT/SRS) versus conventional chemotherapy plus radiotherapy or radiotherapy alone [46, 47]. Both meta-analyses found that TKI-group produced significantly higher RR, better median OS, and higher CNS time to progression than non-TKI-group, *at the expense of increased incidence of adverse effects*, especially skin toxicity.

To summarize, the efficacy of TKI concurrently administered with WBRT in molecularly unselected NSCLC BM patients, has not been confirmed in four randomized trials; nonetheless two recent meta-analyses suggest different results. The safety of the combination has been usually reported as acceptable, whereas some studies warned against unexpected ‘in field’ skin toxicity and a meta-analysis reported higher incidence rate of overall adverse effects, especially rash and dry skin [46]. Consequently, the concurrent use of TKIs with WBRT must be prescribed with caution, particularly with regard to the concomitant use of other medication such as steroids. Moreover, considering not only the EGFR mutational status, but also EGFR-mutation patterns might provide further insight into the role of TKIs and RT in NSCLC BM patients [48].

### Multi-kinase inhibitors

RT increases VEGF expression (one of the most important angiogenesis cytokine), as well as it enhances the expression/inhibition of other angiogenesis factors (Ang-2, Ang-1, and their receptor Tie-2), and of tumor growth factors (TGF $\alpha$ , MAPK) [26, 49–51].

Table 3. RT and TKIs

Study	Primary	n	RT	Drug	Brain control	Local	Median Survival	Toxicity/type	Median follow-up (months)
RTOG 0320 [38]	NSCLC EGFR status unknown	41	WBRT + SRS	Erlotinib Concurrent with WBRT	Brain 80%	Local NR	6.1	Grade 3-4: 49% (versus 11% WBRT+SRS alone) Grade 4=BN Grade 5=HS Increased rash rate (20% versus 5% with placebo) Neurotoxicity not increased Grade 3 rash: 15% Neurotoxicity: 5% (1dementia, 1 RN) No treatment-related neurotoxicity Unusual grade 3-4 toxicities: 2 grade 3 hepatotoxicity 2 grade 3-4 lymphocytopenia 1 grade 4 neutropenia → † 3 grade 3-5 hyponatremia	33.6
Lee et al. [32]	NSCLC Molecularly unselected	40	WBRT	Erlotinib Concurrent with WBRT	(2 mo) 38.9%	NR	3.4	No increased toxicity Grade 3-4: Skin: 2.6%, diarrhea: 2.6%, hepatotoxicity: 2.6%, headache: 5.1%	12.6
Zhuang et al. [43]	NSCLC Molecularly unselected	23	WBRT	Erlotinib Concurrent with WBRT	NR	(1-y) 91.3%	10.7	No increased toxicity	NR
Welsh et al. [40]	NSCLC Molecularly unselected	40	WBRT	Erlotinib Concurrent with WBRT	(1y) 70%	NR	11.8	Grade 3 rash: 15% Neurotoxicity: 5% (1dementia, 1 RN)	28.5
Lind et al. [33]	NSCLC Molecularly unselected	11	WBRT	Erlotinib Concurrent with WBRT	(3 mo) 100%	NR	4.3	No treatment-related neurotoxicity	3
Olmez et al. [36]	NSCLC EGFR status unknown	8	WBRT	Erlotinib Concurrent with WBRT	NA	NA	1.5	Unusual grade 3-4 toxicities: 2 grade 3 hepatotoxicity 2 grade 3-4 lymphocytopenia 1 grade 4 neutropenia → † 3 grade 3-5 hyponatremia	3
Lu and Fan [34]	EGFR-mutated NSCLC	39	WBRT	Erlotinib Gefitinib Icotinib Concurrent with WBRT	NR	NR	26	No increased toxicity Grade 3-4: Skin: 2.6%, diarrhea: 2.6%, hepatotoxicity: 2.6%, headache: 5.1%	25
Kim et al. [31]	EGFR-mutated NSCLC	18	SRS	Erlotinib Gefitinib	83%	NR	37.1	No increased toxicity	NR

Continued

Table 3. Continued

Study	Primary	n	RT	Drug	Brain control	Median Survival	Toxicity/type	Median follow-up (months)
Cai et al. [28]	NSCLC Molecularly unselected	65	WBRT	Erlotinib (43) Gefitinib (22) Concurrent with WBRT	NR	10.6	No increased toxicity	21
Pesce et al. [37]	NSCLC EGFR status unknown	16	WBRT	Gefitinib Concurrent with WBRT	NR	6.3	No relevant toxicity	34
Wang et al. [39]	NSCLC Molecularly unselected	37	WBRT	Gefitinib Concurrent with WBRT	NR	13.3	No relevant toxicity	13.6
Zeng et al. [42]	NSCLC Molecularly unselected	15	WBRT	Gefitinib Concurrent with WBRT	NR	15.4	No relevant toxicity	15.4
Ma et al. [35]	NSCLC EGFR status unknown	21	WBRT	Gefitinib Concurrent with WBRT	NR	13	No increased toxicity	15
Zeng et al. [41]	NSCLC Molecularly unselected	45	WBRT	Gefitinib Concurrent with WBRT	NR	23.4	No increased toxicity	23
Fan et al. [29]	NSCLC Molecularly unselected	20	WBRT	Icotinib Concurrent with WBRT	NR	14.6	No relevant toxicity	20

RT, radiation therapy; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; NSCLC, non-small cell lung cancer; OS, overall survival; BN, brain necrosis; HS, hemorrhagic stroke; RN, radiation necrosis; NR, not reported; NA, not applicable.

Table 4. Multi-kinase inhibitors and RT

Study	Primary	n	RT	Drug	Brain control	Median survival	Toxicity	Median follow-up (months)
Bates et al. [52]	RCC	25 KI: 7 No KI: 18	WBRT (5) SRS (2)	Sorafenib Sunitinib Pazopanib temsirolimus	NS	NS	No increased toxicity	NR
Verma et al. [56]	RCC	81 KI: 40 No KI: 41	SRS	Sorafenib Sunitinib Before BM After BM No TKI	1-y: 53% 1-y: 90% 1-y: 74%	Better in patients receiving TKI at the onset of BM	No increased toxicity	5.4
Cochran et al. [53]	RCC	61 KI: 24 No KI: 37	SRS	TKI mTORi bevacizumab	1-y LC: 93.3% (versus 60% without TT)	16.6 mo (versus 7.2 mo without TT)	No increased toxicity	NR
Stahler et al. [54]	RCC	51	SRS	Sorafenib (29) Sunitinib (22)	1-y: 100% 2-y: 96.6%	11.1 mo	3 seizures 1 BH gr5	14.7
Stahler et al. [55]	RCC	3	WBRT	Sunitinib	NR	NR	No increased toxicity	14.3
Wuthrick et al. [58]	multiple	15	WBRT PBRT	Sunitinib	NR	NA	2 grade 3 fatigue	34.2
Langrand-Escure et al. [57]	RCC	20	WBRT	Sunitinib Sorafenib Axitinib mTORi bevacizumab	NR	NR	2 grade 3: Confusion IHT	9.5

BH, brain hemorrhage (supposed due to systemic progression); IHT, intracranial hypertension; RT, radiation therapy; RCC, renal cell carcinoma; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; PBRT, partial brain radiotherapy; NR, not reported; NS, not significant; NA, not applicable; TKI, tyrosine kinase inhibitors; mTORi, mammalian target of rapamycin inhibitors.

In murine experimental models, low doses of ionizing radiation have indeed been shown to promote tumor growth and metastasis through VEGFR2 activation. Prior use of TKI targeting VEGFR prevented this effect [50].

Data from retrospective studies assessing the multi-kinase inhibitors (mKI) impact on LC and survival are conflicting [52–56] (Table 4). Nonetheless, they all agree on a good toxicity profile of the combination, allowing the continuation of this systemic treatment when brain RT is considered.

Three studies retrospectively compared BM patients treated with brain RT with or without mKI [52, 53, 56]. Whatever the RT scheme (WBRT, SRS, or both), the combined therapy was safely administered without significantly increased toxicity compared with patients treated with RT alone. Concurrent mKI use seemed to improve LC in only one out of these three studies [53], improving median survival in two reports [53, 56]; in the Verma et al.'s study, there was an imbalance for further systemic treatment between the groups [56]. An improved OS was observed only in the group taking TKI *at the onset* of BM, but not in those developing BM while on mKI.

Four other studies retrospectively analyzed BM patients treated with brain RT and combined KI, without control group [54, 55, 57, 58]. Two of them found that both SRS and WBRT did not enhance the adverse effects of mKI, although one among 22 patients

treated with sunitinib and SRS experienced fatal bleeding while on treatment with sunitinib 3 months after SRS [54, 55]. In one another study, 7 out of 15 patients (47%) experienced grade 3 toxicity, only two were thought to be attributable to the combination treatment (fatigue) [58]. The fourth study reported two grade 3 toxicities (10%) in patients treated with mKI and WBRT (one confusional state, and one intracranial hypertension). Two trials reporting RRs found excellent LC with SRS-mKI combination, whereas sunitinib and WBRT combination achieved partial response in 20% of patients [54, 58].

In summary, there is no definitive argument to conclude on the efficacy/toxicity ratio of RT and mKI.

### Anti-angiogenic agents

The combination of anti-angiogenic agents with RT had initially been avoided due to the potential risk of brain hemorrhage. Subsequently, some studies (particularly in primary brain tumors), proved its safety, with some efficacy on tumor control. The anti-angiogenic agents and RT combination was thus considered with the objective to increase tumor brain control.

Anti-angiogenic agents mainly act through vascular endothelial growth factor (VEGF) inhibition. Their objective is to deprive the tumor of oxygen and nutrients. However, many other



signaling pathways, some of them radiation-activated, are able to promote angiogenesis, thus, the optimal use of anti-angiogenic agents, including as radiosensitizers, remains a wide field to be elucidated. Experimental studies showed that the advantage of antiangiogenic agents given concomitantly with RT partly relies on their ability to modify the neo-vasculature structure, becoming less ‘anarchic’, at least during a critic period (named ‘normalization window’), in which hypoxia could be decreased, allowing enhancement of RT anti-tumor activity [59, 60]. Other mechanisms leading to increased tumor cells apoptosis have also been described [61, 62].

Bevacizumab combined with focal brain RT has been shown to improve progression-free survival in primary brain tumors [63, 64]. Its efficacy and safety profile have been suggested in a phase I study when combined with WBRT in BMs patients [65]. To our knowledge, there is no more advanced study relative to this treatment combination in the setting of BMs.

## Anti-HER2

**Trastuzumab.** Curie Institute retrospectively assessed 31 HER2+ breast cancer (BC) patients with BMs receiving WBRT and Trastuzumab concomitantly [66]. The median time to progression was 10.5 months. A complete resolution of symptoms was observed for 74.2% of the patients. Six patients (19.4%) had a complete radiological response, and partial response was achieved in 17 patients (54.8%). Treatment was well tolerated, only 7 patients (23%) had nausea grade 1 and 2, asthenia and headache. The passage of Trastuzumab through the blood–brain barrier into the cerebrospinal fluid (CSF) could be improved after radiotherapy. Stemmler et al., found a ratio serum/CSF of 420 : 1 in 5 patients irradiated in the brain against 76 : 1 in 3 patients without brain RT [67]. These results suggest a potential tumor response benefit of trastuzumab continued during radiotherapy.

**Lapatinib.** A phase I trial attempted to define the maximum tolerated dose of concurrent lapatinib with WBRT. This trial was not conclusive due to important toxicity other than neurologic. However, among 28 assessable patients, the brain objective RR was 79% [68]. The data of the phase II WBRT concurrently administered with lapatinib in patients with BM from HER2+ BC are pending for 2018.

Yomo et al. [69] retrospectively analyzed 40 HER2+ BC patients treated with ( $n = 26$ ) or without ( $n = 14$ ) lapatinib. The median follow-up time after SRS was 10.3 months. There was no significant difference in OS between the two groups but the lapatinib group was associated with an improved 1-year LC rate (86% versus 69%;  $P < 0.001$ ), which suggests a synergic action of lapatinib and SRS. Tolerance was acceptable.

**T-DM1.** There is a strong rationale supporting the combination of antibodies–drug conjugates (ADCs) and RT, since ADCs are considered to specifically target cancer cells (overexpressing targeted antigen). There is no pre-clinical available data about the combination of radiotherapy and T-DM1. Clinical data remain scarce, mainly based on case reports. While T-DM1 associated with WBRT showed encouraging RR without side-effects [70, 71], three case reports raised the problem of recall effect in patients previously treated with SRS, then with T-DM1 [72–74].

Carlson et al. reported a high number of significant RN, in a series of seven patients with BM from HER2+ BC, treated with T-DM1 and SRS. Four out of seven patients experienced shortly after T-DM1 infusion, a symptomatic cerebral edema. One patient had to undergo resection of a metastasis and pathology revealed severe RN with no viable tumor cells [72]. Recently, Mitsuya et al. reported on two cases of RN aggravation, far away from SRS delivery, at the time of T-DM1 initiation [74]. A significant number of RN has been reported in a series of eight patients treated with T-DM1 concomitant with SRS for HER2+ BC BM.

In summary, keeping in mind the paucity of data, LC was commonly improved with anti-HER2 agents associated with RT, but, whereas the association of Trastuzumab and RT has not shown any tolerance issue, as well as lapatinib combined with SRS or T-DM1 combined with WBRT, concomitant delivery of SRS with T-DM1 or lapatinib with WBRT should require caution [68, 73].

## RT and immune checkpoint blockade

RT is well known to induce immunological changes both in the tumor and in its microenvironment (through the promotion of effector immune cells recruitment), and to potentially induce systemic responses due to anti-tumor immunity promotion (‘abscopal’ effect), via several mechanisms, including enhancement of tumor antigens release, exposure of novel tumor antigens, increase of immunogenic cell death, and increase of pro-inflammatory cytokines activating T cells [75]. Through its action, particularly on the tumor microenvironment, RT might ‘facilitate’ immunotherapies such as ICI, but has also immunosuppressive effects [75]. Recent pre-clinical studies have suggested a synergy between RT and immunotherapies [76–79], potentially more efficient when ICI is not delayed after the RT completion [76]. The efficiency of RT and ICI combination is currently under investigation, in order to identify the optimal timing of the combination, the optimal RT dose per fraction and the effect of the combination according to the irradiated site [80].

Most available clinical studies are retrospective. They included melanoma BM patients, mainly treated with Ipi (a fully human monoclonal antibody that promotes anti-tumor T cells) and RT (mainly SRS). These studies suggested an increased OS with the combined treatment (specifically when Ipi was administered concurrently with RT), without increased toxicity, *although delayed RN, intra-tumor hemorrhage and edema remain to be fully assessed* [81–87] (Table 5).

## SRS+/- Ipi

Four studies retrospectively compared patients treated with SRS with or without Ipi [83–86]. Three of them compared LC, as well as toxicity and response rates [84–86]. RRs as well as toxicity were similar between patients treated with SRS with or without Ipi. All the four studies compared median survivals; two of them found comparable survival outcomes [84, 85]; two other studies found improved median survival in patients treated with Ipi, possibly suggesting that an optimal timing of the combination might have an impact on patient outcome.

Four studies investigated the impact of Ipi administration timing relative to RT [82, 83, 85, 86]. Two studies found a positive

Table 5. Immune checkpoint inhibitors and RT

Study	Primary	n	RT	Drug	Brain control	Median survival	Toxicity	Median follow-up (months)
Patel et al. [85]	Melanoma	20	SRS	Ipilimumab 1 during SRS 12 before SRS 7 after SRS	Not improved versus SRS alone	Not improved versus SRS alone (8 versus 9.1 mo)	No increased toxicity	7.3
Knisely et al. [83]	Melanoma	77	SRS	Ipilimumab 27 + SRS: 11 before SRS 16 after SRS	Brain 37% local NR	21.3 mo (versus 4.9 without ipi) No ≠ before/after	NR	NR
Silk et al. [86]	Melanoma	70	WBRT (16) SRS (17)	Ipilimumab 33 + RT: 12 before RT 21 after RT	Not significantly increased in ipi group	18.3 mo (versus 5.3 without ipi) 8.1 mo 18.4 mo (OS 6 mo) 56%	No neuro-toxicity (ipi)	10
Mathew et al. [84]	Melanoma	58	SRS	Ipilimumab 25 + SRS 4 before SRS 7 during SRS 10 after SRS	65%	56%	No increased toxicity	6
Kiess et al. [82]	Melanoma	46	SRS	33 without ipi Ipilimumab 15 during SRS, 19 before SRS, 12 after SRS	63% brain 31% 36% 8% 89%	46% (NS) (1-y OS) 65% 56% 40%	during SRS : no relevant toxicity before SRS: ITH (13%/0 <sup>a</sup> ), seizure (13%/0 <sup>a</sup> ) after SRS: ITH (6/3 <sup>a</sup> )	22
Tazi et al. [87]	Melanoma	10	SRS	Ipilimumab During or after SRS	56%	16.5 mo 3-y OS: 50% 4 mo	No increased toxicity	NR
Gerber et al. [88]	Melanoma	13	WBRT	Ipilimumab 4 before WBRT 6 during WBRT 3 after WBRT	56%		1 grade 3 cognitive change 100% new or worsening ITH	4
Cohen-Inbar et al. [89]	Melanoma	46	SRS	Ipilimumab 14 before SRS 32 during/after SRS	33.6% 50.4% 100%	64 mo 13.8 mo NA	RN and post-SRS edema increased when Ipi was administered during or after SRS pseudo clinical and radiological progression	7.9 6
Alomari et al. [90]	Melanoma NSCLC	2	SRS	Pembrolizumab Nivolumab + ipilimumab	100%			6
Ahmed et al. [91]	Melanoma	26	SRS	Nivolumab During (washout 6d)/ before/after	(1-y) 53%	(1-y) 85%	ITH: 5% Grade 3 oedema: 10%	9.4

<sup>a</sup>x%/x%= grade 3/grade 4.

ipi, ipilimumab; RT, radiation therapy; SRS, stereotactic radiosurgery; OS, overall survival; WBRT, whole-brain radiation therapy; NSCLC, non-small-cell lung cancer; NR, not reported; NS, non-significant; NA, not applicable; ITH, intra-tumor hemorrhage.

Table 6. Ongoing trials of RT combined with TT or ICB

Pharmaceutic class	Study reference	RT scheme and drug	Title	State
BRAF-I	NCT01721603	SRS, dabrafenib	A phase 2 prospective trial of dabrafenib with stereotactic radiosurgery in BRAFV600E melanoma brain metastases	Completed
	NCT02974803	SRS, dabrafenib and trametinib	Concurrent dabrafenib and trametinib with stereotactic radiation in patients with BRAF mutation-positive malignant melanoma and brain metastases	Not yet recruiting
TKIs	NCT01130779	WBRT/SRS, erlotinib	The continuation of erlotinib	Unknown
	NCT02882984	WBRT/HFSRS, gefitinib/tarceva/lotinib	Hypofractionated brain radiation in EGFR-mutated adenocarcinoma cranial disease (hybrid)	Recruiting
	NCT01234740	WBRT/SRS, bafetinib	Bafetinib in treating patients with recurrent high-grade glioma or brain metastases	Completed
Multi-KI	NCT00981890	SRS, sunitinib	Stereotactic radiosurgery with sunitinib for brain metastases	Active, not recruiting
	NCT02019576	SRS, sunitinib	Stereotactic radiotherapy for metastatic kidney cancer being treated with sunitinib	Recruiting
	NCT01276210	SRS, sorafenib	Sorafenib tosylate and stereotactic radiosurgery in treating patients with brain metastases	Active, not recruiting
	NCT02132598	WBRT/SRS, cabozantinib	Trial of cabozantinib (XL184) in non-small cell lung cancer with brain metastases	Recruiting
Antiangiogenic agents	NCT02672995	SRS, bevacizumab	Fractionated stereotactic radiosurgery with concurrent bevacizumab for brain metastases: a phase I dose-escalation trial	Recruiting
	NCT02162537	WBRT/SRS, cisplatinemetrexed-bevacizumab	Multicentric, randomized, Phase III Trial Comparing 2 strategies in patients with non-squamous non-small cell lung cancer with asymptomatic	Recruiting
Anti-HER2	NCT01622868	WBRT/SRS, lapatinib ditosylate	Whole-brain radiation therapy or stereotactic radiosurgery with or without lapatinib ditosylate in treating patients with brain metastasis From HER2-positive breast cancer	Recruiting
Anti-CTLA4	NCT02097732	SRS, ipilimumab	Ipilimumab induction in patients with melanoma brain metastases receiving stereotactic radiosurgery	Active, not recruiting
	NCT02662725	SRS, ipilimumab	Ipilimumab combined with a stereotactic radiosurgery in melanoma patients with brain metastases	Completed
	NCT01703507	SRS, ipilimumab	Phase I Study of Ipilimumab Combined With Whole Brain Radiation Therapy or Radiosurgery for Melanoma	Active, not recruiting
	NCT01950195	SRS, ipilimumab	A Pilot Study of stereotactic radiosurgery combined with ipilimumab in patients with newly diagnosed melanoma metastases in the brain and spine	Terminated
	NCT02107755	SRS, ipilimumab	Stereotactic radiation therapy and ipilimumab in treating patients with metastatic melanoma	Active, not recruiting
Anti-PD-1	NCT02716948	SRS, nivolumab	A Pilot Study of stereotactic radiosurgery combined with nivolumab in patients with newly diagnosed melanoma metastases in the brain and spine	Recruiting
	NCT02696993	SRS/WBRT, nivolumab/ipilimumab	Trial of nivolumab with radiation or nivolumab and ipilimumab with radiation for the treatment of intracranial metastases from non-small cell lung cancer	Recruiting
	NCT02978404	SRS, nivolumab	Combining radiosurgery and nivolumab in the treatment of brain metastases	Not yet recruiting
	NCT02858869	SRS, pembrolizumab	Pembrolizumab and stereotactic radiosurgery for melanoma or non-small cell lung cancer brain metastases	Recruiting
Anti-PD-L1	NCT02886585	SRS, pembrolizumab	Pembrolizumab in central nervous system metastases	Recruiting
	NCT02669914	WBRT/SRS, durvalumab	MEDI4736 (durvalumab) in patients with brain metastasis from epithelial-derived tumors	Recruiting

impact on survival in patients treated with Ipi during or after RT [82, 86]. One study found that OS seemed improved in patients treated with Ipi within 14 days of RT [85], and another study found no difference in survival whether the drug was started before or after SRS [83].

Studying 46 patients treated with SRS plus Ipi, Kiess et al. [82] observed an increase in BM diameter in 50% of patients receiving Ipi during or after SRS (in patients receiving Ipi after SRS, BM increase occurred only after Ipi introduction). Grade 3 and 4 toxicities were observed in 20% of patients (Table 5), and were slightly more frequent in patients receiving Ipi during SRS.

### Ipi+/- SRS

One study retrospectively compared 31 patients treated with Ipi with or without SRS [87]. The authors found no increased toxicity with the addition of SRS to Ipi, and no median survival difference between the two groups.

### Clinical reports without 'comparison' arm

Du Four et al. reported on three patients experiencing an RN after brain RT (SRS with or without WBRT), combined with Ipi started either before or a few months after RT [81]. Gerber et al. retrospectively analyzed 13 patients treated with concurrent WBRT and Ipi (within 30 days of one another) [88]. Only early toxicity was reported. They observed one grade 3 cognitive change during WBRT in a patient suffering from acute seizure and subsequent hemorrhage during WBRT. All patients with follow-up imaging had new or worsening (mainly asymptomatic) intra-tumor hemorrhage, leading the authors to require further prospective studies of combined WBRT and ipi. Recently, Cohen-Inbar et al. reported a retrospective series of 46 patients, strongly suggesting that *delivering SRS before or during Ipi treatment could enhance both efficacy and toxicity* [89].

In summary, the retrospective design of these small sample size series does not allow either to definitely conclude on the impact of Ipi on the survival of melanoma BM patients treated with RT, or to categorically indicate an optimal administration sequence. Nonetheless, giving the amount of evidence that RT acts as an immune-modulator, and on the fact that a limited proportion of patients will respond to ICI alone, the combination of RT and ICI deserves intensive further exploration, and results of ongoing studies are eagerly awaited.

Two retrospective studies reported the outcome of BM patients treated with SRS and PD-1 (Programmed death-1) monoclonal antibodies (mAb) (targeting the PD-1 human cell-surface receptor, expressed on activated T-cells, and leading to T-cell effector function suppression when engaged by its ligand) [90, 91]. In two cases of patients treated with SRS followed by PD-1 mAb therapy (Pembrolizumab or Nivolumab + Ipi), Alomari et al. observed, shortly after PD-1 mAb introduction, a clinical and radiological pseudo-progression of the recently treated BM, which, on pathologic examination, proved to be radiation-induced changes with no viable tumor cells, assumed to be an accelerated response to SRS [91]. The concomitant use of PD-1 mAb and SRS has been suggested to improve distant intra-cranial control compared with the concomitant use of anti-CTLA4 and SRS, this remains to be confirmed [90]. Interestingly, but using a debatable endpoint,

(the 'early radiographic response'), Qian et al. [92] suggested different profiles of response combining SRS with Ipi *versus* nivolumab and pembrolizumab.

## Discussion

### Conclusion

Overall, studies assessing RT and systemic agent combination are currently mainly focused on the concomitant use of TT or ICI and SRS, since SRS nowadays seems to supplant WBRT in BM RT. Most of available studies appear to advocate for TT or ICI combination with RT, without altering the clinical safety profiles, allowing the maintenance of systemic treatments when SRS is considered. Moreover, RR assessment has to be standardized, better using the Response Assessment in Neuro-Oncology (RANO) group [93], to actually assess the impact of combined therapies. Further investigations are warranted, with longer follow-up, and better understanding of RT-immune effects. Numerous prospective studies are ongoing (Table 6), with the objective to better define the safety of these combinations. Cognitive functions, health-related quality of life and RN risk remain to be assessed. The results of prospective studies are awaited in order to complete and validate the above discussed retrospective data.

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### References

- Nabors LB, Portnow J, Ammirati M et al. Central nervous system cancers, version 2.2014. Featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw* 2014; 12: 1517–1523.
- Kumari A, Simon SS, Moody TD et al. Immunomodulatory effects of radiation: what is next for cancer therapy? *Future Oncol* 2016; 12: 239–256.
- Kohutek ZA, Yamada Y, Chan TA et al. Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases. *J Neurooncol* 2015; 125: 149–156.
- Chung EJ, Brown AP, Asano H et al. In vitro and in vivo radiosensitization with AZD6244 (ARRY-142886), an inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 kinase. *Clin Cancer Res* 2009; 15: 3050–3057.
- Sambade MJ, Peters EC, Thomas NE et al. Melanoma cells show a heterogeneous range of sensitivity to ionizing radiation and are radiosensitized by inhibition of B-RAF with PLX-4032. *Radiother Oncol* 2011; 98: 394–399.
- Anker CJ, Ribas A, Grossmann AH et al. Severe liver and skin toxicity after radiation and vemurafenib in metastatic melanoma. *J Clin Oncol* 2013; 31: e283–e287.
- Harding JJ, Barker CA, Carvajal RD et al. Cutis verticis gyrata in association with vemurafenib and whole-brain radiotherapy. *J Clin Oncol* 2014; 32: e54–e56.

8. Hecht M, Zimmer L, Loquai C et al. Radiosensitization by BRAF inhibitor therapy—mechanism and frequency of toxicity in melanoma patients. *Ann Oncol* 2015; 26: 1238–1244.
9. Lang N, Sterzing F, Enk AH et al. Cutis verticis gyrata-like skin toxicity during treatment of melanoma patients with the BRAF inhibitor vemurafenib after whole-brain radiotherapy is a consequence of the development of multiple follicular cysts and milia. *Strahlenther Onkol* 2014; 190: 1080–1081.
10. Peuvrel L, Ruellan AL, Thillays F et al. Severe radiotherapy-induced extracutaneous toxicity under vemurafenib. *Eur J Dermatol* 2013; 23: 879–881.
11. Reigneau M, Granel-Brocard F, Geoffrois L et al. Efflorescence of scalp cysts during vemurafenib treatment following brain radiation therapy: a radiation recall dermatitis? *Eur J Dermatol* 2013; 23: 544–545.
12. Satzger I, Degen A, Asper H et al. Serious skin toxicity with the combination of BRAF inhibitors and radiotherapy. *J Clin Oncol* 2013; 31: e220–e222.
13. Schulze B, Meissner M, Wolter M et al. Unusual acute and delayed skin reactions during and after whole-brain radiotherapy in combination with the BRAF inhibitor vemurafenib. *Strahlenther Onkol* 2014; 190: 229–232.
14. Forschner A, Zips D, Schraml C et al. Radiation recall dermatitis and radiation pneumonitis during treatment with vemurafenib. *Melanoma Res* 2014; 24: 512–516.
15. Narayana A, Mathew M, Tam M et al. Vemurafenib and radiation therapy in melanoma brain metastases. *J Neurooncol* 2013; 113: 411–416.
16. Rompoti N, Schilling B, Livingstone E et al. Combination of BRAF inhibitors and brain radiotherapy in patients with metastatic melanoma shows minimal acute toxicity. *J Clin Oncol* 2013; 31: 3844–3845.
17. Ahmed KA, Freilich JM, Sloot S et al. LINAC-based stereotactic radiosurgery to the brain with concurrent vemurafenib for melanoma metastases. *J Neurooncol* 2015; 122: 121–126.
18. Liebner DA, Walston SA, Cavaliere R et al. Radiation necrosis mimicking rapid intracranial progression of melanoma metastasis in two patients treated with vemurafenib. *Melanoma Res* 2014; 24: 172–176.
19. Patel KR, Chowdhary M, Switchenko JM et al. BRAF inhibitor and stereotactic radiosurgery is associated with an increased risk of radiation necrosis. *Melanoma Res* 2016; 26: 387–394.
20. Gaudy-Marqueste C, Carron R, Delsanti C et al. On demand Gamma-Knife strategy can be safely combined with BRAF inhibitors for the treatment of melanoma brain metastases. *Ann Oncol* 2014; 25: 2086–2091.
21. Xu Z, Lee CC, Ramesh A et al. BRAF V600E mutation and BRAF kinase inhibitors in conjunction with stereotactic radiosurgery for intracranial melanoma metastases. *J Neurosurg* 2017; 126: 726–734.
22. Ly D, Bagshaw HP, Anker CJ et al. Local control after stereotactic radiosurgery for brain metastases in patients with melanoma with and without BRAF mutation and treatment. *J Neurosurg* 2015; 123: 395–401.
23. Wolf A, Zia S, Verma R et al. Impact on overall survival of the combination of BRAF inhibitors and stereotactic radiosurgery in patients with melanoma brain metastases. *J Neurooncol*. 2016; 127: 607–615.
24. Patel BG, Ahmed KA, Johnstone PA et al. Initial experience with combined BRAF and MEK inhibition with stereotactic radiosurgery for BRAF mutant melanoma brain metastases. *Melanoma Res* 2016; 26: 382–386.
25. Akimoto T, Hunter NR, Buchmiller L et al. Inverse relationship between epidermal growth factor receptor expression and radiocurability of murine carcinomas. *Clin Cancer Res* 1999; 5: 2884–2890.
26. Dent P, Reardon DB, Park JS et al. Radiation-induced release of transforming growth factor alpha activates the epidermal growth factor receptor and mitogen-activated protein kinase pathway in carcinoma cells, leading to increased proliferation and protection from radiation-induced cell death. *Mol Biol Cell* 1999; 10: 2493–2506.
27. Schmidt-Ullrich RK, Mikkelsen RB, Dent P et al. Radiation-induced proliferation of the human A431 squamous carcinoma cells is dependent on EGFR tyrosine phosphorylation. *Oncogene* 1997; 15: 1191–1197.
28. Cai Y, Wang JY, Liu H. Clinical observation of whole brain radiotherapy concomitant with targeted therapy for brain metastasis in non-small cell lung cancer patients with chemotherapy failure. *Asian Pac J Cancer Prev* 2013; 14: 5699–5703.
29. Fan Y, Huang Z, Fang L et al. A phase II study of icotinib and whole-brain radiotherapy in Chinese patients with brain metastases from non-small cell lung cancer. *Cancer Chemother Pharmacol* 2015; 76: 517–523.
30. Huang YJ, Liu SF, Wang CJ et al. Exacerbated radiodermatitis and bilateral subdural hemorrhage after whole brain irradiation combined with epidermal growth factor receptor tyrosine kinase inhibitors for brain metastases in lung cancer. *Lung Cancer* 2008; 59: 407–410.
31. Kim HJ, Kim WS, Kwon DH et al. Effects of an epithelial growth factor receptor-tyrosine kinase inhibitor add-on in stereotactic radiosurgery for brain metastases originating from non-small-cell lung cancer. *J Korean Neurosurg Soc* 2015; 58: 205–210.
32. Lee SM, Lewanski CR, Counsell N et al. Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases. *J Natl Cancer Inst* 2014; 106.
33. Lind JS, Lagerwaard FJ, Smit EF et al. Phase I study of concurrent whole brain radiotherapy and erlotinib for multiple brain metastases from non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009; 74: 1391–1396.
34. Lu Y, Fan Y. Combined action of EGFR tyrosine kinase inhibitors and whole-brain radiotherapy on EGFR-mutated non-small-cell lung cancer patients with brain metastasis. *Onco Targets Ther* 2016; 9: 1135–1143.
35. Ma S, Xu Y, Deng Q et al. Treatment of brain metastasis from non-small cell lung cancer with whole brain radiotherapy and Gefitinib in a Chinese population. *Lung Cancer* 2009; 65: 198–203.
36. Olmez I, Donahue BR, Butler JS et al. Clinical outcomes in extracranial tumor sites and unusual toxicities with concurrent whole brain radiation (WBRT) and erlotinib treatment in patients with non-small cell lung cancer (NSCLC) with brain metastasis. *Lung Cancer* 2010; 70: 174–179.
37. Pesce GA, Klingbiel D, Ribic K et al. Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03). *Eur J Cancer* 2012; 48: 377–384.
38. Sperduto PW, Wang M, Robins HI et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys* 2013; 85: 1312–1318.
39. Wang F, Ning F, Liu C et al. Comparison of Gefitinib versus VMP in the combination with radiotherapy for multiple brain metastases from non-small cell lung cancer. *Cell Biochem Biophys* 2015; 71: 1261–1265.
40. Welsh JW, Komaki R, Amini A et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol* 2013; 31: 895–902.
41. Zeng YD, Zhang L, Liao H et al. Gefitinib alone or with concomitant whole brain radiotherapy for patients with brain metastasis from non-small-cell lung cancer: a retrospective study. *Asian Pac J Cancer Prev* 2012; 13: 909–914.
42. Zeng YD, Liao H, Qin T et al. Blood–brain barrier permeability of gefitinib in patients with brain metastases from non-small-cell lung cancer before and during whole brain radiation therapy. *Oncotarget* 2015; 6: 8366–8376.
43. Zhuang H, Yuan Z, Wang J et al. Phase II study of whole brain radiotherapy with or without erlotinib in patients with multiple brain metastases from lung adenocarcinoma. *Drug Des Devel Ther* 2013; 7: 1179–1186.
44. Zhou L, Liu J, Xue J et al. Whole brain radiotherapy plus simultaneous in-field boost with image guided intensity-modulated radiotherapy for brain metastases of non-small cell lung cancer. *Radiat Oncol* 2014; 9: 117.
45. Zhou L, He J, Xiong W et al. Impact of whole brain radiation therapy on CSF penetration ability of Icotinib in EGFR-mutated non-small cell lung cancer patients with brain metastases: Results of phase I dose-escalation study. *Lung Cancer* 2016; 96: 93–100.
46. Jiang T, Min W, Li Y et al. Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis. *Cancer Med* 2016; 5: 1055–1065.

47. Luo S, Chen L, Chen X et al. Evaluation on efficacy and safety of tyrosine kinase inhibitors plus radiotherapy in NSCLC patients with brain metastases. *Oncotarget* 2015; 6: 16725–16734.
48. Zhu Q, Sun Y, Cui Y et al. Clinical outcome of tyrosine kinase inhibitors alone or combined with radiotherapy for brain metastases from epidermal growth factor receptor (EGFR) mutant non small cell lung cancer (NSCLC). *Oncotarget* 2017; 8: 13304–13311.
49. Deng Z, Huang H, Wu X et al. Distinct expression of various angiogenesis factors in mice brain after whole-brain irradiation by X-ray. *Neurochem Res* 2017; 42: 625–633.
50. Sofia Vala I, Martins LR, Imaizumi N et al. Low doses of ionizing radiation promote tumor growth and metastasis by enhancing angiogenesis. *PLoS One* 2010; 5: e11222.
51. Zingg D, Riesterer O, Fabbro D et al. Differential activation of the phosphatidylinositol 3'-kinase/Akt survival pathway by ionizing radiation in tumor and primary endothelial cells. *Cancer Res* 2004; 64: 5398–5406.
52. Bates JE, Youn P, Peterson CR, III et al. Radiotherapy for brain metastases from renal cell carcinoma in the targeted therapy era: The University of Rochester Experience. *Am J Clin Oncol* 2015 February 26 [Epub ahead of print].
53. Cochran DC, Chan MD, Aklilu M et al. The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery. *J Neurosurg* 2012; 116: 978–983.
54. Staehler M, Haseke N, Nuhn P et al. Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma. *BJU Int* 2011; 108: 673–678.
55. Staehler M, Haseke N, Stadler T et al. Feasibility and effects of high-dose hypofractionated radiation therapy and simultaneous multi-kinase inhibition with sunitinib in progressive metastatic renal cell cancer. *Urol Oncol* 2012; 30(3): 290.
56. Verma J, Jonasch E, Allen PK et al. The impact of tyrosine kinase inhibitors on the multimodality treatment of brain metastases from renal cell carcinoma. *Am J Clin Oncol* 2013; 36: 620–624.
57. Langrand-Escure J, Vallard A, Rivoirard R et al. Safety assessment of molecular targeted therapies in association with radiotherapy in metastatic renal cell carcinoma: a real-life report. *Anticancer Drugs* 2016; 27: 427–432.
58. Wuthrick EJ, Kamrava M, Curran WJ, Jr et al. A phase 1b trial of the combination of the antiangiogenic agent sunitinib and radiation therapy for patients with primary and metastatic central nervous system malignancies. *Cancer* 2011; 117: 5548–5559.
59. Winkler F, Kozin SV, Tong RT et al. Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. *Cancer Cell* 2004; 6: 553–563.
60. Dings RP, Loren M, Heun H et al. Scheduling of radiation with angiogenesis inhibitors anigex and Avastin improves therapeutic outcome via vessel normalization. *Clin Cancer Res* 2007; 13: 3395–3402.
61. Masood R, Cai J, Zheng T et al. Vascular endothelial growth factor (VEGF) is an autocrine growth factor for VEGF receptor-positive human tumors. *Blood* 2001; 98: 1904–1913.
62. Truman JP, Garcia-Barros M, Kaag M et al. Endothelial membrane remodeling is obligate for anti-angiogenic radiosensitization during tumor radiosurgery. *PLoS One* 2010; 5.
63. Fu P, He YS, Huang Q et al. Bevacizumab treatment for newly diagnosed glioblastoma: Systematic review and meta-analysis of clinical trials. *Mol Clin Oncol* 2016; 4: 833–838.
64. Chinot OL, Nishikawa R, Mason W et al. Upfront bevacizumab may extend survival for glioblastoma patients who do not receive second-line therapy: an exploratory analysis of AVAglio. *Neuro Oncol* 2016; 18: 1313–1318.
65. Levy C, Allouache D, Lacroix J et al. REBECA: a phase I study of bevacizumab and whole-brain radiation therapy for the treatment of brain metastasis from solid tumours. *Ann Oncol* 2014; 25: 2351–2356.
66. Chargari C, Idrissi HR, Pierga JY et al. Preliminary results of whole brain radiotherapy with concurrent trastuzumab for treatment of brain metastases in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2011; 81: 631–636.
67. Stemmler HJ, Schmitt M, Willems A et al. 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: 23–28.
68. Lin NU, Freedman RA, Ramakrishna N et al. A phase I study of lapatinib with whole brain radiotherapy in patients with Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer brain metastases. *Breast Cancer Res Treat* 2013; 142: 405–414.
69. Yomo S, Hayashi M, Cho N. Impacts of HER2-overexpression and molecular targeting therapy on the efficacy of stereotactic radiosurgery for brain metastases from breast cancer. *J Neurooncol* 2013; 112: 199–207.
70. Borges GS, Rovere RK, Dias SM et al. Safety and efficacy of the combination of T-DM1 with radiotherapy of the central nervous system in a patient with HER2-positive metastatic breast cancer: case study and review of the literature. *Ecancermedicallscience* 2015; 9: 586.
71. Jacot W, Pons E, Frenel JS et al. Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases. *Breast Cancer Res Treat* 2016; 157: 307–318.
72. Carlson JA, Nooruddin Z, Rusthoven C et al. Trastuzumab emtansine and stereotactic radiosurgery: an unexpected increase in clinically significant brain edema. *Neuro Oncol* 2014; 16: 1006–1009.
73. Geraud A, Xu HP, Beuzebec P et al. Preliminary experience of the concurrent use of radiosurgery and T-DM1 for brain metastases in HER2-positive metastatic breast cancer. *J Neurooncol* 2017; 131: 69–72.
74. Mitsuya K, Watanabe J, Nakasu Y et al. Expansive hematoma in delayed cerebral radiation necrosis in patients treated with T-DM1: a report of two cases. *BMC Cancer* 2016; 16: 391.
75. Shabason JE, Minn AJ. Radiation and immune checkpoint blockade: from bench to clinic. *Semin Radiat Oncol* 2017; 27: 289–298.
76. Dewan MZ, Galloway AE, Kawashima N et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* 2009; 15: 5379–5388.
77. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. *J Natl Cancer Inst* 2013; 105: 256–265.
78. Kalbasi A, June CH, Haas N et al. Radiation and immunotherapy: a synergistic combination. *J Clin Invest* 2013; 123: 2756–2763.
79. Vatner RE, Cooper BT, Vanpouille-Box C et al. Combinations of immunotherapy and radiation in cancer therapy. *Front Oncol* 2014; 4: 325.
80. Dhermain F, Deutsch E. Stereotactic radiation and checkpoint inhibitors in melanoma patients with BM: a question of drug, timing or both? *Ann Oncol* 2016; 27: 371–372.
81. Du Four S, Wilgenhof S, Duerinckx J et al. Radiation necrosis of the brain in melanoma patients successfully treated with ipilimumab, three case studies. *Eur J Cancer* 2012; 48: 3045–3051.
82. 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: 368–375.
83. Knisely JP, Yu JB, Flanigan J et al. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. *J Neurosurg* 2012; 117: 227–233.
84. Mathew M, Tam M, Ott PA et al. Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. *Melanoma Res* 2013; 23: 191–195.
85. 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* 2015 May 16 [Epub ahead of print].
86. Silk AW, Bassetti MF, West BT et al. Ipilimumab and radiation therapy for melanoma brain metastases. *Cancer Med* 2013; 2: 899–906.
87. Tazi K, Hathaway A, Chiuzan C et al. Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery. *Cancer Med* 2015; 4: 1–6.
88. Gerber NK, Young RJ, Barker CA et al. Ipilimumab and whole brain radiation therapy for melanoma brain metastases. *J Neurooncol* 2015; 121: 159–165.
89. 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: 1007–1014.

90. Ahmed KA, Stallworth DG, Kim Y et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy. *Ann Oncol* 2016; 27: 434–441.
91. Alomari AK, Cohen J, Vortmeyer AO et al. Possible interaction of anti-PD-1 therapy with the effects of radiosurgery on brain metastases. *Cancer Immunol Res* 2016; 4: 481–487.
92. 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: 3051–3058.
93. Lin NU, Lee EQ, Aoyama H et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol* 2015; 16: e270–e278.