

## Research Article

# Immuno-radiotherapy for brain metastases

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## Abstract

Brain metastases (BM) are a lethal consequence of systemic dissemination of cancer. The most common malignancies that metastasize to the brain are lung, breast, and melanoma. Eighty percent of patients present with brain metastases within the cerebral hemispheres; 15% are within the cerebellar hemispheres and 5% are within the brainstem. The incidence of brain metastases is increasing because of better detection from improved imaging techniques (also for staging asymptomatic patients), and more effective systemic treatment regimens that can prolong life, permitting the cancer to disseminate to the brain, a sanctuary site.

## Introduction

Prognostic scores as an estimation of a patient's prognosis may guide therapy customized for these patients. Different outcomes have been shown in multiple studies in patients stratified with different prognostic scoring systems: most of them have some limitations considering primarily age, KPs and number of BM in multiple primary subsites. The role of genetic signature and other tumor-related features in BM remains unclear [1-4].

One of the challenges in the development of effective therapies for BM is the presence of the blood-brain barrier (BBB), a highly selective permeability barrier made of capillary endothelial cells connected by tight junctions and astrocyte foot processes that limit entry of systemic therapies into the brain [5]. In addition, active transport mechanisms of drug efflux and high plasma protein binding of agents further lower the volume of distribution of agents in the brain parenchyma [6].

However BBB is not efficient in metastatic disease and several studies showed that BBB permeability changed over time as BM developed [7].

Due to the long cancer history patients with BM are usually heavily pretreated with tumors that are more likely to be resistant to therapy. Median overall survival (OS) from diagnosis of BM ranges from 3 to 6 months [8].

The standard therapeutic options include surgery, whole brain radiation therapy (WBRT), stereotactic radiation (SRS), systemic therapy and symptom management only.

The role of systemic therapy (chemotherapy, targeted agents, or immunotherapy) in brain metastases is palliation, because there is no level-1 evidence favouring the use of systemic therapy compared with local approaches, systemic therapies are used when disease control rate is researched also in other sites. In recent years, the development of novel cytotoxic agents and targeted therapies with better blood-brain barrier penetration have increased the interest in use of systemic therapies in brain metastases. Although patients with BM are under represented or excluded from the majority of clinical trials testing new drugs. Considering the tumours with most common cerebral involvement: 10-40% of patients with metastatic melanoma develop BM during their lifetime and >75% have BM at autopsy, with median

survival in the order of 2.5-4 months despite use of WBRT and surgery. Among those with NSCLC, 10% have brain metastases at presentation and another 30% develop them over the course of their disease. Survival after the development of brain metastases is as dismal in those with NSCLC as it is for melanoma. Multifocal disease is common in both of these diseases, with about half of patients with CNS disease presenting with more than one brain lesion [9].

Advances in the understanding of the biology of BM and molecularly defined disease subsets have facilitated an emerging role of novel therapeutic agents, such as targeted therapies and immunotherapy. In particular, there is a great interest in the association between radiation treatment and immunotherapy especially given case reports and animal studies that suggest combined treatment may generate abscopal responses outside the radiation field.

A limit in the development of immunotherapy is the large use of steroids in this settings; steroids (dexamethasone) are recommended in symptomatic BM to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema. Steroids have a wide immunosuppressive action, including reduction of CD8<sup>+</sup>, CD4<sup>+</sup> cells and monocyte/neutrophils ratio (depending on the expression of GCR), macrophage dysfunction and T<sub>reg</sub> induction [10]. Although successful clinical experience would lead to the conclusion that the role of steroids is firmly established in the management of brain metastases, there is a great variability in recommendations and a general lack of well-controlled studies addressing this specific issue. Moreover no clear evidence supported a contraindication of combining steroids with immunotherapy.

The aim of this review is to point out the main experiences on treatment of BM with radiation and the possible development of immune radiotherapy combination.

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## Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for the conduct and reporting of this systematic review [11].

### Search strategy

Studies were identified by a computerized search of the PubMed data-base with the string “brain metastases”, radiotherapy AND “(ipilimumab OR pembrolizumab OR avelumab OR atezolizumab OR nivolumab)” (Figure 1). The search was performed on December 2016. Moreover, abstracts published by the ASCO,ESMO and ESTRO between 2010 and 2016 were reviewed and considered for inclusion if full paper was not published. Reference lists of original articles and review articles were considered as additional sources of information (Figure 1).

### Inclusion and exclusion criteria

English-language studies which reported any survival outcome (median OS and/or landmark analysis of survival) of patients treated with immunotherapy and BM were included in this review. The following information was extracted from each report: tumor primary, number of patients with BM, treatment regimens and line of treatment (i.e. pre-treated or treatment-naïve patients), previous BM local treatment, median OS, landmark analysis of survival, median progression-free survival (PFS) in brain?, overall response rate, disease control rate, intracranial response rate, presence of “central nervous system” (CNS) symptoms, incidence of G3–4 toxicities, discontinuation rate, CNS specific adverse events (for safety outcomes, we included studies for patients with BM only or reporting outcomes for BM patients separately).

Exclusion criteria for study selection were the following: (1) studies investigating the immuno checkpoint not involving brain metastases or radiotherapy; (2) those published in language other than English; (3) duplicate publications.

### Extraction and analysis

Data were independently extracted by 4 investigators (N.D., MO, CC and AM.). To ensure homogeneity of collection and to rule out the effect of subjectivity in data gathering and entry, disagreements

were resolved by interaction, discussion, and consensus. Analysis of extracted data was performed by all the Authors. Revision was performed by MM.

## Biological background

Immune checkpoint targeting used sequentially with RT in melanoma/lung brain metastases may potentiate durable brain response [12]. The optimal treatment sequence has not been delineated. Several pre-clinical studies have demonstrated the variable permeability of the BBB to immune cells, in pathological settings such as septic encephalopathy, experimental autoimmune encephalomyelitis (EAE), or tumorigenesis [13]. Moreover a lymphatic communication exists between the CNS and the periphery (from the brain parenchyma, along the Virchow-Robbins spaces, through the cribriform plate, and out to the deep cervical lymph nodes). [14,15]. Subsequent studies found that APCs (antigen presenting cells) could migrate from the brain to the cervical lymph nodes, and that the type and extent of inflammation in the brain correlates with the frequency of CNS antigens found in those draining nodes [16].

Furthermore, while in brain parenchyma immune population seems to be not significant, innate and adaptive immune reactivity in the ventricles, leptomeninges, and perivascular spaces is similar to that seen in the periphery [17].

In brain disease (both tumoral and non tumoral) effector T cells are capable of entering the parenchyma to proliferate, home or migrate to the tumor, and initiate an active inflammatory response or pro versus antitumoral treatment. Goldberg et al evidenced that T-cells are an integral part of the CNS and shape its function *via* the choroid plexus.

This strong biologic background led in the last few years to a new interest on immunotherapy also in brain cancers (primitive and secondary). Although only a few of the growing number of checkpoint inhibitors (namely, CTLA-4 and PD-1) have been studied until now in this setting, the use of immune modulators appears promising.

A potential limit to immune therapy is the wide use of steroids in BM. The steroids are used specifically to decrease oedema associated with primary and secondary tumors of the central nervous system. The glucocorticoids (GCs) induce immunosuppressive and anti-inflammatory effects predominantly through binding to the

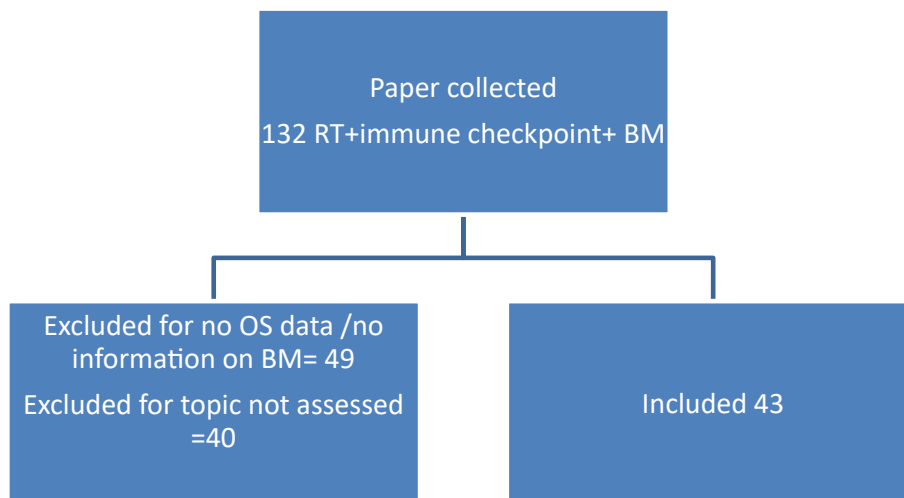


Figure 1. Inclusion and exclusion criteria.

glucocorticoid receptor (GCR) [18]. It is known that dexamethasone and other GCs can modulate the immune system in a wide variety of ways, with varying mechanisms of action in different cell types [19,20].

Dex -induced immunological effects, including a large-scale lymphodepletive effect particularly affecting CD4+ T cells but also CD8+ T cells. The proportion of regulatory T cells within the CD4C compartment did not change after Dex was administered, however a significant increase in proliferation and activation of regulatory T cells as well as a proportional changes in dendritic cell (DC) subtypes was observed.

However, no clinical data exist giving a clear evaluation of the immunosuppressive effect of steroids during immune therapy.

## Radiotherapy

Radiotherapy uses high energy radiation to locally treat cancer inducing DNA damage and endoplasmic reticulum (ER) stress *via* reactive oxygen species (ROS) thus causing cycle arrest of the tumor cells that try to repair the induced damage and reducing their clonogenic potential. In addition to these targeted effects, an increased expression of MHC-I and MHC-II molecules, CD80, CD86 adhesion molecules, stress ligands, Hsp70 and death receptors on tumor cell surfaces can be observed. All these non-targeted effects may result in activation of death cascade and DCs activation [21].

The induction of immunogenic cancer cell death seems to be a common mechanism for most RT schemes. Activation of DCs is a process that has to be tightly controlled to avoid tolerance. In addition to lack of activation of DCs, tolerance is also supported by a number of other mechanisms such as the expression of immune check-points. Cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) on T cells are two major checkpoints.

## Immunotherapy

Significant advances in treatment of metastatic solid tumors have been made with immunotherapy. Checkpoint inhibitors treatments represent a standard treatment in first and second line of melanoma and lung cancer and in second line of renal cancer.

Blockade of CTLA-4 (ipilimumab and tremelimumab), PD-1 (nivolumab, pembrolizumab, pidilizumab and others), and PD-L1 (BMS 936559, durvalimumab Avelumab, and atezolizumab) can produce significant improvement in overall survival in several solid tumors. A better characterization of primary tumors and BM is necessary as mutational status of EGFR, levels of STAT3 and chemokines correlates with immunotherapy response.

For example in NSCLC patients with ALK-rearranged or EGFR-mutated tumour exhibit low response to antibodies against PD-1 or PD-L1 compared with high responses in patients without known actionable mutations, probably because of the absence of CD8 T-cells [22].

## Ipilimumab

Ipilimumab is a monoclonal antibody that antagonizes cytotoxic T-lymphocyte antigen-4 (CTLA-4), It has been optimum timing and sequencing of immunomodulation and radiation therapy in humans is undefined. Because the effects of ipilimumab and other types of immunotherapy can be both delayed in onset and prolonged over many years [23], a warming immune response could potentially be boosted by radiation therapy even some time after the drug is discontinued. Timing was investigated in a retrospective study by Saraceni et al.

They reported a cohort of 30 patients in which patients who received immunotherapy > 30d after RT had statistically significant better OS (median OS 58.00 vs. 34.72 wk),  $p = 0.0493$ . The majority of patients received anti-CTLA4 (76.67%) and gammaknife (66.67%). Brain responses included partial, 42.86%; progressive, 35.71%; stable, 14.29%; and complete, 7.14% [24].

Radiation given prior to ipilimumab could ostensibly liberate antigen and recruit T-cells to the tumor microenvironment as a priming event, which would later be amplified by checkpoint blockade. In the case of ipilimumab delivered first, radiotherapy could boost immunogenic cell death, as the host would have tumor-reactive T cells activated by initial treatment with checkpoint blockade. Further studies will be needed to understand and exploit such mechanisms. Results on combination with RT are summarized in Table 1.

## Pembrolizumab

The anti-PD1 antibody pembrolizumab prolonged progression-free survival and overall survival in advanced melanoma and in PDL1pos NSCLC and other advanced solid cancer (phase III studies on going).

In the registrative study KEYNOTE 006 8.2%, 9.7%,10.1% had no-active brain metastases respectively in the biweekly and triweekly pembrolizumab arms and ipilimumab arm. However no data are separately reported about them. Recently results of a phase II trial NCT02085070 (pembrolizumab in patients with untreated brain metastases from melanoma or NSCLC) were published. Goldberg SB et al reported 22% brain metastasis response (95% CI 7-48) in patients with melanoma and 33%(95% CI 14-59) in patients with NSCLC. Responses were durable, with all but one patient with NSCLC who responded showing an ongoing response at the time of data analysis on June 30, 2015 [22].

## Avelumab

Avelumab is a fully human IgG1 MAb targeting the co-regulatory protein PD-L1. Avelumab is shown to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) of several types of human tumor cell lines (e.g., breast, lung, bladder carcinomas) *in vitro*, with tumor cell lysis mediated mainly by human CD16+ monocytes and natural killer (NK) cells [25]. Due to results of Phase I/II studies in patients with advanced cancer Avelumab is under investigation in several cancers such as Hodgkin, Merkel, Ovarian, Renal, Gastric, NSCLC, breast and urothelial cancer. No data are published on combination with RT in BM patients. (clinicaltrials.gov) <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4910121/> - bib16

## Atezolizumab

Atezolizumab is an engineered humanized monoclonal immunoglobulin G1 antibody that binds selectively to PD-L1, and prevents its interaction with PD-1 and B7-1 (also known as CD80).

Efficacy and safety of atezolizumab has been demonstrated in phase 2 trials in urothelial carcinoma, NSCLC, renal carcinoma, and other solid tumours. Phase 3 trials are ongoing in several diseases. The studies excluded patients who had symptomatic or corticosteroid-dependent brain metastases. And specifically, no outcome information about patients enrolled in the studies who had brain metastases or patient who had radiation therapy. In the phase 1a RCC expansion study (PCD4989g - RCC) included 70 patients with metastatic clear cell or non-clear cell renal carcinoma. In the baseline patient's characteristic

**Table 1.** Patients treated with immunoradiotherapy in clinical trials

Study (author, year)	Study type	primary	N° PTS	line of treat	active systemic disease	systemic treatment regimen	RT(WB vs SRS)	steroid	Timing	median median F-up	Median OS	median PFS	DCR	IRR	G3-4 CTCAE 3.0	discontinuation rate	CNS specific adverse events	RT necrosis requiring surgery	Influence of timing	ABE
Schoenfeld et al. 2015	R	M	16	nd	97% systemic lesions	81% at least 4 cycles ipilimumab 3 mg mq q 21 14 pts, 10 mg mq 2 pts	90% SRS (median 22 Gy 1fx), 10% WBRT	no	RT +IPI (<3 mo) 7 pts, RT after IPI (<3.5 mo) 9 pts	nd	14.4 mo	nd	nd	nd	nd	19% for PD	nd	no	Ipi after RT > OS vs Ipi before RT (26 m vs 6 m)	>RR if Ipi within the 3m to RT (63% vs 7%, p = 0.003)
Chandra 2015	R	M	47	nd	nd	mean 4 cycles ipilimumab 3 mg mq q 21 (43 pts) 10 mg mq (4 pts)	51% brain RT (28 SRS; 23 WBRT), SRS median dose 20 Gy	nd	25 pts Ipi before RT (<3 mo), 22 Ipi after RT (<3 mo), Median time between RT and ipilimumab <1 mo	24 mo (range: 24–112 mo)	28 mo	nd	nd	nd	nd	nd	nd	nd	no association between the temporal proximity of the first dose of ipilimumab to radiation and the response of the index lesions.	RR-> if multiple fraction RT < / = 3 Gy.
Kiess 2015	R	M	46	87% II 13% I	nd	54% 3 mg/kg 4 cycles, 46% 10 mg/kg 4 cycles. 28% received maintenance therapy every 3 months.	SRS 2.1 Gy (15-24), 20% WBRT after recurrence	83% short course steroids with SRS (4 mg dexamethasone for 2 days).	15 pts SRS during Ipi, 19 pts SRS before Ipi, 12 pts SRS after Ipi.	22 mo (range 6-89)	12.4 mos (range, 2-89)	nd	Regional (off-fld) brain 1-year recurrence 92% SRS after Ipi, 69% SRS during Ipi, 64% SRS before Ipi	nd	nd	nd	typical systemic immune-related adverse events associated with Ipi (enterocolitis, pruritus, and hepatitis).	5 pts	SRS during or before Ipi better OS than SRS after Ipi (p=0.008).	nd
Knisely 2012	R	M	27	II or III	nd	(35%) received ipilimumab	40% WBRT, 60% SRS, 22% salvage WBRT	no	nd	21.55 mo (range 6.6–50.93)	21.3 mo (with Ipi) vs 4.9 months (no Ipi)	nd	nd	nd	nd	nd	nd	3 pts (12%)	Median OS 19.8 m (Ipi before SRS) vs 21.3 mo (Ipi after SRS), NS	nd

Tazi 2015	R	Mathew 2013	Silk 2013	Gerber 2015	Patel 2015
R	R	R	R	R	R
M	M	M	M	M	M
10	25 SRS+Ipi	33 Ipi +RT,	13	20 SRS+ Ipi	20 SRS+ Ipi
nd	nd	42.4% II	62% II	nd	nd
nd	72%	nd	nd	85% in Ipi arm systemic active lesions	85% in Ipi arm systemic active lesions
ipi 3mg/kg 2-11 cycles	4 cycles ipilimumab 3 mg mq q 21	4 cycles ipilimumab 3 mg mq q 21	70% 4 cycles ipilimumab 3 mg mq q 21, 30% 2 cycles	Ipi 3 mg/kg within 4 months. No maintenance.	Ipi 3 mg/kg within 4 months. No maintenance.
SRS	SRS 20 Gy	50% WBRT (30-37.5 Gy 10-13 fx), 50% SRS (14-24 Gy 1 fx)	WBRT mean 30 Gy	SRS. BM up to 20 mm in diameter were typically treated to 21Gy, 21 to 30mm in diameter to 18Gy, and 31 to 40mm in diameter to 15Gy	SRS. BM up to 20 mm in diameter were typically treated to 21Gy, 21 to 30mm in diameter to 18Gy, and 31 to 40mm in diameter to 15Gy
nd	prophylactic steroids	nd	77% during RT	5.6% steroid with Ipi	5.6% steroid with Ipi
SRT prior or concomitant	10 pts Ipi after SRS, 7 pts concurrent, 4 pts Ipi prior SRS, 3 unknown	21 pts Ipi after RT, 12 Ipi before RT.	7 pts WBRT prior Ipi, 6 pts concomitant (all within 25 days)	One patient (5%) was treated concurrently, 12 (60%) were treated with ipilimumab before SRS, and 7 (35%) were treated with ipilimumab after SRS. None of the SRS alone patients received ipilimumab before or after 4 months of SRS.	One patient (5%) was treated concurrently, 12 (60%) were treated with ipilimumab before SRS, and 7 (35%) were treated with ipilimumab after SRS. None of the SRS alone patients received ipilimumab before or after 4 months of SRS.
nd	6 mo (range 0.3-47)	nd	4 mo	7.3 mo	7.3 mo
28.3 mo	56 mo (with Ipi) vs 45 mo . NS	5.3 vs 19.9 mo (WBRT vs SRS)	4 mo	nd	nd
nd	nd	TTP 3 mo	nd	nd	nd
nd	freedom from new brain mts 3.5% (with Ipi) vs 47% (no Ipi) 6 mo NS	nd	nd	The 1-year LC rate was similar between the ipilimumab and SRS and SRS alone groups (71.4% vs. 92.3%, P = 0.40).	The 1-year LC rate was similar between the ipilimumab and SRS and SRS alone groups (71.4% vs. 92.3%, P = 0.40).
nd	6mo 63% vs 65% (SRS vs SRS with Ipi) NS	PR 56.7	PR/SD 56%	nd	nd
10% diarrhea/colitis	nd	nd	nd	nd	nd
nd	nd	nd	30% CNS progression	nd	nd
no	intracranial hemorrhage 28% (with Ipi) vs 34% (no Ipi) NS	3.9% hemorrhage	new or increased intratumoral hemorrhage in all 10 pts with follow-up images. 8% G3 cognitive changes. 15% grade 2 seizure during the course of WBRT. Visual changes 23% (G1-2)	At 1 year, the ipilimumab and SRS cohort had a trend toward developing higher rates of radiation necrosis (30.0% vs. 20.92%, P = 0.078)	At 1 year, the ipilimumab and SRS cohort had a trend toward developing higher rates of radiation necrosis (30.0% vs. 20.92%, P = 0.078)
no	no	no	no	no significant difference (15.0% vs. 14.7%, P = 1.00) between ipilimumab and nonipilimumab	no significant difference (15.0% vs. 14.7%, P = 1.00) between ipilimumab and nonipilimumab
nd	no difference	RR 40.0% Ipi before/during RT 16.7% Ipi after RT . OS Ipi after RT as compared to patients who received ipilimumab prior to RT (median of 18.4 months vs. 8.1 months). RR more reliable	nd	SRS + Ipi within 14 d > 1- and 2- y OS	SRS + Ipi within 14 d > 1- and 2- y OS
nd	nd	nd	CR (10%), PR (10%), 2 SD (20%), PD (50%).	nd	nd







## Results

### Population

Fifteen retrospective studies [23, 28-36] reported results of 594 melanoma patients with BM. Only 4 studies (Schoenfeld, Patel, Mathew, Qian) reported active systemic disease in the majority of patients (range 72%-96%). The described prognostic factors were KPS, DS-GPA, less frequently LDH serum levels and rarely B-RAF mutational state.

### Intervention

Among the 594 with melanoma BM of the analyzed papers, 150 were treated with RT alone, 409 were treated with radiotherapy and Ipi, 26 with RT and nivolumab (Ahmed) and 12 with RT and pembrolizumab (3 previously treated also with ipilimumab) (Qian). The majority of patients received Ipi 4 cycles 3 mg mq q 21, some with maintenance every 3 months. Radiotherapy was in 84% a SRS treatment (mean 20 Gy in 1 fraction) and in 16% WBRT (mean 30 Gy 10 fractions). The majority of the studies did not report about steroid use. When declared it was a short course prophylactic use during RT [37-40].

Timing of the combination of radiotherapy and immunotherapy was described differently between studies where this aspect was considered. To define a concomitance between RT and immunotherapy some Authors have considered adequate that the treatments were not administered to more than 4 weeks, 3 months, 5.5 months of each other. In other cases, despite being administered with an interval less than a month the Authors distinguish patients in whom the immunotherapy was administered before, during or after the RT. Others described RT as administered before, during or after immunotherapy without a clear time interval [41,42].

### Outcome

The median of mean follow-up reported in the selected studies is 7.4 months (range 4-24).

The median survival shows great variability (range 4-56 months) as well as the survival at 1 year (range 15.4% -90%).

Prognostic correlations on multivariate analysis reveal a better OS for patients with single brain metastasis and controlled systemic disease (Patel), higher msGPA scores, lower ECOG and LDH. Studies that compare patients treated with RT alone or with immunotherapy. find contradictory results on the impact of Ipi on OS with a significant better OS with the adjunct of ipilimumab in 2 studies (even if in the study by Silk and colleagues it was observed only in patients treated with SRS) whereas ipi has not a significant prognostic impact in the other two studies.

Influence of timing of the association between RT and immunotherapy on oncological end-points is analyzed in 8 papers (Schoenfeld, Kiess, Knisley, Patel, Silk, Mathew, Qian, Jiang). Only Mathew and colleagues find no correlation of the outcome with timing of administration of RT and Ipi. In the other 7 studies is reported a better OS with RT performed before or during immunotherapy and this correlation is statistically significant in 4 studies. Median PFS is reported only in 2 studies and is around 3 months.

Where reported, intracranial Response Rate is 56% and 85% at 1 year, or 65% at 6 months. Abscopal effect is reported in 4 studies with rates ranging from 20% to 68%. A better "out-of-field" response was associated with fraction size  $\leq 3$  in one study, Ipi administered less than 3 months apart from SRS and local response. Incidence of systemic toxicity is reported only in 2 studies and referred to typical

immune-related adverse events as diarrhea, colitis, pruritus, hepatitis. Discontinuation rate was analyzed in 3 studies with a range of 17-30%, due to disease progression. CNS specific toxicity is reported in 9 studies. Radiation necrosis requiring surgery appears in 3%-15% of patients. Where feasible a comparison between patients treated with RT alone and RT+immune no differences of incidence of radiation necrosis emerge between groups. G3 CNS bleeding is reported in 15% of patients, again without differences in patients treated with RT alone. Khoja et al. report an incidence of radiation necrosis in 41% of patients treated SRS compared with 0% in the WBRT group. Kiess et al show a higher CNS toxicity when RT is administered during Ipi (13% G3 CNS bleeding vs 6%, 13% G3 seizures vs 0%).

### Ongoing trials

The discovery that immunotherapy is safety in patients Table 2 summarizes the most impressive ongoing advanced clinical trials.

### Conclusion

Immunotherapy is now a key player in Oncology. Brain metastasis are associated with poor prognosis and lack of effective systemic treatments. Data on combination of immune checkpoints inhibitors and Rt are heterogeneous because of retrospective series, different population and response evaluation. Timing of immunoradiotherapy combination differ in many studies, some trials report benefit with irradiation after the last dose of immunotherapy, other during the treatment.

Another limit of a systematic review on immunoradiotherapy of BM is the assessment of tumor response. As already reported several instruments and end points were used in the different studies. Another limitation is that in the majority of studies no endpoints other than survival is addressed. Results from ongoing trials on BM immunoRT will help to define the optimal association, schedule and the ideal setting of patients.

**Table 2.** Ongoing trials with rt and immunotherapy.

Study	Setting	Drug	Expedted results
CA209-322	Mel symptomatic BM	Nivo in symptomatic BM	Jan April 2017
NCT02681549	BM in NSCLC	Pembro ± Beva in melanoma e NSCLC	May October 2019
NCT01727531	BM*	Chloroquine	Jan 2017
NCT02085070	BM in NSCLC	Pembro and Beva	Dec 2018
NCT02097732	Melanoma BM	Ipi→SRT	May 2017
GEM study GRAY-B*	Melanoma BM	Ipilimumab	Oct 2016
NCT02374242	Melanoma BM	Nivo ± Ipi	Dec 2017
NCT02808416	BM*	PERCELLVAC3	Jun 2018
NCT02886585	BM*	Pembro+SRT	April2020
NCT02669914	BM*	durvalumab	Dec 2021
NCT02858869	Lung and melanoma BM	Pembro+SRT	Oct 2019
NCT01703507	Melanoma BM	Ipi+SRT	Oct 2019
NCT02696993	Lung BM	Nivo± Ipi+SRT/ WBRT	Dec 2020
NCT02320058	Melanoma BM	Nivo+Ipi□Nivo	Jun2018

Abbreviations BM= brain metastases; NSCLC= non small cell lung cancer; SRT stereotactic RT; Nivo= nivolumab; Ipi= Ipilimumab;Pembro=pembrolizumab;\*advanced solid tumours;AB.E abscopal effect. Early result presented at ESMO 2016 1y survival rate 31.4%



## Evaluation

Response to cancer therapy has been historically defined using RECIST criteria, however in the era of immunotherapy discordance in clinical and instrumental behaviour led to the identification of more suitable criteria. Using RECIST 1.1 in immunotherapy trials would lead to declaration of progressive disease (PD) too early, when the treatment effect is not yet fully evident. RECIST also neglects the importance of the 'flare effect' - pseudo-progression effect within the so-called flare time window.

Immune related Response Criteria (irRC) based on WHO criteria were published with an aim to provide better assessment of the effect of immunotherapeutic agents. Hodi et al demonstrated in Keynote 001 that conventional RECIST might underestimate the benefit of pembrolizumab in approximately 15% of patients.

Only in the last two three years patients with BM were enrolled in clinical trials. These studies assessed BM response using alternatively modified RECIST, RANO-BM (Response Assessment in Neuro-Oncology) criteria, and functional outcomes. For example, in recent times a number of trials have used time to neurologic progression or decline as primary endpoint. Focusing not only on survival could lead to differentiate between death resulting from systemic cancer progression or neurological decline from BM. Other outcomes include proportion of patients using steroids to control of cerebral edema for greater than 96h and brain progression free survival. Recent trials investigated response using interval changes in dynamic MRI parameters such as perfusion, blood volume, vascular permeability and diffusion tensor imaging; moreover the change in 3D tumor volume is also under investigation.

A new instrumental evaluation includes FET PET (18F-fluoroethyl-tyrosine [FET]), that is actually compared to MRI brain scans to assess metabolic response of the BM to immune therapy. Several studies showed that FET-PET is very sensitive in the management of brain tumours. It is hypothesized FET-PET may overcome the difficulty of MRI to evaluate lymphocytic infiltration.

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