Combination treatments with immunotherapy in brain metastases patients

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Combination treatments with immunotherapy in brain metastases patients

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Immune checkpoint inhibitors (ICI) have revolutionized the treatment of many advanced cancers. However, in most pivotal trials, patients with brain metastases (BM) were either excluded, or only selected patients were allowed. Therefore, there are still some concerns about the safety/efficacy ratio of ICI in patients with BM. In this special report we will provide an overview on the biological rationale for using ICI in the treatment of BM, the reported BM-related outcomes of clinical trials with a focus on ICI plus chemotherapy and ICI plus ICI combinations. Last, we will provide future challenges with this strategy, as well as directions for future research.

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The incidence of brain metastases (BM) in cancer patients is high, especially in melanoma (7–60%), lung (30–50%), breast (5–50%) and renal cell cancer (RCC; 8%) patients [1–10]. Quality of life (QoL) and overall survival (OS) are negatively influenced by the occurrence of BM [9,11]. Based on the longer OS of cancer patients, this incidence may increase over time. Therefore, treatment strategies for effectively treating (or even preventing) BM are eagerly awaited in daily clinical practice. Immune checkpoint inhibitors (ICI) have revolutionized the treatment landscape of many cancer types. PD-1/PD-L1 inhibitors with/without CTLA4 inhibitors or chemotherapy have become standard of care (SoC) in the first-line setting (and/or beyond) for many advanced solid tumors, such as non-small-cell lung cancer (NSCLC), small cell lung cancer (SCLC), *BRAF* wild-type melanoma and clear cell RCC (ccRCC) [12–16]. For several other histologies, ICI are still under evaluation in clinical trials.

Although ICI are widely being used across diverse tumor types, patients with untreated and/or symptomatic BM were either excluded from pivotal clinical trials or the percentage included was very low, with those patients enrolled being hyper-selected [17–27]. Therefore, there are still some concerns about the safety/efficacy ratio of ICI in patients with BM.

In this special report, we will provide an overview on the biological rationale for using ICI for treatment of BM and the reported BM related outcomes of clinical trials with a focus on ICI plus chemotherapy and ICI plus ICI combinations. Last, we will provide future challenges with this strategy, as well as directions for future research.

Immune environment of brain metastases

It was long thought that the brain was an immune privileged organ due to lack of traditional lymphatic structures. Recently, it has become clear that immune surveillance also takes place in the brain, as T-cells can cross the blood–brain barrier (BBB) and blood–tumor barrier [28,29]. However, in NSCLC, PD-L1 expression (a predictive biomarker for better outcome on anti-PD-[L]1 treatments), is lower in the brain than in extracranial metastases (30 vs 44%) [30]. Furthermore, despite a higher tumor mutational burden (TMB) in NSCLC BM [31] as well as in ccRCC BM [32], the BM immune environment is more ignorant compared with extracranial disease sites [30,33,34].

Table 1. Tumor immune microenvironment in primary tumors and brain metastases matched samples.

Study (year)	Samples	Sample type	Analysis	Main finding	Ref.
Cimino-Mathews <i>et al.</i> (2013)	n = 6 (PT) + 6 (BM)	FFPE	TMA	BM contained fewer TIL compared with extra cranial metastatic sites for lung, gastrointestinal or gynecologic sites	[37]
Breast cancer					
Ogiya <i>et al.</i> (2017)	n = 46 (PT) + 46 (BM)	FFPE	TIL, IHC	The numbers of CD4/CD8/Foxp3-positive cells were significantly higher in breast PT compared with BM (paired <i>t</i> -test, <i>p</i> < 0.05). In triple-negative breast cancer patients, low TILs was associated with shorter overall survival (log-rank test, <i>p</i> = 0.04)	[38]
Sobottka <i>et al.</i> (2016)	n = 87 (PT) + 87 (BM)	FFPE	TIL (iTIL, sTIL, imTIL), IHC	There were fewer TIL in BM than in PT (<i>p</i> < 0.001) but within the tumor compartments, imTIL were more frequent than sTIL and iTIL both within BM and the matched breast PT (<i>p</i> < 0.001)	[39]
Melanoma					
Kluger <i>et al.</i> (2015)	n = 95 (ExM and PT) + 5 (BM)	FFPE	TMA	Although not significant, PD-L1 expression was lower in BM compared with other sites. BM displayed lower T-cell infiltration (<i>p</i> < 0.01)	[40]
Renal cell carcinoma					
Steindl <i>et al.</i> (2019)	n = 6 (PT) + 4 (ExM(lung)) + 10 (BM)	FFPE and frozen samples	TMB, TIL	TMB and TIL were higher in BM than in matched samples, although not statistically significant	[32]
Zhou <i>et al.</i>	n = 25 (PT) + 25 (BM)	FFPE	PD-L1, TIL	CD8 ⁺ TILs were significantly fewer in BM than in PT. Low stromal CD8 ⁺ TILs numbers in BMs were associated with shorter OS	[41]
NSCLC					
Mansfield <i>et al.</i> , 2016	n = 73 (PT) + 73 (BM)	FFPE	PD-L1, TIL	Discordance on tumor cells' PD-L1 and TILs' PD-L1 between BM and PT was observed in 14 and 19%, respectively	[30]
Mansfield <i>et al.</i> (2018)	n = 20 (PT) + 20 (BM)	FFPE	TCR-β sequencing, WES for TMB assessment and neoantigens detection	BM displayed a higher TMB, contained fewer T-cell clones than PT matched samples. Most of the T-cell clones differed between BM and PT	[33]
Kudo <i>et al.</i> , 2019	n = 39 (PT) + 39 (BM)	FFPE	770 genes expression panel, TCR-β sequencing, IHC	Hotspot mutations were mostly shared between PT and BM (71%). 161 genes were differentially expressed between PT and BM, including downregulation of immune pathways, <i>p</i> < 0.01. T-cell and macrophages infiltration was reduced in BM compared with PT (<i>p</i> < 0.001)	[34]

BM: Brain metastasis; ExM: Extracranial metastasis; FFPE: Formalin-fixed paraffin-embedded; IHC: Immunohistochemistry; imTIL: invasive-margin lymphocyte; iTIL: intratumoral lymphocytes; PT: Primary tumor; sTIL: Stromal lymphocyte; TMA: Tissue microarray; TMB: Tumor mutational burden; TCR-β: T-cell receptor-β; TIL: Tumor infiltrating lymphocyte; WES: Whole exome sequencing.

This spatial tumor microenvironment differences between primary and metastatic sites may explain heterogeneous responses rates on ICI.

Increasing data suggest that the brain micro-environment is immunosuppressive by itself [35], and may therefore promote BM development in various tumor histologies [36] as well as hamper anti-tumor immune response compared with other organ microenvironments (Table 1) [30,32–34,37–41]. Therefore, monotherapy strategies with ICI might be impaired and combination strategies could be more suitable/appropriate. All completed trials are summarized in Table 2 and are described in more detail below.

ICI in monotherapy: data from clinical trials

Despite a more immune ignorant phenotype in BM, for NSCLC, intracranial objective response rates (icORR) mirror extracranial ORR (ecORR). For example, in the single arm phase II trial (NCT02085070) evaluating pembrolizumab in melanoma or NSCLC patients with untreated BM (asymptomatic, maximum diameter 20 mm), the updated results on 37 PD-L1-positive NSCLC patients showed an icORR of 29.7% [47]. Similar results were found in a retrospective series: icORR was 27% in 73 NSCLC with active BM [39]. Interestingly, in 13–21% a dissociated response was described (response in brain and extracranial progression or *vice versa*) [47,48]. Except the

Table 2. Completed trials reporting outcomes in patients with brain metastases.

Trial reference	Phase	Combination therapy	Population	BM subgroup	Total popula- tion	BM patients	Total population outcomes			BM population outcomes				Ref
							ORR/DCR	PFS	OS	CNS RR/ORR; CNS DCR/oDCR	CNS PFS	PFS	OS	
ICI/chemotherapy														
NCT01654692	II	Ipilimumab 10 mg/kg q3W × 4 cycles, followed by 10 mg/kg q12W + fotemus-tine 100 mg/m2 q3W	Advanced melanoma	Asymptomatic BM (7 patients were pretreated by RT)	n = 20		DCR: 46.5% (95% CI: 35.7–57.6)	4.5 months (95% CI: 3.1–5.9 months) (irPFS)	12.9 months (95% CI: 7.1–18.7 months)	CNS DCR: 10/50%, oDCR: 50.0% (95% CI: 27.2–72.8)	3.0 months (95% CI: 2.3–3.1 months) (irPFS)	3.4 months (95% CI: 2.3–4.5 months)	12.7 months (95% CI: 2.7–22.7 months)	[42,43]
NCT02039674; NCT02578680; NCT02775435	III	Pembro (P) + chemo (C) vs Pembro (P) only	Advanced NSCLC	Asymptomatic BM	n = 1298	n = 171 (P+C; n = 105; P: n = 86)	ORR: P+C: 54.6% vs P: 31.8	HR: 0.55 (0.48–0.63)	HR: 0.63 (0.53–0.75)	CNS RR/DCR not reported; ORR: P+C: 39.0% vs P: 19.7% (0.32–0.70)	Not reported	HR: 0.44 (0.31–0.62)	vs 7.6 months (P), HR: 0.48 (0.32–0.70)	[17]
ICI/ICI														
NCT02374242†	II	Nivolumab 1 mg/kg q3W + Ipilimumab 3 mg/kg q3W (cohort A)/Nivolumab 3 mg/kg q2W (cohort B and C)	Advanced melanoma with BM	Asymptomatic BM (cohort A and B), or symptomatic BM (cohort C)	NA	n = 35 + 25 + 16	NA	NA	NA	Cohort A: 46% Cohort B: 20% Cohort C: 6%	Cohort A: Not reached/ Cohort B: 2.5 months/ Cohort C: 2.3 months	Cohort A: 13.8 months/ Cohort B: 2.6 months/ Cohort C: 2.6 months	Cohort A: Not reached/ Cohort B: 18.5 months/ Cohort C: 5.1 months	[21]
NCT02320058†	II	Nivolumab 1 mg/kg q3W + Ipilimumab 3 mg/kg q3W × 4 cycles, followed by Nivolumab 1 mg/kg q2W	Advanced melanoma with BM	Asymptomatic BM	NA	n = 94	NA	NA	NA	CNS DCR: 55% (95% CI: 45–66)/50% (95% CI: 40–60)	Not reported	Not reported	Not reported	[44]
NCT02320058†	II	Nivolumab 1 mg/kg q3W + Ipilimumab 3 mg/kg q3W × 4 cycles, followed by Nivolumab 1 mg/kg q2W	Advanced melanoma with BM	Symptomatic BM	NA	n = 18	NA	NA	NA	CNS DCR: 22.2% (6.4–47.6) (vs 58.4% (48.2–68.1) in asymptomatic cohort)	Not reported	Not reported	Not reported	[45]
† Trials marked included only BM metastatic patients. ‡ Total population results of CheckMate209 trial have not been reported yet. Outcomes of nivolumab plus ipilimumab combination in general advanced RCC population have been reported in Checkmate 214 trial. BM: Brain metastasis; CNS DCR: Central nervous system disease control rate; Combo: Combination; icORR: Intracranial objective response rate; ICT: Immune checkpoint inhibitor; NSCLC: Non-small-cell lung cancer; oDCR: Overall disease control rate; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; Ref: Reference.														

† Trials marked included only BM metastatic patients.

‡ Total population results of CheckMate209 trial have not been reported yet. Outcomes of nivolumab plus ipilimumab combination in general advanced RCC population have been reported in Checkmate 214 trial.

BM: Brain metastasis; CNS DCR: Central nervous system disease control rate; Combo: Combination; iORR: Intracranial objective response rate; ICI: Immune checkpoint inhibitor; NSCLC: Non-small-cell lung cancer; oDCR: Overall disease control rate; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; Ref: Reference.

Table 2. Completed trials reporting outcomes in patients with brain metastases (cont.).														
Trial reference	Phase	Combination therapy	Population	BM subgroup	Total population	BM patients	Total population outcomes				BM population outcomes			Ref.
							ORR/DCR	PFS	OS	CNS RR/ORR; CNS DCR/oDCR	CNS PFS	PFS	OS	
NCT02982954	IIIb/IV	Nivolumab (N) 3 mg/kg q3W + Ipilimumab (I) 1 mg/kg q3W × 4 cycles, followed by Nivolumab 480 mg q4W	Advanced clear cell renal carcinoma	Asymptomatic BM (no indication for radiation and not steroid allowed)	Not reported yet	n = 28	Not reported yet ‡ NB: Checkmate 214; I+N: 41% (37–46) vs S: 34% (30–38)	Not reported yet ‡ NB: Checkmate 214; I+N: 9.7 months (95% CI 8.1–11.1), S: 9.7 months (95% CI 8.1–11.1); p = 0.027	Not reported yet ‡ NB: Checkmate 214; I+N: median OS not reached (95% CI 13.2–48.7)	Not reported	9.0 months (95% CI 2.9–NE)	Not reached (95% CI 13.1–NE)	[46]	
ICI/targeted therapy														
No published data on BM outcomes	–	–	–	–	–	–	–	–	–	–	–	–		
ICI/ angiogenesis inhibitor														
No published data on BM outcomes	–	–	–	–	–	–	–	–	–	–	–	–		
† Trials marked included only BM metastatic patients. ‡ Total population results of CheckMate209 trial have not been reported yet. Outcomes of nivolumab plus ipilimumab combination in general advanced RCC population have been reported in Checkmate 214 trial. BM: Brain metastasis; CNS DCR: Central nervous system disease control rate; Combo: Combination; iCORR: Intracranial objective response rate; IC: Immune checkpoint inhibitor; NSCLC: Non-small-cell lung cancer; oDCR: Overall disease control rate; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; Ref: Reference.														

single arm phase II trial mentioned above, no lung cancer trials specifically focusing on ICI efficacy in BM patients have been reported yet. However, data have been reported regarding NSCLC BM patients treated within clinical trials. The largest clinical trial report comes from a pooled analysis ($n = 3170$, of which 292 PD-L1 positive patients with BM) of four KEYNOTE studies (001, 010, 024 and 42). In the BM subgroup, median OS was longer with pembrolizumab compared with chemotherapy (13.2 vs 10.3 months), with a hazard ratio (HR) of 0.83 (95% CI: 0.62–1.10). 159 BM patients had a PD-L1 $\geq 50\%$; and the HR for OS was 0.78 (95% 0.71–0.85) [18]. However, stratification for BM was not performed.

In advanced/metastatic melanoma, the first data with ICI in patients with BM come from ipilimumab, although only radiotherapy pretreated BM patients were included. In a retrospective cohort study, ipilimumab showed equivalent efficacy in pretreated BM versus non-BM patients [49], questioning whether the benefit of ICI in BM is linked to the drug or previous radiotherapy. A phase II study evaluated ipilimumab in asymptomatic and symptomatic BM patients who had at least one measurable index BM (diameter 5–30 mm), and/or two measurable BM > 30 mm on baseline MRI [50]. In this study, patients could have been pretreated by whole-brain or stereotactic radiation (WBRT/SRT), but the index BM should either have been excluded from radiation fields or be progressive after any radiation. Ipilimumab achieved the highest disease control rate (DCR) in asymptomatic BM patients (12/51, 24%, range (12–38)) compared with those with symptomatic BM on a stable dose of corticosteroids (2/21, 10% [range 1–30%]) [50].

In the precited NCT02085070 phase II trial evaluating pembrolizumab in melanoma and NSCLC asymptomatic untreated BM patients, pembrolizumab monotherapy resulted in melanoma in an icORR of 22% (95% CI: 7–48%) [51]. Long-term update analysis was in line with this finding with an icORR of 26% and evidence of sustained clinical benefit with a 24-month OS of 48% [52].

In advanced/metastatic ccRCC, nivolumab monotherapy resulted in a low icORR in a phase II study (12% in 39 patients with previously untreated BM, 0% in the subgroup with multiple BM or BM larger than 1 cm). The 1-year OS was 67% in previously untreated BM patients and 59% in patients with BM that underwent prior therapy [53]. On the contrary, ORR was 25% with nivolumab monotherapy in the randomized phase III CheckMate025 study (nivolumab vs everolimus in pretreated ccRCC patients) [54] and 21% with nivolumab in a ‘real life cohort’ of 729 pretreated ccRCC patients (81 baseline BM, 12.3%), in the multicenter NIVOREN GETUG AFU 26 study [55].

Combination ICI/ICI trial data

Rationale

The synergistic effects of the combination of PD-(L)1 and CTLA4 inhibitors are supported by preclinical studies, as monotherapy ICI might increase compensatory alternative immune checkpoints, and combination therapies increase T-cell infiltration and reduce regulatory T-cells [56].

For NSCLC, ICI/ICI combination data in BM patients are scarce. In the CheckMate 22 trial (nivolumab plus ipilimumab vs platinum-based chemotherapy) patients with treated BM were eligible, but outcomes of this subgroup have not been reported [57]. One cohort of the CheckMate 817 trial (first line nivolumab plus ipilimumab) included special populations (hepatic or renal impairment, HIV or untreated asymptomatic BM, with an ECOG PS of 0–1) [58]. Primary end point was toxicity. 50 out of the 198 included patients in the special population group had BM (25%). BM-specific outcomes were not reported. 67% of patients had an adverse event, of which 28% was grade 3–4. Median progression free survival (PFS) was 3.9 months (95% CI: 2.8–5.4), 1-year PFS was 26% and median OS was 9.9 months (95% CI: 7.0–13.7). Median duration of response (DoR) was 13.8 months (9.6–not reached), with 1-year DoR of 57% [58].

In melanoma, nivolumab/ipilimumab is superior to nivolumab alone. Data also support the use of this combination in BM patients.

The Checkmate 204 trial [44] evaluated four cycles of nivolumab plus ipilimumab, followed by nivolumab alone in BM patients with ≥ 1 measurable and nonirradiated BM measuring 0.5–3.0 cm. Patients were divided into two cohorts according to their neurological symptoms. Cohort A included patients with no neurological symptoms or steroids ($n = 101$, 94 with median follow-up ≥ 6 months) and cohort B included those with neurological symptoms, with or without steroids ($n = 20$, 18 with median follow-up ≥ 6 months). Median follow-up was 14 months. In cohort A, the intraCNS clinical benefit (percentage of patients with stable disease [SD] ≥ 6 months, partial or complete response [PR/CR]) was 57% (95% CI: 47–68), which was comparable to the 56% (95% CI: 46–67) extraCNS clinical benefit. CR, PR, and SD ≥ 6 months were observed in 26, 30 and 2%, respectively. 55% had grade 3–4 adverse events. In an updated analysis of this trial [45], intracranial benefit rate was $> 50\%$ reduced in

cohort B versus cohort A: 22.2% (6.4–47.6) versus 58.4% (48.2–68.1), respectively. Another Phase II trial [59] compared nivolumab versus nivolumab/ipilimumab. Asymptomatic, nonirradiated BM patients were randomized in two cohorts: nivolumab alone (A, n = 36), or nivolumab/ipilimumab (B, n = 27). Cohort C (n = 16) enrolled patients with symptomatic or recurrent BM after local treatment, or leptomeningeal disease and was treated by nivolumab monotherapy. IcORR was 46% in cohort A (95% CI: 29–63), 20% in cohort B (95% CI: 7–41), and 6% in cohort C (95% CI: 0–30). Intracranial CR were observed in 17%, 12% and none, in cohort A, B and C, respectively.

In conclusion, limited data (only cohort B of Checkmate 204 trial) exist concerning the use of ICI combinations as the sole induction treatment for symptomatic previously untreated melanoma BM, and these patients often require multidisciplinary approach [60].

In advanced RCC patients with BM, nivolumab/ipilimumab results were reported in an interim analysis of the Checkmate 920 trial, a Phase IIIb/IV safety trial of nivolumab combined with ipilimumab in previously untreated advanced/metastatic RCC [46]. Although CNS icORR is not yet available and OS not reached, this combination was safe in BM patients, with an overall ORR of 28.6% (95% CI: 13.2–48.7) and median PFS of 9.0 months (95% CI: 2.9–NE). Comparatively, extended follow-up efficacy results of nivolumab/ipilimumab in treatment naive advanced or metastatic ccRCC have been reported in the pivotal phase III CheckMate 214 trial comparing ICI doublet with sunitinib: OS was not reached in the ICI combo arm, (95% CI: 35.6–not estimable), median PFS was 8.2 months (95% CI: 6.9–10.0) and ORR was 41% (37–46) in the intention to treat population [54,61].

Combination ICI/chemo data

Rationale

It is currently well established that chemotherapy may increase ICI efficacy by increasing neoantigens release by inducing immunogenic cell death, increasing T-cell response and disrupting immune suppressive cells' activity [62].

Pembrolizumab/chemotherapy has become standard of care first line treatment for NSCLC regardless of PD-L1 expression and histologic subtype. In a pooled analysis of the KEYNOTE 021, 189 and 407 trials, 171 out of 1298 patients (13%) had BM at baseline. In the KEYNOTE 189 and 407 trials, untreated, asymptomatic and small (maximum diameter 15 mm) BM were allowed; however the percentage of these patients enrolled in both trials was not reported. Like the monotherapy trials, patients with BM also derived clinical benefit from the chemotherapy/pembrolizumab combination, as median OS was 18.8 months versus 7.6 months, with a HR of 0.48 (95% CI: 0.32–0.70). Outcome of BM patients according to PD-L1 status was not reported. Percentage of neurological treatment related AEs (TRAEs) was similar, reaching approximately 30% in both arms [17].

For metastatic SCLC, ICI plus chemotherapy improved the OS compared with chemotherapy alone (IMpower133: atezolizumab plus chemotherapy [63], CASPIAN: durvalumab plus chemotherapy [13]). In the IMpower 133 study, 35/403 patients had baseline BM (9%). In this small subgroup, the addition of atezolizumab did not result in an OS benefit (HR 1.07; 95% CI: 0.47–2.43) [63]. In the CASPIAN trial there was a trend for an OS benefit in the small subgroup (55/537, 10%) of patients with baseline BM. HR for OS was 0.69 (95% CI: 0.35–1.31) [13].

In melanoma, fotemustine combined with ipilimumab was evaluated in the NIBIT trial, which allowed inclusion of asymptomatic BM patients (n = 20/86) [42,43]. IcORR was 40% with a median and CNS PFS of both 3 months and OS of 13.4 months. Three-year follow-up analysis revealed a median OS of 12.9 months (95% CI: 7.1–18.7) for the whole study population, and 12.7 months (95% CI: 2.7–22.7) for the BM subpopulation.

Combination ICI-targeted therapy

Rationale

For melanoma, combination therapies of targeted therapy and ICI are supported by robust preclinical data [64]. For example, it has been shown that MAPK inhibition may increase neoantigens, enhance function of immune cells (dendritic cells, T cells, NKs) and decrease the function of immunosuppressive cells (cancer associated fibroblasts, tumor associated macrophages) [65,66]. Data for lung cancer are lacking.

ICI/targeted therapy combinations that are under investigation for advanced/metastatic melanoma include PD(L)-1 or CTLA4 inhibitors ± BRAF and/or MEK inhibitors. Some of these trials allowed asymptomatic BM (e.g., NCT01673854 [67]) or treated/inactive BM (e.g., NCT02908672, NCT02130466, NCT02967692) but BM specific outcomes have not been reported. Besides, several trials are ongoing evaluating these combinations either in concurrent or sequential settings (NCT02631447, NCT02224781, NCT01940809, NCT03235245,

NCT02902029, NCT02902042, NCT02967692, NCT02818023), but none of these trials allows active and/or nontreated BM patients.

Interestingly, the phase I/II trial NCT02910700 (nivolumab combined with trametinib with or without dabrafenib), was amended to allow the inclusion of patients with untreated BM. BM patients are divided into two cohorts according to their symptom or CNS progression status; recruitment is ongoing (Table 3).

Combination ICI-radiotherapy for brain metastases

Rationale

Radiotherapy increases immunogenicity [68] by release of cytokines, neoantigens and may promote BBB permeability as well as reduce peritumoral edema hence enabling to reduce steroid dosage. Cranial irradiation improves intracranial responses and disease control. Furthermore, radiation acts synergistically with ICI [69]. Therefore, it is of interest to combine these two treatment modalities. However, prospective trial data are lacking.

Based on retrospective series, the combination of anti-PD-[L]1 inhibition and ICI is safe, but the combination of anti-CTLA4 and ICI seems to increase the risk of radiation necrosis [19,70]. However, detailed neurotoxicity assessments for the combination treatment are not available. Based on the available retrospective data, concurrent ICI/radiotherapy results in an improved survival compared with sequential treatment strategies [19,70]. A drawback of these retrospective series is the bias for selecting patients for a certain treatment sequence. For example, those that are treated with cranial irradiation because of brain progression on ICI, obviously have a poorer survival than those that can be treated concurrently. Moreover, those that need to be treated with cranial irradiation before start of ICI because of symptoms, are probably another group of patients than those in the concurrent group.

A series of ongoing trials aim at evaluating the combination of radiotherapy plus ICI (Table 3).

Combination ICI/angiogenesis inhibitors for brain metastases

Rationale

Angiogenesis inhibitors may normalize the vasculature and increase T-cell migration within the tumor bed, hence fostering ICI efficacy [71]. Moreover, adding an angiogenesis inhibitor to ICI may allow to reduce peritumoral edema for BM patients, enabling the reduction of steroid dosage.

For metastatic NSCLC, the combination of atezolizumab plus bevacizumab and carboplatin/paclitaxel is the other approved first-line chemotherapy/ICI regimen based on the phase III IMpower150 trial, however BM specific outcomes have not been reported in this trial [72]. This is unfortunate, as in the phase II BRAIN trial, the addition of bevacizumab to chemotherapy has reported an iORR of 61% in NSCLC patients with asymptomatic and untreated BM. Indeed, there is a rationale for the synergism between antiangiogenic treatment and ICI. Furthermore bevacizumab may overcome radionecrosis [72–74].

In ccRCC, the combination of ICI and VEGF targeting therapies has shown promising efficacy [75–77] leading to FDA+EMA approval of pembrolizumab plus axitinib and avelumab plus axitinib in first line in advanced settings. Patients with BM were allowed in the pembrolizumab/axitinib trial (KEYNOTE-426) if asymptomatic, but data for this subgroup is not yet available. Similarly, the IMmotion 151 trial (atezolizumab/bevacizumab vs sunitib) included only patients with treated BM and data of this subgroup is not available.

Future perspective

As outcome of patients with BM is still often poor, efforts should be put in improving treatment as well as selection for treatment. Possible options are:

Alternative ICI combinations

Numerous other potential ICI combinations should also be tested in BM patients including IDO/CTLA4/PD-(L)1, LAG-3/PD-(L)1 inhibition [78]. Moreover, in advanced melanoma, combination of talimogene laherparepvec (T-VEC) with pembrolizumab is under evaluation to study its ability to revert pembrolizumab resistance [79] (NCT02965716). Regarding BM, only those with treated BM are eligible in this study. One report of CR of T-Vec/pembrolizumab associated with WBRT confirms that this association is feasible and might be envisioned after failure of ICI/ICI combination therapy in BM patients [80]. Furthermore, TKI combined with ICI is an interesting option, especially in melanoma. Future trials should also include subgroups of BM patients. Last, combinations of ICI and epigenetic targeting therapy or DNA repair targeting agents are currently under investigation and might bring benefit as well for BM patients.

Table 3. Ongoing trials evaluating immune checkpoint inhibition combination therapy in patients with brain metastases.

Trial name	Phase	Combo treatment	Primary end point	Secondary end point	Population	Patient BM subgroup	Status	Trial reference
ICI/chemotherapy								
A study of fotemustine (FTM) vs FTM and Ipilimumab (IpI) or IpI and nivolumab in melanoma brain metastasis (NIBIT-M2)	III	Fotemustine + Ipilimumab	OS	PFS, AEs, DCR, ORR, TTR, DOR, B PFS	Melanoma	Active BM	Recruiting	NCT02460068
Atezolizumab in combination with carboplatin plus pemetrexed in chemotherapy-naïve patients with asymptomatic brain metastasis (ATEZO-BRAIN)	II	Atezolizumab + Carboplatin + Pemetrexed	PFS	NANO, time to radiation therapy, number of patients with neurological deterioration, EORTC QLQ-BN20	1st line nonsquamous NSCLC (ALK-/EGFR-)	Active asymptomatic/oligosymptomatic BM	Recruiting	NCT03526900
Pembrolizumab and doxorubicin hydrochloride or anti-estrogen therapy in treating patients with triple-negative or hormone receptor-positive metastatic breast cancer	II	Pembrolizumab + Doxorubicin (TN) or Pembrolizumab + Anastrozole/ Exemestane/ Letrozole (HR+)	AEs, ORR	Clinical benefit, TTE, OS, PFS, duration of response	Breast cancer	Active BM	Recruiting	NCT02648477
ICI/ICI								
Evaluation of safety and efficacy of combined treatment with ipilimumab and nivolumab in patients with four and more symptomatic brain metastases of melanoma	II	Ipilimumab + Nivolumab	Intracranial control rate at 6 months	OS, PFS, AE, BOR of CR/PR, QoL, neurocognitive assessment	Melanoma	Active BM	Recruiting	NCT03728465
Efficacy of immunotherapy in melanoma patients with brain metastases treated with steroids	II	Pembrolizumab alone or Ipilimumab + Nivolumab with 2 levels of steroid dosing	6-months OS and PFS	PFS, OS, ORR, B ORR, ExB ORR, intracranial CBR, blood/tissue biomarkers of response/progression	Melanoma	Active BM	Recruiting	NCT03563729
A Phase II study of open label low dose ipilimumab in combination with pembrolizumab in metastatic melanoma patients with brain metastases	II	Pembrolizumab + Ipilimumab	CBR	OS, PFS, AEs, Cytokine levels, Blood and CSF T-cell population characterization, cfDNA	Melanoma	Active BM	Active, not recruiting	NCT03873818
ICI/targeted therapy								
Induction therapy with vemurafenib and cobimetinib to optimize nivolumab and ipilimumab therapy (COWBOY)	II	Vemurafenib + cobimetinib directly followed by ipilimumab + nivolumab (Arm A) or standard first line ipilimumab + nivolumab (Arm B)	Best overall response rate at week 18	PFS, OS, AEs, G3-4 toxicities, % of ongoing response, % of patients requiring re-induction, response percentage upon re-induction, changes in tumor-specific T-cell responses	Melanoma BRAFV600E	Active asymptomatic BM allowed	Active, Not recruiting	NCT02968303

AE: Adverse event; B: Brain; BM: Brain metastasis; CBR: Clinical benefit rate; CR: Control Rate; ccRCC: clear cell renal cell carcinoma; CSF: Cerebrospinal fluid; DLT: Dose limiting toxicity; cfDNA: Circulating-free DNA; DOR: Duration of response; EXM: Extra-brain; HR: Hormone receptor; ICI: Immune checkpoint inhibitors; NANO: Neurologic assessment in neuro-oncology; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PRO: Patient reported outcome; QoL: Quality of life; RP2D: Recommended dose for Phase II; RR: Response rate; SCLC: Small cell lung cancer; SRS: Stereotactic radiosurgery; TTR: Time to response; TTE: Time to treatment failure; TN breast cancer; Triple-negative breast cancer; WBRT: Whole brain radiotherapy.

Table 3. Ongoing trials evaluating immune checkpoint inhibition combination therapy in patients with brain metastases (cont.).

Trial name	Phase	Combo treatment	Primary end point	Secondary end point	Population	Patient BM subgroup	Status	Trial reference
Phase II study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in patients harboring the BRAFV600 mutation	II	Pembrolizumab alone vs pembrolizumab with dabrafenib + trametinib short scheme, vs pembrolizumab with dabrafenib + trametinib intermediate scheme, vs pembrolizumab with dabrafenib + trametinib long scheme	Safety, feasibility, T-cell response	ORR, AEs, PFS	Melanoma BRAFV600E	Active asymptomatic BM allowed	Unknown	NCT02625337
Nivolumab and Trametinib with or without dabrafenib in treating patients with BRAF mutated or wild-type metastatic stage III–IV melanoma that cannot be removed by surgery	II	Nivolumab and Trametinib with or without dabrafenib	ORR	AEs, OS, PFS, circulating markers	Melanoma BRAFV600E or BRAF wt	Active and symptomatic BM allowed (Cohort A: inactive/treated BM, Cohort B: 1. untreated but asymptomatic and had previous PD-1 treatment, or 2.untreated and symptomatic but symptoms are controlled on stable, or 3. untreated leptomeningeal disease)	Active, recruiting	NCT02910700
ICI/angiogenesis inhibitor								
Study of bevacizumab in combination with atezolizumab in patients with untreated melanoma brain metastases (BEAT-MBM)	II	Bevacizumab + Atezolizumab	B ORR, safety/tolerability/efficacy	AEs, intracranial and extracranial ORR, DOR, PFS, OS	Melanoma	Active BM	Recruiting	NCT03175432
Pembrolizumab plus bevacizumab for treatment of brain metastases in metastatic melanoma or non-small-cell lung cancer	II	Pembrolizumab + Bevacizumab	B ORR	ORR, PFS, AEs, proportion of pts upon steroids, PD-L1 expression another potential biomarkers in CNS/tumors/blood	Melanoma and NSCLC	Active BM	Recruiting	NCT02681549
ICI/RT								
Anti-PD 1 Brain Collaboration + Radiotherapy (ABC-X Study) (ABC-X)	II	Nivolumab + Ipilumab + SRS vs Nivolumab + Ipilumab alone	Neurological specific cause of death	B and ExB ORR, ORR, PFS, OS, Non neurological cause of death, incidence of radionecrosis, requirement for salvage RT or neurosurgery, neurocognitive assessment, QoL and ECOG, AEs, tissue/blood/gut biomarkers	Melanoma	Active BM	Recruiting	NCT03340129

AE: Adverse event; B: Brain; BM: Brain metastasis; CBR: Clinical benefit rate; CR: Control Rate; ccRCC: clear cell renal cell carcinoma; CSF: Cerebrospinal fluid; DLT: Dose limiting toxicity; ctDNA: Circulating-free DNA; DOR: Duration of response; EXM: Extra-brain; HR: Hormone receptor; ICI: Immune checkpoint inhibitors; NANO: Neurologic assessment in neuro-oncology; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PRO: Patient reported outcome; QoL: Quality of life; RP2D: Recommended dose for Phase II; RR: Response rate; SCLC: Small cell lung cancer; SRS: Stereotactic radiosurgery; TTR: Time to response; TTF: Time to treatment failure; TN breast cancer: Triple-negative breast cancer; WBRT: Whole brain radiotherapy.

Table 3. Ongoing trials evaluating immune checkpoint inhibition combination therapy in patients with brain metastases (cont.).

Trial name	Phase	Combo treatment	Primary end point	Secondary end point	Population	Patient BM subgroup	Status	Trial reference
Pembrolizumab and stereotactic radiosurgery (SRS) of selected brain metastases in breast cancer patients	I	Pembrolizumab + SRS	AEs	B and ExB ORR, OS, PFS, intracranial brain failure rate, rate of leptomeningeal disease, rate of local recurrence, rate of symptomatic radionecrosis, serum biomarkers	Melanoma and NSCLC	Active BM	Recruiting	NCT02858869
Pembrolizumab and stereotactic radiosurgery (SRS) of selected brain metastases in breast cancer patients	I/II	Pembrolizumab + SRS	RECIST 1.1 tumor response	OS, correlation of abscopal responses	Breast cancer	Active BM (n = 2 to 10)	Recruiting	NCT03449238
A Phase II study of atezolizumab in combination with stereotactic radiation for patients with triple-negative breast cancer and brain metastasis	II	Atezolizumab + SRS	PFS 24 months	ExB ORR, clinical benefit, OS, PROs, abscopal effects, DLT, NANO	TN breast cancer	Active BM requiring SRS (N <5)	Recruiting	NCT03483012
Avelumab with radiotherapy in patients with leptomeningeal disease	I	Avelumab + WBRT	AEs	CSF T-cell nbr; CSF T-cell activation, CNS RR/ExB RR	Any solid cancer	Leptomeningeal disease	Recruiting	NCT03719768
Immunotherapy with or without SBRT in patients with stage IV non-small-cell lung cancer	III	Pembrolizumab +/- SRS	PFS	OS, rate of failure, Time of progression, number of participants with new sites of disease, AE	NSCLC (ALL-/EGFR-)	Residual ExBM and BM after 4 cycles chemo-immunotherapy with at least SD	Recruiting	NCT03867175
Phase II trial of pembrolizumab in central nervous system metastases from multiple histologies (cohort D)	II	Pembrolizumab + SRS (cohort D)	ORR, ExB ORR, OS rate	AE, B and ExB PFS, B and ExB RR	Melanoma (cohort D)	Active BM requiring SRS (N <4)	Recruiting	NCT02886585
Combining radiosurgery and nivolumab in the treatment of brain metastases	II	Nivolumab + SRS	B PFS	B CR, OS, PFS, neurocognitive assessment (various scales), QoL, correlation between PD-L1 status and outcomes, AEs	NSCLC, SCLC, melanoma or ccRCC	Active BM	Recruiting	NCT02978404
Nivolumab and radiation therapy with or without ipilimumab in treating patients with brain metastases from non-small-cell lung cancer	I/II	Nivolumab + SRS	RP2D of Nivolumab, RP2D of Nivolumab + ipilimumab, intracranial PFS	Neurocognitive assessment	NSCLC	Active BM requiring SRS	Recruiting	NCT02696993

AE: Adverse event; B: Brain; BM: Brain metastasis; CBR: Clinical benefit rate; CR: Control Rate; ccRCC: clear cell renal cell carcinoma; CSF: Cerebrospinal fluid; DLT: Dose limiting toxicity; cDNA: Circulating-free DNA; DOR: Duration of response; ExM: Extra-brain; HR: Hormone receptor; ICI: Immune checkpoint inhibitors; NANO: Neurologic assessment in neuro-oncology; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PRO: Patient reported outcome; QoL: Quality of life; RP2D: Recommended dose for Phase II; RR: Response rate; SCLC: Small cell lung cancer; SRS: Stereotactic radiosurgery; TTR: Time to response; TTF: Time to treatment failure; TN breast cancer; WBRT: Whole brain radiotherapy.

Predictive biomarkers & prognostic scores

ICI, especially ICI combination therapy data for BM patients is still limited, and data available cannot be extrapolated to daily clinical practice as patients included in clinical trials were usually very selected (good performance, no or only low dose corticosteroids, small, asymptomatic and often locally pretreated BM). Furthermore, predictive markers for BM response are not well known.

Therefore, trials should incorporate BM-specific end points, as was recommended by a recent Response Assessment in Neuro-Oncology (RANO) working group statement. They state that if there is a signal for intracranial efficacy (as is the case for ICI combinations), clinical trials should have bicompartamental response assessments (separate cranial and extracranial end points) [81]. Moreover, predictive factors and biomarkers should be evaluated prospectively, also in ICI combination treated patients. For example, in a retrospective series, disease-specific Graded Prognostic Assessment (ds-GPA) was associated with survival in monotherapy ICI treated NSCLC patients [48]. In the pooled analysis of the monotherapy pembrolizumab NSCLC trials, those with PD-L1 $\geq 50\%$ had the best outcome [18] but it is not clear whether these results can be translated to patients treated with ICI combinations.

Response assessment end points

Furthermore, it is known that with ICI treatment, dissociated responses can occur [47,48]. The RANO working group advises to incorporate in the clinical trial protocols the actions that are allowed in case progression occurs in one compartment (e.g., SRT for a growing BM, with the continuation of the ICI, as the extracranial disease is under control) [81]. Intracranial response assessments can be challenging, as pseudoprogression can occur with ICI [82] and radiation necrosis (with as a result a growing BM) can occur especially after SRT [73]. The RANO group has published specific criteria for response assessment in BM patients (depending on clinical condition and time since initiation of ICI: discontinue ICI or continue ICI with follow-up brain imaging) [83], but these criteria should be prospectively validated. Furthermore, it is not clear whether these criteria also apply for ICI/chemotherapy treated patients as the rate of pseudoprogression is probably lower in this patient population. New imaging techniques such as perfusion-weighted magnetic resonance imaging (PWI) and diffusion-weighted magnetic resonance imaging (DWI) are promising tools to differentiate pseudoprogression/radiation necrosis from real progression, and should be prospectively evaluated, as are several positron emission tomography tracers such as 18F-fluoroethyl-L-tyrosine, 18-F-fluorothymidine and 11C-methyl-L-methionine [84]. Alternate contrast agents may also address this question, as exemplified by NCT03325166 which currently evaluates a new contrast agent (ferumoxylol) to differentiate pseudoprogression and real progression.

Last, attention should be paid to long-term neurotoxicity of ICI. Severe neurotoxicity is rare in ICI treated patients [85] but data regarding low-grade toxicity are lacking.

Conclusion

ICI, especially ICI combinations are promising treatments strategies for patients with BM, but factors associated with response and survival should be prospectively evaluated. Furthermore, the optimal treatment sequence (upfront systemic treatment vs upfront SRT followed by systemic treatment) should be defined, as well as the potential deleterious effect of steroids at baseline. New imaging techniques could be helpful for differentiating between pseudoprogression and real progression. As delayed neurotoxicity remains unknown, improving survival with maintaining QoL is mandatory in a population who may achieve prolonged outcomes.

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Executive summary

ICI in monotherapy: data from clinical trials

- Monotherapy ICI icORR mirrors ecORR.

Combination ICI/ICI trial data

- Symptomatic BM patients seem to less benefit from ICI combinations compared with neurologically asymptomatic patients.
- ICI/ICI combinations are effective in the treatment of melanoma BM. Other tumor types should be further evaluated.

Combination ICI/chemo data

- ICI/chemotherapy combinations are effective in the treatment of NSCLC BM.

Combination ICI-radiotherapy for brain metastases

- ICI/radiotherapy combinations are being tested in clinical trials, the optimal sequence needs to be defined.

Future perspective

- With prolonged survival, long-term toxicity becomes more and more important and should be evaluated.

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