The forgotten role of adjuvant immune checkpoint inhibitors in preventing melanoma brain metastasis

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“Although the available evidence for ICI activity in preventing CNS metastasis is very limited, its implication in early disease is high relevant to clinical practice given the natural history of melanoma with CNS metastasis. The ICI adjuvant regimens have shown clinically meaningful reduction in the risk of melanoma recurrence”

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Localized melanoma is commonly cured with simple excision except for high-risk stage III melanoma that is often complicated with distant metastasis and death. A significant portion of these relapses develop in the CNS, which results in a shortened survival and altered quality of life [1]. Initial attempts to prevent the metastatic spread to the CNS relied on the administration of adjuvant therapies following resection [1]. Unfortunately, these attempts failed and active efforts were needed to identify more efficacious adjuvant regimens. Recently, the immune checkpoint inhibitors (ICI) showed high activity in metastatic melanoma, which constituted the backdrop for its evaluation in the adjuvant setting [2–4]. The dilemma remains whether ICI would prevent CNS relapse in resected high-risk stage III melanoma.

Melanoma tends to metastasize in the CNS according to the ‘seed and soil’ theory with a specific interaction between the melanoma cells and the CNS (Figure 1). A CNS metastasis-initiating melanoma cell escapes the immune surveillance during intravasation, adhesion to endothelial cells, extravasation into the parenchyma, vascular co-option, angiogenesis and proliferation [5]. The interaction of the melanoma cells with the soil microenvironment after extravasation seems the rate limiting step of the process. The immune system at this level may promote or hamper metastasis within the perivascular niche by switching between M1 (tumor-suppressive) and M2 (tumor-tolerant) phenotype [6]. The M2 component of the immune system alters the adaptive immunity through immunosuppressive factors such as PD-L1 and PD-1 [7]. Thus metastasis may not soil the CNS either due to the failure of solitary melanoma cells to initiate growth or early micrometastases to continue growth into macroscopic tumors [8].

As preclinical models have shown that ICI activate T-cells trafficking across the blood–brain barrier into the perivascular niche, adjuvant ICI may be protective of CNS metastasis in completely resected high-risk melanoma that has already circulating tumor cells. To date, three adjuvant ICI trials have enrolled 1895 patients with resected stage III melanoma (Supplementary Table 1). These patients were characterized by BRAF mutations in 41.3–47.7%, macroscopic lymph node involvement in 33.9–58.8% and ulceration of the primary tumor in 36.9–41.5%. After a median follow-up of 1.25–2.74 years, the rate of 1-year relapse-free survival was 60.8–75.4%. Unfortunately, none of these trials reported on the pattern of CNS relapse following adjuvant ICI [2–4].

The activity of ICI in CNS metastasis has not been recognized until recently [9,10]. The pivotal ICI trials in metastatic melanoma did not report the intracranial response rates probably due to the small numbers of patients with CNS metastasis (3–10%) [11–13]. One study evaluating the combination of nivolumab plus ipilimumab in metastatic melanoma reported the lowest rate of CNS progression in comparison to nivolumab and ipilimumab (nivolumab plus ipilimumab 11%, nivolumab 17% and ipilimumab 14%) [14]. A recently published Phase II

Figure 1. The successive 'seed and soil' steps in the development of central nervous system metastasis in melanoma. Reproduced with permission from <http://smart.servier.com>.

trial (NCT02374242) reported on the safety and efficacy of nivolumab plus ipilimumab in melanoma patients with CNS metastasis [15]. The intracranial response rate in melanoma patients with untreated asymptomatic CNS metastases was 46% (14 of 35 patients) with nivolumab plus ipilimumab and 20% (5 of 25 patients) with nivolumab monotherapy [15]. Another Phase II trial, NCT02320058, assessed the intracranial response rate of the combination nivolumab plus ipilimumab in metastatic melanoma with nonirradiated brain metastasis (tumor diameter between 0.5 and 3 cm and no neurologic symptoms) [16]. Among the 94 patients eligible for this study, the intracranial response rate was 57% and treatment-related grade 3/4 adverse events rates was 55% (CNS events in 7%). The safety profile of nivolumab plus ipilimumab was similar among patients with or without CNS metastasis [16]. Interestingly, the combination of nivolumab plus ipilimumab prevented intracranial progression for >6 months in 64% of patients [16]. Pembrolizumab has also shown promising intracranial response rates of 22% (4 of 18 patients) in small asymptomatic CNS metastasis [17].

Although the available evidence for ICI activity in preventing CNS metastasis is very limited, its implication in early disease is high relevant to clinical practice given the natural history of melanoma with CNS metastasis. The ICI adjuvant regimens have shown clinically meaningful reduction in the risk of melanoma recurrence but did not report on the occurrence of CNS metastasis at recurrence [18]. Similarly, targeted therapy adjuvant regimens present the same issue although it presents an intracranial response rate of 58% among melanoma patients with *BRAF* V600 mutation and asymptomatic brain metastases [19,20]. This achieves similar intracranial response rates to nivolumab plus ipilimumab; however, the duration of intracranial response was shorter with the combination of dabrafenib plus trametinib (6.5 months vs not reached after median follow-up of 14 months) [15,16,20].

The longer duration of systemic control for ICI compared with targeted therapy and the higher intracranial responses with combination ICI compared with monotherapy ICI lead us to speculate that adjuvant ICI combination therapy seems the best option to reduce the risk of CNS metastasis in high-risk melanoma patients. The main concern remains in identifying the risk factors for CNS metastasis in melanoma to avoid overtreatment and excessive toxicities. Herein raises the need to enhance the understanding of the patient and tumor-related factors that may increase the risk of CNS metastasis. These factors may be considered to build risk models that would stratify the risk of CNS metastasis thus the necessity for aggressive adjuvant treatment with high intracranial activity. Such data may be collected from the adjuvant trials of ICI in high-risk melanoma.

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Supplementary data

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