Editorial Commentary



# Triple combinations of immunotherapy and targeted therapy in patients with melanoma with brain metastases

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The occurrence of brain metastases is the most common cause of death among melanoma patients. They may develop in 50% of patients with stage IV disease (1). Till introduction of novel therapeutic methods the median survival of patients with melanoma brain metastases (MBM) was 4–5 months (1). The progression-free and overall survival of these patients improved substantially with new systemic therapies, e.g., immune checkpoint inhibitors (ICI) and BRAF/MEK inhibitors (BRAF/MEKi). However, patients with central nervous metastases in melanoma are still underrepresented in clinical trials (2-4). Moreover, many patients with MBM require multimodal therapy including surgery/radiotherapy and systemic treatment (5,6). The majority of clinical studies included asymptomatic MBM patients (Checkmate 204, Australian ABC, COMBI-MB) (7-9) and demonstrated that those patients has the best outcomes from the modern treatment approach of combined immunotherapy (nivolumab with ipilimumab) or combined BRAF/MEK inhibitor therapy. TRICOTEL was a two-cohort (*BRAF*-mutated and *BRAF*-wild type), phase 2 trial with optimized design for real population of MBM patients including metastases at size at least 5 mm, ECOG performance status up to 2, concomitant corticosteroids (up to 8 mg/day dexamethasone or equivalent) was allowed (10). Prior stereotactic radiotherapy (SRT) or surgery of brain metastases was allowed, as well as treatment beyond progression and SRT could be performed for patients with oligometastatic progressive disease int the brain. Sixty-five patients were enrolled to *BRAF*-mutated cohort, *BRAF*-wild type cohort was closed prematurely after 15 patients enrolled. Sixty patients in *BRAF*-mutated group received triple combination with atezolizumab plus vemurafenib and cobimetinib (5 without atezolizumab), 15 BRAF-negative patients received atezolizumab plus cobimetinib. Treatment-related adverse events grade ≥3 occurred in 68% of triplet-treated patients but were manageable in majority of them. Intracranial objective response rate (IRR) was 42% in *BRAF*-mutated cohort and 27% in BRAF-wild type. The final analysis concentrated on activity of triplet combination [anti-programmed death ligand-1 (PD-L1) + BRAF/MEKi]. Intracranial disease control rate at 16 weeks assessed by independent review was 38% with median duration of response—7.4 months. Median intracranial progression-free survival was 5.8 months. IRR (assessed by IRC) in symptomatic patients was 46% (n=24) with median duration of response 9.9 months. IRR in asymptomatic patients is similar to other available systemic therapies, but the combination of ipilimumab and nivolumab gives longer duration of responses and progression-free survival and combined immunotherapy is currently considered as gold standard in this group of patients. It must be remembered that in the CheckMate 204—nivolumab + ipilimumab—trial corticosteroids therapy use was not allowed per protocol, while in the COMBI-MB—dabrafenib + trametinib—trial steroid treatment was not used by majority of patients and corticosteroids treatment at baseline was associated with lower intracranial response rate (39%). The optimal treatment for patients who require concomitant steroid was not defined until now. Nevertheless, triplet combination of immunotherapy and targeted therapy used in TRICOTEL

trial gives promising activity especially in patients with high unmet need—requiring corticosteroids, symptomatic MBM, or both. It seems that short initial therapy with targeted therapy before addition of immunotherapy enables the reduction of corticosteroids what may facilitate the benefit from subsequent combination treatment with immunotherapy. TRICOTEL was the first clinical trial reporting intracranial outcomes of combined targeted therapy and immunotherapy in MBM patients. The positive outcomes of subgroup in SECOMBIT clinical trial with sandwich approach with short course of targeted therapy followed by combined immunotherapy still raise the questions about the optimal combination/sequencing in patients with MBM, especially *BRAF*-mutated. The subgroup of MBM patients treated within the TRIDeNT trial (NCT02910700) with nivolumab and dabrafenib with trametinib has also achieved significant benefit in terms of intracranial responses. Currently the phase 2 SWOG-S2000 clinical trial on triplet combination therapy with nivolumab plus encorafenib plus binimetinib compared to nivolumab and ipilimumab is ongoing in asymptomatic MBM population (NCT04511013). The further clinical trials are necessary in the group of patients with MBM, as well as using the objective and uniform definition of symptomatic metastases to the brain. It should also be considered that steroid doses equivalent to more than 20 mg/day of prednisone administered for 2 or more weeks are considered immunosuppressive that hinders immunotherapy responses by impeding both activation and effector functions of T-cells.

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