



BRAF-MEK inhibitors as steroid-sparing bridge prior to checkpoint blockade therapy in symptomatic intracranial melanoma

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Practice points

- Standard of care is lacking regarding the best approach in treating patients with symptomatic intracranial *BRAF*-mutated melanoma.
- Symptomatic patients with intracranial metastatic melanoma are often treated with dexamethasone to control brain edema.
- The use of steroids at baseline can decrease the antitumor efficacy of immune checkpoint blockade (ICB) and lead to poor outcomes.
- Objective response to ICB in symptomatic metastatic intracranial melanoma is low and is associated with short duration of response.
- Objective response rate to combined BRAF-MEK inhibitors in *BRAF*-mutated intracranial melanoma is high, albeit short duration of response prior to progression.
- Presence of mutations such as *CDKN2A* is associated with a shorter duration of response to BRAF-MEK inhibitors in patients with *BRAF*-mutated melanoma.
- Preclinical and clinical data suggest the efficacy of ICB might be compromised in patients who receive ICB after progressing during treatment with BRAF-MEK inhibitors.
- Using BRAF-MEK inhibitors (short course) in *BRAF*-mutated symptomatic intracranial metastatic melanoma might allow the discontinuation of steroids and lead to higher intracranial response. This might optimize the effect of ICB if started prior to progression of the disease.

The introduction of immune checkpoint blockade (ICB) and BRAF-MEK inhibitors has substantially improved outcomes in patients with metastatic melanoma. However, several challenging factors may hinder the efficacy of ICB in patients with symptomatic intracranial metastatic melanoma who are immunosuppressed due to the use of steroids prior to the administration of ICB. This has resulted in the exclusion of patients treated with high dose steroid at baseline from the majority of ICB clinical trials. In addition, despite the high efficacy of BRAF-MEK inhibitors in *BRAF*-mutant intracranial metastatic melanoma, most tumors will eventually progress. This demonstrates a gap in addressing the best management in such patients. Here, we present a case demonstrating our approach in this patient population.

Tweetable abstract: Management of symptomatic *BRAF*-mutated intracranial melanoma.

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Keywords: BRAF-MEK • brain • immune checkpoint blockade • intracranial • ipilimumab • metastatic melanoma • nivolumab • steroids • symptomatic • targeted therapy

Melanoma brain metastases represent a unique spectrum of metastatic melanoma due to high associated morbidity and mortality. This is of importance as a high proportion of patients (~36%) have evidence of intracranial metastases at the time of diagnosis [1]. Survival has improved significantly with the introduction of immune checkpoint blockade (ICB) and BRAF-MEK inhibitors. However, some patients have a high disease burden (defined as ≥ 3 intracranial lesions), and often demonstrate neurological symptoms. These cases represent a challenge in clinical practice as most clinical trials excluded patients with symptomatic brain metastases. Moreover, the immunosuppressive state caused by baseline use of dexamethasone, which is used to relieve neurological symptoms and brain edema, can

attenuate the response to ICB and lead to poorer responses and outcomes [2–5]. Furthermore, despite the high efficacy of targeted treatment with combination BRAF and MEK inhibitors in intracranial metastatic *BRAF*-mutated melanoma, most tumors will eventually progress due to acquired resistance. Genomic alterations such as the loss of expression of *CDKN2A* can contribute to acquired resistance leading to a short-lived response to targeted therapy [6,7]. Therefore, the heterogenous molecular nature of melanoma could further compromise the duration of response to targeted therapy. Here, we report the case of a patient successfully treated with planned sequential BRAF-MEK inhibitors followed by ICB after presenting with high-burden, symptomatic intracranial metastatic melanoma requiring high dose dexamethasone. The patient had detectable *BRAF*^{V600E} and *CDKN2A* mutations. The treatment course included administration of BRAF-MEK inhibitors for 8 weeks while discontinuing dexamethasone followed by ipilimumab-nivolumab administration. The patient had a near-complete radiological resolution of intracranial disease after initiating ICB with an ongoing durable response at 8 months of follow-up.

Case presentation

A 50-year old female presented with new left arm weakness, headache, slurred speech and vision disturbance. Her past medical history was significant for stage IA melanoma in the left chest wall diagnosed 5 years prior for which she underwent wide local excision. She had another lesion in the left lower extremity 2 years later consistent with malignant melanoma (Stage IB: T1bN0M0), which was treated with wide local excision and sentinel lymph node biopsy. The patient underwent brain magnetic resonance imaging (MRI) due to presence of neurological symptoms which showed numerous scattered lesions (30 lesions) involving the supratentorial and infratentorial compartments bilaterally, consistent with metastatic disease (Figure 1A). The patient was started on dexamethasone (4 mg orally, three-times daily) due to symptomatic vasogenic edema (Figure 2A). Chest computed tomography (CT) revealed a 3 cm right upper lobe pulmonary mass which was biopsied and confirmed malignant melanoma. Next-generation sequencing revealed presence of a *BRAF*^{V600E} mutation (VAF 41.1%), *CDKN2A* copy number loss, and tumor mutation burden of 11.1 mutation per megabase (Tempus xT assay). The patient completed whole brain radiation WBRT (total of 30 Gy over 10 fractions) prior to referral to our hospital for further evaluation and management. Repeat brain MRI confirmed persistence of intracranial metastatic lesions. We tapered off dexamethasone within 3-week period after starting treatment with BRAF inhibitor (encorafenib 300 mg once daily orally) and MEK inhibitor (binimetinib 45 mg twice daily orally) as a bridge to control the symptomatic brain lesions prior to initiation of ICB. There were no side effects noted during treatment, and brain MRI after 8 weeks demonstrated partial response in several lesions without new neurological symptoms (Figure 1B). There was also continued resolution of brain edema after starting targeted therapy (Figure 2B). CT showed partial response in pulmonary metastatic lesion. Encorafenib and binimetinib were discontinued 8 weeks after their initiation despite no evidence of progressive disease, and the patient switched to ICB combination therapy including ipilimumab (3 mg/kg intravenously) and nivolumab (1 mg/kg intravenously) every three weeks. Given the risk of rebound disease and flare-up after the discontinuation of targeted therapy, the patient was closely monitored in the clinic but did not demonstrate any concerning signs or symptoms. After the second cycle of ICB, there was near-complete resolution noted on brain MRI. In addition, repeat CT demonstrated complete resolution of the pulmonary metastatic lesion. The patient developed hepatitis (immune related adverse event grade 3) which required holding off ICB and a treatment with 4-week course of high-dose prednisone taper (started 1 mg/kg/day). The patient later started maintenance ICB therapy with nivolumab (480 mg intravenously every 4 weeks). She remains without neurological symptoms and brain MRI continues to show a durable response in intracranial brain metastases after 8 months of initiating treatment (Figure 1C).

Discussion

The integration of ICB into the treatment paradigm of patients with intracranial metastatic melanoma has substantially improved overall survival compared with the pre-immunotherapy era based on data collected from the national cancer database [1]. Further prospective trials have corroborated the high and durable efficacy of ICB in intracranial metastatic melanoma. One such example is the CheckMate-204 Phase II open-label trial, which prospectively evaluated combination ICB (ipilimumab and nivolumab) followed by maintenance nivolumab in 94 patients with asymptomatic intracranial metastases [8]. This trial demonstrated a high intracranial response rate of 57% (including complete and partial responses) which was similar to the extracranial metastatic response rate. Moreover, the estimated overall survival rate was 81.5% at 1-year which further substantiated the evidence of the intracranial durable response attained through treatment with ICB [8]. Nevertheless, the evidence supporting

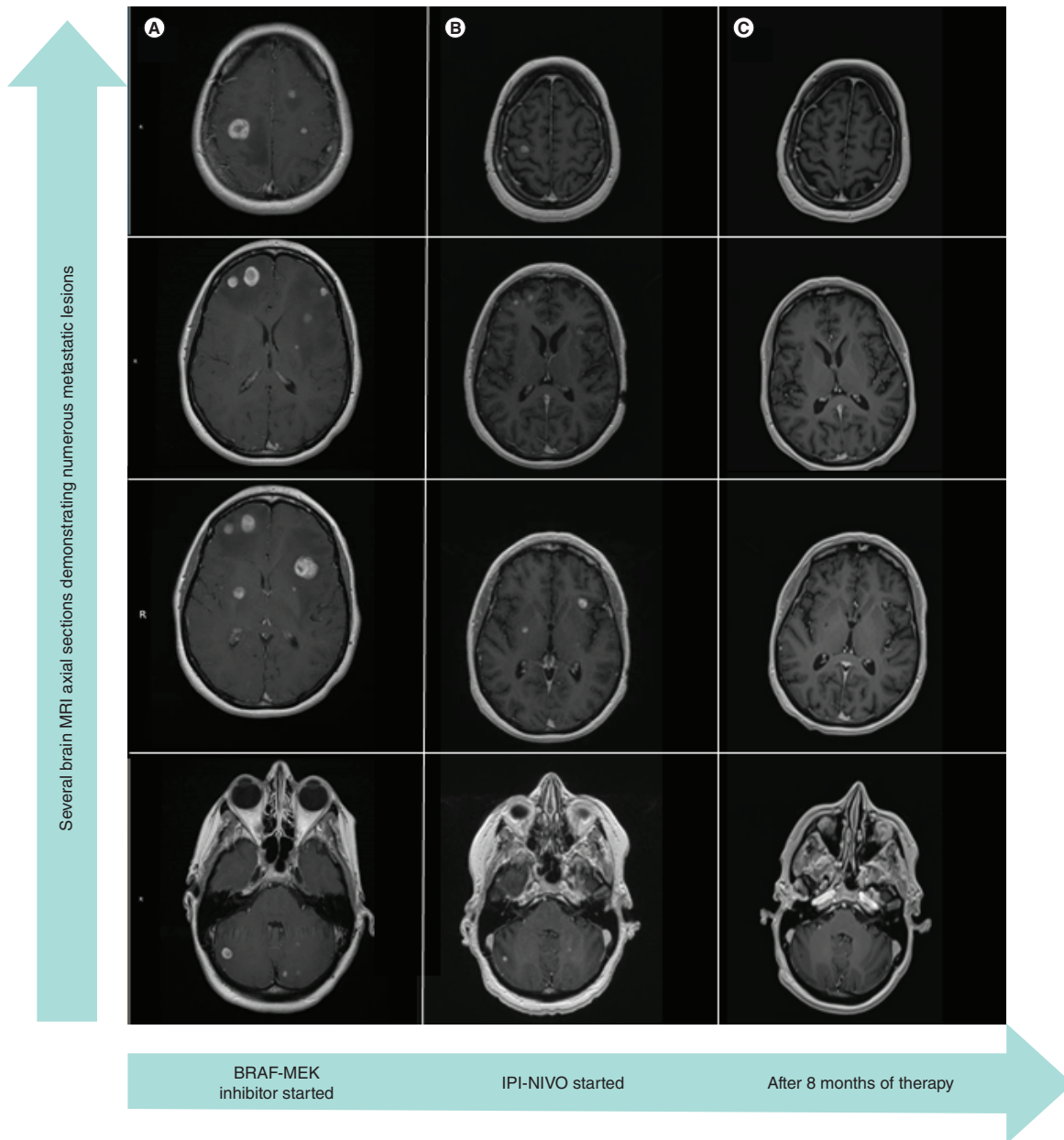


Figure 1. Brain MRI demonstrating intracranial metastatic changes during treatment of the patient in the case report. (A) Axial section of brain MRI in T1 post contrast phase prior to treatment with BRAF-MEK inhibitors which demonstrates 30 scattered enhancing lesions in the supratentorial and infratentorial compartments bilaterally with associated edema. **(B)** Demonstrates reduction in the size and the number of several lesions 8 weeks after treatment with BRAF-MEK inhibitors and prior to administration of immunotherapy. **(C)** Marked decrease in the size of bilateral cerebral and cerebellar metastatic lesions with near-complete resolution of several lesions after 6 months of treatment with ICB. ICB: Immune checkpoint blockade.

the use of ICB in patients with high burden symptomatic intracranial metastatic melanoma and those who are treated with a high dose of steroids at baseline is lacking as most clinical trials have excluded patients with the previous characteristics. This stems from the notion that immunosuppression at baseline (including the use of steroids) could reduce the antitumor efficacy of ICB and lead to short-lived response. To this end, another cohort of the CheckMate-204 study addressed this issue by evaluating the efficacy of ipilimumab and nivolumab in 18 patients with symptomatic melanoma brain metastases of which 39% had three or more brain lesions and 61%

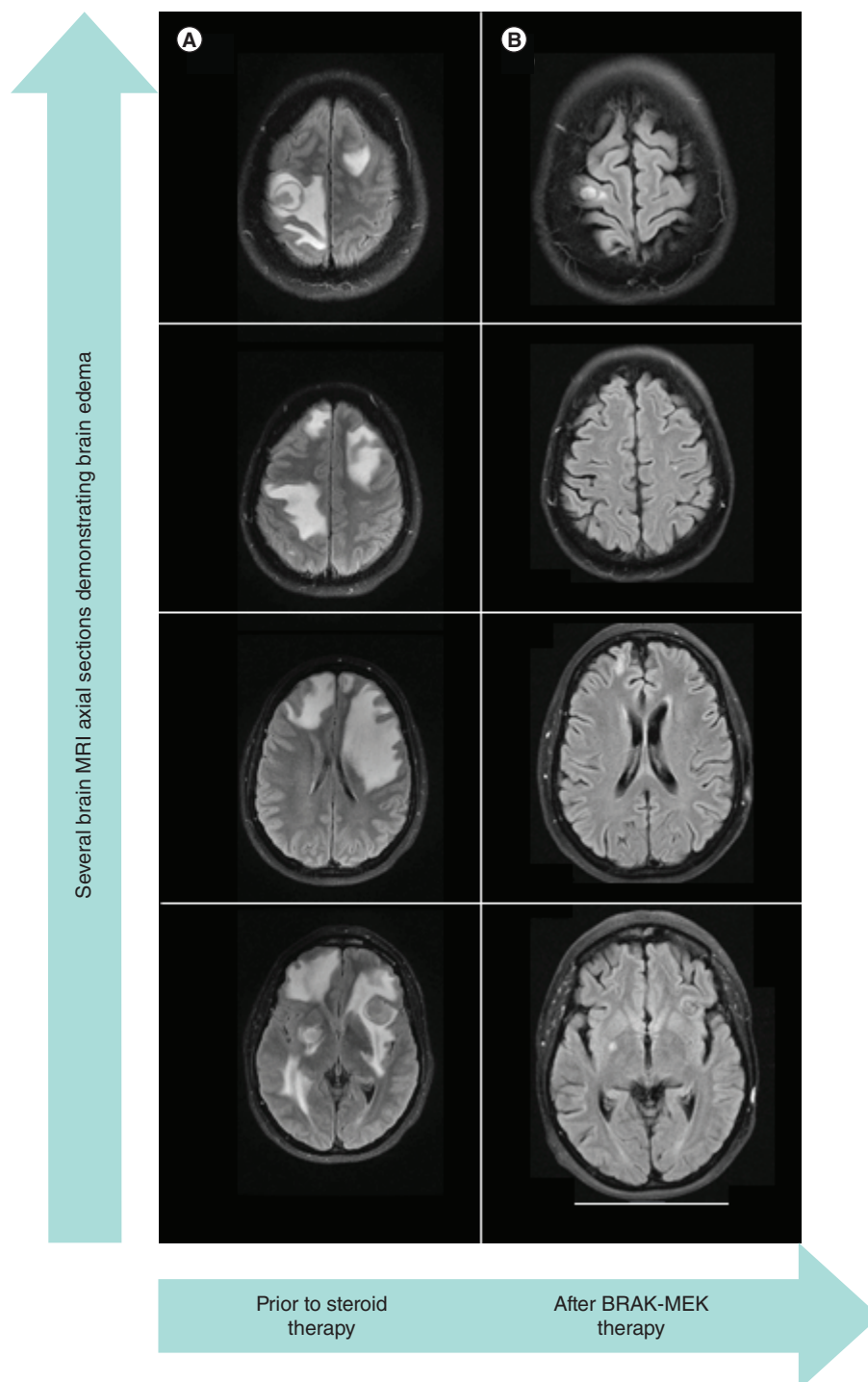


Figure 2. Brain MRI demonstrating with FLAIR signal demonstrating brain edema. (A) Axial section of brain MRI with FLAIR signal showing large diffuse signal abnormality throughout the brain prior to treatment with steroids. **(B)** Significant reduction of the signal abnormality at end of treatment with BRAF-MEK inhibitors.

were on dexamethasone (4 mg or less) [9]. The results demonstrated an objective response rate (ORR) of 22% which was inferior to the response rate observed in patients with asymptomatic brain metastases and those who are not receiving steroids at baseline (ORR = 57%) [9].

Interestingly, BRAF-MEK inhibitors have an advantage over ICB given the high response rates in patients with both asymptomatic and symptomatic intracranial metastatic melanoma whose tumors harbor *BRAF*^{V600} mutations

(>50 and 59%, respectively) [10]. Nevertheless, the high response rates in intracranial metastases are temporary, as the majority of patients treated with targeted therapy progress eventually, which is likely secondary to acquired resistance mechanisms [10,11]. The presence of *CDKN2A* copy number loss has been suggested to contribute to resistance to BRAF-MEK inhibitors in melanoma and lead to a shorter duration of response and inferior outcomes [6,7,12]. In addition, the duration of response in intracranial melanoma metastases is shorter compared with extracranial disease [10,13,14]. Of importance, one concern upon discontinuation of BRAF-MEK inhibitors is the rebound effect caused by reactivation of the BRAF kinase which could result in a flare-up and worsening of the metastatic disease [15]. Collectively, the previous evidence supports the high efficacy of BRAF-MEK inhibitors in patients with *BRAF*^{V600E} melanoma brain metastases, albeit short duration of response with early progression during treatment and the concern of possible flare-up upon discontinuation of targeted therapy.

Our case highlights the challenge often encountered in clinical practice when making a decision to treat patients with *BRAF*-mutated and symptomatic intracranial metastatic melanoma who are receiving baseline high dose steroids. The use of ICB as a front-line therapy in these patients is expected to be associated with low efficacy and short durable response based on the available evidence. As such, BRAF-MEK inhibitors in these patients can offer an advantage in obtaining high response as their efficacy is not compromised by steroids. However, the obtained response with targeted therapy is sustained for a short period prior to progression. Therefore, we followed an approach using BRAF-MEK inhibitors as a bridge to allow the discontinuation of glucocorticoid and to obtain a response in the intracranial metastatic disease prior to initiating ICB (evidenced by the partial radiological response, decrease in intracranial lesion numbers and control of neurological symptoms). We hypothesized such an approach would allow the resolution of the immunosuppressive effect of steroids and optimize the response to ICB. The presence of *CDKN2A* copy number loss further supported our rationale to use BRAF-MEK inhibitors temporarily given the short duration of response associated with this genetic alteration [6,7]. It should be noted that whole-brain radiotherapy could have contributed to the response obtained in the intracranial disease, however, we believe that most of the benefit obtained in the intracranial disease in our case was secondary to the use of BRAF-MEK inhibitors given the depth of response.

Recently, there has been an increased interest in evaluating the use of BRAF-MEK inhibitors with ICB in the treatment of metastatic melanoma. These efforts are assessing several approaches in clinical trials including combination targeted and immunotherapy or the sequential use of BRAF-MEK inhibitors followed by ICB and is summarized in Table 1 [16–21]. This is based on the role of BRAF-MAPK pathway in the modulation of the tumor biology in melanoma. Preclinical research supports this notion as *BRAF*^{V600E} mutant melanoma is associated with immunosuppressive tumor microenvironment leading to diminished antigen presentation and decreased CD8⁺ T cells [22]. As such, inhibition of the BRAF-MAPK pathway can alter tumor microenvironment favoring an immune permissive effect, which can facilitate the action of ICB [23]. To this end, the concurrent use of BRAF-MEK inhibitors and ICB or the sequenced use could favor a higher response with improved survival and is currently under investigation. Of importance, it has been suggested that when using an approach utilizing targeted therapy followed by ICB, waiting until progression while on BRAF-MEK inhibitors prior to starting immunotherapy could lead to an immunosuppressive environment and downregulation of effector T cells, which could negatively impact the efficacy of ICB [24]. This further supports our approach of switching BRAF-MEK inhibitors to ICB prior to an evidence of progressive disease in our patient.

The preclinical evidence of the compromised outcome with ICB treatment in patients who progressed on BRAF-MEK inhibitors has been echoed by a recent Phase-II trial (ABC trial), which evaluated the efficacy of ICB in 76 patients with melanoma brain metastases [25]. This study included a cohort of 16 patients with symptomatic or leptomeningeal brain metastases of which 75% received ICB treatment after they progressed while on BRAF-MEK inhibitors, and were found to have low response rates (ORR = 6%, progressive disease 81%) [25].

Conclusion

This report describes a patient with *BRAF*-mutant symptomatic intracranial metastatic melanoma who was successfully treated with BRAF-MEK inhibitors as a bridge to allow discontinuation of steroids prior to ICB therapy. The patient had significant clinical and radiographic response ongoing at 8 months after initiating therapy. Our observation with the previous reported literature suggest: treatment with BRAF-MEK inhibitors may allow the discontinuation of steroids in patients with symptomatic *BRAF* mutant intracranial metastatic melanoma; bridging temporarily with BRAF-MEK inhibitors prior to evidence of progressive disease may optimize the efficacy of ICB and lead to a durable response; and; integration of tumor molecular characteristics such as *CDKN2A* copy number

Table 1. Selected studies of sequenced or combined targeted therapy with immune checkpoint blockade in metastatic melanoma.

Study (year)	Study design	Patients (n)	Modality of treatment	Presence of intracranial metastases	Primary end point	Survival results	Ref.
Gutzmer <i>et al.</i> (2020)	Prospective randomized double blinded Phase III	256	Combination atezolizumab, vemurafenib and cobimetinib	Yes (5 patients in the study arm)	PFS	15.1 vs 10.6 months	[16]
Puzanov <i>et al.</i> (2020)	<i>Post hoc</i> Pooled analysis of three clinical trials	271	Previously treated with BRAFi with or without MEKi and later were treated with pembrolizumab	Yes (46 patients in the study arm)	ORR, PFS, OS	Lower ORR, PFS and OS [†]	[17]
Dummer <i>et al.</i> (2020)	Single arm safety run in from Phase III COMBI-I trial	36	Combination spartalizumab, dabrafenib, trametinib	Not included	Dose limiting toxicity biomarker analysis [‡]	24 months PFS was 41%	[18]
Burton <i>et al.</i> (2019)	Single arm Phase II	24	Combination nivolumab, dabrafenib, trametinib	Included	Safety and ORR [§]	Not provided	[19]
Ribas <i>et al.</i> (2015)	Phase I	50	Combination durvalumab, dabrafenib, trametinib	Not included	Safety	Not provided	[20]
Amin <i>et al.</i> (2016)	Phase II	46	Vemurafenib followed by ipilimumab	Not included	Safety	mPFS was 4.5 months	[21]

[†] Baseline characteristics were significantly different in the compared subgroups.
[‡] PFS was a secondary end point in the study.
[§] ORR was 89% in 19 evaluable patients.
 BRAFi: BRAF inhibitor; MEKi: MEK inhibitor; PFS: Progression-free survival; ORR: Objective response rate; OS: Overall survival.

loss can aid in planning treatment (favoring a short course with targeted therapy and considering other treatments prior to disease progression). While this case report provides proof-of-concept, further clinical trials are needed to confirm stated conclusions.

Future perspective

To date, the management of patients with metastatic intracranial melanoma and symptomatic disease remains challenging with very limited therapeutic options. The use of steroids to relieve symptom associated morbidity might hinder the efficacy of ICB. The role of targeted therapy in such patients with *BRAF*-mutated melanoma is a possible avenue to circumvent the use of steroids. Research is currently ongoing to investigate the efficacy and safety of an approach combining versus sequencing BRAF-MEK inhibitors and ICB in metastatic melanoma which will offer further insight on the possible role of utilizing short-term targeted therapy prior to ICB in patients with symptomatic intracranial melanoma.

Author contributions

This case report was conceptualized by K Khaddour and G Ansstas. K Khaddour reviewed the literature, wrote the manuscript and created Table 1. K Khaddour, G Ansstas and TM Johanns reviewed the manuscript.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

- Iorgulescu JB, Harary M, Zogg CK *et al.* Improved risk-adjusted survival for melanoma brain metastases in the era of checkpoint blockade immunotherapies: results from a National Cohort. *Cancer Immunol. Res.* 6(9), 1039–1045 (2018).
- Petrelli F, Signorelli D, Ghidini M *et al.* Association of steroids use with survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Cancers (Basel)* 12(3), 546 (2020).
- Menzies AM, Johnson DB, Ramanujam S *et al.* Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann. Oncol.* 28(2), 368–376 (2017).
- **Systematic-review demonstrates negative impact on overall survival in patients receiving steroids for brain metastases and are treated with immune checkpoint blockade (ICB).**
- Arbour KC, Mezquita L, Long N *et al.* Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. *J. Clin. Oncol.* 36(28), 2872–2878 (2018).
- Chasser F, Pages C, Biard L *et al.* Single-center study under a French Temporary Authorization for Use (TAU) protocol for ipilimumab in metastatic melanoma: negative impact of baseline corticosteroids. *Eur. J. Dermatol.* 25(1), 36–44 (2015).
- Flaherty K, Davies MA, Grob JJ *et al.* Genomic analysis and 3-y efficacy and safety update of COMBI-d: a Phase III study of dabrafenib (D)+trametinib (T) versus D monotherapy in patients (pts) with unresectable or metastatic BRAF V600E/K-mutant cutaneous melanoma. *J. Clin. Oncol.* 34(Suppl.), Abstract 9502 (2016).
- Dummer R, Brase JC, Garrett J *et al.* Adjuvant dabrafenib plus trametinib versus placebo in patients with resected, BRAF^{V600}-mutant, stage III melanoma (COMBI-AD): exploratory biomarker analyses from a randomised, Phase III trial. *Lancet Oncol.* 21(3), 358–372 (2020).
- Tawbi HA, Forsyth PA, Algazi A *et al.* Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N. Engl. J. Med.* 379(8), 722–730 (2018).
- **Prospective trial shows efficacy of ICB in patients with asymptomatic intracranial melanoma who were not being treated with steroids.**
- Tawbi HAH, Forsyth PA, Hodi FS *et al.* Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). *J. Clin. Oncol.* 37, 9501 (2019).
- **Prospective trial demonstrates lower efficacy of ICB in patients with symptomatic intracranial melanoma.**
- Davies MA, Saiag P, Robert C *et al.* Dabrafenib plus trametinib in patients with BRAF^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, Phase II trial. *Lancet Oncol.* 18(7), 863–873 (2017).
- **Prospective trial demonstrates high efficacy of BRAF-MEK inhibitors in treatment of intracranial metastatic melanoma but with a short duration of response.**
- Sullivan RJ, Flaherty KT. Resistance to BRAF-targeted therapy in melanoma. *Eur. J. Cancer* 49(6), 1297–304 (2013).
- Hartman ML, Sztiller-Sikorska M, Gajos-Michniewicz A *et al.* Dissecting mechanisms of melanoma resistance to BRAF and MEK inhibitors revealed genetic and non-genetic patient- and drug-specific alterations and remarkable phenotypic plasticity. *Cells* 9(1), 142 (2020).
- Grob JJ, Amonkar MM, Karaszewska B *et al.* Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a Phase III, open-label, randomised trial. *Lancet Oncol.* 16(13), 1389–98 (2015).
- Long GV, Stroyakovskiy D, Gogas H *et al.* Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, Phase III randomised controlled trial. *Lancet* 386(9992), 444–51 (2015).
- Luke JJ, Ott PA. New developments in the treatment of metastatic melanoma - role of dabrafenib-trametinib combination therapy. *Drug Healthc. Patient Saf.* 6, 77–88 (2014).
- Gutzmer R, Stroyakovskiy D, Gogas H *et al.* Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, Phase III trial. *Lancet* 395(10240), 1835–1844 (2020).
- Puzanov I, Ribas A, Robert C *et al.* Association of BRAF V600E/K mutation status and prior BRAF/MEK inhibition with pembrolizumab outcomes in advanced melanoma: pooled analysis of 3 clinical trials. *JAMA Oncol.* 6(8), 1256–1264 (2020).
- Dummer R, Lebbé C, Atkinson V *et al.* Combined PD-1, BRAF and MEK inhibition in advanced BRAF-mutant melanoma: safety run-in and biomarker cohorts of COMBI-i. *Nat. Med.* 26(10), 1557–1563 (2020).
- Burton EM, Amaria RN, Glitza IC *et al.* Safety and efficacy of TRIPlet combination of nivolumab (N) with dabrafenib (D) and trametinib (T) [TRIDEnt] in patients (pts) with BRAF-mutated metastatic melanoma (MM): a single center Phase II study [abstract

- 1312PD]. *Poster presented at: European Society for Medical Oncology Congress. European Society for Medical Oncology Congress*. Barcelona, Spain, 27 September–1 October 1, 2019.
20. Ribas A, Butler M, Lutzky J *et al*. Phase I study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma [abstract 3003]. *Oral presentation at: American Society of Clinical Oncology Annual Meeting* Chicago, IL, USA, 29 May–2 June, 2015.
 21. Amin A, Lawson DH, Salama AK *et al*. Phase II study of vemurafenib followed by ipilimumab in patients with previously untreated BRAF-mutated metastatic melanoma. *J. Immunother. Cancer* 4, 44 (2016).
 22. Bradley SD, Chen Z, Melendez B *et al*. BRAFV600E co-opts a conserved MHC Class I internalization pathway to diminish antigen presentation and CD8+ T-cell recognition of melanoma. *Cancer Immunol. Res.* 3(6), 602–9 (2015).
 - **Study shows that BRAF-mutated melanoma is associated with immunosuppressive tumor microenvironment.**
 23. Frederick DT, Piris A, Cogdill AP *et al*. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clin. Cancer Res.* 19(5), 1225–31 (2013).
 - **Study shows that BRAF inhibition counteract the immunosuppressive effect mediated through BRAF mutation.**
 24. Dummer R, Ascierto PA, Nathan P *et al*. Rationale for immune checkpoint inhibitors plus targeted therapy in metastatic melanoma: a review. *JAMA Oncol.* doi:10.1001/jamaoncol.2020.4401 (Epub ahead of print).
 - **Comprehensive review suggests reduced efficacy of immune checkpoint blockade when administered in melanoma patients after progressing while on BRAF-MEK inhibitors.**
 25. Long GV, Atkinson V, Lo S *et al*. Long-term outcomes from the randomized Phase II study of nivolumab (nivo) or nivo + ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets): anti-PD1 brain collaboration (ABC). *Ann. Oncol.* 30(Suppl. 5), 13110 (2019).
 - **Prospective study shows that response rate and survival to immunotherapy are worse in patients with intracranial metastatic melanoma who previously had disease progression while being treated with BRAF-MEK inhibitors.**