Dear Editors,

Treatment with targeted therapies and immune checkpoint inhibitors have greatly improved outcomes for patients with advanced melanoma [1]. Clinical data suggest that first-line PD-1 inhibitor monotherapy and first-line BRAF/MEK inhibitor therapy result in similar median overall survivals (OS, 25–37.6 months) [2–6].

Targeted therapy offers pronounced early responses and is often the first-line choice for symptomatic patients with a high tumor burden, although acquired resistance is a significant concern [7]. Therapeutic effects of immune checkpoint inhibitors are evident later, but may be durable in a subset of patients regardless of the BRAF mutation status [7]. Compared to targeted agents, the response rates to anti-PD-1 monotherapy are lower and after an initial response to checkpoint immunotherapy the disease may progress due to secondary resistance.

The ideal frontline regimen and treatment sequence of targeted therapy and checkpoint immunotherapy are not well established. Preliminary results indicate that PD-1/PDL-1 inhibitors can be combined with targeted therapy with manageable toxicity and demonstrate encouraging efficacy [8, 9].

Here we report results from a compassionate use of combination therapy with PD-1 blockade and targeted therapy in five patients with predominantly treatment-refractory BRAF V600E-mutant metastatic melanoma. Informed consent was obtained after detailed explanation of off-label use and unknown side effects. All patients had stage IV M1d (AJCC 2018) with symptomatic brain metastases. They received BRAF and MEK inhibitor therapy in 2015 and concomitant anti-PD-1 immunotherapy at the recommended dose for at least two months due to rapid progression or poor response to initial targeted therapy. The combination of PD-1 and CTLA-4 inhibitors was not approved in Europe at this time point.

Physical examination and laboratory tests, including glucose, urea, creatinine, total bilirubin, C-reactive protein, sodium, chloride, potassium, calcium, liver enzymes, LDH, lipase, creatine kinase, differential blood count, basal TSH, ACTH, cortisol and troponin T were performed every two to three weeks. Computed tomography and/or magnetic resonance imaging were carried out every three months. Efficacy endpoints were RECIST 1.1 response, progression-free survival (PFS: time period from the first administered triple combination to the first documented progression), overall survival (OS: time period from first administered triple combination to the last patient visit) and adverse events (AEs).

The patients’ baseline characteristics are summarized in Table 1. Isolated brain metastases were treated with stereotactic radiosurgery (SRS) in two patients. Two patients underwent whole brain radiotherapy (WBRT) because of multiple symptomatic metastases. Two patients had elevated

| Pat. | Age (years) | Sex | Metastases | Symptomatic brain metastases | LDH | Treatment history (months before triple therapy) |
|------|-------------|-----|------------|-------------------------------|-----|--------------------------------------------------|
| 1    | 23          | F   | > 3 cerebral | Yes                           | > 3 x ULN | WBRT (5 mo.), dabrafenib + trametinib (12 mo.)/PD |
| 2    | 46          | M   | < 3 cerebral | Yes                           | Normal      | None                                               |
| 3    | 45          | F   | 3 + cerebral | Yes                           | Normal      | SRS (17 mo.), dabrafenib + trametinib (15 mo.)/PD |
| 4    | 59          | F   | > 3 cerebral | Yes                           | Normal      | SRS (1 mo.), vemurafenib + cobimetinib (13 mo.)/PD |
| 5    | 60          | M   | > 3 cerebral | Yes                           | < 3 x ULN   | WBRT (7 mo.), dabrafenib + trametinib (15 mo.)/PD |

Abbr.: f, female; m, male; mo., month; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; PD, progressive disease; ULN, upper limit of normal.
baseline serum LDH and more than three metastasis sites. In four patients, anti-PD1 therapy was added after failure of BRAF and MEK inhibitor therapy. Only patient 2 was treatment-naive and received the triple combination as first-line treatment because of a high tumor burden with symptomatic brain metastases. The mean duration of triple therapy was 7.2 months (range 2.5–12 months) (Table 2).

Four patients responded to the triple therapy (Table 3): patients 2 and 5 had a partial response (PR), and patients 3 and 4 had a complete response (CR). In patient 3 with CR, targeted therapy and PD-1 inhibitors were stopped at 14 months and 28 months respectively after the commencement of triple therapy. In patient 4 with CR, targeted therapy and PD-1 immunotherapy were discontinued twelve months and 22 months respectively after the start of triple therapy. Patients 3 and 4 have been without cancer therapy for 23 and 18 months and their CRs are still ongoing. Patient 2 experienced a PR for 7.5 months, but died due to cerebral bleeding of progressing brain metastases with development of leptomeningeal melanomatosis. Patients 1 and 5 died two and six months after introduction of triple combination therapy due to disease progression. The mean OS was 20.4 months and the mean PFS was 17.7 months (Table 3).

The most common AEs were rash (resolving with topical corticosteroids), followed by arthralgia and fever (both resolving with paracetamol) and fatigue (all grade 1 and 2) (Table 2). Arthralgia and fatigue persisted for several months. Grade 1 and grade 2 hematological AEs occurred in two patients and resolved without immunosuppressive therapy or discontinuation of triple combination therapy. These AEs emerged within the first three months except for patient 2, who developed grade 1 transaminitis and grade 3

### Table 2  Treatment protocol and adverse events.

| Pat. | Targeted therapy started before combined with PD-1 | Targeted therapy started with PD-1 | Duration of triple therapy (months) | AEs |
|------|-----------------------------------------------|-----------------------------------|----------------------------------|-----|
|      | Yes                                           | No                                | 2                                | Rash, arthralgia, fatigue |
| 2    | No                                            | Yes                               | 4                                | Rash, transaminitis |
| 3    | Yes                                           | No                                | 14                               | Rash, arthralgia, fatigue, fever, leukopenia, neutropenia |
| 4    | Yes                                           | No                                | 12                               | Rash, arthralgia, fatigue, fever |
| 5    | Yes                                           | No                                | 4                                | Pancytopenia |

**Abbr.:** AEs, adverse events.

*Considered as a complication of the progressing brain metastases and not of the triple therapy.

### Table 3  Efficacy.

| Pat. | Best response | PFS (months) | OS (months) | Survival |
|------|---------------|--------------|-------------|----------|
| 1    | PD            | 0            | 2           | No       |
| 2    | PR            | 7.5          | 8           | No       |
| 3    | CR            | > 39         | > 47        | Ongoing* |
| 4    | CR            | > 36         | > 39        | Ongoing§ |
| 5    | PR            | 6            | 6           | No       |

**Abbr.:** CR, complete response; PR, partial response; PD, progressive disease.

*23 months without therapy; §18 months without therapy.
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pneumonitis after six months. The pneumonitis required systemic corticosteroids and discontinuation of triple therapy. Patient 2 subsequently received targeted therapy alone but died due to progressive disease. Two patients developed cerebral bleeding which was regarded as a complication of the progressing brain metastases and not the triple therapy.

This is the first clinical report to assess the efficacy and tolerability of a combination of PD-1 inhibitor and targeted therapy in a series of BRAF V600E mutant melanoma patients with symptomatic brain metastases. Dual inhibition of BRAF and MEK can delay the development of acquired resistance and decrease toxicity [3, 10]. However, the majority of patients treated with this combination still experience disease progression. There is emerging preclinical evidence that BRAF and MEK inhibitors provide an immunostimulatory microenvironment due to their ability to recruit lymphocytes into the tumor and to increase tumor antigen and PD-L1 expression [11]. Adding PD-1/PDL-1 inhibitors to targeted therapy can help to activate these lymphocytes. This synergistic mode of action may lead to improved treatment efficacy and durability.

Recently, a phase 1b study combining vemurafenib and cobimetinib with the PDL-1 inhibitor atezolizumab showed promising data with a high response rate of 72 %, which included 20 % complete responses and 39 % ongoing responses. In general, the safety profile was managed by dose interruptions or modifications [8]. Similar results were obtained from a phase 1 study that determined the safety and activity of the triple combination of dabrafenib, trametinib plus pembrolizumab. 73 % of patients developed grade 3/4 AEs, 73 % had an objective response, and 40 % of them were durable [9]. In contrast, a phase 2 trial using the same triple therapy failed to improve the PFS significantly, and response rates in patients with treatment-naïve BRAF V600E/K-mutant metastatic melanoma, when compared with dual dabrafenib and trametinib inhibition, were associated with a substantial number of grade 3/4 AEs (58 % versus 27 %). A subgroup of patients with poor performance status and elevated LDH may benefit most from triple therapy [2]. The phase 3 TRILOGY IMspire 150 trial and COMBI-i trial will provide additional information about the efficacy and safety of the triple combination.

In the present compassionate use pilot study, four of five patients received anti-PD-1 therapy in addition to dual BRAF and MEK inhibition after treatment failure, and one patient received the triple combination as first-line treatment. All patients had symptomatic brain metastases, and two patients had elevated baseline serum LDH with more than three metastasis sites. Despite poor prognostic factors, combining PD-1 inhibitors with targeted therapy resulted in clinical responses in four patients, and two patients even achieved CR and are now without treatment. Most side effects were grade 1 and 2. Severe AEs occurred in one patient, with discontinuation of triple therapy. Our results confirm preliminary findings that this triple combination has clinical activity in patients who have poor prognostic factors and require rapid responses. Triple therapy with targeted agents and PD-1 inhibitors emerges as a therapeutic off-label option for patients who have a progressive disease while under therapy with either targeted treatment or PD-1 inhibitors. Continued exploration of the triple combination is needed in larger studies with short or intermittent schedules and long-term data.

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Conflict of interest

None.

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