

Trametinib

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application. The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: [8. Immunomodulators and antineoplastics](#) > [8.2. Antineoplastics and supportive medicines](#) > [8.2.2. Targeted therapies](#)

ATC codes: [L01EE01](#)

Indication	Other specified melanoma of skin ICD11 code: 2C30.Y
INN	Trametinib
Medicine type	Chemical agent
List type	Complementary
Formulations	Oral > Solid: 0.5 mg ; 2 mg
EML status history	Application rejected in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	binimetinib (ATC codes: L01EE03) cobimetinib (ATC codes: L01EE02)
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.

Tags

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Expert Committee recommendation

The Expert Committee noted the increasing incidence of melanoma globally and that treatment of metastatic melanoma is complex. With the availability of an increasing number of targeted treatments, outcomes have markedly improved for patients, at least in settings where these treatments are available. Treatment of melanoma now encompasses a series of options associated with clinically important benefits such as surgery, immunotherapy, targeted inhibition of the mitogen-activated protein kinase pathway, and radiation therapy of symptomatic anatomical sites of metastases. The Committee recalled that the 2019 recommendation to include the anti-PD-1 receptor monoclonal antibodies nivolumab and pembrolizumab on the EML for the treatment of metastatic melanoma was based on survival data from several phase III randomized controlled trials, which suggested that about 50% of patients with advanced melanoma receiving immunotherapies are alive at 5 years (historically 5-year survival rates were very low). However, responses to immunotherapy may develop slowly and patients may have a transient worsening of disease before the disease stabilizes or regresses. Furthermore, some patients may have contraindications to immunotherapy. The Committee noted that BRAF/MEK inhibitor combinations are associated with meaningful gains in terms of overall survival, but the magnitude of benefit is not as large as that seen with immune checkpoint inhibitors. The Committee considered that the three combinations proposed in the application were associated with similar benefits, suggestive of a class effect. However, it was noted that the combinations have not been compared with each other in direct randomized trials. The Committee noted that the different BRAF/MEK inhibitor combinations can vary in terms of toxicity. In real-life settings, toxicities often lead to discontinuation or dose reductions of these medicines. The Committee also noted the requirement to monitor for toxicity and adverse events in patients treated with these combinations. The Committee considered that the optimal place in therapy for BRAF/MEK inhibitors was likely

to be as second-line options in patients who fail treatment with immune checkpoint inhibitors, or as first-line options for patients with rapidly progressive disease in whom a rapid response is required. The Committee noted the limited availability of genomic testing for identification of the BRAF V600 oncogenic driver mutation in some settings, which would be a potential barrier to access and appropriate use of BRAF/MEK inhibitors. In addition, in settings where genomic testing is unavailable or underutilized, there is a risk of unintended, harmful consequences (such as overuse of in patients who are unlikely to benefit and underuse in patients who could benefit). Overall, the Committee considered that immune checkpoint inhibitors are still the preferred therapy for metastatic melanoma for most patients. Therefore, the Committee did not recommend listing of BRAF/MEK inhibitor combinations on the EML for the treatment of metastatic melanoma in patients with the BRAF V600 mutation.

Background

BRAF/MEK inhibitors have not previously been considered for inclusion on the EML. In 2019, the Expert Committee recommended the addition of the PD-1 immune checkpoint inhibitors nivolumab and pembrolizumab to the complementary list of the EML for use as first-line monotherapy for treatment of patients with unresectable and metastatic melanoma, on the basis of evidence of significantly increased overall survival and in the absence of other EML-listed treatment options for this indication. Nivolumab was listed with a square box, with pembrolizumab specified as a therapeutic alternative (1).

Public health relevance

The global incidence of melanoma is increasing (2). By 2020, the number of newly diagnosed cases of melanoma worldwide was expected to reach almost 280 000 with an estimated 68 000 deaths (2). As a cancer related to the exposure of the skin to sunlight, melanoma has greater variation in incidence rates across different ethnic groups and is more commonly found in fair-skinned populations of European ancestry (3). The global age-standardized incidence rate of melanoma is 3.4 per 100 000 persons a year, but it is much higher in Australia, New Zealand, Europe and North America than in African and Asian countries. About 40–60% of cutaneous melanomas have mutations in the BRAF oncogene encoding a serine/threonine protein kinase called B-Raf which is involved in the regulation of cell division. The most commonly observed BRAF mutation is V600E (valine [V] is substituted by glutamic acid [E] at amino acid 600), which accounts for about 90% of the mutations in the BRAF gene seen in melanoma (4). BRAF inhibitors can block the increased activity of the mutated B-Raf kinase; however, development of resistance is common when BRAF inhibitors are used as monotherapy. For this reason, they are combined with MEK inhibitors that block the downstream mitogen-activated protein kinase pathway. Melanoma patients with BRAF V600 mutated melanoma can be treated with PD-1 blocking immunotherapy, which is indicated for use in both BRAF mutated and wild-type melanoma. Although there are no direct comparisons of BRAF/MEK inhibitors with immunotherapy, meta-analyses suggest that while patients treated with BRAF/MEK inhibitors may have better progression-free survival, overall survival may be better in patients treated with immune checkpoint inhibitors (5–7). Targeted therapy may be preferred in patients who require a fast response, such as those with higher tumour volume, symptomatic disease, a high risk of organ or function deterioration due to metastases, and in patients in whom immunotherapy is unsuitable (e.g. patients with severe autoimmune diseases). As mentioned before, BRAF inhibitor monotherapy for advanced BRAF-mutated melanoma has been shown to induce high response rates but is followed shortly afterwards by resistance (8–10). The use of BRAF inhibitors in combination with MEK inhibitors serves to overcome the issue of resistance and the short duration of response with BRAF inhibitor monotherapy (11). Monotherapy with BRAF inhibitors is no longer the standard of care in advanced melanoma since the combination of BRAF/MEK inhibitors improved both progression-free survival and overall survival compared with BRAF inhibitor monotherapy (12–14). Monotherapy with BRAF inhibitors should be used only if an absolute contraindication for MEK inhibitors exists (4).

Benefits

The combined use of BRAF and MEK inhibitors has been investigated in randomized phase III trials and compared with BRAF inhibitor monotherapy and showed improved survival outcomes in BRAF V600 mutated melanoma. Dabrafenib/trametinib COMBI-d and COMBI-v were double-blind, randomized, phase III studies comparing dabrafenib/trametinib versus dabrafenib monotherapy or versus vemurafenib monotherapy, respectively, as first-line treatment of BRAF V600 mutated metastatic melanoma (13,15,16). In COMBI-d, after more than 3 years of follow-up, median overall survival in patients receiving combination therapy was 25.1 months (versus 18.7 with monotherapy), median progression-free survival was 11.0 months (versus 8.8 months with monotherapy), and overall response rate was 69%. In COMBI-v, after 23 months follow-up, median overall survival was 26.1 months in patients

receiving dabrafenib/trametinib, median progression-free survival was 12.1 months and the overall response rate was 68% (18% complete response). A pooled analysis of these studies evaluated patient survival after a median follow-up of 5 years and found the overall survival rate was 34%. A complete response was observed in 19% of the patients and, in this subgroup, the 5-year overall survival rate was 71% (17). Based on results of the COMBI-d and COMBI-v studies, dabrafenib/trametinib received scores of 4 and 5 on the European Society for Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1 for first line treatment of unresectable or metastatic melanoma with the BRAF V600E mutation (18). Encorafenib/binimetinib The COLUMBUS study was a two-part randomized, open-label phase III study comparing encorafenib/binimetinib with vemurafenib or encorafenib as monotherapy in patients with unresectable or metastatic melanoma with BRAF V600 mutation who were treatment naïve, or had progressed following first-line immunotherapy. After 36.8 months follow-up, median overall survival was 33.6 months with the combination treatment versus 16.9 months for vemurafenib monotherapy. Median progression-free survival for the combination treatment was 14.9 months and the overall response rate was 64% (19,20). Based on results of the COLOMBUS study, encorafenib/binimetinib received a score of 4 on the ESMO-MCBS v1.1 for treatment of unresectable or metastatic melanoma with the BRAF V600E or BRAF V600K mutation (18). Vemurafenib/cobimetinib The coBRIM trial was a double-blind, randomized, placebo-controlled study comparing vemurafenib/cobimetinib with vemurafenib monotherapy as first-line treatment of BRAF V600 mutated unresectable or metastatic melanoma (21,22). After a median follow-up of 18.5 months, median overall survival was 22.5 months for the combination treatment compared with 17.4 months for vemurafenib monotherapy, median progression-free survival was 12.3 months versus 7.2 months and the overall response rate was 70% for the combination treatment. Based on results of the coBRIM study, vemurafenib/cobimetinib received a score of 4 on the ESMO-MCBS v1.1 for first-line treatment of unresectable or metastatic melanoma with the BRAF V600E mutation (18). No direct comparisons of the different combinations are available. An indirect analysis comparing all three combinations showed a non-significant risk reduction in progression and death in the subgroup of patients with elevated baseline lactate dehydrogenase (a well known negative prognostic marker (23)) receiving vemurafenib/cobimetinib compared with dabrafenib/trametinib and encorafenib/binimetinib. Therefore, in this subgroup of patients, the combination of vemurafenib/cobimetinib might be preferred (24). Targeted therapy in patients with melanoma brain metastases Melanoma brain metastases pose a particular therapeutic challenge and patients with this disease have a worse prognosis than other stage IV cancer patients (25). The studies evaluating systemic therapy in patients with advanced melanoma have systematically excluded patients with brain metastases. Trials specifically investigating immunotherapy and targeted therapy in patients with melanoma brain metastases have shown that these therapies are also effective intracranially. The intracranial response rate is similar to the extracranial response (26–29). There is currently evidence that PD-1-based immunotherapy, particularly combination immunotherapy with nivolumab and ipilimumab, might be more effective than BRAF/MEK inhibitors in treatment of melanoma brain metastases (5,30). The COMBI-MB trial evaluated dabrafenib plus trametinib in patients with BRAF-mutant melanoma brain metastases (28). The primary and secondary endpoints were the investigator-assessed intracranial response. Preliminary data suggest that subgroups of patients with BRAF V600 mutated melanoma with asymptomatic melanoma brain metastases who had received previous local brain therapy have better progression-free survival and overall survival than other subgroups. According to ESMO recommendations, targeted therapy is preferred to immunotherapy in patients with melanoma brain metastases who have continuous dependency on corticosteroids (> 10 mg prednisolone or equivalent) at the start of systemic treatment (31). Treatment sequence Patients with BRAF V600 mutated melanoma can receive treatment with both targeted therapy and immunotherapy. However, the optimal sequence of therapy is not defined as there are no randomized controlled trials with direct comparisons. In the first-line setting, patients treated with targeted therapy seem to respond better during the first 12 months and when progression-free survival is evaluated, with immunotherapy showing a survival benefit after the first 12 months. In the second-line setting, data indicate that targeted therapy may provide greater benefit. Clinical trials evaluating the optimal therapeutic sequence of targeted and immunotherapy are ongoing (32).

Harms

The frequency of adverse events with the three available combinations of BRAF/MEK inhibitors is similar (33). However, the type of adverse event differs and this frequently leads to choosing one or the other combination in clinical practice. Dabrafenib induces almost no photosensitivity compared with vemurafenib, where it has been reported in 41% of patients. Dabrafenib might be a preferred treatment choice for patients living in countries with high solar exposure. Dabrafenib is also associated with fewer keratoacanthomas and squamous cell carcinomas than vemurafenib (7% versus 20–30%). The most commonly reported adverse events with vemurafenib include arthralgia (56%), fatigue (46%) and rash (41%) (8,34). Pyrexia is the most common adverse event associated with dabrafenib treatment, seen in almost half of patients treated, and this often leads to (temporary) treatment

interruption (33,35). For encorafenib/binimetinib, the most frequently reported adverse events are gastrointestinal (28–40%). Cutaneous adverse events were manageable, similar to dabrafenib/trametinib and lower than for vemurafenib/cobimetinib (19). Treatment with MEK inhibitors is associated with ophthalmological toxicity (such as uveitis, conjunctivitis, dry eyes), which is a class effect and typically requires treatment delay and/or suspension. The frequency of surveillance for ocular events is not uniform and depends on the MEK inhibitor type used (36–38). Regular ophthalmological evaluations might be useful for asymptomatic patients and are mandatory in cases of visual disturbances to identify potential complications of retinal vein occlusion such as macular oedema, decreased visual function, neovascularization and glaucoma. Patients with a previous history of ophthalmological problems should be evaluated before the start of treatment (39). Treatment with MEK inhibitors, alone or in combination with BRAF inhibitors, is associated with cardiomyopathy. Decreased left ventricular ejection fraction (LVEF) was found in 4–9% of the patients in trials evaluating treatment with targeted therapy (12,13,40,41). Patients should have a cardiological assessment, particularly assessment of left ventricular ejection fraction by echocardiogram or a multigated acquisition scan before therapy initiation, after 1 month and at 2- to 3-month intervals while on treatment. A decrease in left ventricular ejection fraction is usually managed with treatment interruption, dose reduction or discontinuation. Rarely, QTc prolongation is observed with vemurafenib therapy, but not with MEK inhibitor monotherapy. In patients with QTc > 500 ms, long QT syndrome and/or being treated with medicines known to prolong the QT interval, treatment with vemurafenib is not recommended.

Cost / cost effectiveness

An economic evaluation of the systemic treatments for advanced melanoma that included vemurafenib/cobimetinib, dabrafenib/trametinib, ipilimumab, pembrolizumab, nivolumab and nivolumab/ipilimumab has shown that the targeted combinations were not cost-effective at current prices (often more than US\$ 10 000 per month of treatment) in any jurisdiction (43). However, it was noted that a large number of patients treated in the real-life setting do not meet the criteria for inclusion in clinical trials (44,45). The exact cost-effectiveness in a real-world setting has not been established and reimbursement decisions have involved price negotiations or managed entry agreements with national authorities. Globally, there is significant discrepancy in access to innovative therapies for metastatic melanoma, which is correlated with economic and health system performance factors (46). No defined treatment duration exists for targeted therapy in the advanced setting, or for patients deriving benefit (i.e. with stable disease, partial response or complete response) (42). In general, patients are treated for as long as they benefit (until disease progression) or as long as the therapy is well tolerated (i.e. without unacceptable toxicity). Targeted therapy is restricted to patients with a BRAF V600 mutation, while PD-1 based immunotherapy can be given to all patients with unresectable or metastatic melanoma (a higher number of patients). Access and costs associated with testing for the presence of BRAF V600 mutation should also be considered.

WHO guidelines

WHO guidelines for the treatment of metastatic melanoma are not available. The ESMO guidelines (4) and the guidelines of the United States National Comprehensive Cancer Network (42) include BRAF/MEK combinations among the preferred regimens for first-line treatment of unresectable or metastatic melanoma with BRAF V600 activating mutations.

Availability

The proposed BRAF and MEK inhibitors are all patented medicines. Primary patents are in place until 2023 (binimetinib), 2024–2026 (vemurafenib), 2025 (trametinib), 2026 (cobimetinib) and 2019 (dabrafenib and encorafenib).

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of BRAF/MEK inhibitors on the EML for the treatment of metastatic melanoma. The Working Group acknowledged a relevant benefit associated with BRAF/MEK inhibitors in second-line treatment for metastatic melanoma, and that this is the main place for therapy with BRAF/MEK inhibitors for melanoma (after failure of immunotherapy). However, BRAF/MEK inhibitors could be used as first-line therapy in patients for whom immunotherapy is not suitable or in patients for whom a rapid response is required. The Working Group noted a preference to prioritize inclusion of first-line therapies on the Model List and the established role of immunotherapy in the first-line treatment for melanoma. It therefore did not support listing of BRAF/MEK inhibitors because first-line treatment with these drugs would apply to

only the small subgroup of patients for whom first-line immunotherapy is not recommended or rapid response induction is required, and approval might result in their inappropriate use for patients outside this subgroup, with the associated toxicity risks and high cost. Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that given comparisons to immunotherapy for melanoma already included on the Model List since 2019, the balance does not strongly favour adopting the class of combination BRAF/MEK inhibitors at this time.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; <https://apps.who.int/iris/handle/10665/330668>, accessed 12 June 2021).
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394–424.
3. Cormier JN, Xing Y, Ding M, Lee JE, Mansfield PF, Gershenwald JE, et al. Ethnic differences among patients with cutaneous melanoma. *Arch Intern Med.* 2006;166(17):1907–14.
4. Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2019;30(12):1884–901.
5. Franken MG, Leenenman B, Gheorghe M, Uyl-de Groot CA, Haanen J, van Baal PHM. A systematic literature review and network meta-analysis of effectiveness and safety outcomes in advanced melanoma. *Eur J Cancer.* 2019;123:58–71.
6. Ugurel S, Röhmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. *Eur J Cancer.* 2017;83:247–57.
7. Ugurel S, Röhmel J, Ascierto PA, Becker JC, Flaherty KT, Grob JJ, et al. Survival of patients with advanced metastatic melanoma: The impact of MAP kinase pathway inhibition and immune checkpoint inhibition – Update 2019. *Eur J Cancer.* 2020;130:126–38.
8. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011;364(26):2507–16.
9. Amaral T, Sinnberg T, Meier F, Krepler C, Levesque M, Niessner H, et al. MAPK pathway in melanoma part II-secondary and adaptive resistance mechanisms to BRAF inhibition. *Eur J Cancer.* 2017;73:93–101.
10. Amaral T, Sinnberg T, Meier F, Krepler C, Levesque M, Niessner H, et al. The mitogen-activated protein kinase pathway in melanoma part I – Activation and primary resistance mechanisms to BRAF inhibition. *Eur J Cancer.* 2017;73:85–92.
11. Villanueva J, Vultur A, Lee JT, Somasundaram R, Fukunaga-Kalabis M, Cipolla AK, et al. Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. *Cancer Cell.* 2010;18(6):683–95.
12. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet.* 2015;386(9992):444–51.
13. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med.* 2014;372(1):30–9.
14. Larkin J, Ascierto PA, Dreno B, Atkinson V, Liskay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med.* 2014;371(20):1867–76.
15. Grob JJ, Amonkar MM, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, 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 3, open-label, randomised trial. *Lancet Oncol.* 2015;16(13):1389–98.
16. Long GV, Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAFV600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. *Ann Oncol.* 2017;28(7):1631–9.
17. Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med.* 2019;381(7):626–36.
18. ESMO-magnitude of clinical benefit scale. The ESMO-MCBS score card [internet]. Lugarno: European Society for Medical Oncology; 2015 (<https://www.esmo.org/score/cards>, accessed 12 June 2021).
19. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liskay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2018;19(5):603–15.
20. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liskay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2018;19(10):1315–27.
21. Ascierto PA, McArthur GA, Dréno B, Atkinson V, Liskay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAF/V600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2016;17(9):1248–60.
22. Ascierto PA, Dréno B, Larkin J, Ribas A, Liskay G, Maio M, et al. 5-Year Outcomes with Cobimetinib plus Vemurafenib in BRAF (V600) Mutation-Positive Advanced Melanoma: Extended Follow-up of the coBRIM Study. *Clin Cancer Res.* 2021.
23. Weide B, Martens A, Hassel JC, Berking C, Postow MA, Bisschop K, et al. Baseline biomarkers for outcome of melanoma patients treated with pembrolizumab. *Clin Cancer Res.* 2016;22(22):5487.
24. Glutsch V, Amaral T, Garbe C, Thoms K-M, Mohr P, Hauschild A, et al. Indirect comparison of combined BRAF and MEK inhibition in melanoma patients with elevated baseline lactate dehydrogenase. *Acta Derm Venereol.* 2020;100(13):adv00174.
25. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin.* 2017;67(6):472–92.
26. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol.* 2018;19(5):672–81.
27. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med.* 2018;379(8):722–30.
28. Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol.* 2017;18(7):863–73.
29. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(11):1087–95.
30. Rulli E, Legramandi L, Salvati L, Mandala M. The impact of targeted therapies and immunotherapy in melanoma brain metastases: a systematic review and meta-analysis. *Cancer.* 2019;125(21):3776–89.
31. Keilholz U, Ascierto PA, Dummer R, Robert C, Lorigan P, van Akkooi A, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. *Ann Oncol.* 2020;31(11):1435–48.
32. Ascierto PA, Mandala M, Ferrucci PF, Rutkowski P, Guidoboni M, Fernandez AMA, et al. LBA45 First report of efficacy and safety from the phase II study SECOMBIT (SEquential COMBo Immuno and Targeted therapy study). *Ann Oncol.* 2020;31:S1173–S4.
33. Heinzerling L, Eigentler TK, Fluck M, Hassel JC, Heller-Schenck D, Leipe J, et al. Tolerability of BRAF/MEK inhibitor combinations

- : adverse event evaluation and management. *ESMO open*. 2019;4(3):e000491-e.
34. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358–65.
35. Menzies AM, Ashworth MT, Swann S, Kefford RF, Flaherty K, Weber J, et al. Characteristics of pyrexia in BRAFV600E/K metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial. *Ann Oncol*. 2015;26(2):415–21.
36. Summary of product characteristics – mekinist. Amsterdam: European Medicines Agency; 2020 (https://www.ema.europa.eu/en/documents/product-information/mekinst-epar-product-information_en.pdf, accessed 12 June 2021).
37. Summary of product characteristics – cotelllic. Amsterdam: European Medicines Agency; 2015 (https://www.ema.europa.eu/en/documents/product-information/cotelllic-epar-product-information_en.pdf, accessed 12 June 2021).
38. Summary of product characteristics – mektovi. Amsterdam: European Medicines Agency; 2021 (https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information_en.pdf, accessed 12 June 2021).
39. Stjepanovic N, Velazquez-Martin JP, Bedard PL. Ocular toxicities of MEK inhibitors and other targeted therapies. *Ann Oncol*. 2016;27(6):998–1005.
40. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012;367(18):1694–703.
41. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367(2):107–14.
42. NCCN clinical practice guidelines in oncology. Melanoma: cutaneous. Version 2.2021. Plymouth Meeting, PA:National Comprehensive Cancer Network; 2021 (https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf, accessed 12 June 2021).
43. Gorry C, McCullagh L, Barry M. Economic evaluation of systemic treatments for advanced melanoma: a systematic review. *Value Health*. 2020;23(1):52–60.
44. Donia M, Kimper-Karl ML, Høyer KL, Bastholt L, Schmidt H, Svane IM. The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials. *Eur J Cancer*. 2017;74:89–95.
45. Sam D, Gresham G, Abdel-Rahman O, Cheung WY. Generalizability of clinical trials of advanced melanoma in the real-world, population-based setting. *Med Oncol*. 2018;35(7):110.
46. Kandolf Sekulovic L, Guo J, Agarwala S, Hauschild A, McArthur G, Cinat G, et al. Access to innovative medicines for metastatic melanoma worldwide: Melanoma World Society and European Association of Dermato-oncology survey in 34 countries. *Eur J Cancer*. 2018;104:201–9.

