Cancer Treatment Reviews 110 (2022) 102463

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Systematic or Meta-analysis Studies

Comparative efficacy and safety of targeted therapies for BRAF-mutant unresectable or metastatic melanoma: Results from a systematic literature review and a network meta-analysis

Pippa Corrie [a], Nicolas Meyer [b,c], Rossana Berardi [d], Massimo Guidoboni [e], Maximilian Schlueter [f], Spyros Kolovos [g], Bérengère Macabeo [h,i], Jean-Baptiste Trouiller [h,i], Philippe Laramée [h,i,*]

[a] Oncology Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK
[b] Institut Universitaire du Cancer et CHU de Toulouse, Toulouse, France
[c] Inserm UMR 1037 – CRCT, Toulouse, France
[d] Clinica Oncologica, AOU Ospedali Riuniti, Ancona, Università Politecnica delle Marche, Ancona, Italy
[e] Experimental and Clinical Oncology of Immunotherapy and Rare Tumors, IRCCS IRST "Dino Amadori", Meldola, FC, Italy
[f] IQVIA, London, UK
[g] IQVIA, Athens, Greece
[h] Aix-Marseille Université, Marseille, France
[i] Pierre Fabre Laboratories, Paris, France

ARTICLE INFO

Keywords:
Metastatic melanoma
BRAF inhibitor
Network-meta analysis
Indirect comparison
Encorafenib
Dabrafenib
Vemurafenib

ABSTRACT

Background: The objective of this study was to estimate the relative efficacy and safety of targeted therapies for the treatment of metastatic melanoma using a network meta-analysis (NMA).
Methods: A systematic literature review (SLR) identified studies in Medline, Embase and Cochrane published until November 2020. Screening used prespecified eligibility criteria. Following a transitivity assessment across included studies, Bayesian NMA was conducted.
Results: A total of 43 publications reporting 15 targeted therapy trials and 42 reporting 18 immunotherapy trials were retained from the SLR and considered for the NMA. Due to substantial between-study heterogeneity with immunotherapy trials, the analysis considered a network restricted to targeted therapies. Among combination therapies, encorafenib + binimetinib was superior to dabrafenib + trametinib for overall response rate (OR = 1.86; 95 % credible interval [CrI] 1.10, 3.17), superior to vemurafenib + cobimetinib with fewer serious adverse events (SAEs) (OR = 0.51; 95 % CrI 0.29, 0.91) and fewer discontinuations due to AEs (OR = 0.45; 95 % CrI 0.21, 0.96), and superior to atezolizumab + vemurafenib + cobimetinib with fewer SAEs (OR = 0.41; 95 % CrI 0.21, 0.82). Atezolizumab + vemurafenib + cobimetinib and encorafenib + binimetinib were generally comparable for efficacy endpoints. Among double combination therapies, encorafenib + binimetinib showed high probabilities of being better for all efficacy and safety endpoints.
Conclusions: This NMA confirms that combination therapies are more efficacious than monotherapies. Encorafenib + binimetinib has a favourable efficacy profile compared to other double combination therapies and a favourable safety profile compared to both double and triple combination therapies.

Introduction

A number of approved treatment options currently exist for BRAF-mutant patients with unresectable or metastatic melanoma (MM), and effective diagnosis tools are available for assessing BRAF mutational status [1–3]. Clinician judgment drives individualized treatment decisions based on characteristics of the patient and of the disease [4]. Since multiple options exist, it is essential that treatment decisions are informed by relevant and contemporary clinical research, including efficacy and safety data. Systemic treatment options for BRAF-mutant MM

* Corresponding author at: 33 avenue Emile Zola, 92100 Boulogne, Billancourt, France.
E-mail address: philippe.laramee@pierre-fabre.com (P. Laramée).

https://doi.org/10.1016/j.ctrv.2022.102463
Received 27 May 2022; Received in revised form 30 August 2022; Accepted 30 August 2022
Available online 6 September 2022

can be categorised by monotherapies or combinations of immunotherapies (IO), selective/targeted BRAF inhibitors (BRAFi), double therapy combining a BRAFi and a MEK inhibitor (MEKi) and, most recently, triple therapy combinations of BRAFi + MEKi coupled with an immunotherapy [1].

Selecting the most appropriate therapy for an individual patient is hampered by limited direct treatment comparisons from head-to-head randomised controlled trials (RCTs) [5–6]. Indirect treatment comparisons can offer a robust statistical approach for the estimation of relative treatment effects between these therapies. Such approaches are routinely used by national health technology assessment (HTA) authorities for decisions on public reimbursement for new interventions.

The aim of this study was to conduct a systematic literature review (SLR) of trials investigating the efficacy and safety associated with all currently available treatment options for patients with BRAF-mutant MM and to perform an indirect treatment comparison of the relative efficacy and safety of targeted therapies – and IO if feasible – using a Bayesian network meta-analysis (NMA).

Methods

Identification of studies (systematic literature review)

An SLR was conducted to identify relevant RCTs for evidence synthesis of efficacy and safety outcomes. The SLR was conducted in accordance with the guidelines published by the Cochrane Collaboration and by the Centre for Reviews and Dissemination of the University of York [7]. Eligibility criteria for study inclusion were developed using the Population, Intervention, Comparator, Outcomes, Study design (PICOS) statement [8]. The inclusion and exclusion criteria applied, and the search terms can be found in the supplementary material.

The databases searched included Medline (including Ovid MEDLINE® Epub Ahead of Print, Medline In-Process and other non-indexed citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions®), Embase, and the Cochrane Library. The original searches were conducted through the OVID platform using the advanced search technique and were run on 14th April 2017. Updates of the SLR were run on 3rd April 2018 and on 5th November 2020. Two reviewers independently screened the studies identified from those searches and the eligible studies were included in this analysis.

The methodological quality of included studies was assessed using the criteria for methodological quality as specified by the Cochrane Risk of Bias tool [9]. Additional information for the SLR can be found in the supplementary material.

Network meta-analysis

Feasibility assessment

A feasibility assessment was carried out to determine whether a connected network of direct and indirect evidence for a given outcome of interest could be established and whether the comparability/transitivity assumption was violated. Eligible trials were assessed for presence and extent of between-trial heterogeneity by means of a comparison of trial design characteristics for all included trials to identify potential sources of bias (e.g., crossover, open label) that impact the outcomes of interest, and a comparison of baseline patients' characteristics to assess the comparability of patient populations in all included trials.

Outcomes

The outcomes included in the NMA were selected based on their relevance for investigating the efficacy and safety of therapies for MM, and their clinical relevance. The included efficacy outcomes were overall survival (OS), progression-free survival (PFS), and overall response rate (ORR). The included safety outcomes were those leading to clinical events and being similarly defined in the included studies: any serious adverse events (SAEs; any untoward medical occurrence that at any dose results in death, or is life-threatening, or requires in patient hospitalisation or prolonging of existing hospitalisation, or results in persistent or significant disability/incapacity [10] and treatment discontinuation due to AEs [11–12].

Analysis

Bayesian NMA was conducted using OpenBUGS version 3.2.3 [13] based on scripts recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document 2 [14]. The methodology followed the guidance from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons [15–16]. Additional information about the analysis can be found in supplementary material.

OS and PFS were analysed using log transformed hazard ratios (HR) and corresponding standard errors (SE) from each trial, assuming a normal likelihood and identity link [17]. Visual inspection of log cumulative hazard plots was conducted to verify the proportional hazards assumption was not violated in the survival outcomes reported by included trials. This involved digitisation of Kaplan-Meier curves from all included studies considered in the networks for the OS and PFS outcomes. ORR and the two safety outcomes were analysed as binary outcomes. Relative treatment effects are presented in the form of matrices for all outcomes of interest, presenting each outcome with associated 95 % credible intervals (95 % CrI) [18]. In Bayesian statistics, 95 % credible intervals denote a probability of 95 % of an effect falling within this range given the observed data. Similar to confidence intervals in frequentist statistics, one may interpret treatment comparisons as superior/inferior when 95 % credible intervals (CrI) do not cross unity (i.e., '1'). Although, the Bayesian approach treats parameters of interest as random variables, which are therefore described with probability distributions from observed data, and in this context, the probability of a treatment being better than another treatment is calculated.

The Bayesian concept of credible interval from observed data is sometimes seen as a more practical concept than the confidence interval in frequentist statistics, being based on the hypothesized repeats of the experiment. Bayesian statistics allows to calculate the probability of a treatment being better than another treatment from observed data, offering a different interpretation of results than frequentist statistics with confidence intervals [19]. The relevance of the Bayesian results of the probability of a treatment being better than another one is also justified by the fact that substantial trial power reduction strongly reduces the likelihood of demonstrating superiority between interventions when trials are introduced into an NMA [20]. Then, even when 95 % CrI cross unity, these results should not be discarded and probabilities of an intervention being better than another one should be further assessed with regards to their clinical relevance for a complete interpretation of Bayesian results.

Description of inconsistency assessment, stochastic convergence and the deviance information criterion (DIC) is provided in the supplementary material.

Results

Trial selection

The cumulative results from the original search and the two subsequent updates identified a total of 10,882 unique references after removal of duplicate records. After abstract and full-text screening, 85 citations met the inclusion criteria and were retained for extraction of relevant data. Of the 85 citations, 43 publications covered 15 targeted therapy RCTs, while 42 publications reported 18 IO therapy RCTs (Table 1). For each RCT, the latest data cut-off identified was used for the analysis, under the assumption for survival outcomes of proportional hazards over time. The assumption of proportional hazard functions over time was not violated both for OS and PFS.

Table 1
Trials included and extracted from the systematic literature search.

Trial/NCT/EU ID	Treatments	Line of therapy	Patient population	References
Trials of BRAF-targeted therapies, including monotherapies and combination therapies with or without IO				
BREAK-3 (Ph III)	DB; DTIC	1st line therapy – no prior therapy for metastatic cancer permitted	BRAF mutant advanced (Stage III) or metastatic (Stage IV) melanoma	Hauschild 2012 [21], Hauschild 2013 [22], Latimer 2015a [23]
BRF113220 Part C (Ph II)	DB; DB + TM; 1 mg; DB + TM; 2 mg	1st or 2nd line therapy No prior exposure to BRAF or MEK inhibitors Up to one regimen of chemotherapy and/or interleukin-2 is permitted	Adult patients who have BRAF mutant positive melanoma or colorectal cancer, measurable disease and ECOG 0 or 1	[24] [24], Flaherty 2014 [25], Long 2016 [26],[89] Part C [27]
BRIM-3 (Ph III)	VM; DTIC	1st line therapy	Histologically confirmed melanoma that is either Stage IIIC (unresectable) or Stage IV, and BRAF V600E mutation positive	Chapman 2011 [28],[29] [29], Chapman 2017 [30], Hauschild et al., 2016 [31]
coBRIM (Ph III)	VM + PBO; VM + COB	No prior systemic anti-cancer therapy for advanced disease; stage IIIc and IV). Prior adjuvant immunotherapy (including ipilimumab) is allowed	Patients with histologically xonfirmed melanoma either unresectable stage IIIc or stage IV metastatic melanoma naïve to treatment for locally advanced unresectable or metastatic disease and documentation of BRAF V600 mutation positive	[32] [32],[33] [33], Dreno 2017 [34], NCT01689519 (EUDRACT 2012–003008-11) [35], Dreno et al ASCO 2018 [36]
COLUMBUS (Ph III)	VM 960 mg bid; Enco + Bini450; Enco	1st or 2nd line therapy (prior first-line immunotherapy only)	Patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation	Dummer 2018 [37], Dummer 2018 (ASCO) Dummer et al., 2018;36 38:9504–., Gogas 2018 (ASCO) [39], NN 2016 [40],[95] [41],[42] [42],[43,37] [43], Liszkay et al 2019 [44], Gogas et al 2020 [45]
COMBI-d (Ph III)	DB + TM 2 mg; DB + PBO	Any-line therapy but no prior treatment with BRAF or MEK inhibitors and only prior systemic treatment in the adjuvent setting	Histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV, and BRAF V600E/K mutation positive	Long 2014 [46], Long 2015 [47], Long 2017 [48], NCT01584648 (EUDRACT 2011–006087-49) [49]
COMBI-I	Spar + DB + TM; PBO + DB + TM	1st line therapy	Histologically confirmed, unresectable or metastatic melanoma with BRAF V600 mutationAspartate transaminase (AST) $< 2.5 \times$ ULN and Alanine transaminase (ALT) $< 2.5 \times$ ULN ECOG performance status ≤ 1	Nathan et al ESMO 2020 [50]
COMBI-v (Ph III ol)	DB + TM 2 mg; VM	Any-line therapy but no prior treatment with BRAF or MEK inhibitors and only prior systemic treatment in the adjuvent setting	Histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV, and BRAF V600E/K mutation positive	Robert 2015a [51], Robert 2016 [52], NCT01597908 (EUDRACT 2011–006088-23) [53]
EUDRACT 2011–002545-35	Pacli; GSK1120212 + Pacli; Pazo + Pacli	No prior MEK inhibitor or recent systemic therapy or radiotherapy	18 years or older with measurable unresectable BRAF-wild type stage 3 or 4 melanoma, an Eastern Cooperative Oncology Group score of 0 or 1, and acceptable haematological, renal, and hepatic function	EUDRACT 2011–002545-35 [54]
IMspire150	Atez + VM + COB; VM + COB	Naive to prior systemic anti-cancer therapy for melanoma except adjuvant therapy with interferon, interleukin or vaccine therapies	Patients with previously untreated BRAFv600 mutation-positive metastatic or unresectable locally advanced melanoma	[55] [55], Ascierto et al ESMO 2020 [56]
KEYNOTE-022*	Pembro Q3W + DB + TM; DB + TM	1st line therapy	Histologically-confirmed diagnosis of advanced (unresectable Stage III) or metastatic (Stage IV) melanoma excluding mucosal, or ocular melanoma	[69] [57]
METRIC (TMT212A2301)	TM; DTIC + Pacli; TM	–	Patients with unresectable or metastatic cutaneous melanoma with a BRAF V600 E/K mutation	Robert et al 2019 [58], EUDRACT 2010–022838-85 [59]
NCT02314143	DB + TM; TM + BD; TM + BD	Any-line, but no prior BRAF or MEK inhibitor therapies	BRAF mutant metastatic unresectable stage IIIc or IV melanoma.	NCT02314143 [60] , EUDRACT 2012–004577-12 [61]
S1320**	DB + TM (Continuous dosing); DB + TM (Intermittent dosing)	Any-line, but no prior BRAF or MEK inhibitor therapies	Patients with histologically or cytologically confirmed stage IV or unresectable stage III BRAF V600E or BRAF V600K mutant melanoma	[62] [62]
Trials of immunotherapies* **				
CA184-024	Ipi + DTIC; PBO + DTIC	1st line therapy and only prior adjuvent therapy was permitted	Untreated Unresectable Stage III or IV Melanoma with ECOG 0 or 1	[63] [63],[64] [64]
CheckMate 037	Nivo; DTIC or Carbo + Pacli	–	Adult advanced melanoma patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 and histologically confirmed Stage III (unresectable)/Stage IV melanoma	[65] [65],[66] [66]
CheckMate 066	Nivo; DTIC	Prior adjuvent therapy was not an exclusion criteria	Adult advanced melanoma patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 and histologically confirmed Stage III (unresectable)/Stage IV melanoma	Robert 2015c [67], Robert et al 2019 [68],[69] [69], Robert et al 2020 [70]

(*continued on next page*)

Table 1 (*continued*)

Trial/NCT/EU ID	Treatments	Line of therapy	Patient population	References
CheckMate 067	Nivo + Ipi; Nivo; Ipi	1st line therapy as patients were required to be treatment naive	Adult advanced melanoma patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 and histologically confirmed Stage III (unresectable)/Stage IV melanoma BRAF positive patients excluded	[71] [71], Wolchok 2018 [72], Larkin et al., 2017 [73],[74] [74],[75] [75],[76] [76],[72],[74] [77]
CheckMate 069	Nivo + Ipi; Ipi + PBO	No prior systemic anticancer therapy for unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to date of first dose	Adult advanced melanoma patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 and histologically confirmed Stage III (unresectable)/Stage IV melanoma BRAF positive patients excluded	[77] [78], Postow 2015 [79]
CheckMate 511 Trial	Nivo + Ipi; Nivo + Ipi	1st line therapy in the metastatic setting	Patients were age 18 years or older with unresectable stage III or stage IV melanoma, an Eastern Cooperative Oncology Group performance status of 0 or 1, no prior systemic therapy for metastatic melanoma	Lebbe et al 2019 [80]
EUDRACT2016-001941–26	Nivo + Ipi (Fixed Combination); Nivo + Ipi (Sequential Combination)	1st line therapy Subjects have not been treated by systemic anticancer therapy for unresectable or metastatic melanoma	Males and Females, ages 15 years ≥ of age diagnosed with stage III or/and stage IV histologically confirmed melanoma that is unresectable or metastatic Eastern Cooperative Oncology Group (ECOG) performance status of 0–1	EUDRACT 2016–001941-26 [81]
KEYNOTE 002	Pembro; Pembro; ICC; ICC → Pembro; ICC → Pembro	Patients have progressed on prior therapy	Histologically or cytologically confirmed diagnosis of unresectable Stage III or metastatic melanoma not amenable to local therapy Participants with BRAF gene mutant melanoma must have had a prior treatment regimen that included vemurafenib, dabrafenib, or an approved BRAF or MEK protein inhibitor and ECOG status 0 or 1	NCT01704287 (EUDRACT 2012–003030-17) [82]
KEYNOTE-006	Pembro Q3W; Pembro Q2W; Ipi	No prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (first line) or one prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for melanoma (second line)	Histologically-confirmed diagnosis of unresectable Stage III or metastatic melanoma not amenable to local therapy (excluding uveal or ocular melanoma) with ECOG 0 or 1	Robert 2015b [83], Robert et al 2019 [84],[84] [85], NCT01866319 (EUDRACT 2012–004907-10) [86]
KEYNOTE-029	Pembro + Ipi; Pembro + Ipi	1st line therapy	Histologically- or cytologically-confirmed diagnosis of advanced/unresectable or metastatic melanoma with predominantly clear cell elements. Previously untreated stage III/IV advanced or metastatic melanoma	[87] [87]
KEYNOTE-252/ ECHO-301	Epac + Pembro; PBO + Pembro	No prior systemic treatment for metastatic melanoma but BRAF directed therapyis permitted	Patients were age 18 years or older with unresectable stage III or stage IV melanoma, an Eastern Cooperative Oncology Group performance status of 0 or 1, no prior systemic therapy for metastatic melanoma	[87] [88],[27] [89], NCT02752074 (EUDRACT 2015–004991-31) [90]
NCCTG N0879 (Alliance)	Carbo + pacli + Beva; Carbo + pacli + Beva + Evero	1st or 2nd line therapy in the metastatic setting	Histologic proof of stage IV malignant melanoma not amenable to surgery,, measurable disease, life expectancy of ≥ 4 months, age ≥ 18 years, adequate blood counts and organ function, and ECOG performance score 0–1, and no more than one prior chemotherapy based regimen for metastatic melanoma	[90] [91]
NCT01152788	Interleukin 21; DTIC	Previous therapy permitted as long as it is not a systemic therapy (except for MEK inhibitors)	Histologic diagnosis of malignant melanomaChemotherapy naive Stage IV melanoma (AJCC 2010) Life expectancy of ≥ 12 weeks Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	NCT01152788 [92]
NCT01258855	Ziv-Afi + Aldes; Aldes	1st, 2nd or 3rd line therapy (up to two prior regimens for metastatic cancer are permitted)	Patients With Inoperable Stage III or Stage IV Melanoma	NCT01258855 [93]
NCT01515189	Ipi 3 mg/kg; Ipi 10 mg/kg	–	Unresectable Stage III or Stage IV melanoma Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	EUDRACT 2011–004029-28 [94],[94] [95]
NCT01740297	Talimogene laherparepvec + Ipi; Ipi	1st line therapy with no prior systemic anticancer therapy	Treatment naive Histologically confirmed diagnosis of malignant melanoma. Stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c disease that is not suitable for surgical resection	[97] [96], Chesney et al 2018 [97], Chesney et al ESMO 2019 [98], Chesney et al SMR 2018 [99]

(*continued on next page*)

Table 1 (*continued*)

Trial/NCT/EU ID	Treatments	Line of therapy	Patient population	References
NCT02545075	Ipi; DTIC	Chemotherapy naive patients	Histologic diagnosis of malignant melanomaChemotherapy naive Stage IV melanoma (AJCC 2010) Life expectancy of ≥ 16 weeks Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	NCT02545075 [100]
NCT03273153	Pembro; COB + Atez	1st line therapy	Treatment-naive participants with advanced BRAFV600 wild-type melanoma	NCT03273153 [101],[101] [102], NCT03273153 (EUDRACT 2016–004387-18) [103]

* KEYNOTE-022 did not meet its primary endpoint.
** DB + TM (Intermittent dosing) is not approved by the European Medicines Agency, and trial S1320 did not meet its primary endpoint. Both trials excluded from the analysis.
*** Trials including IO were not analysed as established by the feasibility assessment.
Abbreviations: Aldes: Aldesleukin; Atez: Atezolizumab; Beva: Bevacizumab; BiniEnco: encorafenib + binimetinib; BRAF: v-raf murine sarcoma viral oncogene homolog B1; Carbo: carboplatin; COB: cobimetinib; DB: dabrafenib; DTIC: dacarbazine; ECOG: Eastern Cooperative Oncology Group; Epac: Epacadostat; Evero: Everolimus; ICC: Investigator-Choice Chemotherapy; Ipi: ipilimumab; MEK: mitogen-activated extracellular signal-regulated kinase; Nivo: nivolumab; Pacli: paclitaxel; Pazo: Pazopanib; PBO: placebo; Pembro: pembrolizumab; Spar: Spartalizumab; TM: trametinib; VM: vemurafenib; Ziv-Afi: Ziv-Aflibercept.

Risk of bias

Results of the quality assessment of RCTs overall suggest low to medium risk of bias. Additional details on the assessment can be found in the supplementary material.

Effect modification assessment

The feasibility assessment showed that connected networks of evidence could be created for the outcomes of interest. Moreover, patient populations across trials of targeted therapies were similar with respect to their baseline characteristics. Heterogeneity between IO trial populations and targeted therapy trial populations was detected for potential effect modifiers, such as BRAF mutation status, Eastern Cooperative Oncology Group (ECOG) performance status score, LDH level, and number and stage of metastasis. In addition, the only IO trial connecting to the network of targeted therapies, CheckMate 066, excluded subjects with BRAF mutant tumours.

Since positive BRAF mutation status is associated with poorer outcomes for patients with MM [104], the asymmetrical distribution of this effect modifier between populations enrolled in targeted therapy trials compared with IO trials is most likely to introduce a major bias into a network comprised of both types of treatments. Therefore, it was deemed methodologically inappropriate to include IO trials in the same network of evidence as targeted therapy trials. The network of evidence for targeted therapy regimens investigated in patients with BRAF-mutant MM is shown in Fig. 1.

Excluded trials

Considering that Keynote-022 (comparing dabrafenib + trametinib +/- pembrolizumab), COMBI-I (spartalizumab + dabrafenib + trametinib versus placebo + dabrafenib + trametinib), and S1320 (continuous versus intermittent dabrafenib + trametinib)) are negative trials in relation to their respective control arms and the experimental interventions have no marketing authorisation for the treatment of BRAF-mutant MM, they were excluded from the subsequent analyses.

Efficacy outcomes

Bayesian statistics present results with points estimates and their 95 % credible intervals (CrI). The probability of a treatment being better than another treatment is also calculated, with CrI being based on probability distributions from observed data.

Overall survival

Results of the analysis showed that combination therapies generally achieve improved OS outcomes compared to monotherapies (i.e., dabrafenib, vemurafenib and dacarbazine). Comparisons among double therapy combinations favoured encorafenib + binimetinib versus dabrafenib + trametinib (HR = 0.88; 95 % CrI 0.66, 1.18), and versus vemurafenib + cobimetinib (HR = 0.89; 95 % CrI 0.63, 1.25), (Table 2), with probabilities of being better for encorafenib + binimetinib of 80 % and 75 %, respectively (Table 3). Atezolizumab + vemurafenib + cobimetinib and encorafenib + binimetinib showed comparable results (HR = 0.96; 95 % CrI 0.62, 1.49).

Progression-free survival

The analysis of investigator-assessed PFS consistently demonstrated superior results for combination therapies compared to monotherapies. In addition, atezolizumab + vemurafenib + cobimetinib was shown to be superior compared to vemurafenib + cobimetinib (HR = 0.78 95 % CrI 0.63, 0.97) (Table 2). Encorafenib + binimetinib was associated with probabilities of being better to other double regimens, and specifically of 88 % and 73 % versus dabrafenib + trametinib and vemurafenib + cobimetinib, respectively (Table 3).

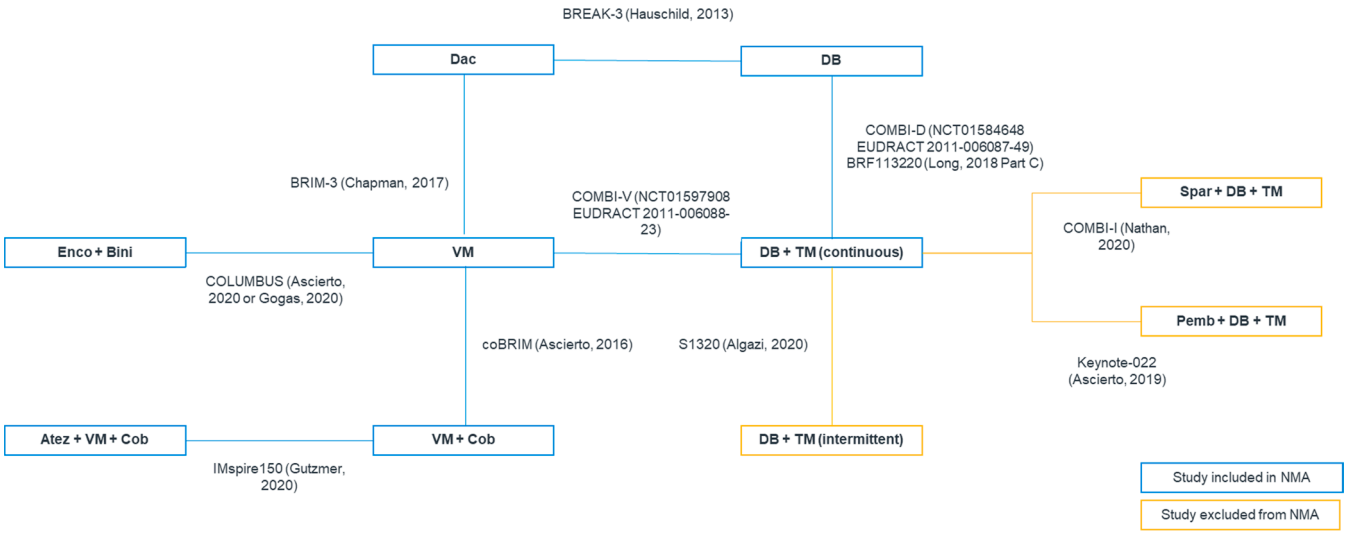

Fig. 1. Network of evidence for efficacy and safety outcomes, Abbreviations: Atez: atezolizumab; Bini: binimetinib; Cob: cobimetinib; DB: dabrafenib; Dac: dacarbazine; Enco: encorafenib; Pemb: pembrolizumab; Spar: spartalizumab; TM: trametinib; VM: vemurafenib, Notes: Due to lack of reported data, IMspire150 was not included for safety outcomes. For COLUMBUS trial, (Ascierto, 2020) provided inputs for ORR and Discontinuation due to AE, [45] provided the OS and PFS input and (Dummer, 2018) provided the SAE outcome. Keynote-022 did not provide SAE data. S1320, COMBI-I and Keynote-022 were excluded from the analysis as they did not meet their primary endpoint, and their experimental intervention have no marketing authorisation for the treatment of BRAF-mutant MM.

Evidence synthesis of PFS using estimates from a blinded independent central review committee (BIRC) to mitigate risk of bias was not performed since only COLUMBUS, CoBRIM and BRF113220 Part C reported BIRC estimates for these outcomes.

Overall response rate

According to our analysis, combination therapies are superior to monotherapies for ORR. For combination therapies, the triple regimen atezolizumab + vemurafenib + cobimetinib demonstrated favourable results compared to double regimens, with the exception of encorafenib + binimetinib (Table 2). Encorafenib + binimetinib was superior to dabrafenib + trametinib (OR = 1.86; 95 % CrI 1.10, 3.17) with a probability of being better of 99 %, and has favourable results compared to vemurafenib + cobimetinib and to atezolizumab + vemurafenib + cobimetinib, with probabilities of being better of 87 % and 79 %, respectively (Table 3).

Safety outcomes

SAEs

Monotherapies were superior with fewer SAEs compared with combination therapies, except for encorafenib + binimetinib compared to vemurafenib and to dabrafenib (Table 2. Encorafenib + binimetinib was superior with fewer SAEs compared to vemurafenib + cobimetinib (OR = 0.51; 95 % CrI 0.29, 0.91) with a probability of being better of 99 %, and compared to atezolizumab + vemurafenib + cobimetinib (OR = 0.41; 95 % CrI 0.21, 0.82) with also a probability of being better of 99 %. Results favoured encorafenib + binimetinib versus dabrafenib + trametinib with a probability of being better of 93 % (Table 3).

Treatment discontinuation due to AEs

Monotherapies were generally associated with fewer treatment discontinuation due to AEs compared with combination therapies (Table 2). For combination therapies, encorafenib + binimetinib (OR = 0.45; 95 % CrI 0.21, 0.96) and dabrafenib + trametinib (OR = 0.49; 95 % CrI 0.25, 0.94) were superior compared to vemurafenib + cobimetinib. Encorafenib + binimetinib showed probabilities of being better of 59 %, 98 % and 88 % versus dabrafenib + trametinib, vemurafenib + cobimetinib and atezolizumab + vemurafenib + cobimetinib, respectively (Table 3).

Discussion

An SLR and NMA were conducted to derive relative effects of indicated targeted therapy regimens for patients with BRAF-mutant MM, since currently there is a lack of RCTs directly comparing the efficacy and safety of these interventions.

Bayesian statistics used for NMAs produce results with 95 % credible intervals (CrI), as compared to confident intervals (CI) in frequentist statistics. The Bayesian approach treats parameters of interest as random variables, and therefore parameters are described with probability distributions from observed data. In this context, the probability of a treatment being better than another treatment is calculated, which is specific to Bayesian statistics as compared with frequentist statistics. For interpretation of results, as in frequentist statistics, superiority between two interventions can be concluded when the 95 % CrI does not cross unity. However, in Bayesian statistics, when 95 % CrI cross unity, the probability of a treatment being better than another one should then be assessed regarding its clinical relevance. This is also justified by the substantial trial power reduction when integrated into an NMA, which strongly reduces the likelihood of demonstrating superiority between interventions [20].

For efficacy outcomes, our study confirmed that combination therapies are generally superior (i.e., 95 % CrI not crossing unity) to monotherapies. Within combination therapies, encorafenib + binimetinib was superior to dabrafenib + trametinib for ORR, and atezolizumab + vemurafenib + cobimetinib was superior to vemurafenib + cobimetinib for PFS. Atezolizumab + vemurafenib + cobimetinib and encorafenib + binimetinib were generally comparable for efficacy endpoints. Furthermore, comparisons among double therapy combinations favoured encorafenib + binimetinib versus dabrafenib + trametinib and versus vemurafenib + cobimetinib in terms of probability of being better for all efficacy endpoints (although with 95 % CrI crossing unity for all endpoints, except for ORR for encorafenib + binimetinib versus dabrafenib + trametinib). These comparisons with high probabilities of being better favouring one intervention are then evaluated for their clinical relevance, and subsequently this evidence can be used to inform clinical decision making.

The favourable results in OS with high probabilities of being better for encorafenib + binimetinib versus dabrafenib + trametinib and versus vemurafenib + cobimetinib are likely to be clinically meaningful,

Table 2
Matrix of Bayesian NMA results.

Overall survival (HR, 95 % CrI)						
DB	1.26 (1.04,1.53)	0.89 (0.70,1.13)	0.73 (0.56,0.95)	1.27 (0.90,1.79)	1.50 (0.96,2.32)	1.44 (1.02,2.02)
0.79 (0.65,0.96)	**DB + TR**	0.70 (0.60,0.83)	0.58 (0.46,0.72)	1.01 (0.75,1.36)	1.19 (0.79,1.77)	1.14 (0.85,1.52)
1.12 (0.89,1.43)	1.42 (1.20,1.68)	**VM**	0.82 (0.69,0.97)	1.43 (1.12,1.83)	1.68 (1.16,2.43)	1.61 (1.27,2.05)
1.38 (1.06,1.80)	1.74 (1.39,2.18)	1.23 (1.03,1.45)	**Dac**	1.75 (1.30,2.37)	2.06 (1.37,3.09)	1.98 (1.47,2.65)
0.79 (0.56,1.11)	0.99 (0.74,1.34)	0.70 (0.55,0.90)	0.57 (0.42,0.77)	**VM + Cob**	1.18 (0.89,1.55)	1.13 (0.80,1.59)
0.67 (0.43,1.04)	0.84 (0.56,1.26)	0.59 (0.41,0.86)	0.48 (0.32,0.73)	0.85 (0.65,1.12)	**Ate + VM + Cob**	0.96 (0.62,1.49)
0.70 (0.50,0.98)	0.88 (0.66,1.18)	0.62 (0.49,0.79)	0.51 (0.38,0.68)	0.89 (0.63,1.25)	1.04 (0.67,1.62)	**Enco + Bini**
TRD	8.14 (2.13, 17.68)					
DIC	−3.782					
Progression-free survival (HR, 95 % CrI)						
DB	1.52 (1.27, 1.83)	0.95 (0.75, 1.19)	0.36 (0.28, 0.47)	1.63 (1.19, 2.25)	2.09 (1.42, 3.08)	1.82 (1.29, 2.58)
0.66 (0.55, 0.79)	**DB + TR**	0.62 (0.53, 0.73)	0.24 (0.19, 0.30)	1.07 (0.81, 1.41)	1.38 (0.97, 1.95)	1.20 (0.88, 1.63)
1.06 (0.84, 1.33)	1.61 (1.37, 1.89)	**VM**	0.38 (0.32, 0.45)	1.73 (1.38, 2.16)	2.21 (1.62, 3.01)	1.93 (1.49, 2.49)
2.77 (2.13, 3.59)	4.21 (3.37, 5.26)	2.62 (2.21, 3.12)	**Dac**	4.52 (3.42, 6.00)	5.80 (4.06, 8.26)	5.04 (3.70, 6.89)
0.61 (0.44, 0.84)	0.93 (0.71, 1.23)	0.58 (0.46, 0.73)	0.22 (0.17, 0.29)	**VM + Cob**	1.28 (1.03, 1.59)	1.12 (0.79, 1.57)
0.48 (0.32, 0.70)	0.73 (0.51, 1.03)	0.45 (0.33, 0.62)	0.17 (0.12, 0.25)	0.78 (0.63, 0.97)	**Ate + VM + Cob**	0.87 (0.58, 1.30)
0.55 (0.39, 0.78)	0.83 (0.62, 1.13)	0.52 (0.40, 0.67)	0.20 (0.15, 0.27)	0.90 (0.64, 1.26)	1.15 (0.77, 1.72)	**Enco + Bini**
TRD	12.13 (6.30, 21.66)					
DIC	−1.525					
Overall response rate (OR, 95 % CrI)						
Enco + Bini	1.86 (1.10, 3.17)	3.19 (2.07, 4.98)	37.82 (21.27,68.36)	1.39 (0.79, 2.48)	1.31 (0.67, 2.60)	4.46 (2.43, 8.21)
0.54 (0.32, 0.91)	**DB + TM**	1.72 (1.28, 2.31)	20.30 (13.04,32.21)	0.75 (0.47, 1.19)	0.71 (0.39, 1.28)	2.39 (1.70, 3.37)
0.31 (0.20, 0.48)	0.58 (0.43, 0.78)	**VM**	11.83 (8.11,17.56)	0.44 (0.30, 0.63)	0.41 (0.25, 0.69)	1.40 (0.91, 2.12)
0.03 (0.01, 0.05)	0.05 (0.03, 0.08)	0.08 (0.06, 0.12)	**Dac**	0.04 (0.02, 0.06)	0.03 (0.02, 0.07)	0.12 (0.07, 0.19)
0.72 (0.40, 1.27)	1.34 (0.84, 2.14)	2.30 (1.59, 3.32)	27.19 (16.02,46.53)	**VM + Cob**	0.94 (0.66, 1.36)	3.20 (1.83, 5.61)
0.76 (0.38, 1.49)	1.42 (0.78, 2.57)	2.43 (1.45, 4.08)	28.82 (15.12,55.08)	1.06 (0.74, 1.53)	**Ate + VM + Cob**	3.39 (1.74, 6.62)
0.22 (0.12, 0.41)	0.42 (0.30, 0.59)	0.72 (0.47, 1.09)	8.48 (5.20,14.14)	0.31 (0.18, 0.55)	0.30 (0.15, 0.58)	**DB**
TRD	20.54 (11.41, 130.6)					
DIC	133.8					
Serious adverse events (OR, 95 % CrI)						
Enco + Bini	0.68 (0.42, 1.13)	0.93 (0.62, 1.41)	3.75 (2.22, 6.40)	0.51 (0.29, 0.91)	1.50 (0.85, 2.67)	0.41 (0.21, 0.82)
1.46 (0.89, 2.40)	**DB + TM**	1.36 (1.02, 1.80)	5.48 (3.67, 8.26)	0.75 (0.47, 1.21)	2.19 (1.58, 3.04)	0.61 (0.33, 1.10)
1.08 (0.71, 1.62)	0.74 (0.55, 0.98)	**VM**	4.04 (2.90, 5.66)	0.55 (0.38, 0.81)	1.61 (1.08, 2.41)	0.45 (0.26, 0.76)
0.27 (0.16, 0.45)	0.18 (0.12, 0.27)	0.25 (0.18, 0.34)	**Dac**	0.14 (0.08, 0.23)	0.40 (0.25, 0.63)	0.11 (0.06, 0.21)
1.94 (1.10, 3.39)	1.33 (0.83, 2.12)	1.80 (1.24, 2.63)	7.29 (4.42,12.08)	**VM + Cob**	2.91 (1.68, 5.03)	0.80 (0.55, 1.18)
0.67 (0.37, 1.18)	0.46 (0.33, 0.63)	0.62 (0.42, 0.93)	2.50 (1.60, 3.98)	0.34 (0.20, 0.60)	**DB**	0.28 (0.14, 0.54)
2.42 (1.22, 4.73)	1.65 (0.91, 3.02)	2.24 (1.32, 3.82)	9.07 (4.84,17.01)	1.24 (0.85, 1.81)	3.62 (1.85, 7.04)	**Ate + VM + Cob**
TRD	25.79 (17.36, 37.95)					
DIC	128.8					
Discontinuation due to AE (OR, 95 % CrI)						
Enco + Bini	0.93 (0.47, 1.81)	0.96 (0.56, 1.64)	3.81 (1.46,11.20)	0.45 (0.21, 0.96)	2.33 (0.95, 5.84)	0.59 (0.24, 1.44)
1.08 (0.55, 2.13)	**DB + TM**	1.03 (0.69, 1.54)	4.10 (1.74,11.12)	0.49 (0.25, 0.94)	2.51 (1.36, 4.82)	0.63 (0.28, 1.45)
1.05 (0.61, 1.79)	0.97 (0.65, 1.44)	**VM**	3.96 (1.80,10.29)	0.48 (0.28, 0.80)	2.44 (1.19, 5.13)	0.61 (0.30, 1.27)
0.26 (0.09, 0.68)	0.24 (0.09, 0.58)	0.25 (0.10, 0.56)	**Dac**	0.12 (0.04, 0.31)	0.61 (0.20, 1.64)	0.15 (0.05, 0.45)
2.20 (1.04, 4.66)	2.04 (1.06, 3.97)	2.10 (1.25, 3.58)	8.38 (3.22,24.59)	**VM + Cob**	5.12 (2.11,12.90)	1.29 (0.78, 2.16)
0.43 (0.17, 1.06)	0.40 (0.21, 0.74)	0.41 (0.20, 0.84)	1.63 (0.61, 4.91)	0.20 (0.08, 0.47)	**DB**	0.25 (0.09, 0.70)
1.70 (0.70, 4.17)	1.58 (0.69, 3.61)	1.63 (0.79, 3.38)	6.49 (2.20,21.17)	0.77 (0.46, 1.28)	3.97 (1.43,11.25)	**Ate + VM + Cob**
TRD	19.5 (10.19, 32.83)					
DIC	115.9					

Abbreviations: Ate: atezolizumab; Bini, binimetinib; CrI, Credible interval; Cob, cobimetinib; DB, dabrafenib; Dac, dacarbazine; DIC, Deviance Information Criterion; Enco, encorafenib; HR, Hazard ratio; OR, Odds ratio; VM, vemurafenib; TRD, Total Residual Deviance; TM; trametinib.
Notes: Results to be read horizontally, e.g. for the comparison of DB + TR vs DB in terms of overall survival the HR (95 % CrI) is 0.79 (0.65, 0.96).

with unadjusted differences in median OS of more than six months for encorafenib + binimetinib versus the other double combination therapies. Differences higher than six months in unadjusted median OS for this patient population was judged clinically relevant by clinicians specialised in the treatment of MM during health technology assessment processes for public reimbursement in England and in Canada for dabrafenib + trametinib and for vemurafenib + cobimetinib [105–109]. Small numerical differences identified in the analysis of OS between atezolizumab + vemurafenib + cobimetinib and encorafenib + binimetinib are unlikely to be clinically meaningful, with an unadjusted difference in median survival between interventions of 4.8 months favouring encorafenib + binimetinib [110,111].

In the analysis of safety outcomes, encorafenib + binimetinib was superior (i.e., 95 % CrI not crossing unity) to atezolizumab + vemurafenib + cobimetinib with fewer SAEs, and was superior to vemurafenib + cobimetinib with fewer SAEs and fewer discontinuations due to AEs. In addition, compared to dabrafenib + trametinib, encorafenib + binimetinib had probabilities of being better of 93 % for SAEs, and of 59 % for discontinuations due to AEs, although with 95 % CrI crossing unity. Based on this assessment of safety outcomes, encorafenib + binimetinib may generate fewer treatment-related hospitalizations and lower health care resource utilisation, which appears important evidence of clinical relevance for choosing an intervention over another one, this choice of regimen potentially resulting in lower costs for health care providers in

Table 3
Matrix of the probability of a treatment of being better compared to another.

Overall survival probability of being better						
DB	1 %	83 %	99 %	8 %	4 %	2 %
99 %	**DB + TM**	100 %	100 %	48 %	21 %	20 %
17 %	0 %	**VM**	99 %	0 %	0 %	0 %
1 %	0 %	1 %	**Dac**	0 %	0 %	0 %
92 %	52 %	100 %	100 %	**VM + Cob**	12 %	25 %
96 %	79 %	100 %	100 %	88 %	**Ate + VM + Cob**	57 %
98 %	80 %	100 %	100 %	75 %	43 %	**Enco + Bini**
Progression-free survival (investigator) probability of being better						
DB	0 %	68 %	100 %	0 %	0 %	0 %
100 %	**DB + TM**	100 %	100 %	31 %	4 %	12 %
32 %	0 %	**VM**	100 %	0 %	0 %	0 %
0 %	0 %	0 %	**Dac**	0 %	0 %	0 %
100 %	69 %	100 %	100 %	**VM + Cob**	1 %	27 %
100 %	96 %	100 %	100 %	99 %	**Ate + VM + Cob**	75 %
100 %	88 %	100 %	100 %	73 %	25 %	**Enco + Bini**
Overall response rate probability of being better						
Enco + Bini	99 %	100 %	100 %	87 %	79 %	100 %
1 %	**DB + TM**	100 %	100 %	11 %	13 %	100 %
0 %	0 %	**VM**	100 %	0 %	0 %	94 %
0 %	0 %	0 %	**Dac**	0 %	0 %	0 %
13 %	89 %	100 %	100 %	**VM + Cob**	38 %	100 %
21 %	87 %	100 %	100 %	62 %	**Ate + VM + Cob**	100 %
0 %	0 %	6 %	100 %	0 %	0 %	**DB**
SAEs probability of being better						
Enco + Bini	93 %	64 %	0 %	99 %	8 %	99 %
7 %	**DB + TM**	2 %	0 %	88 %	0 %	95 %
36 %	98 %	**VM**	0 %	100 %	1 %	100 %
100 %	100 %	100 %	**Dac**	100 %	100 %	100 %
1 %	12 %	0 %	0 %	**VM + Cob**	0 %	87 %
92 %	100 %	99 %	0 %	100 %	**DB**	100 %
1 %	5 %	0 %	0 %	13 %	0 %	**Ate + VM + Cob**
Discontinuation due to adverse event probability of being better						
Enco + Bini	59 %	57 %	0 %	98 %	3 %	88 %
41 %	**DB + TM**	44 %	0 %	98 %	0 %	86 %
43 %	56 %	**VM**	0 %	100 %	1 %	90 %
100 %	100 %	100 %	**Dac**	100 %	83 %	100 %
2 %	2 %	0 %	0 %	**VM + Cob**	0 %	16 %
97 %	100 %	99 %	17 %	100 %	**DB**	100 %
12 %	14 %	10 %	0 %	84 %	0 %	**Ate + VM + Cob**

Abbreviations: Atez: atezolizumab; Bini: binimetinib; Cob: cobimetinib; DB: dabrafenib; Dac: dacarbazine; Enco: encorafenib; TM: trametinib; VM: vemurafenib.

Note: Results to be read horizontally, e.g. for the comparison of DB + TR vs DB in terms of overall survival, the probability of DB + TR being better is 99 %.

terms of AE management.

A number of previous NMAs investigating systemic therapies for the treatment of MM have recently been published [112–116]. An important difference between this study and the previous NMAs is the inclusion of IO trials to the network of evidence, an approach we deem methodologically inappropriate given substantial population heterogeneity and the fact that the only connection between the IO and targeted therapies networks is through the Checkmate 066 trial, which did not allow enrolment of patients with BRAF-mutant melanoma. The current NMA, however, represents the first study to include an approved triple combination therapy for the treatment of BRAF-mutant MM. Consistent with findings from previous NMAs, results of the present NMA indicate the favourable efficacy profile of combination targeted therapies compared to monotherapies, although a comparable or favourable safety profile of monotherapies compared to combination therapies is noted [112–116].

Our study has a number of limitations. Lack of reported data was observed in several included RCTs for potential treatment effect prognostic indicators, such as the number of metastatic sites. As a result, the compatibility of the evidence base could not be exhaustively assessed. Furthermore, the network included a mix of open-label and double-blinded RCTs, and PFS was assessed by BIRC to mitigate risk of bias in only three trials (i.e., COLUMBUS, CoBRIM and BRF113220 Part C) which restricted its assessment. Finally, as previously mentioned, substantial trial power reduction strongly reduces the likelihood of demonstrating superiority between interventions when introduced into an NMA [20], hence probabilities of an intervention being better than another one should not be discarded without further clinical consideration.

Conclusion

Our research represents the first study to compare all currently approved targeted therapies for the treatment of BRAF-mutant MM. It provides an evidence-based framework to inform clinical decision-making given the lack of head-to-head comparisons from RCTs. Overall, results show that combination therapies are more efficacious than monotherapies. Triple combination therapy and encorafenib + binimetinib were found to have the most favourable efficacy profiles, and encorafenib + binimetinib had a favourable safety profile compared to all other combination therapies, including triple combination therapy.

Funding

The study was supported by Pierre Fabre Laboratories, Paris, France.

CRediT authorship contribution statement

Pippa Corrie: Conceptualization, Writing – review & editing, Supervision, Project administration. **Nicolas Meyer:** Conceptualization, Writing – review & editing, Supervision, Project administration. **Rossana Berardi:** Conceptualization, Writing – review & editing, Supervision, Project administration. **Massimo Guidoboni:** Conceptualization, Writing – review & editing, Supervision, Project administration. **Maximilian Schlueter:** Conceptualization, Writing – original draft, Supervision, Software, Validation, Formal analysis, Data curation, Methodology. **Spyros Kolovos:** Writing – original draft, Investigation, Software, Validation, Formal analysis, Data curation, Resources. **Bérengère Macabeo:** Conceptualization, Writing – original draft, Supervision, Project administration. **Jean-Baptiste Trouiller:** Conceptualization, Writing – original draft, Supervision, Project administration. **Philippe Laramée:** Conceptualization, Methodology, Validation, Writing – original draft, Supervision, Project administration.

Declaration of Competing Interest

PC has received speaker/advisory board fees from Pierre Fabre, Novartis, Merck Sharp & Dohme and Bristol Myers Squibb. NM worked as an investigator and/or speaker and/or participated in advisory board and/or received research grants from BMS, MSD, Novartis, Pierre Fabre, Sun Pharma, Sanofi, Merck. RB has received funding to institution and/or for participation to advisory board: Astra Zeneca, Boehringer, Novartis, Merck Sharp & Dohme, Lilly, Roche, Amgen, GSK, Eisai and Bristol Myers Squibb. MG received research funds from Merck Sharp & Dohme and participated in advisory board: Pierre Fabre, Bristol Myers Squibb. PL, BM and JBT were employees of Pierre Fabre Laboratories, Paris, France at the time of the development of this study. SM and KS were employees of IQVIA at the time of the development of this study and IQVIA was funded by Pierre Fabre to support the development of it.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2022.102463.

References

[1] Liu Ye ZX, Guoying W, Xinchang C. Triple combination therapy with PD-1/PD-L1, BRAF, and MEK inhibitor for stage III–IV melanoma: a systematic review and meta-analysis. Front. Oncol. 2021:11:2088.

[2] Ronchi A, Montella M, Zito Marino F, Argenziano G, Moscarella E, Brancaccio G, et al. Cytologic diagnosis of metastatic melanoma by FNA: a practical review. Cancer Cytopathol 2022;130(1):18–29.

[3] Ronchi A, Montella M, Zito Marino F, Caraglia M, Grimaldi A, Argenziano G, et al. Predictive evaluation on cytological sample of metastatic melanoma: the Role of BRAF immunocytochemistry in the molecular era. Diagnostics (Basel) 2021;11 (6).

[4] Lulin ZYE, Asante AH. Complementarity of clinician judgment and evidence based models in medical decision making: antecedents. Prospect Chall Biomed Res Int 2016;1425693.

[5] Crosby TFR, Coles B, Mason M. WITHDRAWN: Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev. 2018;2(2):CD001215.

[6] Pasquali SHA, Chiarion Sileni V, Rossi CR, Mocellin S. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev 2018. Feb 6;2(2): CD011123.

[7] Centre for Reviews and Dissemination, The University of York. Our guidance. [Internet]. Available from: https://www.york.ac.uk/crd/guidance/. (Accessed: 6th October 2017).

[8] Methley AMCS, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC Health Serv Res 2014;14:579.

[9] Cochrane Handbook for Systematic Reviews of Interventions. Available at: http://handbook-5-1.cochrane.org/. (Accessed: 6th October 2017) [Internet].

[10] FDA. What is a Serious Adverse Event?. 2020.

[11] Allen EN, Chandler CI, Mandimika N, Leisegang C, Barnes K. Eliciting adverse effects data from participants in clinical trials. Cochrane Database of Systematic Reviews 2018;1.

[12] James EC, Dunn D, Cook AD, Clamp AR, Sydes MR. Overlap between adverse events (AEs) and serious adverse events (SAEs): a case study of a phase III cancer clinical trial. Trials 2020;21(1):1–8.

[13] Lunn DJTA, Best N, Spiegelhalter D. WinBUGS A Bayesian modelling framework: Concepts, structure, and extensibility Stat Comput 2000;10:325–37.

[14] Dias S WN, Sutton AJ, et al. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials [Internet]. London: National Institute for Health and Care Excellence (NICE); 2014 Apr. Available from: https://www.ncbi.nlm.nih.gov/books/NBK310366/.

[15] Darius N, Lakdawalla JAD, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care—a health economics approach: an ISPOR special task force report [3]. Value in Health 2018;21(2):131–9.

[16] Hoaglin DCHN, Jansen JP, Scott DA, Itzler R, Cappelleri JC, Boersma C, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health 2011 Jun;14(4).

[17] In Jae Myung. Tutorial on maximum likelihood estimation. Journal of Mathematical Psychology. 2003;47 (1):90-100.

[18] AEM J Gail Neely, Rich Jason T, Voelker Courtney CJ, Wang Eric W, Paniello Randal C, Nussenbaum Brian, Bradley Joseph P. A practical guide to understanding systematic reviews and meta-analyses. Otolaryngol – Head Neck Surg. 2010;142(1):6-14.

[19] Hespanhol L, Vallio CS, Costa LM, Saragiotto BT. Understanding and interpreting confidence and credible intervals around effect estimates. Braz J Phys Therapy 2019;23(4):290–301.

[20] Bhatnagar NLP, Jeyashree K. Multiple treatment and indirect treatment comparisons: an overview of network meta-analysis. Perspect Clin Res 2014;5(4): 154–8.

[21] Hauschild A, Grob J-J, 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. The Lancet 2012;380(9839):358–65.

[22] Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. An update on BREAK-3, a phase III, randomized trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM). Am Soc Clin Oncol 2013.

[23] Latimer NR, Abrams, KR, Amonkar MM, Stapelkamp C, Swann RS. Adjusting for the confounding effects of treatment switching - the BREAK-3 trial: dabrafenib versus dacarbazine. The Oncologist 2015;20:798–805.

[24] Flaherty KT. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367:1694–703.

[25] Flaherty K, Daud A, Weber JS, Sosman JA, Kim K, Gonzalez R, et al. Updated overall survival (OS) for BRF113220, a phase 1–2 study of dabrafenib (D) alone versus combined dabrafenib and trametinib (D+ T) in pts with BRAF V600 mutation-positive (+) metastatic melanoma (MM). American Society of. Clinical Oncology 2014.

[26] Long GVWJ, Infante JR, Kim KB, Daud A, Gonzalez R, Sosman JA et al. Overall Survival and Durable Responses in Patients With BRAF V600-Mutant Metastatic Melanoma Receiving Dabrafenib Combined With Trametinib. J Clin Oncol. 2016 Mar 10;34(8):871-8. doi: 10.1200/JCO.2015.62.9345. Epub 2016 Jan 25. Erratum in: J Clin Oncol. 2019 Feb 1;37(4):355. PMID: 26811525.

[27] Long GV, Hauschild A, Santinami M, Atkinson V, Mandala M, Chiarion-Sileni V, et al. Efficacy outcomes in the phase 3 COMBI-AD study of adjuvant dabrafenib plus trametinib vs placebo in patients with stage III BRAFV600E/K-mutant melanoma. SKIN J Cutaneous Med 2018;2(S1):S43.

[28] 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.

[29] McArthur GA. Safety and efficacy of vemurafenib in BRAFV600E and BRAFV600K mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014;15:323–32.

[30] Chapman PB, Robert C, Larkin J, Haanen JB, Ribas A, Hogg D, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. Ann Oncol 2017;28(10): 2581–7.

[31] Hauschild. An update on BRIM-3 study. EADO2016.

[32] Larkin J. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371:1867–76.

[33] Ascierto PA. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17:1248–60.

[34] Dréno B, Ribas A, Larkin J, Ascierto P, Hauschild A, Thomas L, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. Ann Oncol 2017;28(5):1137–44.

[35] A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus GDC-0973 inPreviously Untreated BRAF^600-Mutation Positive Patients with Unresectable Locally Advanced or MetastaticMelanoma [Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003008-11/results.

[36] Dreno B. Efficacy and safety of cobimetinib (C) combined with vemurafenib (V) in patients (pts) with BRAF mutation–positive metastatic melanoma: analysis from the year extended follow-up of the phase 3 coBRIM study. J Clin Oncol 2018;36(15_suppl):9522–95222018.

[37] Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay 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.

[38] Dummer R, Ascierto PA, Gogas H, Arance AM, Mandalà M, Liszkay G, et al. Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma. Journal of Clinical Oncology. 2018;36(15_suppl):9504.

[39] Gogas H, Dummer R, Ascierto PA, Arance AM, Mandala M, Liszkay G, et al. Adverse events of special interest in the phase 3 COLUMBUS study. Am Soc Clin Oncol 2018.

[40] COLUMBUS CSR. COLUMBUS clinical study report: November 2016 Data cut; 2016.

[41] Ascierto PA, Dummer R, Gogas HJ, Flaherty KT, Arance A, Mandala M, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. Eur J Can 2020;126: 33–44.

[42] Gogas HJ, Flaherty KT, Dummer R, Ascierto PA, Arance A, Mandala M, et al. Adverse events associated with encorafenib plus binimetinib in the COLUMBUS study: incidence, course and management. Eur J Can 2019;119:97–106.

[43] Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay 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.

[44] Liszkay G. Update on Overall Survival in COLUMBUS: a randomized phase III trial of encorafenib (ENCO) plus binimetinib(BINI) versus vemurafenib (VEM) or ENCO in patients with BRAF V600–mutant melanoma. J Clin Oncol 2019;37(15_suppl):9512–95122019.

[45] Gogas H. Update on overall survival in COLUMBUS: A randomized phase III trial of encorafenib (ENCO) plus binimetinib(BINI) versus vemurafenib (VEM) or ENCO in patients with BRAF V600-mutant melanoma. Journal of Clinical Oncology, 2020 38(15_suppl): p 10012-10012. 2020.

[46] Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371(20):1877–88.

[47] 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. The Lancet 2015;386(9992):444–51.

[48] Long G, Flaherty K, Stroyakovskiy D, Gogas H, Levchenko E, De Braud F, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol 2017;28(7):1631–9.

[49] A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafeniband the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable(Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma [Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-006087-49/results.

[50] Nathan P, Dummer R, Long GV, Ascierto PA, Tawbi HA, Robert C, et al. LBA43 Spartalizumab plus dabrafenib and trametinib (Sparta-DabTram) in patients (pts) with previously untreated BRAF V600–mutant unresectable or metastatic melanoma: results from the randomized part 3 of the phase III COMBI-i trial. Ann Oncol 2020;31.

[51] Robert C. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30–9.

[52] Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroyakovskiy D, et al. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D)+ trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. Ann Oncol 2016.

[53] A phase III, randomised, open-label study comparing the combination of the BRAF inhibitor, dabrafenib andthe MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) ormetastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma [Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-006088-23/results.

[54] Coupe NCP, Hategan M, Larkin J, Gore M, Gupta A, Wise A, et al. PACMEL: a phase 1 dose escalation trial of trametinib (GSK1120212) in combination with paclitaxel. Eur J Can 2015;51(3):359–66.

[55] Gutzmer R, Stroyakovskiy D, Gogas H, Robert C, Lewis K, Protsenko S, 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 3 trial. The Lancet 2020;395(10240):1835–44.

[56] Ascierto PA, Robert C, Lewis K, Gutzmer R, Stroyakovskiy D, Gogas HJ, et al. 1102P Clinical benefit in BRAFV600 mutation-positive melanoma defined by programmed death ligand 1 (PD-L1) and/or lactate dehydrogenase (LDH) status: exploratory analyses from the IMspire150 study. Ann Oncol 2020;31.

[57] Ascierto PA, Ferrucci PF, Fisher R, Del Vecchio M, Atkinson V, Schmidt H, et al. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. Nat Med 2019;25(6):941–6.

[58] Robert C. Five-year outcomes from a phase 3 METRIC study in patients with BRAF V600E/K-mutant advanced or metastatic melanoma. Eur J Can 2019;2019(109):61–9.

[59] European Union Clinical Trials Register [Internet] Identifier EudraCT Number 2010-022838-85. MEK114267, A Phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjectswith advanced or metastatic BRAF V600E/K mutation-positive melanoma [Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-022838-85/results.

[60] ClinicalTrials.gov [Internet]. National Library of Medicine (US). Identifier NCT02314143, Phase II Biomarker Study Comparing the Combination of BRAF Inhibitor Dabrafenib With MEK Inhibitor Trametinib Versus the Combination After Monotherapy With Dabrafenib or Trametinib; 2013 Sep 25 [cited 2021 Oct 21]; [about 4 screens]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02314143.

[61] Phase II biomarker study evaluating the upfront combination of BRAF inhibitor dabrafenib with MEK inhibitortrametinib versus the combination after eight weeks of monotherapy with dabrafenib or trametinib in patientswith metastatic and unresectable stage III or IV melanoma harbouring an activating BRAF mutation [Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-004577-12/results.

[62] Algazi AP, Othus M, Daud AI, Lo RS, Mehnert JM, Truong TG, et al. Continuous versus intermittent BRAF and MEK inhibition in patients with BRAF-mutated melanoma: a randomized phase 2 trial. Nat Med 2020;26(10):1564–8.

[63] Robert C. Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. . N Engl J Med 2011;364:2517–26 (011).

[64] Maio M. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol 2015;33:1191–6.

[65] Weber JS. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;2015(16):375–84.

[66] Larkin J, Minor D, D'Angelo S, Neyns B, Smylie M, Miller Jr WH, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: a randomized, controlled, open-label phase III trial. J Clin Oncol 2018;36(4):383.

[67] Robert C. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30.

[68] Robert C. Five-year survival outcomes in patients (pts) with BRAF wild-type advanced melanoma who received nivolumab (NIVO) monotherapy in the phase 3 CheckMate 066 study. ESMO2019.

[69] Ascierto PA, Long GV, Robert C, Brady B, Dutriaux C, Di Giacomo AM, et al. Survival outcomes in patients with previously untreated BRAF wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. JAMA Oncol 2019;5(2):187–94.

[70] Robert C. Five-year outcomes with nivolumab in patients with wild-type BRAF advanced melanoma. J Clin Oncol 2020;38.

[71] Larkin J. combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.

[72] Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017;377(14):1345–56.

[73] Larkin JC-S, V Overall survival with nivolumab (NIVO) and ipilimumab ((IPI) combination therapy in a phase III trial of advanced melanoma (CheckMate 067).30, e68 (2017).

[74] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2019;381(16):1535–46.

[75] Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19(11):1480–92.

[76] McDermott DF, Shah R, Gupte-Singh K, Sabater J, Luo L, Botteman M, et al. Quality-adjusted survival of nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone among treatment-naive patients with advanced melanoma: a quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis. Qual Life Res 2019;28(1):109–19.

[77] Larkin JMG, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao C, et al. 5-year survival outcomes of the CheckMate 067 phase III trial of nivolumab plus ipilimumab (NIVO+IPI) combination therapy in advanced melanoma. Ann Oncol 2019;30:v904–5.

[78] Hodi FS. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 2016;17:1558–68.

[79] Postow MA. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. . N Engl J Med 372:2006–17 (15).

[80] Lebbé CMN, Mortier L, Marquez-Rodas I, Robert C, Rutkowski P, Menzies AM, et al. Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: results from the phase IIIb/IV CheckMate 511 trial. J Clin Oncol 2019;37(11):867–75.

[81] PHASE IIIB, RANDOMIZED STUDY OF MULTIPLE ADMINISTRATION REGIMENS FOR NIVOLUMAB PLUSIPILIMUMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED UNRESECTABLE OR METASTATIC MELANOMA [Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-001941-26/results.

[82] Randomized, Phase II Study of Pembrolizumab (MK-3475) versus Chemotherapy in Patients with AdvancedMelanoma (KEYNOTE 002) [Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003030-17/results.

[83] Robert C. Pembrolizumab versus Ipilimumab in Advanced Melanoma. . N Engl J Med 372:2521–32 (015).

[84] Robert C. Pembrolizumab versus ipilimumab in advanced melanoma: post hoc 5-year results and outcomes of patients completing pembrolizumab treatment in the randomised phase 3 KEYNOTE-006 study. Lancet Oncol 2019;20(9):1239–51.

[85] Carlino MS, Long GV, Schadendorf D, Robert C, Ribas A, Richtig E, et al. Outcomes by line of therapy and programmed death ligand 1 expression in patients with advanced melanoma treated with pembrolizumab or ipilimumab in KEYNOTE-006: a randomised clinical trial. Eur J Can 2018;101:236–43.

[86] A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy ofTwo Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Patients With AdvancedMelanoma [Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-004907-10/results.

[87] Long GV. Standard-dose pembrolizumab (pembro) plus alternate-dose ipilimumab (ipi) in advanced melanoma: initialanalysis of KEYNOTE-029 cohort 1C. J Clin Oncol 2019;37(15_suppl):9514–95142019.

[88] Long GV, Dummer R, Hamid O, Gajewski TF, Caglevic C, Dalle S, et al. Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. Lancet Oncol 2019;20(8):1083–97.

[89] Long GV. Epacadostat (E) plus pembrolizumab (P) versus pembrolizumab alone in patients (pts) with unresectable ormetastatic melanoma: Results of the phase 3 ECHO-301/KEYNOTE-252 study. ASCO: J Clin Oncol 36, 2018 (suppl; abstr 108); 2018.

[90] A Phase 3 Randomized, Double-Blind, Placebo- Controlled Study of Pembrolizumab (MK-3475) inCombination With Epacadostat or Placebo in Subjects with Unresectable or Metastatic Melanoma (KEYNOTE-252 / ECHO-301)

[Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-004991-31/results.
[91] McWilliams RR, Allred JB, Slostad JA, Katipamula R, Dronca RS, Rumilla KM, et al. NCCTG N0879 (Alliance): A randomized phase 2 cooperative group trial of carboplatin, paclitaxel, and bevacizumab +/- everolimus for metastatic melanoma. Cancer 2018;124(3):537–45.
[92] ClinicalTrials.gov [Internet]. National Library of Medicine (US). Identifier NCT01152788, Phase II Study of Interleukin-21 (rIL-21) vs Dacarbazine (DTIC) in Patients With Metastatic or Recurrent Melanoma; 2010 June 28 [cited 2021 Oct 21]; [about 4 screens]. Available from: https://clinicaltrials.gov/ct2/show/NCT01152788.
[93] ClinicalTrials.gov [Internet]. National Library of Medicine (US). Identifier NCT01258855, Aldesleukin With or Without Ziv-Aflibercept in Treating Patients With Stage III-IV Melanoma That Cannot Be Removed by Surgery; 2010 Dec 10 [cited 2021 Oct 21]; [about 4 screens]. Available from: https://clinicaltrials.gov/ct2/show/NCT01258855.
[94] A Randomized Double-Blind Phase III Study of Ipilimumab Administered at 3 mg/kg vs at 10 mg/kg inSubjects with Previously Treated or Untreated Unresectable or Metastatic Melanoma [Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-004029-28/results.
[95] Ascierto PA, Del Vecchio M, Mackiewicz A, Robert C, Chiarion-Sileni V, Arance A, et al. Overall survival at 5 years of follow-up in a phase III trial comparing ipilimumab 10 mg/kg with 3 mg/kg in patients with advanced melanoma. J Immunother Can 2020;8(1).
[96] Chesney J, Puzanov I, Collichio F, Milhem MM, Hauschild A, Chen L, et al. Patterns of response with talimogene laherparepvec in combination with ipilimumab or ipilimumab alone in metastatic unresectable melanoma. Br J Can 2019;121(5):417–20.
[97] Chesney J. Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced. Unresectable Melanoma J Clin Oncol 2018;36:1658–67.
[98] Chesney JA, Puzanov I, Collichio F, Singh P, Milhem M, Glaspy J, et al. Talimogene laherparepvec (T-VEC) in combination (combo) with ipilimumab (ipi) versus ipi alone for advanced melanoma: 3-year landmark analysis of a randomized, open-label, phase II trial. Ann Oncol 2019;30:v906–7.
[99] Chesney J. Patterns of response with talimogene laherparepvec (T-VEC) in combination (combo) with ipilimumab (ipi) or ipi alone in patients (pts) with metastatic, unresectable melanoma (MEL). SMR2018.
[100] ClinicalTrials.gov [Internet]. National Library of Medicine (US). Identifier NCT02545075, A Comparative Study in Chinese Subjects With Chemotherapy Naïve Stage IV Melanoma Receiving Ipilimumab (3 mg/kg) vs. Dacarbazine; 2015 Aug 25 [cited 2021 Oct 21]; [about 4 screens]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02545075.
[101] ClinicalTrials.gov [Internet]. National Library of Medicine (US). Identifier NCT03273153, A Study of Cobimetinib Plus Atezolizumab Versus Pembrolizumab in Participants With Previously Untreated Advanced BRAFv600 Wild-Type Melanoma; 2017 Sep 1 [cited 2021 Oct 21]; [about 4 screens]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03273153.
[102] Arance AM, Gogas H, Dreno B, Flaherty KT, Demidov L, Stroyakovskiy D, et al. Combination treatment with cobimetinib (C) and atezolizumab (A) vs pembrolizumab (P) in previously untreated patients (pts) with BRAFV600 wild type (wt) advanced melanoma: Primary analysis from the phase III IMspire170 trial. Ann Oncol 2019;30.
[103] A Phase III, Open-Label, Multicenter, Two Arm, Randomized Study to Investigate the Efficacy and Safety ofCobimetinib Plus Atezolizumab Versus Pembrolizumab in Patients With Previously Untreated Advanced BRAFV600 Wild-Type Melanoma [Internet]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-004387-18/results.
[104] L. Ny MH, Nyakas M, Koivunen J, Oddershede L, Yoon M, Wang X et al. BRAF mutational status as a prognostic marker for survival in malignant melanoma: a systematic review and meta-analysis. Acta Oncologica. 2020;59(7):833–44.
[105] Excellence NIfHaC. Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Technology appraisal guidance TA4142016.
[106] Review P-COD. Cobimetinib (Cotellic) and vemurafenib (Zelboraf) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. 2016.
[107] Excellence NIfHaC. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma. Technology appraisal guidance [TA396]; 2016.
[108] Review P-COD. Dabrafenib and trametinib in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation; 2015.
[109] Excellence NIfHaC. Encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma. Technology appraisal guidance (TA562); 2019.
[110] Gogas H, Ascierto PA, Flaherty K, Arance A, Mandalà M, Liszkay G, et al. Update on overall survival in COLUMBUS: A randomized phase III trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in patients with BRAF V600-mutant melanoma. J Clin Oncol. 2020;38(15_suppl):10012-.
[111] Gutzmer RSD, Gogas H, Robert C, Lewis K, Protsenko S, Pereira RP, 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 3 trial. Lancet 2020;395(10240):1835–44.
[112] Zoratti MJDT, Levine O, Thabane L, Xie F. Network meta-analysis of therapies for previously untreated advanced BRAF-mutated melanoma. Can Treat Rev 2019;74:43–8.
[113] Franken MGLB, Gheorghe M, Uyl-de Groot CA, Haanen JBAG, van Baal PHM. A systematic literature review and network meta-analysis of effectiveness and safety outcomes in advanced melanoma. Eur J Can 2019;123:58–71.
[114] Devji TLO, Neupane B, Beyene J, Xie F. Systemic therapy for previously untreated advanced BRAF-mutated melanoma: a systematic review and network meta-analysis of randomized clinical trials. JAMA Oncol 2017;3(3):366–73.
[115] An Q, Liu Z. Comparative efficacy and safety of combination therapies for advanced melanoma: a network meta-analysis. BMC Cancer 2019;19:43.
[116] Huang Y-f, Xie W-j, Fan H-y, Du J. Comparative risks of high-grade adverse events among FDA-approved systemic therapies in advanced melanoma: systematic review and network meta-analysis. Front Oncol 2020;10(2069).