Dabrafenib plus trametinib versus nivolumab for advanced melanoma

Daniela Lahoz[a]*, Felipe Reyes[b], Camila Quirland[a]

[a] Unidad de Evaluación de Tecnologías Sanitarias, Departamento de Investigación del Cáncer, Instituto Oncológico, Fundación Arturo López Pérez, Santiago, Chile
[b] Departamento de Oncología Médica, Instituto Oncológico, Fundación Arturo López Pérez, Santiago, Chile

*** Corresponding author**
daniela.lahoz@falp.org

Citation
Lahoz D, Reyes F, Quirland C. Dabrafenib plus trametinib versus nivolumab for advanced melanoma. *Medwave* 2023;23(1):e2666

DOI
10.5867/medwave.2023.01.2666

Submission date
Sep 15, 2022
Acceptance date
Jan 20, 2023
Publication date
Feb 27, 2023

Keywords
Dabrafenib, trametinib, nivolumab, advanced melanoma, Epistemonikos, GRADE

Postal address
Fundación Arturo López Pérez Rancagua 878, Santiago, Chile

Abstract

Introduction

The incidence of cutaneous melanoma has increased worldwide over the years, and an incidence of 3 cases per 100,000 men and women is estimated in Chile. Though most of the patients are diagnosed at an early stage of the disease and have a good prognosis, advanced melanoma has poor survival results. For the treatment of melanoma, the combination of dabrafenib plus trametinib has been demonstrated to improve the outcome versus dabrafenib alone, but only indirect evidence is available for its efficacy and safety compared with immunotherapy, like nivolumab. The aim of this study is to review the available evidence to report results of efficacy and safety of dabrafenib plus trametinib in comparison with nivolumab in metastatic melanoma.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews selected, reanalyzed data of primary studies, and generated a summary of the findings table using the GRADE approach.

Results and conclusions

We identified five systematic reviews, including seven studies overall that included one intervention of our interest, of which all were randomized trials. We only found indirect evidence comparing dabrafenib plus trametinib versus nivolumab that came from Network Meta-Analyses. We concluded that it is not possible to decide if dabrafenib plus trametinib is a better strategy for advanced melanoma treatment than nivolumab because the certainty of the evidence is very low for efficacy and safety outcomes.

Main messages

- It is not possible to conclude if dabrafenib plus trametinib versus nivolumab increases the overall survival because the certainty of the evidence is very low.
- It is not possible to conclude if dabrafenib plus trametinib versus nivolumab increase the progression-free survival because the certainty of the evidence is very low.
- It is not possible to conclude if nivolumab increases the response to the treatment and has less toxicity compared to dabrafenib plus trametinib because the certainty of the evidence is very low.

Problem

Melanoma is a type of cancer that develops in skin or mucosal cells as a result of a series of abnormalities in the genetic melanocyte pathway. The most common mutation in melanoma is on the BRAF gene promoting growth deregulation of melanocytes [1].

The incidence of cutaneous melanoma has increased worldwide over the years. In Chile, an incidence of 3 cases per 100,000 men and women has been estimated, which is lower than the worldwide incidence of 3.4 per 100,000 men and women [2]. The melanoma mortality in Chile is greater than mortality worldwide (0.96 in 100,000 versus 0.56 in 100,000) [2]. Whilst most patients are diagnosed at an early stage of the disease and with a good prognosis, patients with advanced melanoma (unresectable stage III and metastatic stage IV) have poor survival results [3].

Multiple innovative therapies are available for the treatment of advanced melanoma, like target therapies and checkpoint inhibitors. Target therapies are focused in BRAF mutation, which is the most common oncogene mutation in melanoma, occurring in 10-30% of these primary tumors [1]. Among the former, dabrafenib plus trametinib, a BRAF inhibitor combined with a MEK inhibitor, has been shown to improve survival and delay the disease progression when compared with dabrafenib alone [4,5]. Within checkpoint inhibitor, Nivolumab is an anti-PD-1, which has been shown to be an effective treatment for melanoma in monotherapy or combined with ipilimumab, a CTLA-4 inhibitor [6–8]. In Chile, Nivolumab is available in public health system, but the other therapies are not funded and are only available for out-of-pocket expenses.

There is no consensus about the best treatment for advanced melanoma. There are no published studies directly comparing the efficacy and safety of treatments with the combination of BRAF/MEK inhibitors versus PD-1 inhibitors. In this review, we show the results of different published network meta-analyses that included the combination of dabrafenib plus trametinib versus nivolumab to determine which treatment has better results in terms of efficacy and safety for patients with advanced melanoma.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), a summary of findings table following the GRADE approach, and a table of other considerations for decision-making.

What is the evidence	We identified five systematic reviews [3,9–12] including seven primary studies [4–8,13,14] reported in seventeen references [4–8,13–24] that included one of the interventions of interest. All the studies were randomized trials.
See evidence matrix in Epistemonikos later	We did not find studies directly comparing dabrafenib plus trametinib versus nivolumab. Therefore, this analysis included network meta-analyses with indirect comparisons. Three systematic reviews [3,10,11] were bayesian network meta-analyses, and two [9,12] were frequentist network meta-analysis. the median follow-up for the trials including the interventions of interest in the network meta-analysis fluctuates between 5.3 and 46.9 months.

What types of patients were included*	All the studies included adults with advanced cutaneous melanoma (unresectable stage III and metastatic stage IV). Five studies [4,6,7,13,14] included patients with no previous treatment. One study [8] included patients who progressed to one previous treatment, and one study [5] included patients with no line of treatment restriction. Four studies [4,5,13,14] included only patients with BRAF mutation. Two studies [6,8] included patients independently of BRAF mutation status, and one [7] included only patients with BRAF wild-type.
What types of interventions were included*	Two studies [4,5] compared dabrafenib plus trametinib versus dabrafenib alone, one study [13] against vemurafenib, and one study against pembrolizumab plus dabrafenib plus trametinib [14]. One study [7] compared nivolumab against dacarbazine, and another study against chemotherapy (dacarbazine plus carboplatin or paclitaxel plus carboplatin) [8]. The last study [6] was a three-arm study and compared nivolumab plus ipilimumab versus, either nivolumab or ipilimumab alone. All studies are part of four network meta-analyses, that indirectly compared the treatments under analysis.
What types of outcomes were measured	The studies reported multiples outcomes, which were aggregated into a systematic review and defined as follows: • Overall survival was defined as the risk of dying from any given cause. • Progression-free survival as the risk of progression using one of the interventions. • Response to the treatment as the probability of having a complete response or partial response to the treatment with one intervention. • Toxicity as the risk of presenting a severe or grade III/IV, adverse event during the treatment with one of the interventions. • Health-related quality of life as a subjective and multidimensional concept that accounts for how an individual perceives their health.

*The information about primary studies is not extracted directly from primary studies but from identified systematic reviews unless otherwise stated.

Summary of findings

The assessment of efficacy and safety of treatment with dabrafenib plus trametinib compared with nivolumab in patients with advanced melanoma is based on seven randomized trials [4–8,13,14]. Regarding these trials, five systematic reviews [3,9–12] performed an indirect comparison using network meta-analysis methods. Three [3,10,11] were bayesian analyses and two [9,12] were frequentist analyses.

Two studies (531 patients) [4,5] evaluated the combination of dabrafenib with trametinib against dabrafenib, one study (704 patients) [13] versus vemurafenib, and one study (120 patients) [14] against a triple combination: pembrolizumab plus dabrafenib plus trametinib.

One study (418 patients) [7] compared nivolumab versus dacarbazine. One study (405 patients) [8] evaluated nivolumab against chemotherapy (dacarbazine/carboplatin and paclitaxel/carboplatin). One study (901 patients) [6] compared the combination of nivolumab and ipilimumab versus nivolumab or ipilimumab alone.

Only three randomized trials [7],[18],[22] included patients from Chile, but is not possible to know their contribution to the intention-to-treat population of the studies.

Because of the structure of a network meta-analysis, no systematic review allowed for the data extraction to be used in a new meta-analysis, therefore, the outcomes were presented as a narrative synthesis. The summary of the results is as follows:

- It is not possible to establish with clarity if the combination of dabrafenib and trametinib increases the overall survival in patients with advanced melanoma compared to nivolumab because the certainty of evidence has been evaluated as very low.
- It is not possible to establish with clarity if the combination of dabrafenib and trametinib increases progression-free survival in patients with advanced melanoma compared to nivolumab because the certainty of evidence has been evaluated as very low.
- It is not possible to establish with clarity if nivolumab increases the response to treatment in patients with advanced melanoma compared with dabrafenib plus trametinib because the certainty of evidence has been evaluated as very low.
- It is not possible to establish with clarity if nivolumab is associated with fewer severe or grade III/IV adverse events in patients with advanced melanoma compared to dabrafenib plus trametinib because the certainty of evidence has been evaluated as very low.
- We did not find studies that evaluated the quality of life in patients with advanced melanoma.

Dabrafenib plus Trametinib versus Nivolumab in advanced melanoma	
Patients	**Patients with advanced melanoma**

Dabrafenib plus Trametinib versus Nivolumab in advanced melanoma		
Intervention	**Dabrafenib plus trametinib**	
Comparison	**Nivolumab**	
Outcome	**Absolute Effect**	**Certainty of evidence (GRADE)**
Overall survival	The information compiled in four systematic reviews is contradictory, and all results have no statistical significance. One review [9] shows that the combination of dabrafenib and trametinib could increase the overall survival in patients (HR 0.87; CI 95% 0.45 - 1.68) when compared with nivolumab, the same as a second review [10] (HR 0.60; CI 95% 0.03 - 10.95). One review [11] shows that the combination of dabrafenib and trametinib could decrease the overall survival of patients (HR 1.21; CI95% 0.66 - 2.13) compared to nivolumab, the same result that four reviews [3] (HR 0.86; CI95% 0.57 - 1.24 in favor to nivolumab)	⨁◯◯◯[1,2,3] Very Low
Progression-free survival	Three reviews show that dabrafenib plus trametinib increase the progression-free survival of patients compared to nivolumab alone. (HR 0.33; CI 95% 0.19 - 0.58 [9]; HR 0.42; CI95% 0.20 - 0.77 [11]; and HR 2.00; CI95% 1.43-2.75 in favor of dabrafenib plus trametinib [3])	⨁◯◯◯[1,3] Very Low
Response to the treatment	One review [9] shows that nivolumab increases the proportion of patients that respond to the treatment (RR 3.08; CI 95% 1.47 - 6.45) compared to dabrafenib plus trametinib, and this result matches another review [10] (OR 5.96; CI 95% 1.88 - 29.25)	⨁◯◯◯[1,2,3] Very Low
Toxicity	Two reviews show that dabrafenib plus trametinib has more serious adverse events compared to nivolumab (RR 1.69; CI 95% 0.45 – 6.59 [11] and RR 1.60; CI 95% 1.04 – 2.49 [12]). Two reviews show that dabrafenib plus trametinib has more grade III or IV adverse events (RR 2.17; CI 95% 1.27 – 3.73 [9] and RR 0.59; CI95% 0.35 - 0.93 in favor of nivolumab [3]).	⨁◯◯◯[1,3] Very Low
Health-related quality of Life	In one review [11], the authors stated that the health-related quality of life could not be reported because the network meta-analysis was not performed due to the poor available information. The other reviews [3,9,10,14] did not evaluate this outcome.	--

Margin of error: 95% confidence interval (CI).
HR: Hazard Ratio.
OR: Odds Ratio
RR: Risk Ratio
GRADE: Evidence grades of the GRADE Working Group (see later).
[1] The certainty of the evidence was downgraded by one level for risk of bias due to some trials including incomplete data, or other biases like crossover, in their network meta-analysis.
[2] The certainty of the evidence was downgraded by one level for the imprecision of the results due to the margin of error, going through the no-effect threshold
[3] The certainty of the evidence was downgraded by two levels for indirect evidence due to the results coming from a network meta-analysis. ,

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate
⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different: a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence in this summary applies to adults with advanced melanoma (non-resectable stage III and metastatic stage IV).

About the outcomes included in this summary

The outcomes included in this review are the most clinically relevant and most reported by the included systematic reviews.

The overall survival represents the risk of dying from any given cause and it is the most clinically relevant outcome in patients with advanced melanoma.

Both progression-free survival and the proportion of patients that respond to the treatment, are efficacy outcomes and drivers of clinical treatment decisions.

The adverse events to treatments are relevant because they impact directly the quality of life and treatment adherence.

Balance between benefits and risks, and certainty of the evidence

The combination of dabrafenib and trametinib has been demonstrated to be effective against vemurafenib or dabrafenib alone, and it has been demonstrated to be effective against chemotherapy. Nivolumab has also been demonstrated to be effective against chemotherapy. However, when comparing the two interventions, it is not possible to determine which treatment is better for advanced melanoma in terms of overall survival, disease-progression, response to treatment, and toxicity, because the certainty of the evidence is very low.

An increase in the certainty of the evidence for this recommendation could occur by the development of a study that evaluates the two interventions directly, because currently there is only indirect evidence published through network meta-analyses.

Resource considerations

One of the systematic reviews had results of cost-effectiveness. Pike et al [11] made a network meta-analysis and carried out a cost-effectiveness study of seven new drugs for the treatment of advanced melanoma, from the Norwegian health system perspective. The results of the aforementioned study showed that nivolumab could be the most cost-effective strategy among the available treatments for advanced melanoma in Norway, but exceeding the willingness-to-pay for this health system.

For this study, the main source of uncertainty was the limited information available for each treatment, and it could be improved if it would exist direct evidence for the evaluated comparators.

What would patients and their doctors think about this intervention

Currently, for the treatment of patients with advanced melanoma, most clinicians use immunotherapy with checkpoint inhibitors as a first option, due to its overall survival advantage and safety profile. For patients with BRAF mutation and a high burden of disease, or a rapidly progressing disease, most doctors prefer dabrafenib plus trametinib, due to its benefits in response rate, progression-free survival and overall survival.

Given the very low certainty of the evidence, it is unlikely that clinicians change their common practice with the results of this review, but it could shed some light on the effects and benefits of target therapies.

Differences between this summary and other sources

One systematic review [3] concluded that anti-PD-1/PD-L1 plus anti-CTLA-4 treatment is the best strategy to treat advanced melanoma regardless of its BRAF mutation status. Two systematic reviews [3],[9] concluded that dabrafenib plus trametinib could be the most effective alternative against advanced melanoma in patients with BRAF mutation. One systematic review [10] concluded that dabrafenib plus trametinib could have the most short-term efficacy among the combined alternatives. One systematic review [11] concluded that combined therapies have similar effectiveness to immunotherapy with PD-1 checkpoint inhibitors, and the last systematic review [12] concluded that immunotherapy, like nivolumab, has better acceptability than most target therapies in severe adverse events.

The results of the systematic reviews agree with the recommendation of international medical societies. The European Society for Medical Oncology (ESMO) [25] recommends PD-1 inhibitors, such as nivolumab, as a "standard of care" in first-line treatment against advanced melanoma, except in patients with BRAF mutations. For those patients, the ESMO recommends the treatment with BRAF/MEK inhibitors such as dabrafenib plus trametinib. This recommendation coincides with that of the National Comprehensive Cancer Network (NCCN) [26], asserting with their highest recommendation grade the use of checkpoint inhibitors as a first-line of treatment in advanced melanoma, and the use of target therapies (like BRAF/MEK) when patients have a BRAF V600 mutation.

All systematic reviews [3],[9],[10],[11],[12] included in this review declare the necessity of more evidence to make direct and indirect analyses, and to be able to increase the certainty of the evidence. This agrees with our results indicating that it is

not possible to draw a conclusion because the certainty of the evidence is very low.

Could this evidence change in the future?

Owing to the uncertainty in the evidence, it is likely that the results of this review could change in the future due to the follow-up of current studies or because new studies may be available at some point.

Actually, five studies included in our review [4],[5],[6],[8],[13] have recently published updated results in clinical outcomes [27],[28],[29],[30],[31]. These updates were not included in the systematic reviews. Two of them [28],[29] were about nivolumab and the other three [29],[30],[31] were about dabrafenib plus trametinib.

Three studies [6],[7],[8] included in this review are currently active, and, thus, might contribute with new evidence in future.

We searched in PROSPERO for new systematics reviews. The search resulted in five new network meta-analysis [32],[33],[34],[35],[36] in development including our comparison of interest. The search in clinicaltrials.gov showed three studies of interest: one study in the stage of recruitment [37] including dabrafenib plus trametinib, and two studies in active stage but with no publications yet, one using nivolumab [38] and the other using a new treatment combination of nivolumab plus dabrafenib plus trametinib [39].

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and presented it as a matrix of evidence.

Follow the link to access the **interactive version** (Figure 1): **Dabrafenib plus trametinib versus nivolumab for advanced melanoma**.

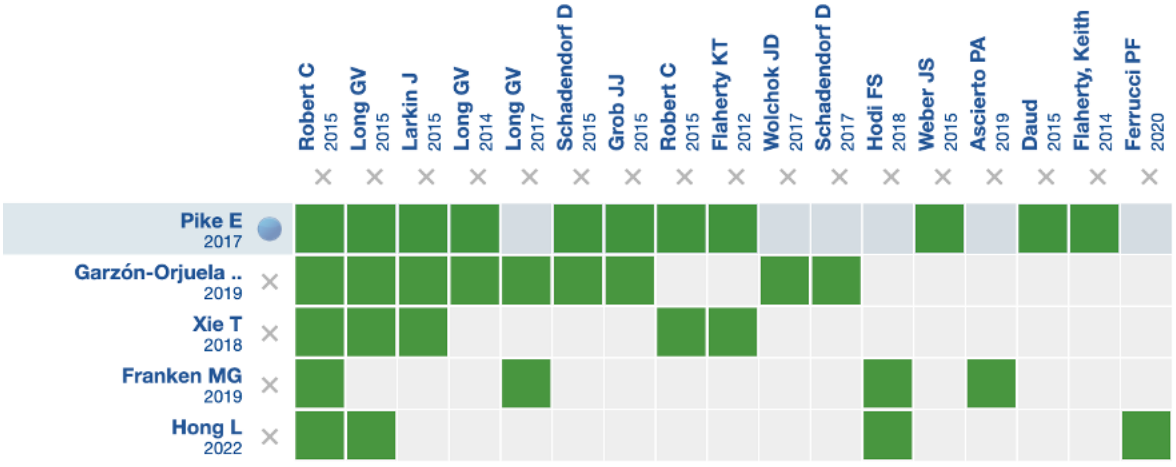
The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence to update the summary, and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save matrices and receive automated notifications any time potentially relevant new evidence appears.

This article is part of the Epistemonikos Evidence Synthesis project. It was elaborated with a pre-established methodology, following rigorous methodological standards and an internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and the analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

Figure 1.



Notes

Contributor roles

Conceptualization: DL, CQ. DL: Formal analysis, data curation, writing, visualization: Investigation: DL, FR, CQ: Supervision. DL: Project administration.

Potential conflicts of interest

The authors do not have relevant interests to declare.

Provenance and peer review

Not commissioned. Externally peer-reviewed by two reviewers, double-blind.

Provenance and peer review

Not commissioned. Externally peer-reviewed by two reviewers, double-blind.

References

1. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. Lancet. 2005;365: 687–701. https://doi.org/10.1016/S0140-6736(05)17951-3
2. World Health Organization International Agency for Research on Cancer (IARC). GLOBOCAN 2022: estimated cancer incidence, mortality and prevalence worldwide in. 2020. https://gco.iarc.fr/today
3. Franken MG, Leeneman B, 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 Cancer. 2019;123: 58–71. https://doi.org/10.1016/j.ejca.2019.08.032
4. 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: 444–51. https://doi.org/10.1016/S0140-6736(15)60898-4
5. 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: 1694–703. https://doi.org/10.1056/NEJMoa1210093
6. Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373: 1270–1. https://doi.org/10.1056/NEJMc1509660
7. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372: 320–30. https://doi.org/10.1056/NEJMoa1412082
8. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. 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;16: 375–84. https://doi.org/10.1016/S1470-2045(15)70076-8
9. Garzón-Orjuela N, Prieto-Pinto L, Lasalvia P, Herrera D, Castrillón J, González-Bravo D, et al. Efficacy and safety of dabrafenib-trametinib in the treatment of unresectable advanced/metastatic melanoma with BRAF-V600 mutation: A systematic review and network meta-analysis. Dermatol Ther. 2020;33. https://doi.org/10.1111/dth.13145
10. Xie T, Huang CY, Kang X, Luo JS, Qin XM, Han F. A Network Meta-Analysis of Short and Long-Term Efficacy of Targeted Therapy With Single or Double-Drug Regimens in the Treatment of Stage III/IV Malignant Melanoma Based on 16 Randomized Controlled Trials. J Cell Biochem. 2018;119: 640–649. https://doi.org/10.1002/jcb.26225
11. Pike E, Hamidi V, Saeterdal I, Odgaard-Jensen J, Klemp M. Multiple treatment comparison of seven new drugs for patients with advanced malignant melanoma: a systematic review and health economic decision model in a Norwegian setting. BMJ Open. 2017;7. https://doi.org/10.1136/bmjopen-2016-014880
12. Hong L, Huang P, Zheng X, Ye X, Zhao H, Wang J, et al. Acceptability of Drugs in the Treatment of Unresectable/Metastatic BRAF V600-Mutant Melanoma: A Systematic Review and Network Meta-Analysis. Front Oncol. 2022;12: 865656. https://doi.org/10.3389/fonc.2022.865656
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. 2015;372: 30–9. https://doi.org/10.1056/NEJMoa1412690
14. Ferrucci PF, Di Giacomo AM, Del Vecchio M, Atkinson V, Schmidt H, Schachter J, et al. KEYNOTE-022 part 3: a randomized, double-blind, phase 2 study of pembrolizumab, dabrafenib, and trametinib in *BRAF*-mutant melanoma. J Immunother Cancer. 2020;8. https://doi.org/10.1136/jitc-2020-001806
15. 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: 1345–1356. https://doi.org/10.1056/NEJMoa1709684
16. Schadendorf D, Larkin J, Wolchok J, Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Health-related quality of life results from the phase III CheckMate 067 study. Eur J Cancer. 2017;82: 80–91. https://doi.org/10.1016/j.ejca.2017.05.031
17. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, 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: 1480–1492. https://doi.org/10.1016/S1470-2045(18)30700-9
18. 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: 187–194. https://doi.org/10.1001/jamaoncol.2018.4514
19. 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: 1877–88. https://doi.org/10.1056/NEJMoa1406037
20. 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 BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol. 2017;28: 1631–1639. https://doi.org/10.1093/annonc/mdx176
21. Schadendorf D, Amonkar MM, Stroyakovskiy D, Levchenko E, Gogas H, de Braud F, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. Eur J Cancer. 2015;51: 833–40. https://doi.org/10.1016/j.ejca.2015.03.004
22. Daud A, Weber JS, Sosman JA, Kim K, Gonzalez R, Hamid O, et al. Updated overall survival (OS) results for BRF113220, a phase I–II study of dabrafenib alone versus combined dabrafenib

and trametinib in patients with *BRAF* V600 metastatic melanoma (MM). JCO. 2015;33: 9036–9036. https://doi.org/10.1200/jco.2015.33.15_suppl.9036
23. 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). JCO. 2014;32: 9010–9010. https://doi.org/10.1200/jco.2014.32.15_suppl.9010
24. 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: 1389–98. https://doi.org/10.1016/S1470-2045(15)00087-X
25. Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019;30: 1884–1901. https://doi.org/10.1093/annonc/mdz411
26. National Comprehensive Cancer Network. Cutaneous Melanoma. 2020. https://www.nccn.org/
27. 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: 1535–1546. https://doi.org/10.1056/NEJMoa1910836
28. Larkin J, Minor D, D'Angelo S, Neyns B, Smylie M, Miller 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: 383–390. https://doi.org/10.1200/JCO.2016.71.8023
29. 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: 626–636. https://doi.org/10.1056/NEJMoa1904059
30. Long GV, Eroglu Z, Infante J, Patel S, Daud A, Johnson DB, et al. Long-Term Outcomes in Patients With BRAF V600-Mutant Metastatic Melanoma Who Received Dabrafenib Combined With Trametinib. J Clin Oncol. 2018;36: 667–673. https://doi.org/10.1200/JCO.2017.74.1025
31. 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: 626–636. https://doi.org/10.1056/NEJMoa1904059
32. Guiqing D. Comparative efficacy and safety of immunotherapy and combined targeted therapy for advanced melanoma: a network meta-analysis. PROSPERO. 2020.
33. Donohue M, Turkstra E, Gordon L, Elliott T. Comparative efficacy and safety of medications for advanced melanoma: a systematic review and network meta-analysis. PROSPERO. 2015.
34. 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. https://doi.org/10.3389/fonc.2020.571135
35. Boutros A, Tanda ET, Croce E, Catalano F, Ceppi M, Bruzzone M, et al. Activity and Safety of First-Line Treatments for Advanced Melanoma: A Network Meta-Analysis. SSRN Journal. 2022. https://doi.org/10.2139/ssrn.4257624
36. Pasquali S, Mocellin S. Novel therapies for patients with metastatic melanoma: a network meta-analysis. PROSPERO. 2016.
37. Straume O. BGB324 in Combination With Pembrolizumab or Dabrafenib/Trametinib in Metastatic Melanoma. NCT02872259.
38. Queirolo P. To evaluate the efficacy beyond progression of Vemurafenib+Cobimetinib associated with local treatment compared to second-line treatment in patients with BRAFV600+ metastatic melanoma in focal progression with first-line Vemurafenib + Cobimetinib. NCT03514901.
39. Tawbi H. Nivolumab and Trametinib with or without Dabrafenib in treating patients with BRAF mutated or wild-type metastatic stage III-IV melanoma that cannot be removed by surgery. NCT02910700.

Dabrafenib más trametinib versus nivolumab para el tratamiento del melanoma avanzado

Resumen

Introducción

La incidencia de melanoma cutáneo ha aumentado a nivel mundial con el paso de los años, estimándose en Chile una incidencia de 3 casos por 100.000 hombres y mujeres. Aunque la mayoría de los pacientes son diagnosticados en etapas tempranas de la enfermedad y tienen un buen pronóstico, el melanoma avanzado tiene malos resultados de sobrevida. Para el tratamiento del melanoma, se ha demostrado que la combinación de dabrafenib más trametinib mejora el resultado frente a dabrafenib solo, pero sólo se dispone de evidencia indirecta sobre su eficacia y seguridad en comparación con la inmunoterapia, como nivolumab.

Métodos

Se realizaron búsquedas en Epistemonikos, la mayor base de datos de revisiones sistemáticas en salud, que se mantiene mediante el cribado de múltiples fuentes de información, incluyendo MEDLINE, EMBASE, Cochrane, entre otras. Se extrajeron los datos de las revisiones sistemáticas seleccionadas, se reanalizaron los datos de los estudios primarios y se generó una tabla de resumen de los hallazgos utilizando el enfoque GRADE.

Resultados y conclusiones

Se identificaron cinco revisiones sistemáticas, incluyendo siete estudios en total que incluían una intervención de nuestro interés, de los cuales todos eran ensayos aleatorizados. Se concluyó que no es posible decidir si dabrafenib más trametinib es una mejor estrategia para el tratamiento del melanoma avanzado que nivolumab porque la certeza de las pruebas es muy baja para los resultados de eficacia y seguridad.