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REVIEW ARTICLE

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Systemic treatments for advanced cutaneous melanoma — Cochrane Systematic Review 2018

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ABSTRACT

The results of the systematic review have the leading place in the hierarchy of clinical data reliability. They allow to extend the conclusions from individual studies to a larger population, minimizing the risk of systematic errors. Meta-analysis is the final step of the review of enough homogenous primary research that allow to quantitatively synthesize their results. In 2018, the Cochrane systematic review and data meta-analysis which assessed the effects of various systemic treatments of metastatic cutaneous melanoma were published. All relevant trials published up to October 2017 were included. This article introduces the assumptions of the meta-analysis and presents its results regarding the effectiveness of the most important systemic treatments of melanoma.

Key words: Cochrane meta-analysis, metastatic melanoma, anti-BRAF/anti-MEK therapy, immunotherapy

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Literature review and meta-analysis — theoretical basis

A systematic review is an essential part of evidence-based medicine (EBM). It is a type of literature review that focuses on a single issue (defined research problem) and identifies, chooses, and evaluates appropriate primary sources (primary research data) that focus on the issue. Included studies (preferably randomised controlled trials, RCTs) should address the same research problem and evaluate similar populations, interventions, study end points, and variables. In further steps, complete collected data are analysed and summarised as results that allow proper conclusions to be drawn. Results of systematic reviews are ranked highly in the hierarchy of clinical data, due to the rigorous methodological standards that facilitate extrapolation of a single trial to a broader population, minimising the risk of systematic mistakes (known as biases). Meta-analysis could be the final step of a systematic review, if it includes sufficiently homogenous trials that allow quantitative synthesis.

Depending on the assessed variables, the results of meta-analysis can be presented using different parameters. Most commonly, relative risk (RR) or hazard ratio (HR) are calculated. Relative risk is a quotient of a probability of defined end point occurrence in an experimental group (which receives assessed intervention) and corresponding probability in a control group. An RR value of more than one means an increase in probability of end point occurrence in an experimental group. When interpreting, HR is analogical to RR, with a difference based on an analysis of survival curves or tables. HR defines the relative probability of event occurrence in evaluated groups in a defined period of time, incorporating also incomplete observations (Kaplan-Meier analysis). For a designated RR and HR, the confidence interval (CI) is calculated. It defines how precise — or rather how imprecise — each estimation is. Usually a 95% CI is used, which determines an interval in which with a 95% certainty (synonym — confidence) a true value of a parameter, in a specific population, can be found.

The homogeneity of an analysed trial is a vital element that influences the reliability of a systematic

review. Therefore, it is crucial to define the degree to which each study contributes to the final results of the meta-analysis and the degree of homogeneity between studies. The heterogeneity of studies is assessed with the χ^2 test. If the p result in the χ^2 test is determined to be less than 0.1, then the differences between studies are deemed as not random. The other parameter used to evaluate homogeneity is I^2, which determines the percentage variation for the calculated effect due to heterogeneity and not due to sample bias [1–3].

The GRADE system (Grading of Recommendations Assessment, Development, and Evaluation) is often used to determine quality of evidence. The basic requirement for good quality data is attributed to their source in a randomised controlled trial. Additional factors can lead to both decrease (including factors such as limitations in trial design, inconsistency in results, imprecision in calculated results) or increase (such as large effect of intervention on evaluated end point) in data grading. As a result, data can be categorised as: high quality of evidence (in which further research probably will not change the assumption regarding accuracy of intervention assessment), moderate quality of evidence (further research might impact the assumption regarding accuracy of intervention assessment and might change the outcomes of assessment), low quality of evidence (further studies would probably impact the assumption regarding the accuracy of intervention assessment and change the outcomes of the assessment), and very low quality of evidence, in which every intervention assessment is questionable [4].

Cochrane

Cochrane was established in 1993 as an international not-for-profit organisation that works as a network of collaborators engaged in health care. One of its main interests is the promotion of undertaking medical decisions based on reliable scientific data (EBM), through Cochrane systematic reviews prepared by collaborators. Reviews published in the Cochrane Library assess, with strictly defined criteria, the effectiveness of therapeutic, prophylactic, and diagnostic interventions [5].

Cochrane meta-analysis of trials evaluating systemic treatment for metastatic melanoma

In 2018 a Cochrane meta-analysis evaluating systemic treatment for metastatic skin melanoma was published [6]. Two independent authors collected data published until October 2017 in the Cochrane registry, CENTRAL, MEDLINE, Embase, and LILACS databases or reported during ASCO meetings and in randomised clinical trial registries. The acquired results were evaluated by a third independent author. Overall, the authors identified 122 RCTs that included 28,561 patients with unresectable skin melanoma and metastases in lymph nodes or distant metastases (including brain metastases). The primary end points of the meta-analysis were: overall survival (OS), defined as the time between randomisation and death from any cause featured as HR (105 RCTs); progression-free survival (PFS), defined as the time between randomisation and local or distant disease recurrence (also featured as HR) (89 RCTs); and toxicity, defined as an occurrence of grade 3 (G3) or worse adverse event according to WHO classification (featured as RR) (118 RCTs). Additional analysis evaluated also: overall response rate (ORR), complete or partial according to WHO or RECIST criteria (effect featured as RR) (117 RCTs); quality of life in a descriptive manner due to the lack of a dedicated scale (12 RCTs); and cost effectiveness expressed as QUALY (1 RCT). From 122 RCTs, the final analysis included 83 trials, 77% of which were phase III, 41% phase II, one was phase I, and 4% of trials were combined phases.

Data inconsistency was assessed as high when I^2 was more than 50%, moderate when I^2 was between 25 and 50%, and low when I^2 was lower than 25%. Additional heterogeneity evaluation was performed using the χ^2 test, with statistically important heterogeneity if a p value of χ^2 was less than 0.1 and/or I^2 was more than 50%.

The described analysis included evidence grading according to GRADE criteria. The quality of most of the data included in direct comparison of OS, PFS, and ORR were high or medium [decrease of data quality was mostly due to heterogeneity of results (inconsistency) and imprecise effect assessment (imprecision)]. Data regarding toxicity was mostly moderate and low quality. In indirect analysis, data quality was conditionally decreased to moderate due to the indirect character of the comparison.

Different systemic therapies developed to treat advanced melanoma during a period of several years were evaluated — therapeutic modalities included were: chemotherapy, both as a monotherapy and in combined regimens; chemotherapy combined with interferon alpha and/or IL-2 (biochemotherapy); chemotherapy combined with antiangiogenic agents; immunotherapy directed at checkpoint inhibitors; as well as molecularly targeted agents and other less commonly used forms of systemic therapy. Conclusions were drawn based on both direct and indirect group comparisons.

Our article summarises the results of meta-analysis concerning the most important treatment modalities only.

Options of systemic treatment for advanced skin melanoma assessed over the years in different clinical trials — meta-analysis based on direct comparisons

Chemotherapy — monotherapy and combined regimens

For nearly 30 years, until 2011, dacarbazine was the basic chemotherapeutic option for advanced, unresectable melanoma. Dacarbazine-based multidrug regimens failed to provide OS prolongation compared to monotherapy, with a limited increase in overall response rate reported only in a few reports. This established dacarbazine monotherapy as a standard of care for many years and a basic comparator in further clinical trials.

The Cochrane meta-analysis confirmed the lack of benefit from multidrug regimens (mostly combinations of dacarbazine with cisplatin, carmustine, lomustine, or epirubicin) in terms of PFS and OS over dacarbazine monotherapy. An increase of overall response rate was confirmed, but at the cost of increased toxicity (Table 1) [6].

Immunotherapy directed at immune checkpoints

Because anti-CTLA-4 antibodies were shown to improve OS in previously treated patients with advanced melanoma in 2010, the so-called "immunotherapy era" began, with several subsequent immunomodulating drugs and their combinations recently developed.

Anti-CTLA-4 antibodies plus chemotherapy *vs.* chemotherapy alone

Ipilimumab, an anti-CTLA-4 antibody, is the first immunomodulating drug that improved OS in the first line of melanoma treatment. A clinical trial comparing a combination of ipilimumab and dacarbazine with dacarbazine and placebo in previously untreated patients with advanced melanoma showed OS of 11.2 and 9.1 months, respectively, and three-year survival of 20.8% and 12.2% [7]. Assessing the combination of anti-CTLA-4 antibodies and chemotherapy, Cochrane evaluated two trials: one with ipilimumab and dacarbazine and the second with tremelimumab combined with either dacarbazine or temozolomide [7, 8]. Anti-CTLA-4 antibody and chemotherapy as first-line treatment probably improve PFS (medium quality of evidence) compared to chemotherapy alone, with a significantly increased toxicity (medium quality of evidence), resulting in a lack of statistically significant improvement in OS. No difference was also seen regarding ORR (Table 2) [6].

Anti-PD-1 antibodies *vs.* chemotherapy

The most important RCTs comparing anti-PD-1 antibodies to different chemotherapy regimens (dacarbazine, paclitaxel with carboplatin, temozolomide) were the CheckMate 037 and 066 trials (assessing nivolumab) and Keynote 006 trial (assessing pembrolizumab). Depending on the trial, patients were previously untreated or treated with ipilimumab, anti-BRAF, or anti-BRAF anti-MEK therapy. Overall survival was a primary end point only in a one study, therefore it was impossible to perform meta-analysis regarding OS [6, 9].

Combined analysis lead to the conclusion that anti-PD-1 agents improved ORR compared to chemotherapy. Probably it also improved PFS and was associated with less toxicity (medium and low quality of evidence, respectively) (Table 3) [6].

Anti-PD-1 antibodies *vs.* anti-CTLA-4 antibodies

Two trials included in the meta-analysis compared anti-PD-1 and anti-CTLA-4 treatment (pembrolizumab *vs.* ipilimumab and nivolumab *vs.* ipilimumab). Only one trial, CheckMate 067, included OS as the primary

Table 1. Comparison of multidrug chemotherapy regimens (experimental group) with single-drug chemotherapy (comparator group)

	N RCTs	N exper.	N comp.	HR/RR	95% CI	Data homogeneity	Quality of evidence	Conclusion
OS	6	312	282	HR = 0.99	0.85–1.16	p = 0.57; I^2 = 0%	High	NS
PFS	5	219	179	HR = 1.07	0.91–1.25	p = 0.93; I^2 = 0%	High	NS
Toxicity	3	313	201	RR = 1.97	1.44–2.71	I^2 = 42%	Medium	Significantly higher in experimental group
ORR	14	1124	761	RR = 1.27	1.02–1.58	p = 0.61; I^2 = 0%	Medium	Significantly higher in experimental group
Quality of life	No data							

N — number; exper. — experimental group; comp. — comparator group; NS — difference not significant; RCT — randomised clinical trial; RR — relative risk; HR — hazard ratio; ORR — overall response rate; PFS — progression-free survival; OS — overall survival

Table 2. Comparison of anti-CTLA-4 and chemotherapy (experimental group) with chemotherapy alone (comparator)

	N RCTs	N exper.	N comp.	HR/RR	95% CI	Data homogeneity	Quality of evidence	Conclusion
OS	2	578	579	HR = 0.81	0.65–1.01	p = 0.08; I^2 = 67%	Low	NS
PFS	1	250	252	HR = 0.76	0.63–0.92	NA	Medium	Significantly longer in experimental group
Toxicity	2	578	579	RR = 1.69	1.19–2.42	p = 0.01; I^2 = 85%	Medium	Significantly higher in experimental group
ORR	2	578	579	RR = 1.28	0.92–1.77	p = 0.41; I^2 = 0%	Medium	NS
Increase in OS corrected for quality of life	1.5 months, 2.36 months, and 3.28 months after, respectively, 2, 3, and 4 years							

NA — not assessed; N — number; exper. — experimental group; comp. — comparator group; RCT — randomised clinical trial; RR — relative risk; HR — hazard ratio; ORR — overall response rate; PFS — progression-free survival; OS — overall survival

Table 3. Comparison of anti-PD-1 antibodies (experimental group) with chemotherapy alone (comparator)

	N RCTs	N exper.	N comp.	HR/RR	95% CI	Data homogeneity	Quality of evidence	Conclusion
OS	1	210	208	HR = 0.42	0.37–0.48	NA	High	Significantly reduced risk of death in experimental group
PFS	2	570	387	HR = 0.49	0.39–0.61	p = 0.13; I^2 = 56%	Medium	Significantly longer in experimental arm
Toxicity	3	847	520	RR = 0.55	0.31–0.97	p = 0.0008; I^2 = 86%	Medium	Significantly less toxicity in experimental arm
ORR	3	847	520	RR = 3.42	2.38–4.92	p = 0.31; I^2 = 15%	High	Significantly higher in experimental group
Quality of life	Less worsening in experimental arm							

NA — not assessed; N — number; exper. — experimental group; comp. — comparator group; RCT — randomised clinical trial; RR — relative risk; HR — hazard ratio; ORR — overall response rate; PFS — progression-free survival; OS — overall survival

endpoint (data from the study are included in Table 4). Compared to anti-CTLA-4 treatment, anti-PD-1 antibodies increased ORR and PFS, and reduced risk of death. Probably (low quality of evidence) it is also characterised by a better toxicity profile [6].

Combination of anti-PD-1 antibodies and anti--CTLA-4 antibodies *vs.* anti-CTLA-4 antibodies alone

The data regarding the effectiveness of anti-CTLA-4 and anti-PD-1 antibody combination come from two RCTs, both of which assessed nivolumab and ipilimumab. Neither of these trials assessed OS as a primary end point. Combined analysis showed that combination treatment resulted in improved PFS and ORR. Despite increased toxicity observed in the experimental arm of CheckMate 067 [10], the meta-analysis deemed the difference as statistically insignificant, probably due to poor data quality (Table 5) [6].

Molecularly targeted therapy

The discovery of a role of MAPK pathway activation and *BRAF V600* mutation (present in about 50% of skin and 11% of mucosal melanoma) led to a significant breakthrough in melanoma treatment: the development of BRAF serine-threonine kinase small molecule inhibitors and MEK inhibitors. Anti-BRAF/anti-MEK drugs are now — along with immunotherapy — one of the basic treatment modalities for advanced melanoma. Unfortunately, their application is limited to patients with *BRAF* mutated melanoma.

BRAF inhibitors *vs.* chemotherapy

The analysis included two trials comparing vemurafenib and dabrafenib to dacarbazine monotherapy [11, 12] and showed improvement of OS, PFS, and ORR in patients receiving BRAF inhibitors with a probable similar toxicity (low quality of evidence) (Table 6) [6].

Table 4. Comparison of anti-PD-1 antibodies (experimental group) with anti-CTLA-4 antibodies (comparator)

	N RCTs	N exper.	N comp.	HR/RR	95% CI	Data homogeneity	Quality of evidence	Conclusion
OS	1	556	208	HR = 0.63	0.60–0.66	NA	High	Significantly reduced risk of death in experimental group
PFS	2	872	593	HR = 0.54	0.50–0.60	p = 0.72; I^2 = 0%	High	Significantly longer in experimental arm
Toxicity	2	872	593	RR = 0.70	0.54–0.91	p = 0.14; I^2 = 53%	Low	Significantly less toxicity in experimental arm
ORR	2	872	593	RR = 2.47	2.01–3.04	p = 0.35; I^2 = 0%	High	Significantly higher in experimental group
Quality of life	No data							

NA — not assessed; N — number; exper. — experimental group; comp. — comparator group; RCT — randomised clinical trial; RR — relative risk; HR — hazard ratio; ORR — overall response rate; PFS — progression-free survival; OS — overall survival

Table 5. Comparison of anti-CTLA-4 and anti-PD-1 antibody combination (experimental group) with anti-CTLA-4 antibody alone (comparator)

	N RCTs	N exper.	N comp.	HR/RR	95% CI	Data homogeneity	Quality of evidence	Conclusion
OS	2	NA	NA	NA	NA	NA	NA	None
PFS	2	386	352	HR = 0.40	0.35–0.46	p = 0.78; I^2 = 0%	High	Significantly longer in experimental group
Toxicity	2	386	352	RR = 1.57	0.85–2.92	p = 0.03; I^2 = 80%	Low	NS
ORR	2	386	352	RR = 3.50	2.07–5.92	p = 0.20; I^2 = 39%	High	Significantly higher in experimental group
Quality of life	No data							

NA — not assessed; N — number; exper. — experimental group; comp. — comparator group; RCT — randomised clinical trial; RR — relative risk; HR — hazard ratio; ORR — overall response rate; PFS — progression-free survival; OS — overall survival

Table 6. Comparison of BRAF inhibitors (experimental arm) to chemotherapy (comparator)

	N RCTs	N exper.	N comp.	HR/RR	95% CI	Data homogeneity	Quality of evidence	Conclusion
OS	2	524	401	HR = 0.40	0.28–0.57	p = 0.31; I^2 = 4%;	High	Significantly lower risk of death in experimental group
PFS	2	524	401	HR = 0.27	0.21–0.34	p = 0.63; I^2 = 0%	High	Significantly longer in experimental group
Toxicity	2	524	401	RR = 1.27	0.48–333	p = 0.004; I^2 = 88%	Low	NS
ORR	2	524	401	RR = 6.78	4.84–9.49	p = 0.75; I^2 = 0%	High	Significantly higher in experimental group
Quality of life	Based on EORTC QLQ-C30 questionnaire, patients in experimental group showed improvement in emotional and social functioning and reduction in certain symptoms: drowsiness, vomiting, apathy, diarrhoea, fatigue, dyspnoea, insomnia							

N — number; exper. — experimental group; comp. — comparator group; RCT — randomised clinical trial; RR — relative risk; HR — hazard ratio; ORR — overall response rate; PFS — progression-free survival; OS — overall survival

Anti-MEK agents *vs.* chemotherapy

In two out of three trials evaluating monotherapy with MEK inhibitors (trametinib, selumetinib), no improvement regarding OS was seen when compared to chemotherapy alone (dacarbazine, docetaxel, paclitaxel) [13–15]. The meta-analysis supports a similar conclusion, but the level of evidence is low. Two trials showed a positive impact of MEK inhibition on PFS, as confirmed by the meta-analysis, along with an improvement of ORR when compared to chemotherapy. However, anti-MEK treatment is probably associated with more severe toxicity (data from 3 trials [15]) (Table 7) [6].

Combination of anti-BRAF and anti-MEK agents *vs.* anti-BRAF agents alone

A combination of BRAF and MEK inhibition improved treatment outcomes and reduced rates of skin cancers induced by BRAF inhibitors. Trials included in the meta-analysis evaluated: dabrafenib and trametinib *vs.* vemurafenib; dabrafenib and trametinib *vs.* dabrafenib (two trials); and vemurafenib and cobimetinib *vs.* vemurafenib [16–19]. Improvement of OS was seen in two trials, and all studies showed an improvement in PFS. The meta-analysis demonstrated that anti-BRAF/anti-MEK inhibition leads to improvement in ORR, OS, and probably PFS, without increased toxicity (medium quality of evidence) (Table 8) [6].

Table 7. Comparison of MEK inhibitors (experimental group) with chemotherapy (comparator)

	N RCTs	N exper.	N comp.	HR/RR	95% CI	Data homogeneity	Quality of evidence	Conclusion
OS	3	300	196	HR = 0.85	0.58–1.25	p = 0.10; I^2 = 57%;	Low	NS
PFS	3	300	196	HR = 0.58	0.42–0.80	p = 0.09; I^2 = 58%	Medium	Significantly longer in experimental group
Toxicity	3	300	196	RR = 1.61	1.08–2.41	NA	Medium	Significantly higher in experimental group
ORR	3	300	196	RR = 2.01	1.35–2.99	p = 0.47; I^2 = 0%	High	Significantly higher in experimental group
Quality of life	Evaluation of EORTC QLQ-C30 questionnaire results suggested improvement in physical performance and social functioning in experimental group, along with reduction of fatigue, pain, insomnia, nausea and vomiting, constipation, and dyspnoea							

NA — not assessed; N — number; exper. — experimental group; comp. — comparator group; RCT — randomised clinical trial; RR — relative risk; HR — hazard ratio; ORR — overall response rate; PFS — progression-free survival; OS — overall survival

Table 8. Comparison of dual BRAF and MEK inhibition (experimental arm) with BRAF inhibition alone (comparator)

	N RCTs	N exper.	N comp.	HR/RR	95% CI	Data homogeneity	Quality of evidence	Conclusion
OS	4	918	866	HR = 0.70	0.59–0.82	p = 0.98; I^2 = 0%;	High	Significantly reduced risk of death in experimental group
PFS	4	918	866	HR = 0.56	0.44–0.71	p = 0.02; I^2 = 69%	Medium	Significantly longer in experimental group
Toxicity	4	918	866	RR = 1.01	0.85–1.20	p = 0.04; I^2 = 64%	Medium	NS
ORR	4	918	866	RR = 1.32	1.20–1.46	p = 0.27; I^2 = 23%	High	Significantly higher in experimental group
Quality of life	A trend in favour of the combinational treatment was seen regarding pain, insomnia, and physical, social, emotional, cognitive, and role functioning An opposite trend was seen regarding nausea, vomiting, diarrhoea, dyspnoea, and constipation, with a significant improvement from baseline values in the group receiving dabrafenib monotherapy							

N — number; exper. — experimental group; comp. — comparator group; RCT — randomised clinical trial; RR — relative risk; HR — hazard ratio; ORR — overall response rate; PFS — progression-free survival; OS — overall survival

Indirect comparison

The meta-analysis included also indirect comparison of agents that were not compared head-to-head in any randomised clinical trial. Due to its indirect character, the value of this analysis was decreased from baseline and therefore a medium quality of evidence was accepted as maximal. Additionally, the authors undertook SUCRA ranking analysis (the surface under the cumulative ranking curve). In this analysis each agent is classified with a probability of taking a specific position in a ranking of therapies, from the best to the worst. For each agent, the SUCRA result might be a value from 1 (clearly the best evaluated therapy) to 0 (clearly the worst evaluated therapy). However, due to the quality of data used, the authors emphasised that the results obtained in the analysis are not unequivocally reliable [6].

Comparison of different therapies regarding OS

Due to insufficient data, it is impossible to properly assess the effects of different therapies on overall survival.

Comparison of different therapies regarding PFS

Combined anti-BRAF/anti-MEK inhibition (HR = 0.17; 95% CI 0.11–0.26) (medium quality of evidence), combined anti-PD-1/anti-CTLA-4 therapy (HR = 0.30; 95% CI 0.17–0.51) (medium quality of evidence), anti-BRAF monotherapy (HR = 0.30; 95% CI 0.20–0.44) and anti-PD-1 monotherapy (HR = 0.44; 95%CI 0.30–0.63) all proved to be superior to chemotherapy. There was no statistically significant difference between anti-CTLA-4 monotherapy and chemotherapy (low quality of evidence). Combined anti-BRAF/anti-MEK therapy was better than either anti-PD-1 monotherapy (HR = 0.38; 95% CI 0.21–0.68) or anti-CTLA-4 monotherapy (HR = 0.22; 95% CI 0.12–0.39) (medium quality of evidence). No difference was seen between both combinations: anti-BRAF/anti-MEK and anti-PD-1/anti-CTLA-4 (very low quality of evidence).

According to SUCRA analysis, the best therapeutic option in terms of PFS is anti-BRAF/anti-MEK combination (0.99), with the combination of anti-PD-1/anti-CTLA-4 agents (0.77) and anti-BRAF monotherapy (0.77) being lower in rank. Clearly inferior options are: anti-PD-1 monotherapy (0.56), anti-MEK monotherapy (0.46), anti-CTLA-4 monotherapy (0.25), and bio-chemotherapy (0.18), with conventional chemotherapy at the very last position (0.02) [6].

Comparison of different therapies regarding toxicity

Both anti-CTLA-4 monotherapy (RR = 1.65; 95% CI 1.09–2.49) (very low quality of evidence) and combination of anti-PD-1/anti-CTLA-4 antibodies (RR = 3.49; 95% CI 2.12–5.77) (medium quality of evidence) were more toxic than chemotherapy according to indirect comparison. Anti-BRAF/anti-MEK therapy was similar to chemotherapy compared to chemotherapy (very low quality of evidence). Combination of anti-PD-1/anti-CTLA-4 blockade was more toxic than both anti-PD-1 monotherapy (RR = 3.83; 95% CI 2.59–5.68) and anti-BRAF/anti-MEK combination (RR = 2.34; 95% CI 1.11–4.96) (medium quality of evidence).

The best toxicity profile according to SUCRA analysis is exhibited by anti-PD-1 monotherapy (0.91), followed by chemotherapy (0.87), BRAF inhibitor monotherapy (0.55), bio-chemotherapy (0.48), combination of anti-BRAF/anti-MEK agents (0.42), MEK inhibitor monotherapy (0.41), and anti-CTLA-4 antibodies (0.36), with the worst safety profile of anti-PD-1/anti-CTLA-4 combination (0.01) [6].

Summary

Optimal management of disease requires administration of the most effective and the least toxic available therapy, with an emphasis on the treatment safety. According to the presented meta-analysis, two options might be considered as the best approach for the treatment of advanced melanoma: anti-BRAF/anti-MEK combination (only in patients with *BRAF* mutated melanoma) and anti-PD-1 therapy (as a monotherapy or in combination with anti-CTLA-4 antibody). In patients with BRAF mutated melanoma, combined anti-BRAF/anti-MEK therapy seems to be the most effective in terms of progression-free survival, but it is less advantageous than anti-PD-1 therapy in terms of toxicity. The lack of quality data hindered drawing conclusions regarding the effects of different treatments on overall survival. Finding the answer will require longer observations of patients receiving immunotherapy or anti-BRAF/anti-MEK inhibitors and, preferably, dedicated RCTs comparing those two modalities with an assessment of overall survival as a primary end point. Until then, the decision regarding systemic treatment in patients with *BRAF*-mutated melanoma should include available data from clinical trials, results of described meta-analyses, as well as the feasibility of performing the planned treatment sequence. It should be assumed that the effectiveness of immunotherapy has not been studied in trials dedicated to patients with *BRAF* mutations, and such a population comprised only a minority of trials evaluating anti-PD-1 or anti-CTLA-4 antibodies, with suboptimal comparators other than anti-BRAF or anti-BRAF/anti-MEK inhibitors.

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