The First Line Treatment of Advanced or Metastatic BRAF Mutant Melanoma: A Network Meta-analysis

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Abstract

Purpose: The treatments for advanced or metastatic BRAF mutant melanoma are flourish, but the most effective treatment is unclear. Here, we conducted a network meta-analysis (NMA) in unresectable stage III or advanced (or metastatic) stage IV BRAF mutant melanoma patients to estimate the efficacy of various first line treatments.

Methods: A comprehensive search for RCTs in PubMed and EMBASE was conducted to January 2021. Randomized control trials of unresectable stage III or advanced stage IV BRAF mutant melanoma were eligible if not receive previously treatment. By a Bayesian network meta-analysis, the effectiveness of each treatment was estimated and ranked based on the odds ratio (OR) for Object response rate (ORR) and hazard ratio (HR) for Overall survival (OS).

Results: Eight trials enrolling 3272 patients were included. Combination dabrafenib and trametinib with pembrolizumab (HR: 0.37; 95% confidence interval [CI]: 0.21-0.66; compared with dacarbazine) ranked as the best effective treatment for OS.

Conclusion: Combination pembrolizumab with trametinib and dabrafenib and combination atezolizumab with trametinib and dabrafenib appear more effective as first line treatments for unresectable stage III or advanced (or metastatic) stage IV BRAF mutant melanoma patients. Whereas, further RCTs are needed to complete the network.

Introduction

Approximate 40% to 60% of cutaneous melanoma patients carry BRAF mutation, which could constitutively activate the downstream signaling through the MAP kinase pathway and increase melanoma cells proliferation and survival.[1, 2] A latest randomized control trial (RCT) indicates a landmark OS rate of 34% after 5years by targeting this signaling pathway.[3] Combination BRAF and MEK inhibitors could increase melanoma antigens and involve in transporting CD8+ and CD4+ cells to melanoma.[4-7] Although this combination therapy leads to a considerable cancer response of 75% in BRAF mutant melanoma patients,[8] most responses are short-lived.[9] Furthermore, patients quickly acquired resistance to it and resulted in relapse within months.[10-12] A three-year pooled analysis indicated that at least 70% of patients experienced relapse or metastasis within the first 3 years of therapy.[13] Interestingly, we found an increased expression of PD-1 and PD-L1 in advanced or metastatic BRAF mutant melanoma patients who accept the treatment of BRAF inhibitors.[4] And anti-PD-1 immune checkpoint inhibitor is a vital coregulatory factor for down-regulation of T-cell activation.[14-16] Therefore, combination immune checkpoint inhibitors (ICIs) and BRAF inhibitors may conduct a more effective treatment for those patients.

Additionally, immune checkpoint inhibitors, BRAF inhibitors and MEK inhibitors all show vital therapeutic effectiveness in advanced or metastatic BRAF mutant melanoma patients.[10, 17-23] Immune checkpoint inhibitors provide more durable responses but their response rates are relatively lower.[24] Therefore, a triple combination therapy of MEK inhibitors, BRAF inhibitors and anti-PD-1 or anti-PD-L1 immune checkpoint inhibitors need to be conducted.[25, 26]

Presently, two randomized controlled trials indicated that triple combination therapy is more effective than combination MEK inhibitors and BRAF inhibitors.[27, 28] Therefore, we compared the efficacy of various treatments by a network meta-analysis and tried to find a best first-line treatment in advanced or metastatic BRAF mutant melanoma patients.

Methods

Literature search

This systematic review and network meta-analysis of RCTs, registered on the PROSPERO database ([CRD42021234924](#)) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Network Meta-analysis ([PRISMA-NMA](#)) reporting guideline,[29] was updated to January, 2021.

Treatments include combination atezolizumab with cobimetinib and vemurafenib, combination vemurafenib and cobimetinib, combination pembrolizumab with dabrafenib and trametinib, combination dacarbazine and selumetinib, combination dabrafenib and trametinib, dabrafenib monotherapy, vemurafenib monotherapy, dacarbazine monotherapy. Two endpoints were all efficacy that measured by objective response rate (ORR), overall survival (OS). A search on PubMed and Embase, following the algorithm: “(BRAF mutation) AND (melanoma)”, was conducted by Mr. Yang and Mrs. Zhong. The conflicts and uncertainties were finally resolved by Mrs. Wu.

The following inclusion criteria were used: 1) neoplasm: unresectable stage III and advanced or metastasis stage IV BRAF mutant melanoma; 2) most of patients (>80%) did not receive treatment before; 3) study design: RCTs reporting on ORR and OS; No language restriction was applied. If there are multiple publications of the same RCTs, the latest data was included.

The Risk of bias

The assessment of the risk of bias was conducted by Mr. Yang and Mrs. Zhong with [the Cochrane Risk of bias tool](#).^[30] All RCTs were assessed by three grades: high risk, unclear risk, or low risk. The extraction of data was carried out by Mr. Yang and Mrs. Zhong and independently verified by Mrs. Wu.

Statistical analysis

we conducted this NMA with R (R Project for Statistical Computing; version 3.6.2; gemtc package).^[31] The OR and 95% CIs were used to estimate ORR. The HR and 95% CIs were used to estimate OS. For any comparison, an OR for ORR bigger than 1 or an HR for OS smaller than 1 means that the treatment was more effective. The heterogeneity between the comparisons was estimated by the I-squared statistic.

DIC was used for model selection. The chain of model was three. The adaptation was 10000 and model iteration was 100000. Edge-splitting was used for the evaluation of inconsistency. Additionally, we ranked all outcomes by the probability.

Results

Characteristics of All Trials

14 articles containing 8 trials were included for subsequent analysis.^[8, 12, 19, 27, 28, 32-40] Trails directly compared the following 8 treatments: combination atezolizumab with cobimetinib and vemurafenib, combination vemurafenib and cobimetinib, combination pembrolizumab with dabrafenib and trametinib, combination dacarbazine and selumetinib, combination dabrafenib and trametinib, dabrafenib monotherapy, vemurafenib monotherapy, dacarbazine monotherapy (Network plot, figure 1). The detailed description of all RCTs was showed in Table 1. All trials were two-arm trials. NMA for ORR (I-square. cons= 0) and OS (I-square. cons= 0) show no heterogeneity and absent inconsistency.

Table. 1

Characteristics of included studies

trial name	treatment	masking	phase	participants, NO.	male, (%)	Median age, years (range)	OR No. (total No.)	OS, HR (95%CI)
IMspire150 (NCT02908672)	vemurafenib+cobimetinib+atezolizumab	double-blind	3	256	59	54.0 (44.8–64.0)	169 (255)	0.85 (0.64–1.11)
	vemurafenib+cobimetinib+placebo			258	58	53.5 (43.0–63.8)	160 (246)	
KEYNOTE-022 (NCT02130466)	dabrafenib+trametinib+pembrolizumab	double-blind	2	60	55	54.0 (18.0–82.0)	38 (60)	0.64 (0.38–1.06)
	dabrafenib+trametinib+placebo			60	60	58.0 (21.0–83.0)	43 (60)	
coBRIM (NCT01689519)	vemurafenib+cobimetinib	triple-blind	3	247	59	56.0 (23.0–88.0)	172 (247)	0.70 (0.55–0.90)
	vemurafenib+placebo			248	56	55.0 (25.0–85.0)	123 (248)	
COMBI-d (NCT01584648)	dabrafenib+trametinib	quadruple-blind	3	211	53	55.0 (22.0–89.0)	144 (210)	0.75 (0.58–0.96)
	dabrafenib+placebo			212	54	56.5 (22.0–86.0)	116 (211)	
COMBI-v (NCT01597908)	dabrafenib+trametinib	open-label	3	352	59	55.0 (18.0–91.0)	226 (351)	0.69 (0.53–0.89)
	vemurafenib monotherapy			352	51	54.0 (18.0–88.0)	180 (350)	
BRIM-3 (NCT01006980)	vemurafenib monotherapy	open-label	3	337	59	56.0 (21.0–86.0)	106 (219)	0.81 (0.67–0.98)
	dacarbazine monotherapy			338	54	52.0 (17.0–86.0)	12 (220)	
BREAK-3 (NCT01227889)	dabrafenib monotherapy	open-label	3	187	60	53.0 (22.0–93.0)	93 (187)	0.82 (0.57–1.18)
	dacarbazine monotherapy			63	59	50.0 (21.0–82.0)	4 (63)	
robert 2013 (NCT00936221)	selumetinib+dacarbazine	double-blind	2	45	49	57.0 (48.0–69.0)	18 (45)	0.93 (0.67–1.28)
	dacarbazine+placebo			46	61	52.0 (40.0–65.0)	12 (46)	

The risk of bias

The risk of bias of the 8 RCTs was estimated by Mr. Yang and Mrs. Zhong. These studies had a low risk of detection, reporting and attrition bias. These RCTs at least double-blind except 3 trials (COMBI-v, BRIM-3, BREAK-3) were considered to have a high quality of evidence.

Outcomes

Objective response rate

Due to the DICs of the random model and fixed model was 31.47, 30.16, respectively, we chose the fixed model to conducted the NMA. The result of the NMA showed in table 2. Combination atezolizumab with cobimetinib and vemurafenib was the most effective treatment in all treatments, despite the OR compared to combination vemurafenib and cobimetinib (OR: 1.1; CI: 0.73-1.5) and combination pembrolizumab with dabrafenib and trametinib (OR: 2.1; CI: 0.80-5.8) and combination dabrafenib and trametinib (OR: 1.4; CI: 0.80-2.6) did not achieve statistical significance. Combination vemurafenib and cobimetinib was more effective than other treatments except combination atezolizumab with cobimetinib and vemurafenib, despite the OR compared to combination pembrolizumab with dabrafenib and trametinib (OR: 2.0; CI: 0.82-5.1) and combination dabrafenib and trametinib (OR: 1.4; CI: 0.86-2.2) did not achieve statistical significance. Combination pembrolizumab with trametinib and dabrafenib was more effective than combination dacarbazine and selumetinib, dabrafenib monotherapy (OR: 1.2; CI: 0.51-2.9), vemurafenib monotherapy (OR: 1.2; CI: 0.50-2.6), dacarbazine monotherapy. Combination dabrafenib and trametinib was more effective than combination dacarbazine and selumetinib, dabrafenib monotherapy, vemurafenib monotherapy and dacarbazine monotherapy.

Table. 2 Results of objective response rate and overall survival

Overall survival (OS)							
Vemurafenib+	0.85	1.3	0.84	0.52	0.62	0.59	0.49
Cobimetinib+	(0.64,1.1)	(0.68,2.6)	(0.55,1.3)	(0.31,0.89)	(0.39,0.98)	(0.41,0.86)	(0.32,0.74)
atezolizumab							
1.1	Vemurafenib+	1.6	0.99	0.62	0.73	0.70	0.57
(0.73,1.5)	cobimetinib	(0.85,2.9)	(0.71,1.4)	(0.40,0.96)	(0.51,1.1)	(0.55,0.90)	(0.42,0.78)
2.1	2.0	Dabrafenib+	0.64	0.40	0.47	0.45	0.37
(0.80,5.8)	(0.82,5.1)	Trametinib+	(0.38,1.1)	(0.21,0.77)	(0.27,0.82)	(0.26,0.79)	(0.21,0.66)
		pembrolizumab					
1.4	1.4	0.68	Dabrafenib+	0.62	0.74	0.71	0.58
(0.80,2.6)	(0.86,2.2)	(0.31,1.5)	Trametinib	(0.41,0.95)	(0.59,0.92)	(0.56,0.88)	(0.45,0.75)
21	20	10	15	Dacarbazine+	1.2	1.1	0.93
(6.5,70)	(6.5,70)	(2.6,38)	(4.9,44)	selumetinib	(0.78,1.8)	(0.78,1.6)	(0.67,1.3)
2.6	2.5	1.2	1.8	0.12	dabrafenib	0.96	0.79
(1.3,5.2)	(1.4,4.5)	(0.51,2.9)	(1.2,2.6)	(0.040,0.37)		(0.73,1.3)	(0.60,1.0)
2.5	2.3	1.2	1.7	0.12	0.95	vemurafenib	0.82
(1.5,4.2)	(1.6,3.4)	(0.50,2.6)	(1.3,2.3)	(0.040,0.34)	(0.60,1.5)		(0.68,0.98)
41	39	19	28	1.9	16	16	dacarbazine
(19,90)	(20,78)	(7.1,52)	(16,53)	(0.79,4.8)	(8.4,31)	(9.6,30)	
Objective response rate (ORR)							

Overall survival

Due to the DICs of the random model and fixed model was 15.06, 14.13, respectively, we chose the fixed model to conducted the NMA. The result of the NMA showed in table 2.

Combination pembrolizumab with trametinib and dabrafenib seemed the most effective treatment, despite the HR compared to combination atezolizumab with cobimetinib (HR: 0.76; CI: 0.39-1.5) and combination vemurafenib and cobimetinib (HR: 0.64; CI: 0.35-1.2) and combination dabrafenib and trametinib (HR: 0.64; CI: 0.38-1.1) did not achieve statistical significance in table 2. Combination atezolizumab with cobimetinib

and vemurafenib seemed the second effective treatment, despite the HR compared to combination vemurafenib and cobimetinib (HR: 0.85; CI: 0.64-1.1) and combination dabrafenib and trametinib (HR: 0.84; CI: 0.55-1.3) did not achieve statistical significance. Combination vemurafenib and cobimetinib seemed the third effective treatment, despite the HR compared to combination dabrafenib and trametinib (HR: 0.99; CI: 0.71-1.4) and dabrafenib monotherapy (HR: 0.73; CI: 0.51-1.1) did not achieve statistical significance in table 2. Combination dabrafenib and trametinib was more effective than combination dacarbazine and selumetinib, dabrafenib monotherapy, vemurafenib monotherapy and dacarbazine monotherapy.

Ranking

Ranking analysis for ORR performed with SUCRA suggested that combination atezolizumab with cobimetinib and vemurafenib had the highest probability to rank at the first place for ORR (0.59), combination vemurafenib and cobimetinib ranked at the second place for ORR (0.57), combination dabrafenib and trametinib ranked at the third place for ORR (0.72), combination pembrolizumab with trametinib and dabrafenib ranked at the fourth place for ORR (0.39) (figure 2). Ranking analysis for OS performed with SUCRA suggested that combination pembrolizumab with trametinib and dabrafenib had the highest probability to rank at the first place for OS (0.78), combination atezolizumab with cobimetinib and vemurafenib ranked at the second place for OS (0.54), combination vemurafenib and cobimetinib ranked at the third place for OS (0.45), combination dabrafenib and trametinib ranked at the fourth place for OS (0.47) (figure 3).

Discussion

In the constant upgrading process of the treatment regimens for unresected stage III or metastatic stage IV BRAF mutant melanoma patients, monotherapy, due to high drug resistance, gradually replaced by double combination therapy.[41] And the combination MEK inhibitors and BRAF inhibitors appears to be the best treatment for BRAF V600 mutant melanoma patients.[42] Then, a previous network meta-analysis including an update to November 2018 of treatments for these special melanoma patients compared various double combination therapy and monotherapy.[43] That NMA showed that combination dabrafenib with trametinib seemed to be the best treatment for PFS while combination nivolumab with ipilimumab seemed to be the best treatment for OS. That NMA also showed that dacarbazine monotherapy seemed to be the worst treatment of these treatments, which was the same as ours.

Interestingly, we found an increased expression of PD-1 and PD-L1 in advanced or metastatic BRAF mutant melanoma patients who accept the treatment of BRAF inhibitors.[4] Pembrolizumab, as an anti-PD-1 immune checkpoint inhibitor, firstly estimated in KEYNOTE-001.[44] Until 2019, these data confirmed its durable antitumor activity in advanced melanoma.[45] In the second course of the phase III KEYNOTE-006,[46] the estimated 5-year survival outcome showed that pembrolizumab was more effective than ipilimumab in advanced and ipilimumab-naive melanoma patients. Atezolizumab, as an anti-PD-L1 immune checkpoint inhibitor, was originally used to cure lung and breast cancer patients alone or combined with other treatments. Then, atezolizumab monotherapy showed an ORR of 30% in advanced melanoma.[47] Immune checkpoint inhibitors provide more durable responses but their response rates are relatively lower.[24] Therefore, a triple combination therapy of MEK inhibitors, BRAF inhibitors and anti-PD-1 or anti-PD-L1 immune checkpoint inhibitors need to be conducted.[25, 26] The first triple combination therapy was conducted in KEYNOTE-022 trials (combination pembrolizumab with dabrafenib and trametinib), which showed that the triple combination therapy was more effective than combination MEK inhibitors and BRAF inhibitors, though it has a higher rate of adverse events.[28] IMspire150 trials found that triple combination therapy (combination atezolizumab with cobimetinib and vemurafenib) was tolerable and safe, and vitally induced a better result of progression-free survival (PFS) in BRAF mutant melanoma patients.[27] Despite the overall survival in IMspire150 trials was not reached, the curves of overall survival began to separate indicated that the triple combination therapy was more effective which was the same as the delayed separation in KEYNOTE-022 trials.

Unlike previous NMA, our NMA included triple combination therapies like combination atezolizumab with cobimetinib and vemurafenib and combination pembrolizumab with trametinib and dabrafenib.[27, 28, 32] The two trials evaluated combination immune checkpoint therapy with MEK inhibitors and BRAF inhibitors in advanced or metastatic BRAF mutant melanomas. This NMA contained 8 phase 2 or 3 RCTs, with 3272 patients, and estimated the effectiveness of various first-line treatments for unresected stage III or metastatic stage IV melanoma patients (table 1). Additionally, our NMA carried out a complete search on PubMed and EMBASE updated to January 2021 with a low risk of bias. The results showed that combination atezolizumab with cobimetinib and vemurafenib was associated with the best ORR. Though not the best, combination pembrolizumab with trametinib and dabrafenib still showed considerable effectiveness for ORR. Combination pembrolizumab with trametinib and dabrafenib was associated with the best OS, and combination atezolizumab with cobimetinib and vemurafenib was the second for OS. According to the result of ORR and OS, these two combination treatments were likely to rank as the most appropriate treatments for unresected stage III or metastatic stage IV BRAF mutant melanoma patients.

Limitations

Although this NMA had no heterogeneity and absent inconsistency, it stills had limitations. First, the same as previous NMA,[43] ICIs may be used in indolent melanoma patients, which limited the universality of our outcomes in all BRAF mutant patients. Second, our NMA for OS was based on HR and its CI, without consideration of survival curves, which need further research to perfect the results. Third, due to the only data, subgroup analysis could not be carried out by stratifying BRAR mutant melanoma patients by age, LDH levels, M1c stage, ECOG performance status, or other factors that may be associated with the results of the treatments. Fourth, the triple combination therapy, including IMspire150 trials and KEYNOTE-022 trials, are still ongoing. Fifth, with the sparseness information of treatment-related adverse events, we could not evaluate and rank the safety of these treatments. Therefore, more extensive researches are needed to conduct a comprehensive NMA.

Conclusion

The two triple combination therapies all show considerable effectiveness in all treatments. Combination atezolizumab with cobimetinib and vemurafenib has a higher ORR. Combination pembrolizumab with trametinib and dabrafenib show a better result in OS. In conclusion, the two triple combination therapies are more preferable for unresectable stage III or advanced (or metastatic) stage IV BRAF mutant melanoma patients.

Declarations

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Conflict of Interest Disclosures:

The authors declare that they have no conflict of interest.

Availability of data and material:

Not applicable

Code availability:

R Project for Statistical Computing; version 3.6.2; gemtc package

Author Contributions:

Mr. Yang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Yang.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Yang.

Critical revision of the manuscript for important intellectual content: Yang, Zhong, Wen.

Statistical analysis: Yang, Zhong.

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Figures

Figure 1

Network of evidence for objective response rate and overall survival

Figure 2

Ranking analysis for objective response rate

Figure 3

Ranking analysis for overall survival

Supplementary Files

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- PRISMA2009ChecklistMSWord.doc
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