REVIEW

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Focus on the dabrafenib, vemurafenib, and trametinib in the clinical outcome of melanoma: A systematic review and meta-analysis

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ABSTRACT

Background: Melanoma is the most severe lethal skin cancer, affecting melanin producer cells (melanocytes). Surgery is the most common treatment, whereas, for the advanced stage, the development of treatment is recommended. BRAF (Dabrafenib and Vemurafenib) inhibitor or MEK inhibitor (Trametinib) is the most frequently targeted melanoma therapy due to more than 80% of patients with positive BRAF mutation. In this review, those treatments will be investigated systematically to identify their clinical outcome.

Method: This systematic literature review (SLR) was performed from Cochrane, Science Direct, Google Scholar, and Pubmed. Cochrane Risk-of-Bias Tool RoB2 is used to assess RCT studies and New-castle Ottawa Scale Assessment to assess cohort studies by three different assessors. Data analysis was carried out by using Review Manager (RevMan 5.4). Heterogenicity test was assessed by *I2* and *Chi*^{2} statistic

Result: There are 20 studies used in this article (13 RCT and seven cohorts). The overall survival (OS) and progression-free survival (PFS) of the survey that using targeted therapy (vemurafenib, trametinib, or dabrafenib) compare other treatments (chemotherapy, immunotherapy, etc.) showed risk ratio (RR) was 1.12 (95%CI 1.07,1.17; I^2=100%; p<0,00001). The OS and PFS with monotherapy compare of vemurafenib, trametinib, or dabrafenib with combination therapy showed RR was 1.09 (95%CI.06,1.13; I^2=99%; p<0,00001).

Conclusion: BRAF and MEK targeted therapy has a good prognosis for a patient with a positive BRAF gene mutation and could be combined with other treatments for better clinical outcomes rather than monotherapy.

Keywords: melanoma, dabrafenib, vemurafenib, and trametinib

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INTRODUCTION

Melanoma is the most serious lethal skin cancer, affects the melanin producer cells (melanocytes).[1] It can be found not only in the skin but also in the throat, nose, eyes, and bowel. Melanoma is less occurred than other skin cancer but causes most death due to its ability to metastasis quickly.[2] The incidence of melanoma increases significantly. Around 77,698 new cases each year in the United States, with 21.9 per 100.000 incidences. The mortality rate is 2.5 per 100.000, with 9,008 people died every year.[3] Melanoma becomes the 5th rank of skin cancer in men and the 6th rank in women.[4] There were reported 5-years survival rates of melanoma in stage 4 is 22.5%, 63.6% stage 3, and 98.4% in stage 0-2. Thus, an improvement of melanoma therapy might also enhance the life expectancy of the patient, particularly in the advanced stage.[5]

According to the specific characteristic-related gene, the most common mutation in melanoma is the BRAF gene.[6] More than 80% of patients with melanoma-positive BRAF mutation.[7] This mutation leads to an alteration in protein and takes control of cell growth aggressively.[8] In addition, the mutated BRAF gene loses the ability to improve antigen recognition by antigen-specific T lymphocytes and dendritic recognition.[9,10] BRAF gene is also able to activate the MAP kinase/ERK-signaling pathway.[11] Therefore, BRAF or MEK inhibitor is used as the targeted therapy of melanoma. There are several specific targeted therapies of BRAF or MEK inhibitor such as Dabrafenib, Vemurafenib, Trametinib.[12]

Dabrafenib and Vemurafenib were tested in a randomized phase 3 study with a higher response rate than dacarbazine (DTIC), 57% vs.

9%, and 50% vs. 6%.[13–16] However, this treatment is associated with hyperkeratosis, rash, alopecia, and skin papilloma in some cases.[13,14] Meanwhile, Trametinib could induce cell death, inhibit cell growth, reduce angiogenesis and proliferation, and increase apoptosis in BRAF mutated genes. Rash, fatigue, peripheral edema, and diarrhea are the most common toxicities of Trametinib.[17] In addition, ocular toxicity has been proven as an adverse event of MEK inhibitor.[18] Besides its adverse event, due to microenvironmental changes, it leads to resistance of BRAF inhibitors targeted therapy.[9]

Thus, in this review, vemurafenib, trametinib, and dabrafenib as specifically targeted therapies of BRAF and MEK inhibitor will be investigated systematically and identify their clinical outcome. The results of this review are expected as consideration and information for further research to enhance the patient's clinical outcome.

MATERIAL AND METHOD

Systematic literature review

This systematic literature review (SLR) was performed by Cochrane, Science Direct, Google Scholar, and Pubmed to identify cohort and randomized clinical trial (RCT) of Melanoma targeted therapy (Vemuravenib, Trametinib, Dabravenib). This SLR accordances with PRISMA guideline 2009, with the study's time frame, is the last ten years. There were several criteria for this SLR such as the study is using a human sample that is already diagnosed in skin melanoma, the patient is treated by MEK dan BRAF inhibitor targeted therapies such as Vemurafenib, Trametinib, Dabravenib that establish the progression survival rate (PFS) and or overall survival rate (OS). The excludes study were as follow the text was using English and inaccessible full-text.

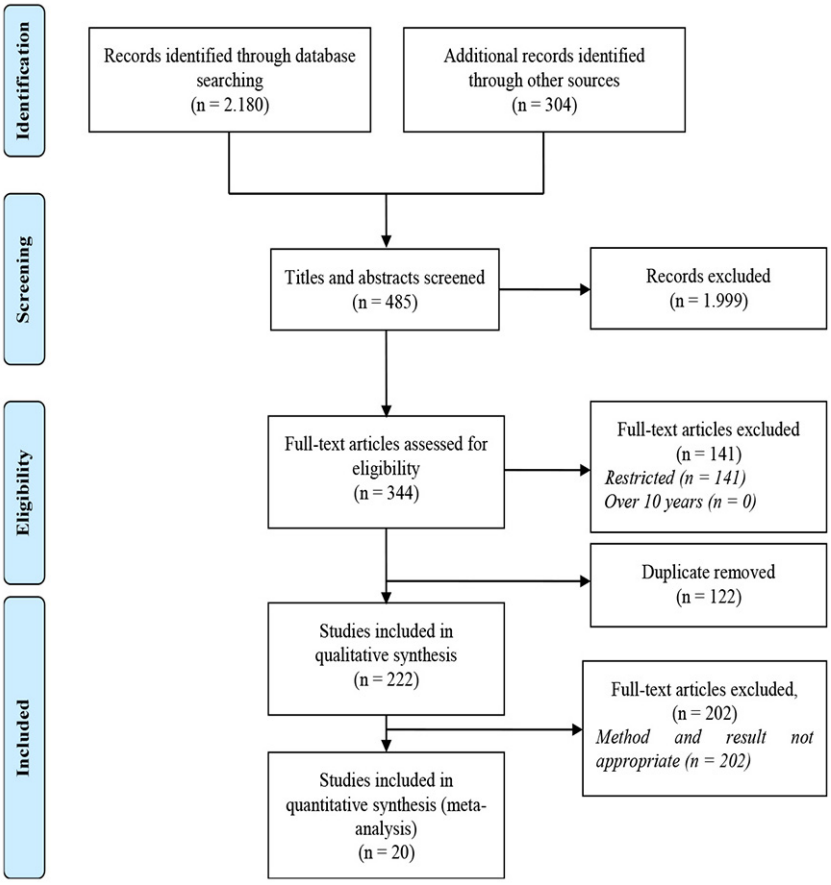

Figure 1. Flow diagram of clinical outcome of targeted teraphies (vemurafenib, dabrafenib, trametinib) in melanoma systematic review

Data extraction and quality assessment

Data were extracted using data collection form in Excel. The following data were extracted: first author, the year of publication, research design, phase of a clinical trial, number of population, stage of melanoma, intervention and comparator, and effectiveness outcomes (hazard ratios [HRs] including 90% and 95% confidence intervals [CIs] for PFS and OS). The search of the formula used boolean "AND" or "OR" by using keywords as follows: "melanoma", "vemurafenib", "dabrafenib", "trametinib", "cohort study", "RCT". There are 20 studies used in this article. Twelve of those researches were RCT, and the remaining eight were cohort. There are four kinds of research not reporting the HRs for PFS and one study not reporting the HRs for OS. One of 20 kinds of research has 90% CIs for PFS and OS. This review included all phases of RCT and obtained phase II-III RCTs (13 studies), the rest was cohort (7 studies) in patients with skin melanoma. We used the Cochrane Risk-of-Bias Tool RoB2 to assess RCT studies and the New-castle Ottawa Scale Assessment to assess cohort studies by three different assessors. In all included RCTs, we used intention-to-treat analysis with five domains (Figure 4), including randomization process, deviations from intended intervention, missing outcomes data, measurement of the outcomes, and selection of the reported result. We also assessed the overall bias based on the mark at five domains. All percentages of the analysis are presented by using a graph (Table 2).

Analysis of data

Data analysis was carried out by using Review Manager (RevMan 5.4). The Heterogenicity test was assessed by I^2 and Chi^2 statistics to determine the variance of the studies that have been analyzed. For Chi^2 analysis, if the p-value is significant ($p<0.05$) indicate the data is heterogeneous, whereas if the value of I^2 around 75%-100% considerable heterogeneity data, 50%-90% may represent as

Table 1. **Data extraction of studies included (n=20) in flow diagram**

First author	Year	Research design	Phase	Population	Staging	Intervention	Comparator	HR for PFS (95% CI)	HR for OS (95% CI)
Flaherty[19]	2012	RCT	III	322 (214 T vs 108 Ch)	IIIC, IV	Trametinib	Chemotherapy	0.45 (0.33-0.63)	0.54 (0.32-0.92)
Schilling[20]	2014	RCT	III	342 (277 V vs 65 D)	IV	Vemurafenib	Dabrafenib	21.3 weeks for V, 21.0 weeks for D*	44.1 weeks for V, 46.3 weeks for D*
Robert[21]	2015	RCT	III	704 (352 D+T vs 352 V)	IIIC, IVM1a, IVM1b, IVM1c	Dabrafenib + Trametinib	Vemurafenib	0.56 (0.46-0.69)	0.69 (0.53-0.89)
Chapman[22]	2017	RCT	III	675 (337 V VS 338 Da)	IIIC or IV	Vemurafenib	Dacarbazine	NR	13.6 (12.0-15.4) for V, 0.81 (0.7-1.0) for Da
Long[23]	2017	RCT	III	423 (211 D+T vs 212 D)	IIIC or IV	Dabrafenib + Treametinib	Dabrafenib	0.71 (0.57–0.88)	0.75 (0.58–0.96)
Amaria[24]	2018	RCT	II	21 (7 standard care [surgery] vs 14 D + T)	IIIB, IIIC, IV	Surgery	Dabrafenib + Trametinib	NR	0.28 (0.026-2.17)
Brzozowska[25]	2018	RCT	III	1310 (759V, 370I, 181D)	NR	Vemurafenib, Ipilimumab, Dabrafenib		NR	9.8 (8.8–10.6) for V, 6.9 (5.7–9.2) for I
Dummer[26]	2018	RCT	III	577 (192 E+B, 194 E, 191 V)	IIIB, IIIC, IVM1a, IVM1b, IVM1c	Encorafenib, Binimetinib, Vemurafenib		0.77 (0.59-1.00)	0.61 (0.47–0.79)
Urbonas[27]	2019	RCT	II	111 (38 Pa, 36 Pa+T, 37 Pa+P)	III or IV	Paclitaxel, Trametinib, Pazopanib		3.4 (2.0–3.8) for Pa*, 5.2 (3.7–7.0) for Pa+T*, and 5.3 (3.4–6.4) for Pa+P*	10.8 (8.8–NE) for Pa*, 9.4 (8.3–13.5) for Pa+T*, and 11.6 (8.0–16.2) for Pa+P*
Robert[28]	2019a	RCT	III	563	II, IVM1a, IVM1b, IVM1c	Dabrafenib + Trametinib		0.79 (17-24) at 4 years, 0.81 (15-22) at 5 years	0.63 (33-42) at 4 years, 0.66 (30-38) at 5 years
Robert[29]	2019b	RCT	III	322 (214 T vs 108 Da or Pa)	IIIC or IV	Trametinib	Dacarbazine or Paclitaxel	0.54 (0.41-0.73)	0.84 (0.63-1.11)
Ascierto[30]	2020	RCT	III	577 (192 COMB450, 194 ENCO300, and 191 VEM).	IIIB, IIIC, IV	Encorafenib + Binimetinib (COMBO 450)	Vemurafenib (VEM) or Encorafenib (ENCO300)	0.51 (0.39-0.67).	33.6 (24.4-39.2) for COMBO450, 23.5 (19.6-33.6) for ENCO300, 16.9 (14.0-24.5) for VEM
Puzanov[31]	2015	Cohort	-	48	M1a, M1b, M1c	Vemurafenib		5.2 (3.9 - 5.6)	14 (1.2–56.1), 26.0 (7.7–56.1)
Scholtens[32]	2015	Cohort	-	70	M1a, M1b, M1c	Dabrafenib + Trametinib, Vemurafenib		1.92 (1.04-3.55)	5.2 (3.8-7.4), 1.4 (0.6-3.4)
Kim[33]	2016	Cohort	-	27 (11 D+T vs 6 V)	NR	Dabrafenib + Trametinib	Vemurafenib	9.2 (1.6-16.7)	NR
Long[34]	2016	Cohort	-	24 vs 54	IIIC, IV	Dabrafenib, Trametinib		10.8 (5.3-18.6) vs 9.4 (8.6-16.6)	27.4 (12.9-not reach) vs 25 (17.5-36.5)
Lang[35]	2018	Cohort	-	80 (40 V vs 40 I)	IIIC, IV	Vemurafenib	Ipilimumab	NR	8.0 (± 1.25: 5.55–10.45) for V, 10.0 (± 3.16: 3.81–16.19) for I
Algarra[36]	2019	Cohort	-	331	IIIC, IV	Dabrafenib		5.2 (4.2–6.1)	12.4 (10.2–15.0)
Lewis[37]	2019	Cohort	-	1027 (717 V vs 310 C+V)	IIIC or IV	Vemurafenib	Cobimetinib + Vemurafenib	0.80 (0.67–0.95)	0.84 (0.68–1.03)
Sullivan[38]	2019	Cohort	-	46 (17 A+V vs 39 A+C+V)	III	Atezolizumab + Vemurafenib	Atezolizumab + Cobimetinib + Vemurafenib	10.9 (5.7-22) for A+V, 12.9 (8.7-21.4) for A+C+V	46.2 (24.1-NE) for A+V, NE (NE-NE) for A+C+V

Abbreviation :
T: Trametinib
V: Vemurafenib
D: Dabrafenib
C: Cobimetinib
E: Encorafenib
B: Binimetinib
P: Pazopanib
A: Atezolizumab
Pa: Paclitaxel
Da: Dacarbazine
Ch: Chemotherapy
HR: Hazard ratio
CI: Confidence interval
PFS: Progression-free survival
OS: Overall survival
EFS: Event-free survival
RFS: Relapse-free survival
DFS: Disease-free survival
NR: Not reported
NE: Not estimable
*Confidence interval of the study is 90% (CI 90%)

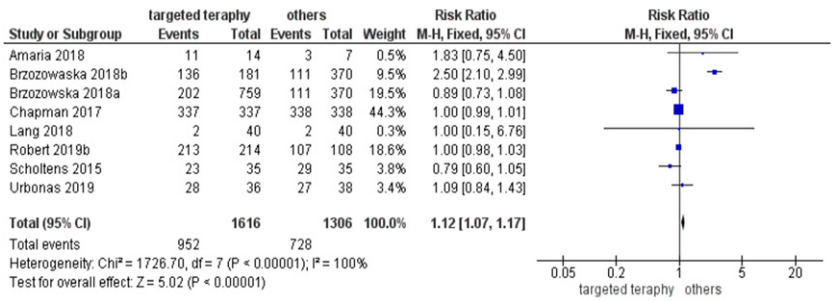

Figure 2. Forest plot of RR of BRAF and MEK inhibitors (vemuravenib, dabrafenib, and trametinib) compare with others treatment such as chemoteraphy, surgery, imunoteraphy,etc in assessing clinical outcome of melanoma in all stages.

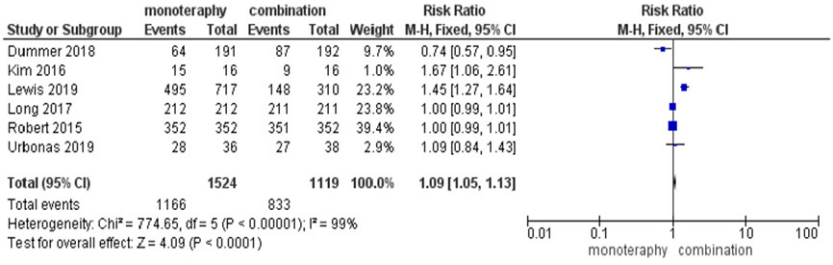

Figure 3. Forest plot of RR of BRAF and MEK inhibitors (vemuravenib, dabrafenib, and trametinib) as a monoteraphy compare with combination teraphy in assessing clinical outcome of melanoma in all stages.

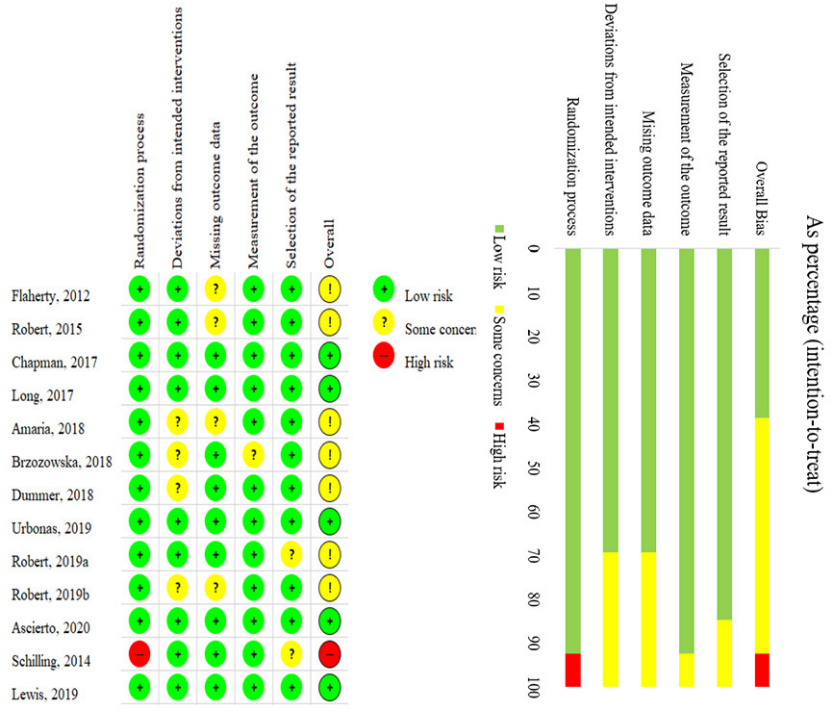

Figure 4. Summary risk of bias in RCT study.

substantial heterogeneity, 30%-60% may present as moderate heterogeneity, and 0%-40% might not be important. Those all also depend on the magnitude and direction of effects, the strength of evidence for heterogeneity. Other estimations have been analyzed as follows risk ratio (RR) for assessing the efficacy and safety, 95% confidence interval (95% CI) as population parameters. Risk ratio and 95% statistically significant if p<0.05.

RESULT

Systematic Literature Review

Initially, 2,180 citations were identified from the selected journal database using keywords and boolean operators. About 304 additional citations were obtained through other sources. All citations are analyzed in the title and abstract screening, 1,999 citations are excluded. The screened citations go through to access eligibility, and 344 citations are obtained based on exclusion criteria (restricted and over ten years). Those citations are checked for duplication and continue to qualitative studies, 222 citations are available. The method and result of citations are analyzed to include them in this review. There are 20 citations in the quantitative synthesis (Figure 1) and summarized in Table 1.

Overall survival rate (OS) and progression-free survival rate (PFS) of treatment response

Two meta-analyses have been assessed. The OS and PFS of the study that was using targeted therapy (vemurafenib, trametinib, or dabrafenib) compare to other treatments (chemotherapy, immunotherapy, etc.) showed RR was 1.12(95% CI 1.07-1.17; I^2=100%; p<0.00001) (Figure 2). Whereas, the OS and PFS with monotherapy compare of vemurafenib, trametinib, or dabrafenib with combination therapy showed RR was 1.09 (95% CI 0.06-1.13; I^2=99%; p<0.00001) (Figure 3)

Risk of Bias Analysis

One included study (8.3%) shows a high risk of bias at domain "randomization process" because there is no evidence that the experimental was randomized.[20] Four included studies (33.3%) show some concerns of bias at domain "deviations from intended interventions" because some experimental context led to additional interventions beyond those specified in the protocol that might also affect the study's outcomes.[24-26,29] Four included study (33.3%) show some concerns of bias at domain "missing outcomes data" because not all participants were interpreted and analyzed, but the result might not be affected.[17,21,24,29]

One included study (8.3%) shows some concerns of bias at domain "measurement of the outcomes"

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Table 2. **Analysis of risk bias in cohort study**

No.	Study ID	Selection	Comparability	Outcome	Quality score
1.	Puzanov, 2015	☆	☆	☆☆☆	**Poor**
2.	Scholtens, 2015	☆☆☆	☆☆	☆☆	**Good**
3.	Kim, 2016	☆☆	☆☆	☆☆	**Good**
4.	Long, 2016	☆☆☆	☆	☆☆☆	**Good**
5.	Lang, 2018	☆☆☆	☆☆	☆☆	**Good**
6.	Algarra, 2018	☆☆	☆	☆☆	**Fair**
7.	Sullivan, 2019	☆☆	☆	☆☆	**Fair**

because some measurement of the outcome has differed between intervention groups.[25] Two included studies (16.7%) show some concerns of bias at domain "selection of the reported result" because the data that produced this study were not analyzed following a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis.[20,28]

On the other hand, we were converting the Newcastle-Ottawa scales to The Agency for Healthcare Research, and Quality (AHRQ) standards included good, fair, and poor quality to define the quality of cohort studies. One included study (14.2%) shows a poor quality because the selection bias due to groups of patients was not prospectively defined. The population was not drawn from the same community as the exposed cohort and no description of ascertainment of exposure.[31] The overall quality of the studies also likely to be affected by the small number of patients in the 3 included studies (42.8%).[31,33,36]

DISCUSSION

Melanoma is highly mutated, particularly for the BRAF gene. Thus, it leads to the worst prognosis.[39] BRAF gene provides instruction for transmitting a chemical signal from the outside cell to the nucleus. It's activated through the membrane tyrosine kinase. Mutation of BRAF gene promoting RAF-MEK-ERK signaling pathway activation thus leads to abnormal cell proliferation. Moreover, BRAF V600E protein mutation in melanoma and thyroid cancer correlates with alteration of the immune system by expressing a high level of FOXP3+ Regulatory T Cells (Tregs) that function to inhibit anti-tumor immune responses. Thus, it makes patient-related BRAF V600E mutation protein in melanoma and thyroid cancer have a poor prognosis. In addition, BRAF inhibitors also increase dendritic cell-mediated antitumor immune responses. Due to many studies discovering BRAF mutation in melanoma, targeted therapies related to BRAF mutation have been developed, such as vemurafenib, which can improve antigen recognition by antigen-specific T lymphocytes (melanocyte differentiation agents), dabrafenib, encorafenib.[9,10] BRAF gene related to MEK gene due to their signaling pathway. Thus, targeted therapy-related MEK inhibitors have been developed. Unfortunately, the only trametinib as a specifically targeted therapy of MEK inhibitor has been approved by FDA.[18] The adverse events of the treatment and the overexpression of EGFR, platelet-derived growth factor receptor-β, gene encoding related to the COT kinase, mutation downstream of MEK1 kinase, NRAS, and or splicing of BRAF gene cause resistance of BRAF inhibitor. Thus, combination therapy could be an alternative way to overcome it.[9]

Several studies establish the clinical outcome related to targeted therapy and its combination. According to the Keith study, trametinib has a longer median duration of progression-free survival (4.8 months) compared with the chemotherapy group (1.5 months), with HR for PFS, 0.45 (95% CI: 0.33-0.63; p<0.001). There was a reduction of mortality rate in the trametinib group (16%) compared to the chemotherapy group (27%), with the most common adverse events in the trametinib group were rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform.[19] The combination of dabrafenib and trametinib had less mortality rate (28%) than monotherapy of vemurafenib (35%). Amaria study reported that this combination therapy has a longer median event-free survival of 19.7 months than standard care (surgery followed by consideration of standard adjuvant therapy) was 2.9 months.[40] Nevertheless, several adverse events have been reported, followed by pyrexia, nausea, diarrhea, chills, fatigue, headache, and vomiting. In vemurafenib therapy, the most frequent adverse events were arthralgia, rash, alopecia, diarrhea, nausea, and fatigue. Skin toxic effects were more frequent in the vemurafenib group than in the combination therapy group, and pyrexia was more frequent in the combination therapy group than in the vemurafenib group.[21] Urbonas study reported the median progression-free survival of paclitaxel and trametinib (5.2 months) was significantly

longer than paclitaxel alone (3.4 months). There was no significant difference in PFS between paclitaxel plus pazopanib and single paclitaxel therapy.[27]

Our meta-analysis study found that patients with targeted therapy were predisposed to a better clinical outcome in a patient with the positive BRAF gene mutation. Moreover, combination therapy has a better prognosis than monotherapy, probably due to the resistance mechanism. Meanwhile, it needs to be proved further. Unfortunately, the limitation in our study is not able to access several full paper inclusion study, thus further research with more databases is needed.

CONCLUSION

BRAF and MEK targeted therapy have a good prognosis for a patient with a positive BRAF gene mutation. In addition, this therapy could be combined with other treatments and has a better clinical outcome rather than monotherapy.

FUNDING

None.

AUTHORS CONTRIBUTION

All authors were contributed to article preparation and publication.

CONFLICT OF INTEREST

There was no conflict of interest regarding the publication.

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