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Cardiovascular adverse events of BRAF and/or MEK inhibitors in cancer patients: a systematic review and meta-analysis of placebo randomized- controlled trials

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DU GRADE DE DOCTEUR EN MÉDECINE

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M. Charles François Hoa-Binh Dolladille

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TITRE DE LA THÈSE :

Cardiovascular adverse events of BRAF and/or MEK inhibitors in cancer patients: a systematic review and meta-analysis of placebo randomized-controlled trials

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Abbreviations

CI: Confidence interval

CTCAE: Common Terminology Criteria for Adverse Events

CVAE: Cardiovascular adverse events

DCR: disease control rate

DFS: disease-free survival

ER: oestrogen receptors

ERK: extracellular signal-regulated kinase

GRADE: Grading of Recommendations Assessment, Development and Evaluation

IM: intramuscular

IV: intravenous

MB: muscle/brain

MD: missing data

MedDRA: Medical Dictionary for Regulatory Activities

MEK: Mitogen-activated extracellular signal-regulated kinase

MeSH: Medical Subject Headings

OR: Odds-Ratio

OS: overall survival

PFS: progression-free survival

PgR: progesterone receptors

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: International Prospective Register of Systematic Reviews

RCT: Randomized controlled-trial

RPCT: Randomized placebo-controlled trial

Summary

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Introduction

Overall survival and progression free survival have dramatically improved in cancer patients with the emergence of new generation antineoplastic therapies represented by kinase inhibitors and more recently immunotherapies¹⁻³. *BRAF* and mitogen-activated extracellular signal-regulated kinase (MEK) selective inhibitors have been evaluated in a variety of cancers such as melanoma, non-small cell lung cancer, breast and pancreatic cancer. *BRAF* mutation in tumors causes a hyperactivation of the RAS-RAF-pathway (mitogen-activated protein-MAP-kinase). This pathway leads to the extracellular signal-regulated kinase (ERK) activation which promotes the transcription of important genes for cell proliferation and differentiation and resistance to apoptosis⁴. *BRAF* and MEK selective inhibitors interrupt this cascade (Figure 1). *BRAF* inhibitors improved progression-free survival in monotherapy^{3,5}. Several meta-analyses of efficacy suggested that *BRAF* and MEK inhibitors combination therapy significantly improved the overall response, progression-free survival and overall survival versus *BRAF* monotherapy^{6,7}. However, these treatments are also responsible for a wide range of toxicities (cutaneous, digestive, rheumatologic⁶), including cardiovascular adverse events (CVAEs). An increased risk of ejection fraction decrease was found in randomized controlled trials (RCTs) regarding trametinib and cobimetinib in association with vemurafenib^{8,9}, and vemurafenib was associated with a higher risk of QT prolongation¹⁰. MEK inhibitors also presented a higher risk of hypertension (risk ratio 1.54, p=0.04) and decrease in ejection fraction (risk ratio 1.85, p=0.05) in a meta-analysis of MEK inhibitors safety¹¹.

Previous safety meta-analyses mostly relied on selected terms of the Medical Dictionary for Regulatory Activities (MedDRA) assessment^{6,7,11}. In these studies, there was no attempt to explore the entire CVAE safety data. Furthermore, monotherapy and combination therapy trials have sometime been pooled altogether in safety evaluation causing some bias in the true effect of each pharmacological class. Finally, there was no previous meta-analysis that focused on randomized placebo-controlled trials (RPCTs) to investigate the cardiac safety of *BRAF* and/or MEK inhibitors and therefore the exact cardiac risk and severity of these agents remained not fully understood. Therefore, we performed a systematic review and meta-analysis of CVAEs in *BRAF* and/or MEK inhibitors RPCTs, in both monotherapy and combination therapy, for any cancer type.

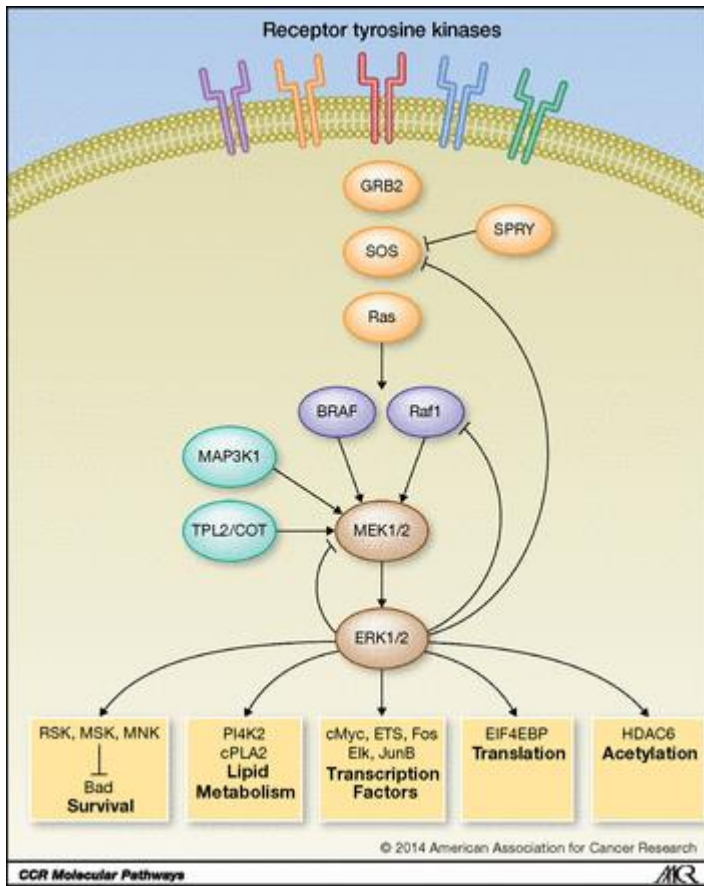


Figure 1 – Reproduced from Johnson et al, 2014, Clinical Cancer Research. Model of the ERK1/2 MAPK signaling network controlled by receptor tyrosine kinases and Ras.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^{12,13} (Supplementary Table 1). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42018094729.

Data Sources and Search strategy

An extensive, computerized MEDLINE, EMBASE and Cochrane Library literature search was conducted according to the pre-specified selection criteria from database inception to September 18th, 2018. There was no language limitations imposed to the search although we finally only included in our analyses studies in English or French languages. As pre-specified in our protocol, the search strategy included the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity maximizing version (2008 revision) filter in MEDLINE and the search filters for identifying randomized trials in EMBASE that are described in the Cochrane Handbook for Systematic Review of Interventions version 5.1.0¹⁴. The Cochrane Library search was not restricted by filters. We also scanned reference lists of included studies and previous relevant reviews to ensure published literature saturation. Trial protocols on trials registry platforms including clinicaltrials.gov (<https://clinicaltrials.gov/>), the World Health Organization international clinical trials registry platform (<http://apps.who.int/trialsearch/>), and data from scientific meeting abstracts and conference were screened for unpublished or ongoing studies (Congress of The European Society for Medical Oncology, Congress of the American Society for Medical Oncology, Congress of the Society for Melanoma Research, the European Cancer congress, the International Melanoma congress, the American Society of Hematology meeting, symposium of the Society of Surgical Oncology). We used both controlled terms (i.e. MeSH-terms in MEDLINE) and free text terms related to *BRAF* and/or MEK inhibitors as sole domain, including industrial codes for each specific molecule. We did not create a secondary domain dedicated to CVAE to prevent a restrictive search strategy since we did not expect them to be reported in title or abstract of RCTs. Supplementary data 1 shows the MEDLINE draft search strategy.

Study selection

Efficacy studies evaluating the effects of *BRAF* and/or MEK inhibitors, alone or in combination therapy for any cancer type in adult and children patients were included. Studies that did not report at least one CVAE as defined in the Outcome section were excluded. A hierarchical study inclusion plan was pre-specified. Our aim was to assess the risk of CVAEs in RPCTs to obtain the highest level of evidence.

Data extraction

We screened study titles and abstracts yielded by the search against eligibility criteria. Full reports were obtained for all eligible articles/abstracts. We extracted data from the selected studies using a standardized data extraction form. Any disagreements were resolved by the senior author (J.A.). Data extracted included patient demographic and baseline characteristics, patient selection, methodology and study design, inclusion and exclusion criteria, follow-up duration, number of patients, type and dosing of *BRAF* and/or MEK inhibitors (when available) and CVAE reported during the follow-up. The detailed list and description of variables collected is shown in Supplementary Data 2. To avoid duplicate study bias, we solely considered the study with the longest follow-up duration when multiple reports of the same trial were available. Additional information were sought by contacting corresponding authors or pharmaceutical industrials through e-mail contact.

Outcomes

The primary outcome was the risk of all-grade hypertension, all-grade ejection fraction decrease and all-grade peripheral oedema with *BRAF* or MEK inhibitors compared with placebo in monotherapy trials. We used as primary outcomes all the CVAEs that had previously been significantly associated with the use of *BRAF* or MEK inhibitors in at least one meta-analysis^{11,15,16}.

Secondary outcomes were the risk of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or more and serious of each of the individual components of the primary outcome (hypertension, ejection fraction decrease and peripheral oedema). We assessed the risk of all the other CVAEs (all-grade, CTCAE grade 3 or more and serious) reported in the safety data of RPCTs in monotherapy trials. We also analyzed the risk of all CVAEs (all-grade, CTCAE grade 3 or more and serious) in combination therapy trials. All CVAEs had to be reported with MedDRA terms in the safety database of the studies. All the MedDRA terms related to the field of cardiovascular diseases were analyzed. To ensure reproducibility, we selected MedDRA terms which belong to MedDRA system organ classes “Cardiac Disorders” and “Vascular Disorders” or to the Standardized MedDRA queries “Cardiac arrhythmia”, “Cardiac failure”, “Cardiomyopathy”, “Embolic and thrombotic events”, “Hypertension”, “Ischaemic heart disease”, “Pulmonary hypertension”, “Thrombophlebitis” and “Torsade de pointes/QT prolongation”. Individual MedDRA terms analyses were performed. Standardized MedDRA queries are validated, standard sets of MedDRA terms that are not confined to the system organ class hierarchy, to improve safety signal detection¹⁷.

Seriousness of an adverse event had to be reported following the Food and Drug Administration definition¹⁸, which mainly corresponds to death, life-threatening issues, hospitalization or prolongation of a current hospital stay, ongoing or significant incapacity issues. Following our hierarchical study inclusion plan, comparison would have been against control other than placebo if we did not find enough RPCTs.

Exploration of heterogeneity of *BRAF* and/or MEK inhibitors-induced CVAE

Subgroup and sensitivity analyses were performed on the summary odds-ratio (OR) of the primary outcome to explore possible sources of heterogeneity or inconsistency. We performed subgroup analyses on the primary outcomes only if the heterogeneity was significant ($I^2 > 50\%$ or Chi^2 p-value < 0.1). In subgroups analyses, the following parameters were studied: patient demographic (study median age < 60 years old or ≥ 60 years old), type of cancer, exclusion or not of patients with clinically significant cardiovascular disease (defined in individual study protocols), treatment dose and follow-up duration (median follow-up < 12 months or ≥ 12 months). In accordance with the Cochrane Handbook, subgroups were designed for exploratory purposes and we qualitatively described the findings (subgroups p-values are for descriptive purpose). Sensitivity analyses included individual study removal, quality component (full-text published studies versus meeting abstracts/non-published studies), risk of bias (by omitting studies presenting a high risk of bias), funding (institutional, industrial), biggest study removal (studies with the highest weight in the main analysis, with threshold depending on the number of included studies) and small study bias (study sample size ≤ 100 patients).

Risk of bias (quality) assessment

The Cochrane Collaboration's Risk of Bias Tool for Randomized Controlled Trials¹⁹ that is described in the Cochrane Handbook version 5.1.0¹⁴ was used to assess the risk of bias in individual randomized controlled clinical trials. Any disagreements were resolved by the senior author (J.A.). With respect to this risk of bias assessment and after careful consideration, studies were classified in "high risk of bias" or "low to moderate risk of bias" to perform sensitivity analyses. The potential for reporting/publication bias was visually explored by funnel plots and Egger's test if 10 studies or more were included.

Assessment of strength of the body of evidence

We planned to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology to assess the quality of evidence for all the outcomes²⁰.

Statistical analysis

Statistical analyses were performed with R software Version 3.4.4 for Windows (R Foundation for Statistical Computing, Vienna, Austria), package meta. Heterogeneity was measured using the Chi^2 and I^2 statistics with Chi^2 p-value. Significant between-study heterogeneity was defined as $I^2 > 50\%$ or Chi^2 p-value < 0.1 . Heterogeneity was low $< 30\%$, moderate between 30 and 50% and substantial $> 50\%$ ¹⁴. We pre-specified to conduct meta-analyses using a fixed-effect model and the OR statistic by Peto if studies were sufficiently homogeneous in terms of design and comparator. However, a random-effect would have been used in case of significant heterogeneity. We computed OR with 95% confidence interval (CI) from the number of each CVAE occurrence in each group (treatment arm versus placebo arm in monotherapy trials and combination arm versus monotherapy plus placebo arm in combination trials) and the total number of patients in the safety groups as

reported in the studies. Sensitivity analyses assessed the robustness of the main result by recalculating the combined OR after excluding study(ies). In subgroup analyses, between-group heterogeneity was computed. A p-value <0.05 was considered statistically significant.

Results

Figure 2 shows the flow diagram of the study selection process. This process allowed to retrieve 11 RPCTs that fulfilled the eligibility criteria. There was 9 monotherapy trials, with 8 studies of *BRAF* or MEK monotherapy on top on standard chemotherapy versus placebo^{8,21-27} and one study of *BRAF* monotherapy alone versus placebo¹⁰. There was 2 *BRAF* and MEK combination therapy versus *BRAF* monotherapy and placebo trials^{28,29}. The inverted funnel plot for the primary outcome did not suggest any significant publication bias (Supplementary Figure 1).

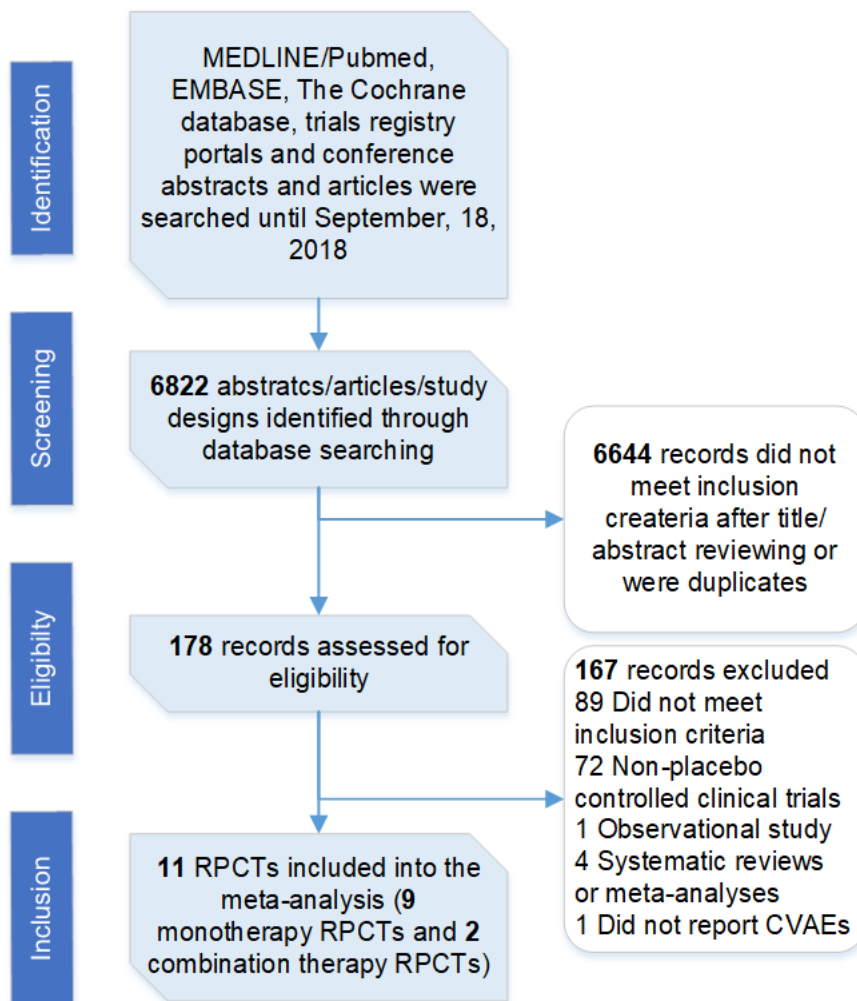


Figure 2 - Flow diagram of study selection. CVAEs: cardiovascular adverse events, RPCTs: randomized placebo-controlled trials.

Description of Included Studies

Table 1 presents the characteristics of the monotherapy studies included. A total of 1,722 adult patients (no study with children patients) were enrolled in monotherapy studies, with 915 patients in the *BRAF* or MEK inhibitor arms (53.1%) and 807 patients in the control arms (46.9%). One study had 3 groups of treatment²⁵ (selumetinib + docetaxel 60mg/m², selumetinib + docetaxel 75mg/m², placebo + docetaxel 75mg/m²), we only included patients of the selumetinib + docetaxel 75mg/m² and placebo + docetaxel 75mg/m² groups. The median age in the *BRAF* or MEK inhibitor groups ranged from 51/55 years (BRIM8 study with 2 cohorts) to 64 years. One study had a non-randomized phase Ib part and a randomized placebo-controlled phase II part²⁶, we only included patients from the phase II part. The administered *BRAF* or MEK inhibitor was selumetinib in 59.4%^{21-25,27}, vemurafenib in 27.0%¹⁰, trametinib in 8.7%⁸ and pimasertib in 4.9%²⁶ of active arm patients. The concomitant standard chemotherapy was docetaxel in 41.4%^{22,23,25}, gemcitabine in 13.7%^{8,26}, dacarbazine in 15.4%^{21,24}, fulvestrant in 2.5%²⁷ and there was no concomitant chemotherapy in 27.0%¹⁰ of patients. The cancer type was melanoma in 41.4%^{10,21,24}, non-small cell lung cancer in 41.7%^{22,23,25}, pancreas cancer in 14.3%^{8,26} and breast cancer in 2.6%²⁷ of patients. Three studies^{8,21,26} included only metastatic cancers, 5 studies^{22-25,27} included both metastatic and non-metastatic cancers and one study¹⁰ did not include metastatic cancers. Five studies were first line treatment trials^{8,10,21,24,26}, which represented 55.7% of patients. Patients cardiovascular comorbidities were exclusion criteria in 4 studies^{8,10,21,27} (detailed list in Supplementary Data 3). Cardiac exclusion criteria were mainly uncontrolled blood pressure, signs and symptoms of ischaemic heart disease, prolonged QT interval and ejection fraction below normal values. Exposition to cardiovascular risk factors was not reported with the exception of smoking status in non-small cell lung cancer trials^{22,23,25}, which ranged from 16% to 26% current smokers and from 62% to 73% former smokers. The included studies did not report the cardiovascular past history, cardiovascular risk factors or the cardiovascular medication intakes of the patients. Median follow-up was available in 7 studies and ranged from 2.7 to 33.5 months. Seven studies used version 4.0 of the CTCAE and two studies used version 3.0^{22,24}. All the studies were published in full-text and had at least a partial industrial funding.

Table 1 presents the characteristics of the combination therapy studies included. In the combination therapy studies, there were a total of 913 patients with 456 (49.9%) in the combination arms and 457 (50.1%) in the monotherapy arms. The combination therapy were dabrafenib + trametinib versus dabrafenib + placebo²⁹ and vemurafenib + cobimetinib versus vemurafenib + placebo²⁸. Both studies included advanced (unresectable stage IIIC or IV) V600 *BRAF* mutant melanoma patients. These 2 studies were updates of the initial studies with long-term survival and safety analysis (combi-d and coBRIM, respectively). Both studies excluded patients with cardiovascular comorbidities (Supplementary Data 3).

Table 1 - Characteristics of the clinical trials included in the meta-analysis

| Authors, study name (if available) | <i>BRAF</i> and/or MEK inhibitor | <i>BRAF</i> and/or MEK inhibitor initial doses | Concurrent cytotoxic chemotherapy | Study Comparator | Duration of treatment | Population size | Safety population size (% of patient in active arm) | Cancer type | Line of treatment | Median age in treatment group | Cardiovascular comorbidities were exclusion criteria | Study primary outcome | Median follow-up duration in months |
|---|----------------------------------|--|---|---------------------------------------|--------------------------------------|-----------------|---|---|-------------------|-------------------------------|--|-----------------------|-------------------------------------|
| <i>BRAF</i> or MEK inhibitors monotherapy trials | | | | | | | | | | | | | |
| Carvajal et al, 2018, SUMIT | Selumetinib | 75mg twice per day | Dacarbazine IV 1,000mg/m ² on day 1 of a 21-day cycle | Placebo + dacarbazine (same schedule) | Until efficacy or major safety event | 129 | 129 (75.2) | Metastatic uveal melanoma | 1 | 63 | Yes | PFS | 2.7 |
| Gupta et al, 2014, DOC-MEK | Selumetinib | 75mg twice per day | Docetaxel 75mg/m ² IV every 3 weeks up to six cycles | Placebo + docetaxel (same schedule) | Until efficacy or major safety event | 83 | 79 (48.1) | Unresectable stage III or IV <i>BRAF</i> wild-type melanoma | 1 | 62 | Yes | PFS | 13.6 |
| Infante et al, 2014 | Trametinib | 2mg per day | Gemcitabine IV 1,000mg/m ² weekly x 7 for 8 weeks, then days 1,8,15 of 28-day cycles | Placebo + gemcitabine (same schedule) | Until efficacy or major safety event | 160 | 160 (50.0) | Metastatic adenocarcinoma of the pancreas | 1 | 64 | Yes | OS | MD |
| Jänne et al, 2013 | Selumetinib | 75mg twice per day | Docetaxel IV 75mg/m ² on day 1 of a 21-day cycle | Placebo + docetaxel (same schedule) | Until efficacy or major safety event | 87 | 86 (51.2) | Stage IIIB-IV <i>KRAS</i> -mutant non-small cell lung cancer | 2 | 59.5 | No | OS | 7.2 |
| Jänne et al, 2017, SELECT-1 | Selumetinib | 75mg twice per day | Docetaxel IV 75mg/m ² on day 1 of a 21-day cycle | Placebo + docetaxel (same schedule) | Until efficacy or major safety event | 505 | 505 (49.7) | Stage IIIB-IV <i>KRAS</i> -mutant non-small cell lung cancer | 2 | 62 | No | PFS | 2.7 |
| Maio et al, 2018, BRIM8 | Vemurafenib | 960mg twice per day | - | Placebo | 52 weeks | 498 | 494 (50.0) | Stage IIC-IIIB in cohort 1 and stage IIIC in cohort 2, <i>BRAF</i> ^{V600} mutation-positive melanoma | 1 | 51/55 | Yes | DFS | MD |
| Robert et al, 2013 | Selumetinib | 75mg twice per day | Dacarbazine IV 1,000mg/m ² on day 1 of a 21-day cycle | Placebo + docetaxel (same schedule) | Until efficacy or major safety event | 91 | 89 (49.4) | <i>BRAF</i> -mutant inoperable stage III or metastatic melanoma | 1 | 57 | No | OS | 12.3 |
| Soria et al, 2017, SELECT-2 | Selumetinib | 75mg twice per day | Docetaxel IV 75mg/m ² on day 1 of a 21-day cycle. | Placebo + docetaxel (same schedule) | Until efficacy or major safety event | 127* | 127 (66.1) | Locally advanced or metastatic non-small cell lung cancer | 2 | 62 | No | PFS | MD |
| Van Cutsem et al, 2018 | Pimasertib | 60mg twice per day | Gemcitabine IV weekly in 28-day cycles for 5 months | Placebo + gemcitabine (same schedule) | Until efficacy or major safety event | 88** | 87 (51.7) | Metastatic pancreatic adenocarcinoma | 1 | 63 | No | PFS | 10.6 |
| Zaman et al, 2013, SAKK21/08 | Selumetinib | 75mg twice per day | Fulvestrant IM on days 1, 15 and 29 of cycle 1, then every 28 ± 3 days | Placebo + fulvestrant (same schedule) | Until efficacy or major safety event | 46 | 45 (51.1) | Advanced-stage endocrine sensitive (ER and/or PgR≥10%) breast cancer | 2 | 66 | Yes | DCR | 22 |

BRAF and MEK inhibitors combination therapy trials

| | | | | | | | | | | | | | |
|-------------------------------------|---------------------------|---------------------------------------|---|---------------------------------------|--|-----|------------|--|---|----|-----|------------|------|
| Ascierto et al, 2016, coBRIM | Vemurafenib / cobimetinib | 960mg twice per day / 60mg 21 days/28 | - | Placebo + vemurafenib (same schedule) | Both: 52 weeks or until efficacy or major safety event | 495 | 493 (50.1) | Unresectable locally advanced or metastatic BRAF V600 mutation-positive melanoma | 1 | 56 | Yes | PFS and OS | 14.2 |
| Long et al, 2017, combi-d | Dabrafenib / trametinib | 150mg twice per day / 2mg per day | - | Placebo + dabrafenib (same schedule) | Both: Until efficacy or major safety event | 423 | 420 (49.8) | Unresectable stage IIIC or stage IV melanoma with BRAF V600E or V600K mutation | 1 | 55 | Yes | PFS | MD |

*All the studies included were full-text, published, randomized placebo-controlled clinical trials and had at least a partial industrial funding. * In the study by Soria et al, we only included patients of the selumetinib + docetaxel 75mg/m² and placebo + docetaxel 75mg/m² groups. ** In the study by Van Cutsem et al, we only included patients of the phase II placebo-controlled part of the study. DCR: disease control rate, DFS: disease-free survival, ER: oestrogen receptors, IM: intramuscular, IV: intravenous, MD: missing data, MEK: mitogen-activated extracellular signal-regulated kinase, OS: overall survival, PFS: progression-free survival, PgR: progesterone receptors*

CVAE incidence

Figure 3 shows the ORs of all-grade hypertension (panel A), ejection fraction decrease (panel B) and peripheral oedema (panel C) between *BRAF* or MEK inhibitors groups and placebo groups in monotherapy trials. *BRAF* or MEK inhibitor groups had a significantly higher incidence of all-grade ejection fraction decrease and peripheral oedema versus placebo groups, with a moderate heterogeneity for peripheral oedema and a low heterogeneity for ejection fraction decrease. Peripheral oedema was only reported in MEK inhibitor studies. There was no difference in the incidence of all-grade hypertension.

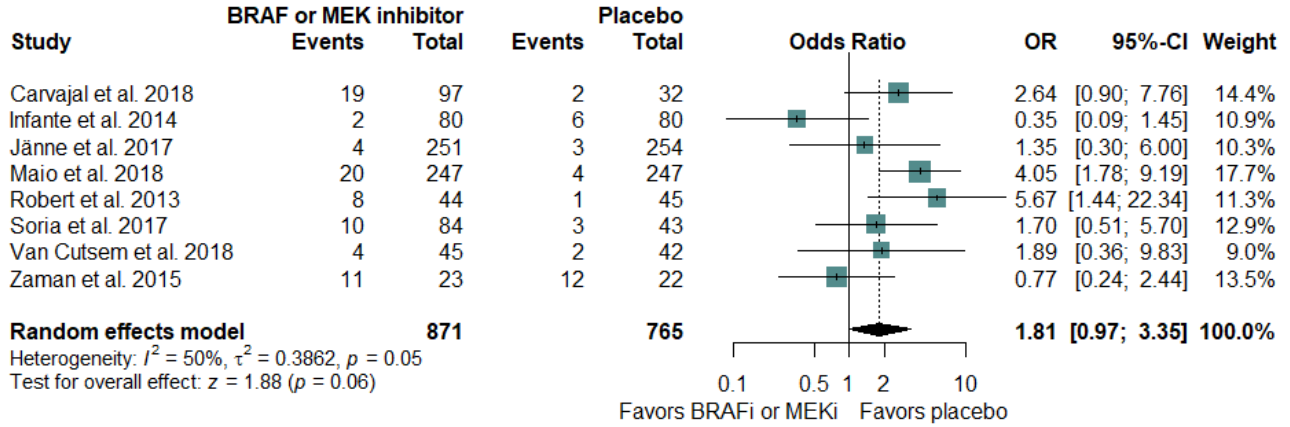
Individual summaries of the other all-grade CVAEs are reported in Table 2 and Supplementary Figure 2. There was 83 individual CVAE related terms in the safety data of monotherapy trials, of whom 35 were reported in at least two studies and eligible for a pooled estimation. *BRAF* or MEK inhibitor groups had a significantly higher incidence of syncope versus placebo and a significantly lower incidence of phlebitis, and atrial flutter. There was a trend for a higher incidence of cardiac failure in *BRAF* or MEK inhibitor groups versus placebo although it was not significant ($p=0.055$). Because QT prolongation was reported in only one study¹⁰, no pooled estimation could be drawn.

The incidence of CTCAE grade 3 or more hypertension was not different between groups in monotherapy trials (OR 1.83, 95%CI 0.85-3.94, $p=0.41$, $I^2=0\%$). There was no CTCAE grade 3 or more ejection fraction decrease reported in monotherapy trials. No other CVAE had a CTCAE grade 3 or more pooled estimation in monotherapy trials. The analyses of serious CVAE risk (Supplementary Table 2) showed that *BRAF* or MEK inhibitor groups had a significantly higher incidence of serious syncope versus placebo, without heterogeneity.

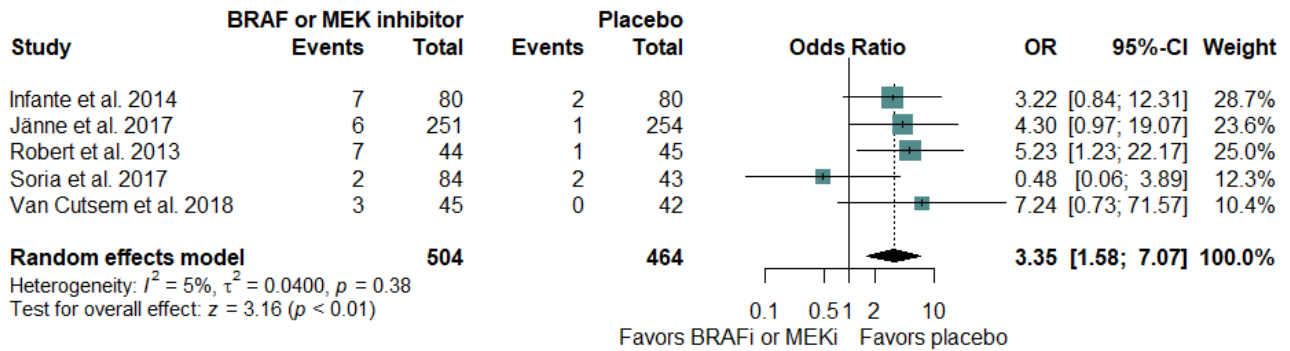
In combination therapy trials, there was 66 individual CVAE related terms in the safety data of whom 11 were reported in at least two studies and eligible for a pooled estimation. Combination groups had a significantly higher incidence of all-grade ejection fraction decrease than monotherapy groups (Figure 4, Table 2 and Supplementary Figure 2). The heterogeneity was low for all-grade ejection fraction decrease. There was no between group difference for the incidence of CTCAE grade 3 or more CVAE and serious CVAE (Supplementary Table 2).

Figure 3 – Forest plots of odds-ratio of (A) all-grade hypertension, (B) all-grade ejection fraction decrease and (C) all-grade peripheral oedema associated with *BRAF* or MEK inhibitors in monotherapy randomized controlled trials. BRAFi: *BRAF* inhibitor, MEK: mitogen-activated extracellular signal-regulated kinase, MEKi: MEK inhibitor, OR: Odds-Ratio, 95%-CI: 95% confidence interval

A.



B.



C.

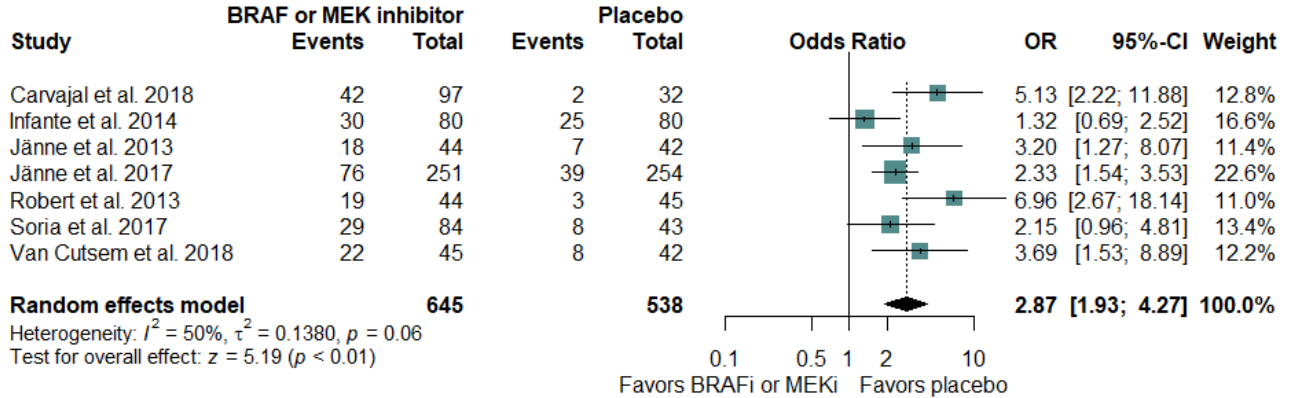
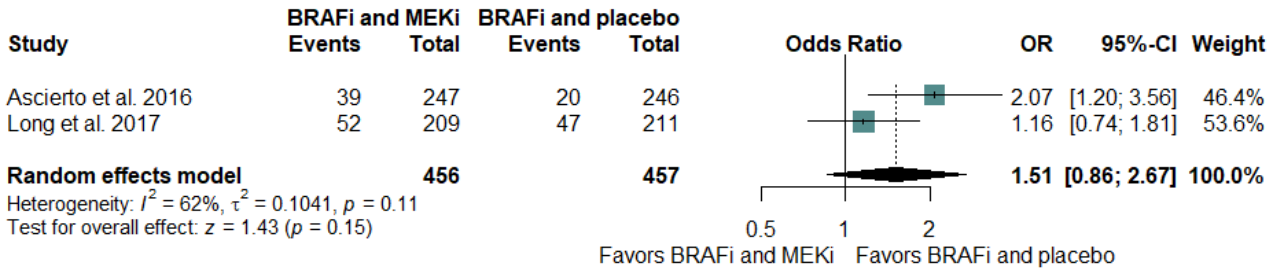
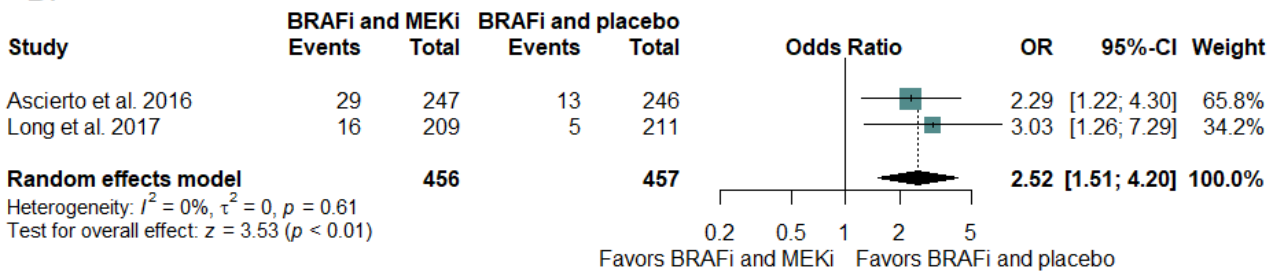


Figure 4 – Forest plots of odds-ratio of (A) all-grade hypertension, (B) all-grade ejection fraction decrease and (C) all-grade peripheral oedema associated with *BRAF* and MEK inhibitors combination therapy versus monotherapy plus placebo in randomized controlled trials. BRAFi: *BRAF* inhibitor, MEK: mitogen-activated extracellular signal-regulated kinase, MEKi: MEK inhibitor, OR: Odds-Ratio, 95%-CI: 95% confidence interval

A.



B.



C.

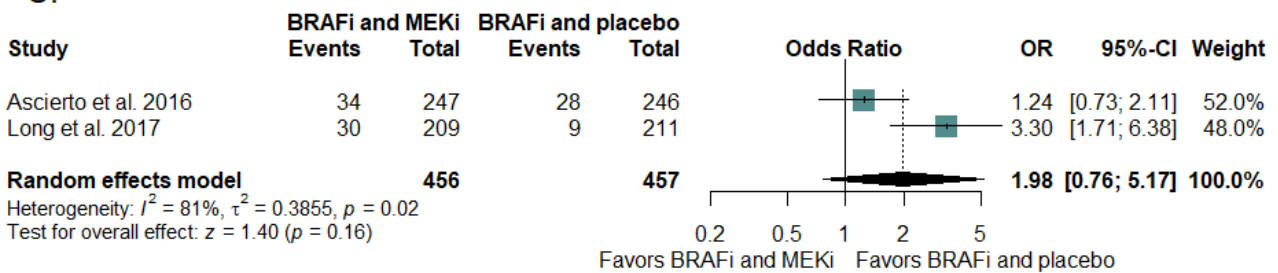


Table 2A – Individual MedDRA term analyses in monotherapy randomized controlled trials of *BRAF* or MEK inhibitors versus placebo

| MedDRA term | Number of studies reporting the outcome | Number of event in <i>BRAF</i> or MEK inhibitor groups | Number of event in placebo groups | Random effect Odds-Ratio | 95% confidence interval | p-value | I ² for heterogeneity | Chi ² p-value for heterogeneity |
|---|---|--|-----------------------------------|--------------------------|-------------------------|---------|----------------------------------|--|
| Atrial fibrillation | 4 | 10 | 6 | 1.43 | (0.53-3.9) | 0.48 | 0% | 0.43 |
| Atrial flutter | 4 | 1 | 4 | 0.16 | (0.02-0.99) | 0.049 | 0% | 0.48 |
| Blood creatine phosphokinase MB increased | 2 | 2 | 0 | 5.90 | (0.34-101.77) | 0.22 | 0% | 0.86 |
| Blood pressure increased | 3 | 5 | 1 | 2.85 | (0.26-31.19) | 0.39 | 42% | 0.18 |
| Cardiac arrest | 2 | 1 | 1 | 0.72 | (0.02-23.41) | 0.85 | 33% | 0.22 |
| Cardiac failure | 3 | 9 | 2 | 3.27 | (0.98-10.98) | 0.055 | 0% | 0.98 |
| Cardiac failure congestive | 3 | 2 | 3 | 0.48 | (0.05-4.21) | 0.50 | 24% | 0.27 |
| Cerebral ischaemia | 2 | 2 | 1 | 1.29 | (0.03-64.19) | 0.90 | 63% | 0.101 |
| Cerebrovascular accident | 2 | 1 | 1 | 0.97 | (0.02-45.38) | 0.99 | 48% | 0.17 |
| Chest pain | 6 | 15 | 6 | 2.24 | (0.92-5.41) | 0.07 | 1% | 0.41 |
| Deep vein thrombosis | 4 | 12 | 10 | 1.21 | (0.51-2.87) | 0.66 | 0% | 0.49 |
| Dyspnoea | 8 | 135 | 88 | 1.33 | (0.92-1.93) | 0.13 | 22% | 0.26 |
| Dyspnoea exertional | 6 | 26 | 17 | 1.45 | (0.77-2.71) | 0.25 | 0% | 0.84 |
| Ejection fraction decreased | 5 | 25 | 6 | 3.35 | (1.58-7.07) | 0.002 | 5% | 0.38 |
| Hemiparesis | 2 | 2 | 0 | 5.66 | (0.33-97.7) | 0.23 | 0% | 0.88 |
| Hypertension | 8 | 78 | 33 | 1.81 | (0.97-3.35) | 0.06 | 50% | 0.05 |
| Left ventricular dysfunction | 2 | 2 | 1 | 1.88 | (0.19-18.23) | 0.59 | 0% | 0.40 |
| Mitral valve incompetence | 2 | 2 | 0 | 5.90 | (0.34-101.77) | 0.22 | 0% | 0.86 |
| Myocardial infarction | 2 | 1 | 2 | 0.49 | (0.05-4.73) | 0.54 | 0% | 0.43 |
| Oedema | 3 | 14 | 11 | 0.71 | (0.04-11.46) | 0.81 | 81% | 0.005 |
| Oedema peripheral | 7 | 236 | 92 | 2.87 | (1.93-4.27) | <0.001 | 50% | 0.06 |
| Orthostatic hypotension | 3 | 6 | 1 | 3.85 | (0.86-17.3) | 0.08 | 0% | 0.73 |
| Palpitations | 4 | 5 | 3 | 1.31 | (0.15-11.11) | 0.80 | 51% | 0.11 |
| Pericardial effusion | 3 | 2 | 5 | 0.89 | (0.05-15.07) | 0.94 | 55% | 0.11 |
| Pericarditis | 2 | 3 | 0 | 6.37 | (0.64-63.86) | 0.12 | 0% | 0.85 |
| Peripheral ischaemia | 2 | 1 | 1 | 0.72 | (0.02-23.38) | 0.85 | 33% | 0.22 |
| Phlebitis | 3 | 0 | 4 | 0.08 | (0.01-0.63) | 0.02 | 0% | 0.90 |
| Pulmonary embolism | 8 | 12 | 9 | 1.22 | (0.51-2.92) | 0.65 | 0% | 0.49 |
| Pulmonary oedema | 2 | 1 | 1 | 0.65 | (0.01-84.88) | 0.86 | 66% | 0.09 |
| Sinus bradycardia | 2 | 2 | 0 | 7.27 | (0.45-116.22) | 0.16 | 0% | 0.98 |
| Sinus tachycardia | 3 | 2 | 6 | 0.27 | (0.06-1.11) | 0.07 | 0% | 0.40 |
| Supraventricular tachycardia | 2 | 3 | 1 | 1.99 | (0.14-29.25) | 0.61 | 43% | 0.18 |
| Syncope | 7 | 26 | 0 | 6.71 | (3-14.99) | <0.001 | 0% | 0.999 |
| Tachycardia | 3 | 5 | 9 | 0.54 | (0.19-1.55) | 0.25 | 0% | 0.37 |
| Thrombosis | 3 | 1 | 2 | 0.39 | (0.02-7.71) | 0.54 | 40% | 0.19 |

Table 2B – Individual MedDRA term analyses in combination therapy randomized controlled trials of *BRAF* and MEK inhibitors versus *BRAF* inhibitor plus placebo

| MedDRA term | Number of studies reporting the outcome | Number of event in BRAF or MEK inhibitor groups | Number of event in placebo groups | Random effect Odds-Ratio | 95% confidence interval | p-value | I ² for heterogeneity | Chi ² p-value for heterogeneity |
|------------------------------|---|---|-----------------------------------|--------------------------|-------------------------|---------|----------------------------------|--|
| Atrial fibrillation | 2 | 11 | 5 | 2.14 | (0.73-6.31) | 0.17 | 0% | 0.36 |
| Cardiac failure | 2 | 1 | 3 | 0.43 | (0.06-2.94) | 0.39 | 0% | 0.85 |
| Cerebrovascular accident | 2 | 3 | 0 | 3.93 | (0.44-35.47) | 0.22 | 0% | 0.82 |
| Dyspnoea | 2 | 31 | 34 | 0.91 | (0.57-1.47) | 0.71 | 0% | 0.50 |
| Ejection fraction decreased | 2 | 45 | 18 | 2.48 | (1.46-4.21) | <0.001 | 0% | 0.53 |
| Hypertension | 2 | 91 | 67 | 1.43 | (0.83-2.45) | 0.20 | 68% | 0.08 |
| Oedema peripheral | 2 | 64 | 37 | 1.94 | (0.71-5.32) | 0.20 | 82% | 0.02 |
| Pulmonary embolism | 2 | 7 | 2 | 3.34 | (0.68-16.46) | 0.14 | 0% | 0.57 |
| QT prolonged | 2 | 11 | 18 | 0.42 | (0.05-3.41) | 0.42 | 56% | 0.13 |
| Supraventricular tachycardia | 2 | 1 | 1 | 1.00 | (0.1-9.61) | 0.998 | 0% | 0.34 |
| Tachycardia | 2 | 11 | 16 | 0.61 | (0.06-5.83) | 0.67 | 83% | 0.01 |

Only cardiovascular adverse events that occurred in at least two studies are presented. MB: muscle/brain, MedDRA: Medical Dictionary for Regulatory Activities, MEK: mitogen-activated extracellular signal-regulated kinase

Subgroup analyses

To further explore study heterogeneity, we performed subgroup analyses based on several pre-specified clinical parameters (Table 3). In the absence of heterogeneity for ejection fraction decrease, we did not performed subgroups analyses on this outcome. The heterogeneity of the incidence of peripheral oedema was different among concomitant chemotherapy administered and cancer type (similar subgroups). There was a trend for a higher incidence in melanoma patients, treated with concomitant dacarbazine. There was no other subgroup difference observed. We could not perform subgroup analyses on treatment dose or dosage regimen because the schedule for *BRAF* and/or MEK administration was similar between the studies (Table 1).

Table 3 – Subgroup analyses for the incidence of all-grade peripheral oedema in monotherapy trials.
95%CI: 95% confidence interval, OR: Odds-Ratio

| Subgroups (number of studies) | OR (95%CI) | I² | Test for subgroup differences |
|--------------------------------------|-------------------|----------------------|--------------------------------------|
| Concomitant chemotherapy | 7 | | 0.04 |
| Dacarbazine | 5.86 (3.12-11.02) | 0% | |
| Docetaxel | 2.40 (1.70-3.38) | 0% | |
| Gemcitabine | 2.11 (0.77-5.77) | 71% | |
| Cancer type | 7 | | 0.04 |
| Melanoma | 5.86 (3.12-11.02) | 0% | |
| NSCLC | 2.40 (1.70-3.38) | 0% | |
| Pancreatic cancer | 2.11 (0.77-5.77) | 71% | |
| Median follow-up | 5 | | 0.19 |
| < 12 months | 2.99 (1.88-4.75) | 29% | |
| ≥ 12 months | 4.93 (2.58-9.43) | 0% | |
| Median age in treatment group | 7 | | 0.15 |
| < 60 years old | 4.67 (2.18-10.01) | 24% | |
| ≥ 60 years old | 2.47 (1.63-3.75) | 46% | |
| Cardiovascular comorbidities | 7 | | 0.35 |
| Excluded | 2.39 (1.26-4.51) | 68% | |
| Not excluded | 3.49 (2.17-5.62) | 13% | |

Sensitivity analyses

Sensitivity analyses on hypertension were equivocal. The association was significant in 2 of 8 (25%) estimations after individual study removal. Biggest and smallest trial removal did not change the association. Sensitivity analyses on ejection fraction decrease did not show any substantial variation in the magnitude or direction of the OR, although the association became non-significant with the removal of biggest and smallest studies (Supplementary Table 3). Sensitivity analyses on peripheral oedema did not change magnitude or direction either. The association remained significant in all the analyses. We could not perform the prespecified analyses regarding quality component, risk of bias and industrial funding because all the studies included were similar regarding quality components and risk of bias for the primary outcome. They also all received at least a partial industrial funding.

Study Quality, meta-biases

Regarding RPCTs quality (Supplementary Table 4), all the studies included had a low to moderate risk of bias. In a majority of studies^{8,21-27,29}, the CTCAE grading was reported for frequent adverse events only and thereby it is missing for more than 80% of the reports. We contacted the authors to gather this information. One additional author²⁷ provided this information. We reduced the quality of evidence for CTCAE grade 3 or more pooled estimations (-1).

According to the GRADE methodology, our primary outcome had a moderate consistency, with low to moderate risk of bias studies, a good precision and no evident publication bias. The heterogeneity was low to moderate. The quality of evidence for the primary outcome was judged to be high for ejection fraction decrease and peripheral oedema, and moderate for hypertension. The quality of evidence of the secondary outcomes (combination trials analyses, other CVAEs, CTCAE grade 3 or more and serious monotherapy trials analyses) was judged to be moderate, except for CTCAE grade 3 or more events where it was judged to be low.

Discussion

We performed an extensive and comprehensive systematic review and meta-analysis regarding the risk of CVAE occurrence in patients treated with *BRAF* and/or MEK inhibitors in RPCTs. We observed that: 1) *BRAF* or MEK inhibitors monotherapy was associated with a significantly higher incidence of ejection fraction decrease, peripheral oedema and syncope compared with placebo, with a low to moderate heterogeneity. 2) There was a trend for a higher incidence a hypertension and cardiac failure in *BRAF* or MEK inhibitors groups. 3) Combination therapy of *BRAF* and MEK inhibitors groups versus monotherapy groups had an even higher incidence of ejection fraction decrease. 4) The heterogeneity could be partially explained by the inclusion of studies of different cancer type and different concurrent cytotoxic chemotherapies use. 5) With the exception of a higher incidence of serious syncope in *BRAF* or MEK inhibitors in monotherapy trials, no grade 3 or more or serious incidences of CVAE were found, in both monotherapy and combination therapy trials.

Our results are consistent with previous findings of meta-analyses regarding ejection fraction decrease and peripheral oedema incidences, with the OR point estimates of the present study being similar to previous ones^{11,15,16}. The higher incidence of all-grade hypertension in *BRAF* or MEK inhibitor groups did not reach statistical significance in our study ($p=0.06$). Previous meta-analysis had very close p-values for the risk of hypertension ($p=0.04$ ¹¹ in a MEK inhibitor meta-analysis, $p=0.02$ ¹⁵ in a combination trial versus monotherapy of *BRAF* and MEK inhibitors). In our sensitivity analyses, this outcome could be significant depending on the included trials (Supplementary Table 3). We only included studies with the highest level of evidence and with the longest follow-up, which gives us confidence in our results. However, we acknowledge that further studies are likely to change the significance of this endpoint and caution should be taken with its interpretation. It is noteworthy that we did not observed higher incidences of either CTCAE grade 3 or more or serious hypertension, ejection fraction decrease and peripheral oedema. We hypothesize that these adverse events would be more frequent with *BRAF* or MEK inhibitors but generally well-tolerated.

The natural history of ejection fraction decrease in *BRAF* and MEK inhibitors was approached in an in-depth safety evaluation of the coBRIM study³⁰. In this study, most of the common adverse events had an early onset whereas ejection fraction decrease had no apparent temporal pattern. The median time to onset of ejection fraction decrease was between 2 and 4 months in both groups but it had a random frequency over the treatment period. Ejection fraction decrease led to a dose modification in 9 patients (21.4%). The median time to resolution was 5.5 and 2.8 months in vemurafenib and vemurafenib and cobimetinib groups respectively, with 60% and 82% of the ejection fraction decrease events resolved at data cut-off in vemurafenib and vemurafenib and cobimetinib groups, respectively. Robert et al. described the ejection fraction decrease in their study as asymptomatic and transient, with return within normal limits while continuing selumetinib in 4 patients and after interruption in 2 patients (of whom one was treated with ramipril plus furosemide)²⁴. It is consistent that whether ejection fraction decrease with *BRAF* and MEK inhibitors is transient, it would usually not be reported as a serious or high-grade adverse event.

All-grade hypertension occurred in 2% to 48% of patients in the included studies. In the management suggestion of adverse events with kinase inhibitors by Welsh et al., stage 2 or higher hypertension shall lead to MEK inhibitors discontinuation³¹. They also suggest that any patient with a decrease in the ejection fraction shall have kinase inhibitors withheld for at least 4 weeks if asymptomatic or permanently discontinued if symptomatic. To date, evidence is missing on the clinical characteristics of these adverse events. It is unknown whether the incidences of hypertension, ejection fraction decrease or peripheral oedema would be dose-dependent, or would alter the prognosis of patients. It is unclear that ejection fraction decrease would be symptomatic³¹ or not²⁴. It has been suggested that peripheral oedema could be a manifestation of cardiac failure and/or ejection fraction decrease in this setting. However, there was no significant association of *BRAF* or MEK inhibitors with dyspnea. Since serial echocardiography were not performed routinely in these trials, it is difficult to confirm this association³¹. We underline that there was no signal for high grade peripheral oedema, which could mean that this sign is either not related to cardiac failure or that cardiac failure in *BRAF* or MEK inhibitors would be subclinical. We believe that a further cardiovascular investigation with echocardiography is advisable in these symptomatic patients. For the management of adverse events, an approach of withholding or discontinuation of medications with adverse events that are potentially well-tolerated or not serious might lead to unjustified loss of chances for patients. An early stage detection and proper management of CVAEs appears crucial to prevent from treatment interruption or dose modification, and ultimately improve the efficiency of these treatments.

Regarding the heterogeneity observed in our analyses, a methodological diversity seems unlikely since we only included RPCTs with low to moderate risk of bias. The clinical diversity was explored through subgroup analyses. Although the studies assessed different drugs, they all belong to a similar pharmacological class and a meta-analysis seemed to be reasonable to evaluate the average effect of these drugs. The cancer type had a marked influence on the heterogeneity. Melanoma does not share many risk factors with cardiovascular disease whereas non-small cell lung cancer, pancreas cancer and breast cancer do (i.e. smoking). There could be a survivorship bias between cardiovascular disease and the development of lung or pancreas cancer, where patients diagnosed with these cancers would be less prompt to develop cardiovascular diseases. The female population of the breast cancer study is likely to have a lower risk than mixed populations as well. The fact that concomitant chemotherapy had an influence on heterogeneity is likely to be correlated with the cancer type. To our knowledge, there is no known pharmacological interaction between these chemotherapies and *BRAF* or MEK inhibitors that could underlie this association. Readers should keep in mind that these subgroups analyses are for exploratory purpose only and that no definitive conclusions should be drawn.

The risk of syncope with MEK 1/2 inhibitors was highlighted since phase I studies. Dose-limiting toxicity in these studies included presyncope for refametinib, syncope for PD0325901 and QTc prolongation in E6201³². QTc prolongation has been observed in individual studies of *BRAF* inhibitors. Syncope with these treatments might result of a rhythm disorder in both MEK and *BRAF* inhibitors. With syncope being the only serious CVAE associated with *BRAF* or MEK inhibitors, routine Holter-electrocardiogram could be relevant even in asymptomatic patients.

We observed a lower incidence of phlebitis and atrial flutter in monotherapy groups versus placebo. Meanwhile, we found no difference for the incidence of pulmonary embolism, thrombophlebitis, deep vein thrombosis or thrombosis with OR point estimate showing alternatively a protective or a negative association. Atrial fibrillation, supraventricular tachycardia and palpitations had an opposite point estimate compared to atrial flutter. This potential protective role on atrial flutter and phlebitis was not seen in previous studies. In safety databases, a similar clinical condition can have been coded with several close individual terms and its true incidence can be confounded. We believe that this situation may have occurred for atrial flutter and phlebitis.

This systematic review was conducted with an appropriate search strategy which allowed us to perform an extensive meta-analysis with all appropriate studies being included. Interestingly, a classic search strategy, i.e. combining search domains as *BRAF* and/or MEK inhibitors domain with cardiovascular diseases domain would have restricted our search, since CVAE are rarely mentioned in the title or abstract of phase II or III efficacy studies.

Previous meta-analyses, including network meta-analyses, were conducted to assess efficacy and safety of *BRAF* and/or MEK inhibitors^{6,7,15,33,34}. Several limitations appear in these studies. 1) The efficacy outcome analyses are the major concern and safety is considered as a second endpoint. In particular, cardiovascular safety is often limited to hypertension and ejection fraction decrease with non-standardized detection protocols^{11,15}. There was no attempt to explore other potential cardiovascular safety signals. 2) Since individual meta-analysis of efficacy were appropriately conducted for one type of cancer, mostly melanoma, they do not cover the entire data of *BRAF* and/or MEK inhibition safety.

Our study is the first study to explore specifically the cardiac safety of *BRAF* and MEK inhibitors alone or in combination. This design is meaningful to distinguish the cardiovascular risk of single inhibitor therapies versus combination therapies. As *BRAF* and MEK inhibitors target the same pathophysiological pathway, we expected an even higher risk for the combination than the monotherapy trials, which was found for other type of toxicities⁶. We observed a similar additive risk for ejection fraction decrease but not for peripheral oedema. The present study is the first safety meta-analysis in this domain to include only RPCTs, which represent the highest level of evidence. This study is also the first to conduct a pragmatic safety signal detection approach with the analyses of all the MedDRA terms related to the field of cardiovascular diseases. We believe this pharmacovigilance perspective could be relevant to find additional CVAE safety signals. Usual meta-analysis methods are focused on efficacy outcome measurements. Definition of a unique primary outcome is the standard. The agnostic approach of pharmacovigilance supposes that safety signals can be unintended and hence a unique adverse event evaluation can be misleading in signal detection. In the absence of dedicated method for safety meta-analysis, we still had to choose a primary adverse event of interest. Standardized MedDRA queries would have been a consistent candidate for primary evaluation¹⁷. However, since it gather together multiple terms of CVAE safety, it can only be used with individual patient level data. The overall rate of CVAE would have been a proper choice as well but this data is usually not reported and would otherwise suppose access to individual

patient level data. Hence, for meta-analyses with study level data, it is unclear which event is to select as primary outcome. We chose the CVAEs that had previously been detected in meta-analyses of safety. Since these adverse events were notorious, we expected them to be reported with care in the RPCTs, which warranted consistency between study and made subgroup analyses relevant.

Study limitations

Several aspects of this systematic review and meta-analysis must be considered when interpreting the results. The overall incidence of CVAE could not be assessed because it was not reported in the studies. We may have missed safety signals that a patient-level data meta-analysis would have provided, with the use of aggregated terms definitions of CVAEs. CVAE reports were not always the result of a systematic assessment and a threshold was often used for the report of non-serious CVAE, although it was quite low (ranged from 0% to 10%, Supplementary Table 4). The consistency of individual terms reporting was uncertain, but we did not observe frequently heterogeneity levels that were above 50% (Table 2).

We did not perform meta-regression since we had less than 10 studies in the primary outcome analysis.

The exposition to cardiovascular risk factors or cardiovascular past history of patients were not reported in the studies. These factors always increase the risk of cardiovascular toxicity for all cancer type and all antineoplastic therapies³⁵. It is probable that these factors were different between studies and could have participated in the observed heterogeneity. Furthermore, the cardiovascular medication intakes were not reported. Presumably, in study accruing patients treated with conversion enzyme inhibitors or beta-blockers for hypertension, the risk of ejection fraction decrease would have been lowered by these drugs.

Conclusion

The incidence of ejection fraction decrease, peripheral oedema, dyspnea and syncope is increased with the use of *BRAF* or MEK inhibitors in monotherapy in cancer patients. Combination therapies have an even higher incidence of ejection fraction decrease. CVAEs were not considered serious or CTCAE high grade in the majority of cases, which supports the hypothesis that they might have a limited impact in clinical practice. Routine practice shall constrains to establish the potential link between cardiovascular symptoms like peripheral oedema or dyspnea with cardiac failure, and possible provoking factor of cardiac failure like hypertension. Systematic echocardiography in symptomatic patients is advisable. In the opposite, asymptomatic patients would not necessarily need close cardiac monitoring, with the possible exception of Holter-electrocardiogram due to the risk of syncope. A better knowledge and ultimately an earlier detection and management of CVAEs could reduce the dose modifications and achieve a better efficiency of these treatments.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Supplementary material

Supplementary Table 1 – PRISMA checklist for the meta-analysis¹³.

| Section/topic | # | Checklist item | Reported section (top-level heading) |
|---------------------------|----------|---|--|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Both, title, abstract |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Abstract |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Introduction |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Introduction |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | CRD42018094729 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Study selection, Outcomes |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Search strategy |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Search strategy, Supplementary data 1 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Study selection |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Data extraction |

| | | | |
|------------------------------------|----|--|--|
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Supplementary data 2 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Risk of bias (quality) assessment |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Statistical analysis |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. | Outcomes, Statistical analysis |

Page 1 of 2

| Section/topic | # | Checklist item | Reported section # (top-level heading) |
|-------------------------------|----------|--|--|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Risk of bias (quality) assessment |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Exploration of heterogeneity on CVAE occurrence in BRAF and/or MEK inhibitors versus placebo Statistical analysis |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Figure 2 (flow diagram) |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Study characteristics, Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Supplementary table 4 Risk of Bias, Study Quality, meta-biases |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | CVAE incidence Odds-Ratio, Subgroup analyses, Figures 3 and 4, Table 2, Supplementary Figures 2 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of | CVAE incidence Odds- |

| | | | |
|-----------------------------|----|--|---|
| | | consistency. | Ratio, Subgroup analyses, Figures 3 and 4, Table 2, Supplementary table 2 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Study Quality, meta-biases Supplementary Table 4 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | CVAE incidence Odds-Ratio, Subgroup analyses, Table 3, Supplementary Figure 2, Supplementary Table 3 |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Study Quality, meta-biases Discussion (1st paragraph) |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Study limitations, discussion |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Conclusion |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Funding sources/sponsors |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Table 2 – Serious and grade 3 or more cardiovascular adverse events summary odds-ratio in monotherapy and combination therapy trials

Supplementary Table 2A – Summary Odds-Ratio of serious cardiovascular adverse events in *BRAF* or MEK inhibitors monotherapy trials versus placebo

| MedDRA term | Number of study reporting the outcome | Number of event in BRAF or MEK inhibitor groups | Number of event in placebo groups | Odds-Ratio (Random effect) | 95% confidence interval | p-value | I ² for heterogeneity | Chi ² p-value for heterogeneity |
|----------------------------|---------------------------------------|---|-----------------------------------|----------------------------|-------------------------|---------|----------------------------------|--|
| Atrial fibrillation | 2 | 2 | 1 | 1.29 | (0.03-63.1) | 0.90 | 63% | 0.102 |
| Atrial flutter | 2 | 1 | 1 | 0.57 | (0.02-15.28) | 0.74 | 18% | 0.27 |
| Cardiac arrest | 2 | 1 | 1 | 0.72 | (0.02-23.41) | 0.85 | 33% | 0.22 |
| Cardiac failure | 3 | 4 | 1 | 2.58 | (0.42-15.93) | 0.31 | 0% | 0.93 |
| Cardiac failure congestive | 3 | 2 | 2 | 0.72 | (0.09-5.83) | 0.76 | 6% | 0.34 |
| Cerebral ischaemia | 2 | 1 | 1 | 1.01 | (0.02-51.3) | 0.998 | 50% | 0.16 |
| Cerebrovascular accident | 2 | 1 | 1 | 0.97 | (0.02-45.38) | 0.99 | 48% | 0.17 |
| Chest pain | 3 | 3 | 1 | 2.24 | (0.3-16.98) | 0.44 | 0% | 0.69 |
| Deep vein thrombosis | 3 | 3 | 4 | 0.80 | (0.09-7.52) | 0.85 | 49% | 0.14 |
| Dyspnoea | 5 | 16 | 8 | 1.75 | (0.77-3.96) | 0.18 | 0% | 0.70 |
| Dyspnoea exertional | 3 | 3 | 0 | 7.36 | (0.77-70.8) | 0.08 | 0% | 0.9997 |
| Hypertension | 2 | 1 | 1 | 0.97 | (0.02-52.19) | 0.99 | 52% | 0.15 |
| Myocardial infarction | 2 | 1 | 2 | 0.49 | (0.05-4.73) | 0.54 | 0% | 0.43 |
| Oedema peripheral | 2 | 2 | 1 | 1.61 | (0.16-16.15) | 0.69 | 0% | 0.56 |
| Pericardial effusion | 3 | 2 | 2 | 1.03 | (0.07-14.76) | 0.99 | 37% | 0.20 |
| Pulmonary embolism | 7 | 11 | 8 | 1.25 | (0.5-3.13) | 0.63 | 0% | 0.58 |
| Sinus bradycardia | 2 | 2 | 0 | 7.27 | (0.45-116.22) | 0.16 | 0% | 0.98 |
| Syncope | 5 | 7 | 0 | 6.86 | (1.54-30.6) | 0.01 | 0% | 0.9997 |
| Thrombosis | 2 | 1 | 1 | 0.65 | (0.01-83.4) | 0.86 | 65% | 0.09 |

Supplementary Table 2B – Summary Odds-Ratio (random effect) of grade 3 or more and serious cardiovascular adverse events in *BRAF* and MEK inhibitors combination therapy trials versus *BRAF* inhibitor and placebo

| MedDRA term | Number of study reporting the outcome | Number of event in combination therapy groups | Number of event in monotherapy + placebo groups | Odds-Ratio (Random effect) | 95% confidence interval | p-value | I ² for heterogeneity | Chi ² p-value for heterogeneity |
|--|---------------------------------------|---|---|----------------------------|-------------------------|---------|----------------------------------|--|
| Grade 3 or more cardiovascular adverse events | | | | | | | | |
| Ejection fraction decreased | 2 | 10 | 7 | 1.44 | (0.55-3.75) | 0.46 | 0% | 0.79 |
| Hypertension | 2 | 27 | 20 | 1.39 | (0.62-3.13) | 0.43 | 48% | 0.17 |
| Pulmonary embolism | 2 | 7 | 2 | 3.09 | (0.83-11.47) | 0.09 | 0% | 0.62 |
| QT prolonged | 2 | 3 | 5 | 0.51 | (0.08-3.23) | 0.48 | 32% | 0.22 |
| Serious cardiovascular adverse events | | | | | | | | |
| Atrial fibrillation | 2 | 6 | 3 | 1.96 | (0.53-7.28) | 0.31 | 0% | 0.37 |
| Cardiac failure | 2 | 1 | 2 | 0.51 | (0.05-4.94) | 0.56 | 0% | 0.42 |
| Cerebrovascular accident | 2 | 3 | 0 | 7.41 | (0.77-71.37) | 0.08 | 0% | 0.997 |
| Ejection fraction decreased | 2 | 13 | 6 | 2.16 | (0.87-5.4) | 0.10 | 0% | 0.56 |
| Hypertension | 2 | 2 | 0 | 7.41 | (0.46-118.46) | 0.16 | 0% | 0.996 |
| Pulmonary embolism | 2 | 4 | 2 | 1.96 | (0.39-9.78) | 0.41 | 0% | 0.56 |
| Supraventricular tachycardia | 2 | 1 | 1 | 1.00 | (0.02-51.21) | 0.999 | 50% | 0.16 |

Only cardiovascular adverse events that occurred in at least two studies are presented. MedDRA: Medical Dictionary for Regulatory Activities, MEK: mitogen-activated extracellular signal-regulated kinase

Supplementary Table 3 – Sensitivity analyses for the odds-ratio of hypertension and peripheral oedema in monotherapy trials.

Supplementary Table 3A – Sensitivity analyses to evaluate the contribution of each study by excluding each of the studies one after the others on the pooled odds-ratio of all-grade hypertension, ejection fraction decrease and peripheral oedema in *BRAF* or MEK inhibitors monotherapy trials.

| Study | Hypertension | | | Ejection fraction decrease | | | Peripheral oedema | | |
|------------------------|---|----------------|---------------------------------|---|----------------|---------------------------------|---|----------------|---------------------------------|
| | Odds-Ratio (95%CI) after single-study exclusion | I ² | Weight of the removed study (%) | Odds-Ratio (95%CI) after single-study exclusion | I ² | Weight of the removed study (%) | Odds-Ratio (95%CI) after single-study exclusion | I ² | Weight of the removed study (%) |
| Carvajal et al. 2018 | 1.68 (0.82-3.45) | 56% | 14.4 | - | - | 0 | 2.62 (1.74-3.93) | 47% | 12.8 |
| Infante et al. 2014 | 2.27 (1.36-3.8) | 23% | 10.9 | 3.27 (1.15-9.31) | 29% | 28.7 | 3.22 (2.25-4.62) | 27% | 16.6 |
| Jänne et al. 2013 | - | - | 0 | - | - | 0 | 2.86 (1.82-4.5) | 58% | 11.4 |
| Jänne et al. 2017 | 1.85 (0.93-3.69) | 57% | 10.3 | 3.01 (1.11-8.16) | 27% | 23.6 | 3.1 (1.85-5.19) | 57% | 22.6 |
| Maio et al. 2018 | 1.52 (0.8-2.9) | 41% | 17.7 | - | - | 0 | - | - | 0 |
| Robert et al. 2013 | 1.57 (0.83-2.97) | 48% | 11.3 | 2.84 (1.09-7.38) | 20% | 25.0 | 2.53 (1.76-3.63) | 36% | 11.0 |
| Soria et al. 2017 | 1.8 (0.88-3.68) | 57% | 12.9 | 4.38 (2.02-9.49) | 0% | 12.3 | 3.04 (1.92-4.83) | 58% | 13.4 |
| Van Cutsem et al. 2018 | 1.78 (0.9-3.54) | 57% | 9.0 | 2.99 (1.26-7.09) | 20% | 10.4 | 2.79 (1.78-4.37) | 56% | 12.2 |
| Zaman et al. 2015 | 2.08 (1.1-3.93) | 46% | 13.5 | - | - | 0 | - | - | 0 |

Supplementary Table 3B – Sensitivity analyses to evaluate the contribution of study characteristics to the pooled estimation of all-grade hypertension, ejection fraction decrease and peripheral oedema incidences in *BRAF* or MEK inhibitors monotherapy trials.

| Study characteristics | Hypertension | | | Ejection fraction decrease | | | Peripheral oedema | | |
|--|---|----------------|-----------------------------------|---|----------------|-----------------------------------|---|----------------|-----------------------------------|
| | Odds-Ratio (95%CI) after removing studies | I ² | Weight of the studies removed (%) | Odds-Ratio (95%CI) after removing studies | I ² | Weight of the studies removed (%) | Odds-Ratio (95%CI) after removing studies | I ² | Weight of the studies removed (%) |
| Removing of studies with institutional funding²⁷ | 2.08 (1.1-3.93) | 46% | 13.5 | - | - | 0 | - | - | 0 |
| Removing of biggest trials | Study weight > 15% | | | Study weight > 25% | | | Study weight > 15% | | |
| | 1.51 (0.46-4.93) | 61% | 17.7 | 2.54 (0.56-11.6) | 46% | 53.7 | 3.78 (2.55-5.62) | 2% | 39.2 |
| Small study bias : Removing of smaller trials^{22,24,26,27} | 1.73 (0.79-3.83) | 56% | 33.8 | 2.33 (0.75-7.25) | 34% | 35.4 | 2.31 (1.44-3.71) | 53% | 69.2 |

95%CI: 95% confidence interval

Supplementary Table 4 – Risk of bias in randomized studies, based on the Cochrane Risk of Bias Tool for Randomized Controlled Trials¹⁹.

Supplementary Table 4A – Assessment of the risk of bias of included studies using The Cochrane Risk of Bias Tool for monotherapy Randomized Controlled Trials

| | Random sequence generation | Allocation concealment | Selective reporting | Other bias | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data |
|------------------------|----------------------------|------------------------|---------------------------|---------------------------|--|--------------------------------|---------------------------|
| Carvajal et al, 2018 | Unclear risk | Unclear risk | Low risk | Unclear risk ² | Unclear risk | Unclear risk | Low risk ³ |
| Infante et al, 2014 | Unclear risk | Unclear risk | Low risk | Unclear risk ² | Unclear risk | Unclear risk | Low risk ³ |
| Jänne et al, 2013 | Low risk | Low risk | Low risk | Unclear risk ² | Low risk | Low risk | Low risk ³ |
| Jänne et al, 2017 | Low risk | Low risk | Low risk | Unclear risk ² | Unclear risk | Unclear risk | Low risk ³ |
| Maio et al, 2018 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk ⁴ |
| Robert et al, 2013 | Low risk | Low risk | Unclear risk ¹ | Unclear risk ² | Low risk | Low risk | Low risk ³ |
| Soria et al, 2017 | Unclear risk | Low risk | Low risk | Unclear risk ² | Unclear risk | Unclear risk | Low risk ³ |
| Van Cutsem et al, 2018 | Unclear risk | Low risk | Unclear risk ¹ | Unclear risk ² | Unclear risk | Unclear risk | Low risk ³ |
| Zaman et al, 2013 | Low risk | Low risk | Unclear risk ¹ | Low risk | Unclear risk | Unclear risk | Low risk ⁵ |

Supplementary Table 4B - Assessment of the risk of bias of included studies using The Cochrane Risk of Bias Tool for combination therapy Randomized Controlled Trials

| | Random sequence generation | Allocation concealment | Selective reporting | Other bias | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data |
|----------------------|----------------------------|------------------------|---------------------|---------------------------|--|--------------------------------|---------------------------|
| Ascierto et al, 2016 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk ⁴ |
| Long et al, 2017 | Low risk | Low risk | Low risk | Unclear risk ² | Low risk | Low risk | Low risk |

1: Cardiac events were collected by non-systematic assessment

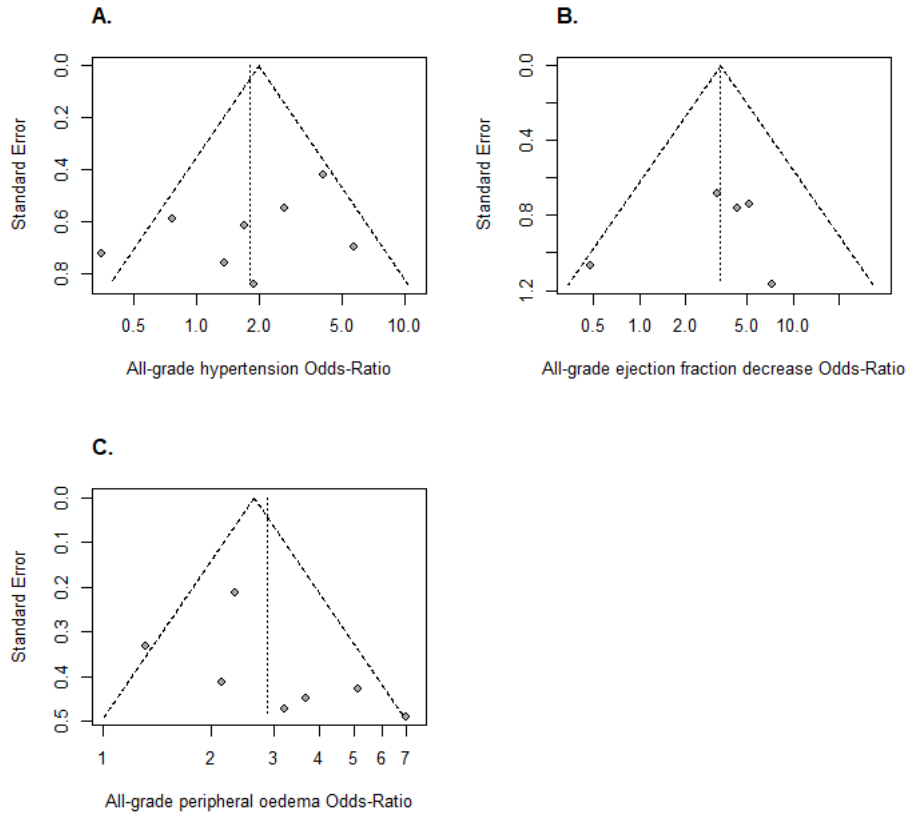
2: Did not systematically report CTCAE grading for every cardiac events

3: Threshold for non-serious adverse events reporting was 5% or less

4: Threshold for CTCAE grade 1-2 adverse events was 10%

5: The author provided an exhaustive detailed list of all the adverse events of the trials for both groups.

Supplementary Figure 1 – Funnel plots of log odds-ratio standard error by odds-ratio to evaluate publication bias for the primary outcomes (A) all-grade hypertension, (B) all-grade ejection fraction decrease and (C) all-grade peripheral oedema in monotherapy trials



Supplementary Figure 2 –

Individual MedDRA

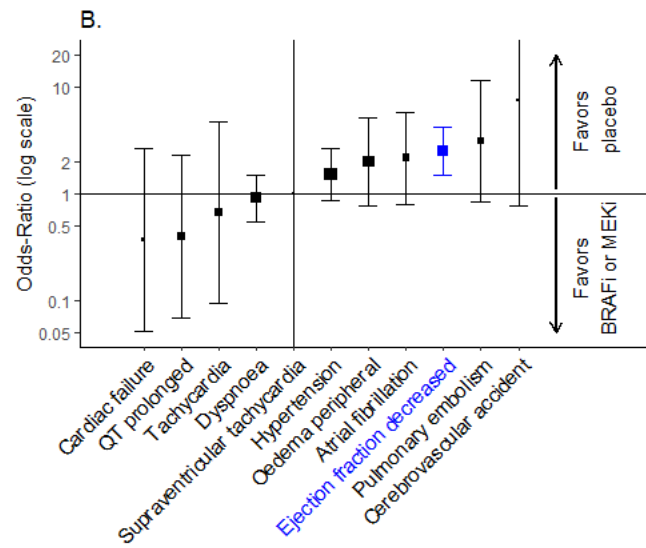
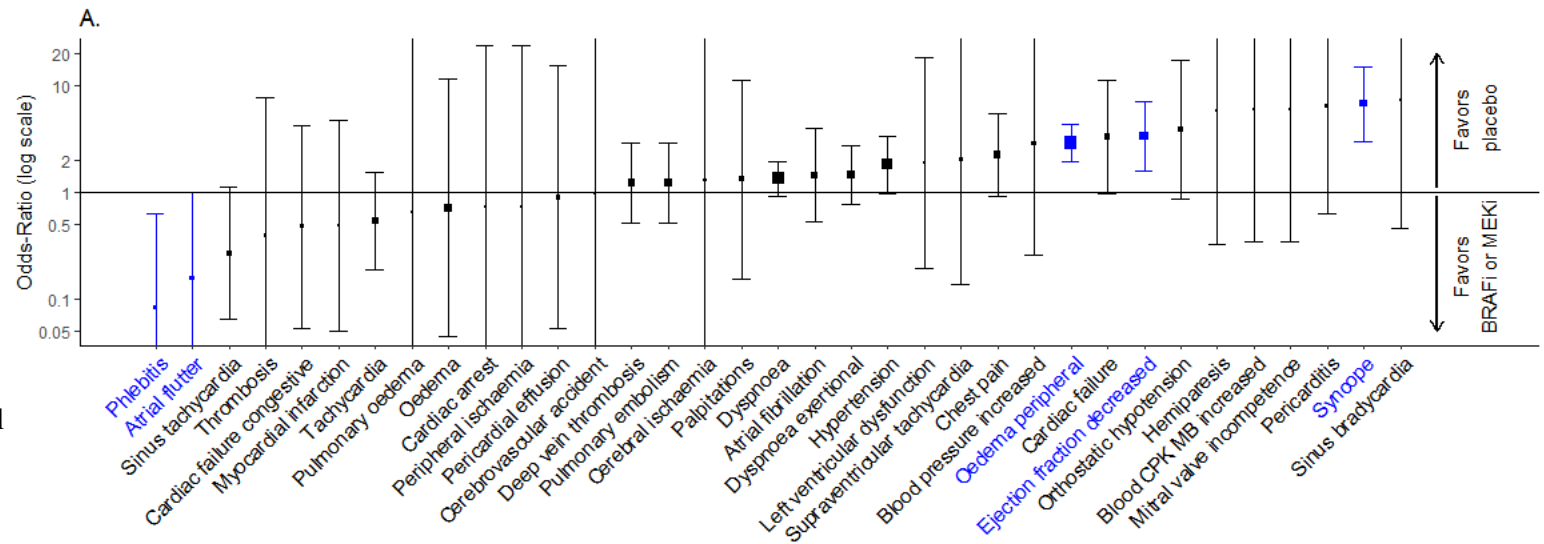
(medical dictionary for regulatory activities) terms random-effect summary Odds-Ratio in

(A) monotherapy trials and
(B) combination therapy trials.

Color square indicates a significant association. Square size is proportional to the number of events.

CPK: creatine phosphokinase

MB: muscle/brain



Supplementary Data 1 (appendix 1) – Draft MEDLINE search with High sensitivity filter for randomized clinical trials – Ovid interface

1. Anti-MEK OR Anti-BRAF
2. MEK inhibitor OR BRAF inhibitor
3. Cobimetinib OR XL-518 OR XL518 OR XL 518 OR GDC-0973 OR GDC 0973 OR GDC0973
4. Trametinib OR GSK-1120212 OR GSK 1120212 OR GSK1120212
5. Binimetinib
6. Selumetinib OR AZD 6244 OR AZD6244 OR AZD-6244
7. Pimasertib OR AS703026 OR AS 703026 OR AS-703026
8. Vemurafenib OR PLX4032 OR PLX 4032 OR PLX-4032 OR RG7204 OR RG 7204 OR RG-7204
9. Dabrafenib OR GSK2118436 OR GSK 2118436 OR GSK-2118436
10. Encorafenib OR arry-142886
11. or/1-10
12. randomized controlled trial[Publication Type]
13. controlled clinical trial[Publication Type]
14. randomized[Title/Abstract]
15. placebo[Title/Abstract]
16. drug therapy[MeSH Subheading]
17. randomly[Title/Abstract]
18. trial[Title/Abstract]
19. groups[Title/Abstract]
20. or/12-19
21. animals [MeSH Terms] NOT humans [MeSH Terms]
22. 20 NOT 21
23. 11 AND 22

Supplementary Data 2 (appendix 2) - List and definition of all the variables for which data were sought and any assumptions and simplifications made.

Study characteristics

General: Study number in our meta-analysis (arbitrary), first author, initial year of publication, last update year of publication, study name, publication type (1: full article 2: abstract 3: poster 4: other, specify), country of publication, NCT (clinical trials number), study DOI (digital object identifier)

Design: Study type (1: RCT (randomized clinical trial) placebo controlled, 2: RCT comparator controlled, 3: Subgroup analyses, 4: Post-hoc analyses, 5: Prospective cohort studies, 6: Retrospective cohort studies), study eligibility (1: Eligible 0: Not eligible), reasons for exclusion, study blinding (0: none, 1:simple, 2:double), association study (0: no, 1: yes), inclusion period (starting date, endpoint date), follow up period (in months), median follow-up (months) or median primary objective follow-up. Protocol of the study previously (yes/no) published, weblink to study protocol. Randomization method (free text), prespecified reporting (1: yes, 0: no, spontaneous reporting of observed event), "If prespecified reporting, is there spontaneous non-prespecified adverse events ?", Version of CTCAE (common terminology criteria for adverse events) used (0: not used 3: version 3.0 4: version 4.0 5: version 5.0). Threshold for report of non-serious adverse event (%), most frequent cardiac event, second adverse event, third adverse event, total number of intervention groups, other intervention (no: 0, else: specify), *BRAF* inhibitor and MEK (mitogen-activated extracellular signal-regulated kinase) inhibitor dosage, median treatment duration, mean dose. Comparator (1:placebo, 2:cytotoxic chemotherapy, other please specify), dosage (if placebo: leave empty), duration (if identical, leave empty), metastatic cancer (0: not included 1: included 2: metastatic only), minors (0: not included, 1: included, 2: minors only), line of treatment (1: first line, etc.), presence of cardiovascular comorbidities (0: excluded, 1: included), "If cardiovascular comorbidities excluded, specify"

Participants: Total number of participants, number of patients in treatment group, number of patients in control group, participants age (mean), treatment group median age, participants sex (%age of men)

Safety: Safety population size, safety treatment group size, safety control group size, %age in treat group

Funding: Authors own work, government funding, industry funding

Individual MedDRA terms

MedDRA term belonging to either MedDRA system organ classes "Cardiac Disorders" and "Vascular Disorders" or to the Standardized MedDRA queries "Cardiac arrhythmia", "Cardiac failure", "Cardiomyopathy", "Embolic and thrombotic events", "Hypertension", "Ischaemic heart disease", "Pulmonary hypertension", "Thrombophlebitis" and "Torsade de pointes/QT prolongation".

For each MedDRA term:

- AE_MEDDRA : MedDRA term of the adverse event
- NUM_AE_TTT : number of patients presenting the adverse event in treatment group
- NUM_AE_CTRL : same in control group
- _NONSERIOUS : number of patients presenting the adverse event which was non serious
- _SERIOUS : number of patients presenting the adverse event which was serious
- _GRADE12 : number of patients presenting the adverse event which was CTCAE grade 1 or 2
- _GRADE3 : number of patients with CTCAE grade 3 or 4 adverse events

Supplementary Data 3 – Cardiovascular related inclusion and exclusion criteria of included studies

| Study | Cardiovascular related inclusion and exclusion criteria |
|-----------------------------|---|
| Carjaval et al. 2014 | <p>Exclusion criteria</p> <p>Uncontrolled hypertension (BP \geq150/95 mmHg despite medical therapy)</p> <p>Acute coronary syndrome within 6 months prior to starting treatment</p> <p>Uncontrolled Angina - Canadian Cardiovascular Society grade II-IV despite medical therapy - Symptomatic heart failure (New York Heart Association [NYHA] Class II-IV,- Prior or current cardiomyopathy</p> <p>Baseline LVEF <55% measured by echocardiography or MUGA. Appropriate correction to be used if a MUGA is performed</p> <p>Severe valvular heart disease</p> <p>Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest</p> <p>QTcF >450 ms or other factors that increase the risk of QTc prolongation</p> |
| Infante et al. 2014 | <p>Exclusion criteria</p> <p>Bazett's corrected QT interval \geq 480 ms</p> <p>History or evidence of congestive heart failure</p> <p>History of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the past 6 months</p> |
| Maio et al. 2018 | <p>Exclusion criteria</p> <p>History of clinically significant cardiac or pulmonary dysfunction, including the following:</p> <p>Current, uncontrolled Grade \geq 2 hypertension</p> <p>Unstable angina</p> <p>Current Grade \geq 2 dyspnea or hypoxia or need for supplemental oxygen</p> <p>History of symptomatic congestive heart failure of Grade II–IV New York Heart Association Class (NYHA)</p> <p>Serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia</p> <p>History of myocardial infarction within 6 months prior to randomization</p> <p>History of congenital long QT syndrome or QTc interval > 450 ms at baseline</p> <p>History of or current uncorrectable electrolyte disorder affecting serum levels of potassium, calcium, or magnesium</p> |
| Zaman et al. 2013 | <p>Inclusion criteria</p> <p>Adequate (...) cardiac function(s) was required</p> <p>LVEF \geq 50%</p> <p>No uncontrolled hypertension (systolic BP > 150 mm Hg and/or diastolic BP > 100 mm Hg, measured repeatedly at more than two visits despite adequate treatment with at least two different antihypertensive drugs)</p> <p>No clinically significant (i.e., active) cardiovascular disease, including any of the following:</p> <ul style="list-style-type: none"> Cerebrovascular accident/stroke or myocardial infarction within the past 6 months Unstable angina NYHA class III-IV congestive heart failure Serious cardiac arrhythmia or AV-block > 1, requiring medication during the trial and which might interfere with regularity of the trial treatment, or not controlled by medication |
| Ascierto et al. 2016 | <p>Exclusion criteria</p> <p>Clinically significant cardiac dysfunction, including the following:</p> |

| | |
|--------------------------------|--|
| | <ul style="list-style-type: none"> a) Current unstable angina b) Current symptomatic congestive heart failure of New York Heart Association class 2 or higher (Appendix 7) c) History of congenital long QT syndrome or mean (average of triplicate measurements) QTcF > 450 msec at baseline or uncorrectable abnormalities in serum electrolytes (sodium, potassium, calcium, magnesium, phosphorus). d) Current uncontrolled hypertension \geq Grade 2 (patients with a history hypertension controlled with anti-hypertensives to \leq Grade 1 are eligible). e) LVEF below institutional lower limit of normal (LLN) or below 50%, whichever is lower |
| <p>Long et al. 2017</p> | <p>Inclusion criteria Left Ventricular Ejection fraction (LVEF) \geq lower limit of normal</p> <p>Exclusion criteria A history or evidence of cardiovascular risk including any of the following:</p> <ul style="list-style-type: none"> a. A QT interval corrected for heart rate using the Bazett's formula (QTcB) \geq480 msec b. A history or evidence of current clinically significant uncontrolled arrhythmias c. Exception: Subjects with atrial fibrillation controlled for > 30 days prior to randomization are eligible. d. A history (within 6 months prior to randomization) of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty e. A history or evidence of current \geqClass II congestive heart failure as defined by the New York Heart Association (NYHA) guidelines f. Treatment refractory hypertension defined as a blood pressure of systolic > 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by antihypertensive therapy; g. Patients with intra-cardiac defibrillators or permanent pacemakers; h. Known cardiac metastases; i. Abnormal cardiac valve morphology (\geqgrade 2) documented by echocardiogram (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study. 12. A history or current evidence/risk of retinal vein occlusion |

BP: blood pressure, ECG: electrocardiogram, LVEF: left ventricular ejection fraction, MUGA: multigated acquisition

« Par délibération de son Conseil en date du 10 Novembre 1972, l'Université n'entend donner aucune approbation ni improbation aux opinions émises dans les thèses ou mémoires. Ces opinions doivent être considérées comme propres à leurs auteurs ».

VU, le Président de Thèse

VU, le Doyen de la Faculté

VU et permis d'imprimer
en référence à la délibération
du Conseil d'Université
en date du 14 Décembre 1973

Pour le Président
de l'Université de CAEN et P.O

Le Doyen

ANNEE DE SOUTENANCE : 2018

NOM ET PRENOM DE L'AUTEUR : DOLLADILLE CHARLES

TITRE DE LA THESE : Effets indésirables cardiovasculaires des inhibiteurs de *BRAF* et MEK en traitement du cancer : une revue systématique et méta-analyse d'études randomisées contrôlées contre placebo

RESUME DE LA THESE EN FRANÇAIS :

Contexte : Les effets indésirables cardiovasculaires (EICV) des inhibiteurs de *BRAF* et de MEK (mitogen-activated extracellular signal-regulated kinase) ne sont pas entièrement caractérisés.

Objectif : Evaluer les risques d'EICV des inhibiteurs de *BRAF* et/ou MEK en monothérapie et en combinaison.

Méthodes : Medline, Embase et la base de données Cochrane Library furent examinées jusqu'au 18 septembre 2018 à la recherche d'études d'efficacité randomisées contrôlées contre placebo (RPCT) recueillant les EICV des inhibiteurs de *BRAF* et/ou MEK. Nous avons effectué une revue systématique avec méta-analyse pour calculer les Odds-Ratio (OR) (effet aléatoire) avec intervalle de confiance à 95% (IC95%) des EICV. Les critères principaux étaient les EICV hypertension, baisse de la fraction d'éjection (BFE) et œdèmes périphériques. Numéro d'enregistrement PROSPERO : CRD42018094729.

Résultats: Onze RPCTs ont été incluses, totalisant 1722 patients dans les études en monothérapie et 953 patients dans les études de combinaison. En monothérapie, il y avait un sur-risque significatif de BFE (OR 3,36, IC95% 1,63-6,94, $p=0,001$, $I^2=5\%$), d'œdèmes périphériques (OR 2,64, 95%CI 2,03-3,42, $p<0,001$, $I^2=50\%$) mais pas d'hypertension (OR 1,81, IC95% 0,97-3,35, $p=0,06$, $I^2=50\%$), des inhibiteurs de *BRAF* ou MEK contre placebo. Les inhibiteurs de *BRAF* ou MEK avaient un sur-risque de syncope contre placebo et un sous-risque de phlébite et flutter atrial. En combinaison, il y avait un sur-risque de BFE versus monothérapie.

Conclusion : Les inhibiteurs de *BRAF* et MEK en traitement du cancer sont associés à un sur-risque de BFE et d'œdèmes périphériques. Le risque de BFE est accru en cas de combinaison des traitements.

MOTS CLES :

Inhibiteurs de *BRAF*, effets indésirables cardiovasculaires, inhibiteurs de mitogen activated extracellular signal-regulated kinase, méta-analyse de sécurité

TITRE DE LA THESE EN ANGLAIS : Cardiovascular adverse events of *BRAF* and/or MEK inhibitors in cancer patients: a systematic review and meta-analysis of placebo randomized-controlled trials

RESUME DE LA THESE EN ANGLAIS :

Background: Cardiovascular adverse events (CVAE) risk of *BRAF* and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors are not fully characterized.

Objectives: We aimed to evaluate the incidence of CVAE in *BRAF* and/or MEK inhibitors used in monotherapy and in combination therapy.

Methods: Medline, Embase and the Cochrane Library databases were searched from database inception through September 18, 2018 for efficacy randomized placebo-controlled trials (RPCTs) of *BRAF* and/or MEK inhibitors with CVAE data collection. We performed a systematic review and meta-analysis to compute random-effect summary odds-ratios (OR) with 95% confidence intervals (CI) of CVAE. The primary outcomes were hypertension, ejection fraction decrease and peripheral oedema occurrences. PROSPERO registration number: CRD42018094729.

Results: We included 11 RPCTs, with a total number of 1,722 patients in monotherapy trials and 953 patients in combination therapy trials. In monotherapy trials, there was a significantly higher incidence of ejection fraction decrease (OR 3.36, 95%CI 1.63-6.94, $p=0.001$, $I^2=5\%$) and peripheral oedema (OR 2.64, 95%CI 2.03-3.42, $p<0.001$, $I^2=50\%$) but not hypertension (OR 1.81, 95%CI 0.97-3.35, $p=0.06$, $I^2=50\%$) in *BRAF* or MEK inhibitor groups versus placebo. *BRAF* or MEK inhibitor groups had a significantly higher incidence of syncope versus placebo and a significantly lower incidence of phlebitis, and atrial flutter. In combination therapy trials, there was an additional higher incidence of ejection fraction decrease in combination groups versus monotherapy plus placebo.

Conclusion: *BRAF* or MEK inhibitors in cancer patients are associated with a higher incidence of ejection fraction decrease and peripheral oedema with an additional higher incidence of ejection fraction decrease in combination therapies.

KEY WORDS: *BRAF* inhibitors, cardiovascular adverse events, mitogen-activated extracellular signal-regulated kinase inhibitors, safety meta-analysis