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Charles Dolladille, Jonaz Font, Theodora Bejan-Angoulvant, Khalil Zaman, Marion Sassier, et al.. Cardiovascular safety of rapidly accelerated fibrosarcoma B-type and/or mitogen-activated extracellular signal-regulated kinase inhibitors: A mixed approach combining a meta-analysis and a pharmacovigilance disproportionality analysis. Archives of cardiovascular diseases, 2020, 113, pp.420 - 432. <10.1016/j.acvd.2020.03.014>. <hal-03491168>

HAL Id: hal-03491168

<https://hal.science/hal-03491168v1>

Submitted on 22 Aug 2022

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Cardiovascular safety of rapidly accelerated fibrosarcoma B-type and/or mitogen-activated extracellular signal-regulated kinase inhibitors: A mixed approach combining a meta-analysis and a pharmacovigilance disproportionality analysis

Abbreviated title: Cardiovascular safety of BRAF and MEK inhibitors

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Summary

Background. – The risk of cardiovascular adverse events from rapidly accelerated fibrosarcoma B-type (BRAF) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors is not fully characterized.

Aim. – To evaluate the cardiovascular adverse events risks related to BRAF and/or MEK inhibitors in randomized placebo-controlled clinical trials and in the real-life setting.

Methods. – We used two approaches. First, we conducted a systematic review and meta-analysis of randomized placebo-controlled clinical trials reporting the incidence of cardiovascular adverse events for BRAF and/or MEK inhibitors in cancer patients. Second, we performed a disproportionality analysis, using age- and sex-adjusted reporting odds ratios (arORs) and their 95% confidence intervals (CIs) from the World Health Organization's pharmacovigilance database (VigiBase®) of anticancer drug-associated reports, to investigate real-life data.

Results. – MEK inhibitors increased the risk of ejection fraction decrease (odds ratio [OR] 3.35, 95% CI 1.58–7.07), peripheral oedema (OR 2.87 95% CI 1.93–4.27) and syncope (OR 6.71, 95% CI 3.00–14.99) compared with placebo in randomized placebo-controlled clinical trials. BRAF and MEK inhibitor combination therapy further increased the risk of ejection fraction decrease. In the disproportionality analysis, we found over-reporting of ejection fraction decrease (arOR 8.42, 95% CI 7.03–10.09), peripheral oedema (arOR 1.39, 95% CI 1.17–1.66), syncope (arOR 1.56, 95% CI 1.22–1.99), torsade de pointes/QT prolongation (arOR 6.13, 95% CI 5.04–7.47) and supraventricular arrhythmias (arOR 1.50, 95% CI 1.21–1.85) for BRAF and MEK inhibitors. BRAF and MEK inhibitors were not associated with hypertension in either approach.

Conclusions. – In conclusion, MEK inhibitors increase the risk of ejection fraction decrease, peripheral oedema and syncope in randomized placebo-controlled clinical trials. Real-life data confirm these findings, and suggested additional risks of torsade de pointes/QT prolongation and supraventricular arrhythmias with BRAF/MEK inhibitors.

Résumé

Contexte. – Le risque d'évènements indésirables cardiovasculaires (EICV) avec les inhibiteurs de BRAF et MEK n'est pas entièrement caractérisé.

Objectif. – Evaluer les EICV associés aux inhibiteurs de BRAF et/ou MEK dans les essais randomisés contrôlés contre placebo (ERCP) et avec des données de vraie vie.

Méthodes. – Nous avons utilisé deux approches. D'abord, une revue systématique et méta-analyse des ERCP rapportant l'incidence des EICV avec les inhibiteurs de BRAF et/ou MEK chez les patients atteints de cancer. Deuxièmement, une analyse de disproportionnalité parmi les cas rapportés d'évènements indésirables sous anticancéreux, avec calcul du reporting Odds-Ratio et son intervalle de confiance (IC) à 95% ajusté sur l'âge et le sexe (arOR) dans la base de pharmacovigilance de l'Organisation Mondiale de la Santé Vigibase® pour étudier les données de vraie vie.

Résultats. – Les inhibiteurs de MEK augmentaient le risque de baisse de la fraction d'éjection (OR 3,35, IC95 % 1,58–7,07), d'œdèmes périphériques (OR 2,87, IC95 % 1,93–4,27) et de syncope (OR 6,71, IC95 % 3,00–14,99) comparé au placebo dans les ERCP. La combinaison d'inhibiteurs de BRAF et MEK augmentait encore le risque de baisse de la fraction d'éjection. Dans l'analyse de disproportionnalité, une sur-notification de baisse de la fraction d'éjection (arOR 8,42, IC95 % 7,03–10,09), d'œdèmes périphériques (arOR 1,39, IC95 % 1,17–1,66), de syncope (arOR 1,56, IC 95% 1,22–1,99), de torsade de pointes/allongement du QT (arOR 6,13, IC95 % 5,04–7,47) et d'arythmies supraventriculaires (arOR 1,50, IC95 % 1,21–1,85) était présente pour les inhibiteurs de BRAF et/ou MEK. Les inhibiteurs de BRAF/MEK n'étaient pas associés à l'hypertension dans les deux approches.

Conclusions. – Les inhibiteurs de BRAF et MEK augmentent le risque de baisse de la fraction d'éjection, d'œdèmes périphériques, de syncope dans les ERCP. Les données de vraie vie confirment ce signal et suggèrent un risque additionnel de torsade de pointes/allongement du QT et d'arythmies supraventriculaires.

KEYWORDS

BRAF inhibitors;

Cardiovascular adverse events;

Disproportionality analysis;

MEK inhibitors;

Safety meta-analysis

MOTS CLÉS

Analyse de disproportionnalité ;

Evènements indésirables cardio-vasculaires ;

Inhibiteurs de BRAF ;

Inhibiteurs de MEK ;

Méta-analyse de sécurité

Abbreviations: BRAF, rapidly accelerated fibrosarcoma B-type; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; CVAE, cardiovascular adverse event; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICSR, individual case safety report; MedDRA, Medical Dictionary for Regulatory Activities; MEK, mitogen-activated extracellular signal-regulated kinase; OR, odds ratio; RPCT, randomized placebo-controlled trials.

Background

Rapidly accelerated fibrosarcoma B-type (BRAF) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors have been evaluated in a variety of cancers, such as melanoma, non-small cell lung cancer, breast cancer and pancreatic cancer. BRAF inhibitors improved progression-free and overall survival in monotherapy versus cytotoxic chemotherapy [1, 2]. Several meta-analyses suggested that combination therapy with BRAF and MEK inhibitors significantly improved surrogate criteria, such as overall response or progression-free survival and overall survival compared with BRAF inhibitor monotherapy [3, 4]. However, a wide range of adverse events has been described with these treatments, including cardiovascular adverse events (CVAEs) [3, 5]. A significantly increased risk of cardiac-related adverse events was found in clinical trials with the MEK inhibitor trametinib (10% vs 6% in the placebo group). The BRAF inhibitor vemurafenib was associated with a higher risk of QT prolongation in clinical trials (4% versus 0% in the placebo group) [6]. MEK inhibitors also displayed a higher risk of hypertension (risk ratio 1.54; $P = 0.04$) and an increased risk of ejection fraction decrease (risk ratio 1.85; $P = 0.05$) in a MEK inhibitor safety meta-analysis [7].

Previous cardiovascular safety meta-analyses focused on a restricted number of CVAEs [7-9], and data from randomized placebo-controlled trials (RPCTs) were pooled with the data from lower level of evidence studies, such as non-placebo-controlled trials. To our knowledge, no attempt has been made to evaluate the broad spectrum of cardiovascular risk in RPCTs. Furthermore, the CVAE risk profile of BRAF and MEK inhibitors in RPCTs has not been compared with real-life pharmacovigilance signals. Therefore, we performed: (1) a systematic review and meta-analysis aimed at broadly evaluating the risk of CVAEs with BRAF and/or MEK inhibitors in RPCTs that included any cancer type; and (2) a disproportionality analysis in the World Health Organization's pharmacovigilance database (VigiBase®) to evaluate the signals of CVAEs in a larger setting.

Methods

Systematic review and meta-analysis

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10, 11] ([Table A.1](#)). The protocol

was registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42018094729).

Data sources and search strategy

An extensive computerized literature search was conducted independently by two reviewers (C. D. and J. F.) in MEDLINE, Embase, the Cochrane Library and clinical trials registry platforms, including ClinicalTrials.gov, according to the pre-specified selection criteria, from database inception up to 18 September 2018. [Appendix A](#) shows details of the search strategy. We used both the controlled terms (i.e. MeSH terms in MEDLINE) and the free text terms related to BRAF inhibitors and/or MEK inhibitors as the sole domain ([Appendix B](#)).

Study selection and data extraction

All RPCTs evaluating a BRAF inhibitor or a MEK inhibitor as monotherapy or the combination of a BRAF inhibitor and a MEK inhibitor for any cancer type in adult patients and reporting at least one CVAE were included. We assessed the risk of CVAEs in RPCTs to provide the highest level of evidence. Data were extracted by two authors (C. D. and J. F.) independently. See [Appendix A](#) and [Appendix C](#) for details of the data extraction procedure.

Outcomes

We gathered CVAEs from the study safety database using Medical Dictionary for Regulatory Activities (MedDRA) terms. A detailed list of MedDRA terms is available in [Appendix A](#).

The primary outcome was the risk of CVAEs under BRAF/MEK inhibitor monotherapy versus placebo. The secondary outcomes were: the risk of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher CVAEs in BRAF/MEK inhibitor monotherapy versus placebo; the risk of serious CVAEs in BRAF/MEK inhibitor monotherapy versus placebo; the risk of all-grade, grade 3 or higher and serious CVAEs in combination therapy versus BRAF/MEK inhibitor monotherapy. We used the adverse event seriousness definition of the Food and Drug Administration [12].

Exploration of heterogeneity of BRAF and/or MEK inhibitor-induced CVAEs

Subgroup and sensitivity analyses were performed for the primary outcome to explore possible sources of heterogeneity or inconsistency ([Appendix A](#)).

Risk of bias (quality) assessment

The Cochrane Collaboration's Risk of Bias Tool for Randomized Controlled Trials [13], described in the Cochrane Handbook, version 5.1.0 [14], was used by two authors (C. D. and J. F.) independently to assess the risk of bias in RPCTs. Any disagreements were resolved by the senior author (J. A.). The risk of bias was finally adjudicated as “high” or “low to moderate” to perform sensitivity analyses.

Assessment of strength of the body of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology was used to assess the quality of evidence for all the outcomes [15].

Disproportionality analysis in the World Health Organization's pharmacovigilance database (VigiBase®)

VigiBase®, the World Health Organization's global individual case safety reports (ICSRs) database was used for this study. VigiBase® contains more than 19 million ICSRs received from 130 member countries since 1967. ICSRs include administrative information (country, type of report, qualification of reporter), patient data (age, sex), date of onset of reaction(s) and the nature of the outcome, using the latest version of the MedDRA terms. The drug(s) involved (name, drug start and stop dates, time to onset, indication, dose) are also indicated. Drugs are coded using the World Health Organization's drug dictionary. Each adverse drug reaction is characterized as “serious” or “non-serious” according to the World Health Organization's definition.

To investigate whether CVAE risks identified in RPCTs were concordant with CVAE risks in the real-life population, we performed a disproportionality analysis. We evaluated the association between BRAF/MEK inhibitor exposure in ICSRs and several CVAE diseases identified with MedDRA preferred

terms or Standardized MedDRA Queries until 01 March 2019. The beginning of the time window was the date of the first ICSR including a BRAF or MEK inhibitor. The study population was restricted to the ICSRs involving at least one Food and Drug Administration (FDA)-labelled or European Medical Agency (EMA)-labelled anticancer drug in the primary analysis ([Appendix D](#)). Sensitivity analyses were performed after: (1) exclusion of reports from study; and (2) inclusion of all the reports in the database (no restriction to anticancer drugs).

Statistical analysis

Statistical analyses were performed with R software, version 3.5.1, for Windows (R Foundation for Statistical Computing, Vienna, Austria), package meta. We computed Peto odds ratios (ORs) with 95% confidence intervals (CIs) for each CVAE in each group (BRAF/MEK inhibitor monotherapy arm versus placebo arm; combination therapy arm versus BRAF inhibitor plus placebo arm) using a random-effects model. Heterogeneity was measured using the I^2 statistic and χ^2 with its P value. Significant between-study heterogeneity was defined by a χ^2 P value < 0.1 . Heterogeneity was considered low for $I^2 < 30\%$, moderate for I^2 between 30% and 50% and substantial for $I^2 > 50\%$ [13]. 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. Reporting/publication bias was visually explored by funnel plots, and statistical tests of asymmetry were performed if 10 or more studies were included.

In VigiBase®, disproportionality analysis compared the proportion of a selected CVAE reported for a BRAF/MEK inhibitor with the proportion of the same CVAE for a control group of drugs (e.g. full database or any subset of it). The result of this comparison can be expressed as a reporting OR; these were computed with a logistic regression model and were adjusted for age and sex. A lower end of the 95% CI > 1 was considered significant and designated as an over-reporting.

Results

After electronic database searches, duplicate removal and screening, we included 12 RPCTs in the qualitative and quantitative analyses ([Fig. 1](#)). There were 10 BRAF/MEK inhibitor monotherapy trials, with

nine studies of MEK inhibitor monotherapy versus placebo on top of standard chemotherapy [16-24] and one study of BRAF inhibitor monotherapy versus placebo [6]. There were two combination therapy trials versus BRAF inhibitor monotherapy plus placebo [25, 26]. The kappa statistic for study selection was 0.86 (95% CI 0.72–0.997; $P < 0.001$), indicating an almost perfect inter-rater agreement. The inverted funnel plot for the primary outcome did not suggest publication bias, but no statistical tests were performed (Fig. A.1).

Description of included studies

A total of 1801 adult patients were enrolled in the BRAF/MEK inhibitor monotherapy studies, with 915 patients in the BRAF/MEK inhibitor arms (53.1%) and 807 patients in the control arms (46.9%) (Table 1, with additional details of the included studies available in Appendix D). Patients with cardiovascular co-morbidities were excluded in four studies [6, 16, 18, 24] (detailed list in Table A.2), mainly because of uncontrolled blood pressure, signs and symptoms of ischaemic heart disease, prolonged QT interval and ejection fraction below normal values. The distribution of cardiovascular risk factors was not reported, with the exception of smoking status in non-small cell lung cancer trials [19, 20, 22], which ranged from 16% to 26% current smokers and from 62% to 73% former smokers. The included studies did not report the patients' cardiovascular past history, cardiovascular risk factors or cardiovascular medications.

In the combination therapy studies, there were 913 patients, with 456 (49.9%) in the combination arms and 457 (50.1%) in the BRAF inhibitor monotherapy plus placebo arms. These two studies were updates of initial studies with long-term survival and safety analyses (COMBI-d and coBRIM, respectively). Both studies excluded patients with cardiovascular co-morbidities (Table A.2).

Risk of CVAEs

The risk of CVAEs under BRAF/MEK inhibitor monotherapy versus placebo is shown in the Central illustration. MEK inhibitor monotherapy was associated with a significantly higher risk of all-grade ejection fraction decrease (OR 3.35, 95% CI 1.58–7.07; I^2 5%), peripheral oedema (OR 2.87, 95% CI 1.93–4.27; I^2 50%) and syncope (OR 6.71, 95% CI 3.00–14.99; I^2 0%) versus placebo. Ejection fraction decrease, peripheral oedema and syncope were only reported in MEK inhibitor monotherapy studies. BRAF/MEK

inhibitor monotherapy was not associated with a higher risk of hypertension, symptomatic heart failure, supraventricular arrhythmias, venous thromboembolism, ischaemic heart disease or ischaemic stroke versus placebo. Details of individual terms identified in RPCTs are shown in [Table A.3](#). Because QT prolongation was reported in only one study [6], no pooled estimation could be done. BRAF/MEK inhibitor monotherapy did not increase the risk of grade 3 or higher or serious CVAEs versus placebo, with few events reported (two to 24 events in two to seven trials) ([Table A.3](#)), with the exception of serious syncope.

In combination therapy trials, combination therapy groups had a significantly higher risk of all-grade ejection fraction decrease than BRAF inhibitor monotherapy plus placebo groups (OR 2.48, 95% CI 1.46–4.21; I^2 0%) ([Table 2](#) and [Table A.3](#)). There was no between-group difference in the risk of high-grade CVAEs or of serious CVAEs ([Table A.3](#)).

Subgroup analysis

Subgroup analyses were performed on CVAEs significantly associated with BRAF/MEK inhibitors and with significant heterogeneity. [Table 3](#) shows the subgroup analysis. Concomitant chemotherapies administered and the cancer type had a significant influence on the heterogeneity of the peripheral oedema analysis (similar subgroups). Also, the risk of hypertension tended to be higher in the BRAF inhibitor only group, although the between group difference was not significant (P for interaction 0.07).

Sensitivity analyses

Sensitivity analyses on hypertension were equivocal. The association was significant in two of eight (25%) estimations after individual study removal. Largest and smallest trial removal did not change the association. Sensitivity analyses on other CVAEs did not show substantial variations in the magnitude or direction of the association ([Table A.4](#)).

Study quality, metabiases

Regarding RPCT quality ([Table A.5](#)), all the studies included had a low-to-moderate risk of bias. In the majority of studies ($n = 10$, 83%) [16-24, 26], the CTCAE grading was reported for frequent adverse

events only, and therefore it is missing from more than 80% of the reports. Additionally, CVAE grading was not similar between CTCAE versions 3 and 4. We contacted the authors to gather this information. Two additional authors [17, 24] provided this information. We reduced the quality of evidence for high-grade CVAE risk pooled estimations (−1).

According to the GRADE methodology, our primary outcome had a moderate consistency, with low-to-moderate risk of bias studies, good precision and no evident publication bias. The heterogeneity was low to moderate. However, a small number of studies evaluated each CVAE. The quality of evidence for the primary outcome was judged to be moderate. The secondary outcomes' quality of evidence was low in the analysis of combination trials and the analysis of high-grade and serious CVAEs.

Disproportionality analysis in VigiBase®

In VigiBase®, 20,548 ICSRs included BRAF inhibitors and/or MEK inhibitors. The first ICSR with a BRAF or MEK inhibitor was reported in 2010. There were 1,810,862 ICSRs including anticancer drugs between 2010 and March 2019 (primary analysis population) and 14,237,423 ICSRs in the entire database during the same time window ([Fig. 1](#)). A significant over-reporting of ejection fraction decrease, supraventricular arrhythmias, torsade de pointes/QT prolongation, peripheral oedema and syncope was found with BRAF/MEK inhibitors compared with other anticancer drugs ([Central illustration](#)). There were 6368 BRAF/MEK inhibitor ICSRs that were reported from studies (34.4% of 18,533 available). Exclusion of these cases did not change the associations. The additional sensitivity analysis in the entire database was consistent with the primary analysis, except for the over-reporting of syncope, which was not significant ([Table A.6](#)).

Discussion

Using data from RPCTs and VigiBase®, we showed that MEK inhibitor monotherapy was associated with a significantly higher risk of ejection fraction decrease, peripheral oedema and syncope compared with placebo, and that BRAF/MEK inhibitors were associated with a higher notification rate of ejection fraction decrease, peripheral oedema, syncope, torsade de pointes/QT prolongation and supraventricular arrhythmias compared with other anticancer drugs. BRAF/MEK inhibitor combination therapy groups

versus BRAF monotherapy plus placebo groups had an even higher risk of ejection fraction decrease. With the exception of a higher incidence of serious syncope in MEK inhibitor monotherapy trials, no increased high-grade or serious CVAE risks were found.

Our results are consistent with previous findings of meta-analyses regarding ejection fraction decrease and peripheral oedema risks with BRAF and MEK inhibitors [7, 9, 27]. Based on RPCT data, ejection fraction decrease with BRAF and MEK inhibitors has been described previously as transient and asymptomatic [21, 28]. We did not find any increase in high-grade or serious risk of ejection fraction decrease either. It has been suggested that peripheral oedema could be a manifestation of cardiac failure and/or ejection fraction decrease in this setting. As serial echocardiography was not performed routinely in RPCTs, it is difficult to confirm this association [29]. We believe that real-life cohorts of BRAF/MEK inhibitor-treated patients with adequate echocardiography monitoring could provide a better understanding of ejection fraction decrease, and could help to identify the ideal schedule of ejection fraction monitoring. Early-stage detection and proper management of CVAEs appear crucial to prevent treatment interruption or dose modification, and ultimately may improve the efficiency of these treatments.

The higher incidence of all-grade hypertension in the BRAF or MEK inhibitor groups did not reach statistical significance in our study ($P = 0.06$), whereas there was a significant association in a MEK inhibitor meta-analysis [7] and in a meta-analysis of BRAF/MEK inhibitor combination therapy versus BRAF inhibitor monotherapy [27]. The disproportionality analysis in VigiBase® was consistent with an absence of association between hypertension and BRAF or MEK inhibitors. Our sensitivity analysis could suggest a sampling fluctuation. Hence, further studies might change the conclusion for this outcome.

The risk of syncope and QT prolongation with MEK-1/2 and BRAF inhibitors has been highlighted since phase I studies. Dose-limiting toxicity in these studies included presyncope for refametinib, syncope for PD0325901 and QTc prolongation for E6201 [30]. QTc prolongation has been observed in individual studies of BRAF inhibitors. Syncope with these treatments might result from a rhythm disorder under both MEK and BRAF inhibitors. The increased risk of syncope and torsade de pointes/QT prolongation in VigiBase® is supportive of this hypothesis. Because syncope is the only serious CVAE associated with MEK inhibitors, extended and continuous Holter monitoring could be relevant, even in asymptomatic patients.

This is the first study to specifically explore the cardiac safety of BRAF and MEK inhibitors with a dual approach of meta-analysis and pharmacovigilance disproportionality analysis. We were able to evaluate CVAEs in both clinical trials and the real-life setting. Cardiovascular safety data extracted from clinical trials encompassed more than 80 different terms related to CVAEs in our study, whereas previous safety meta-analyses were usually restricted to fewer than 10 [3, 4, 7], highlighting the importance of searching sources in safety meta-analyses [31]. We made a distinction between BRAF/MEK inhibitor monotherapy trials and combination therapy trials, and thus we were able to distinguish between the effect of BRAF inhibitors and MEK inhibitors and the potential additional risk of the combination therapy. Unfortunately, CVAEs could have been incompletely or inconsistently reported, and we cannot exclude that events rather than patients were accounted in some analyses. As a consequence, each CVAE occurred in a limited number of patients in RPCTs. Thus, associations may be inconclusive for some events, and we may have missed potential safety signals. In addition, RPCTs cannot detect rare or delayed adverse events. Patients are also highly selected and less prone to develop CVAEs than the real-life population. The pharmacovigilance disproportionality analysis addresses these issues, because patients are not selected. We were able to perform disproportionality analyses on standardized MedDRA queries, which increase the power of safety signal detection for several selected diseases. However, notification may be selective, and there is no control group. Several biases can interfere with the interpretation of a disproportionality analysis, such as time since marketing, media safety alerts and selective notification.

Study limitations

Several aspects of this systematic review and meta-analysis must be considered when interpreting the results. The overall incidence of CVAEs could not be assessed because it was not reported in the studies. The CVAE reports were not always the result of a systematic assessment, and a threshold was often used for the reporting of non-serious CVAEs, although it was quite low, ranging from 0% to 10%.

The heterogeneity in our analyses was low to moderate and might be explained by clinical diversity, with the aggregation of patients with various cancer types, as suggested by our subgroup analysis. A methodological diversity in the monitoring of CVAEs is also possible between RPCTs, with different follow-up schedules and different CTCAE versions being used. This may alter the estimations and the external

validity of our study. Although the studies assessed different drugs, they all belonged to a similar pharmacological class, and a meta-analysis seemed reasonable to evaluate the average effect of these drugs. To our knowledge, there is no known pharmacological interaction between the concurrent cytotoxic drugs and BRAF or MEK inhibitors that could underlie this association. Readers should keep in mind that these subgroup analyses are for exploratory purposes only, and that no definitive conclusions should be drawn. We did not perform metaregression because we had fewer than 10 studies for each CVAE in the primary outcome analysis.

The cardiovascular risk factors, past history and medications of patients were not reported in the studies. These factors always increase the risk of cardiovascular toxicity for all cancer types and all antineoplastic therapies [32]. It is probable that these factors were differentially distributed between studies and could have interfered with the incidence of CVAEs, thus contributing to the heterogeneity.

Conclusions

Our analysis showed that the risks of ejection fraction decrease, peripheral oedema and syncope were increased with the use of MEK inhibitors in cancer patients in RPCTs. Combination therapies increased the risk of ejection fraction decrease. Serious syncope was the only high-grade or serious CVAE associated with MEK inhibitors. Pharmacovigilance analysis suggested an association between BRAF/MEK inhibitors and torsade de pointes/QT prolongation and supraventricular arrhythmias that was not found in RPCTs. Better knowledge and, ultimately, earlier detection and management of CVAEs could improve the risk/benefit balance of these treatments.

Acknowledgements

We express our gratitude to Oxford University for their prompt response to our data request.

Sources of funding

This systematic review was supported by the Caen Normandy University Hospital (CHU de Caen, Normandie, France) and Normandy University (Université de Caen Normandie, France).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Figure legends

Figure 1. Flow diagram of study selection. BRAF: rapidly accelerated fibrosarcoma B-type; CVAE: cardiovascular adverse event; ICSR: individual case safety report; MEK: mitogen-activated extracellular signal-regulated kinase; RPCT: randomized placebo-controlled trial; WHO: World Health Organization.

Central illustration. Forest plot comparing the association between B-type rapidly accelerated fibrosarcoma/mitogen-activated extracellular signal-regulated kinase inhibitors in the meta-analysis of randomized placebo-controlled trials (Peto summary odds ratio [OR]) and the disproportionality analysis in VigiBase® (age- and sex-adjusted reporting odds ratio [rOR]). CI: confidence interval; TdP: torsade de pointes.

^a Excluding ejection fraction decreased and isolated non-specific signs.

Table 1. Characteristics of the clinical trials of rapidly accelerated fibrosarcoma B-type and mitogen-activated extracellular signal-regulated kinase inhibitors (as monotherapy or in combination) that were included in the meta-analysis.

Study	BRAF and/or MEK inhibitor	BRAF and/or MEK inhibitor initial doses	Concurrent cytotoxic chemotherapy	Study comparator	Duration of treatment	Population size	Safety population size (% of patients in active arm)	Cancer type	Line of treatment	Median age in treatment group (years)	CV co- morbidity as exclusion criteria	Study primary outcome	Median follow- up (months)
Monotherapy trials													
Carvajal et al. SUMIT [16]	Selumetinib	75 mg twice per day	Dacarbazine 1000 mg/m ² IV 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. DOC-MEK [17]	Selumetinib	75 mg twice per day	Docetaxel 75 mg/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 BRAF wild-type melanoma	1	62	Yes	PFS	13.6
Infante et al. [18]	Trametinib	2 mg per day	Gemcitabine 1000 mg/m ² IV weekly x 7 for 8 weeks, then days 1, 8 & 15 of 28-day	Placebo + gemcitabine (same schedule)	Until efficacy or major safety event	160	160 (50.0)	Metastatic adenocarcinoma of the pancreas	1	64	Yes	OS	MD

			cycles										
Jänne et al. [19]	Selumetinib	75 mg twice per day	Docetaxel 75 mg/m ² IV 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 NSCLC	2	59.5	No	OS	7.2
Jänne et al. SELECT-1 [20]	Selumetinib	75 mg twice per day	Docetaxel 75 mg/m ² IV 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 NSCLC	2	62	No	PFS	2.7
Maio et al. BRIM8 [6]	Vemurafenib	960 mg twice per day	-	Placebo	52 weeks	498	494 (50.0)	Stage IIC–IIIB (cohort 1) & stage IIIC (cohort 2) <i>BRAF</i> ^{V600} mutation- positive melanoma	1	51/55	Yes	DFS	MD
Robert et al. [21]	Selumetinib	75 mg twice per day	Dacarbazine 1000 mg/m ² IV 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. SELECT-2 [22]	Selumetinib	75 mg twice per day	Docetaxel 75 mg/m ² IV on day 1 of a 21- day cycle.	Placebo + docetaxel (same schedule)	Until efficacy or major safety event	127 ^a	127 (66.1)	Locally advanced or metastatic NSCLC	2	62	No	PFS	MD

Van Cutsem et al. [23]	Pimasertib	60 mg twice per day	Gemcitabine IV weekly in 28-day cycles for 5 months	Placebo + gemcitabine (same schedule)	Until efficacy or major safety event	88 ^b	87 (51.7)	Metastatic pancreatic adenocarcinoma	1	63	No	PFS	10.6
Zaman et al. SAKK21/08 [24]	Selumetinib	75 mg twice per day	Fulvestrant IM on days 1, 15 & 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
Combination therapy trials													
Ascierto et al. coBRIM [25]	Vemurafenib; cobimetinib	960 mg twice per day; 60 mg 21 days out of 28	-	Placebo + vemurafenib (same schedule)	Both: 52 weeks or until efficacy or major safety event	495	493 (50.1)	Unresectable locally advanced or metastatic <i>BRAF</i> ^{V600} mutation-positive melanoma	1	56	Yes	PFS & OS	14.2
Long et al. COMBI-d [26]	DaBRAFeinib; trametinib	150 mg twice per day; 2 mg per day	-	Placebo + daBRAFeinib (same schedule)	Both: until efficacy or major safety event	423	420 (49.8)	Unresectable stage IIIC or IV melanoma with <i>BRAF</i> ^{V600E} or <i>BRAF</i> ^{V600K} mutation	1	55	Yes	PFS	MD

All the studies included were full-text, published, randomized placebo-controlled clinical trials, and had at least partial industrial funding. BRAF: rapidly accelerated fibrosarcoma B-type; CV: cardiovascular; DCR: disease control rate; DFS: disease-free survival; ER: oestrogen receptor; IM: intramuscular; IV: intravenous; MD: missing data; MEK: mitogen-activated extracellular signal-regulated kinase; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; PgR: progesterone receptor.

^a We only included patients from the selumetinib + docetaxel 75 mg/m² and placebo + docetaxel 75 mg/m² groups.

^b We only included patients from the phase II placebo-controlled part of the study.

Table 2 Individual Medical Dictionary for Regulatory Activities term analyses in randomized controlled trials of rapidly accelerated fibrosarcoma B-type and mitogen-activated extracellular signal-regulated kinase inhibitor combination therapy versus BRAF inhibitor plus placebo.

MedDRA term	No. of studies reporting the outcome	Events/obs in BRAF and MEK inhibitor groups	Events/obs in control groups	Random-effects OR	95% CI	<i>P</i>	I ² for heterogeneity	χ^2 <i>P</i> for heterogeneity
Cardiac arrhythmias								
Supraventricular arrhythmias	2	13/456	7/457	1.85	0.76–4.49	0.17	0%	0.79
TdP/QT prolongation	2	11/456	18/457	0.40	0.07–2.32	0.30	0.70%	0.06
Heart failure								
Ejection fraction decreased	2	45/456	18/457	2.48	1.46–4.21	< 0.001	0%	0.53
Symptomatic heart failure ^a	2	1/456	3/457	0.37	0.05–2.61	0.31	0%	0.56
Ischaemic diseases								
Ischaemic heart disease	1	5/247	1/246	-	—	-	-	-
Ischaemic stroke	2	4/456	0/457	7.43	1.04–52.9	0.045	0%	0.99
Hypertension	2	91/456	67/457	1.43	0.83–2.45	0.20	68%	0.08
Venous thromboembolism	2	13/456	3/457	3.57	1.33–9.6	0.01	0%	0.76
Non-specific signs								
Chest pain	1	0/209	1/211	-	—	-	-	-
Dyspnoea	2	31/456	34/457	0.90	0.55–1.5	0.70	0%	0.50

Peripheral oedema	2	64/456	37/457	1.98	0.76–5.17	0.16	80%	0.02
Syncope	2	8/456	5/457	1.60	0.53–4.77	0.40	0%	0.51

BRAF: rapidly accelerated fibrosarcoma B-type; CI: confidence interval; MEK: mitogen-activated extracellular signal-regulated kinase; obs: total number of patients observed; OR: odds ratio; TdP: torsade de pointes.

^a Excluding ejection fraction decreased and isolated non-specific signs.

Table 3 Subgroup analyses for peripheral oedema in rapidly accelerated fibrosarcoma B-type and mitogen-activated extracellular signal-regulated kinase inhibitor trials.

Subgroup (number of studies)	OR (95% CI)	I ²	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	4.67 (2.18–10.01)	24%	
≥ 60 years	2.47 (1.63–3.75)	46%	
CV co-morbidities (7)			0.35
Excluded	2.39 (1.26–4.51)	68%	
Not excluded	3.49 (2.17–5.62)	13%	

CI: confidence interval; CV: cardiovascular; NSCLC: non-small cell lung cancer; OR: odds ratio.

Method

Meta-analysis of RPCTs from MEDLINE/Pubmed, EMBASE, The Cochrane database, trials registry portals and conference abstracts and articles until September, 18th, 2018

Selection process

6,822 abstracts / articles / study designs identified through database searching

6,644 records did not meet inclusion criteria after title / abstract reviewing or were duplicates

178 records assessed for eligibility

166 records excluded

- 89 did not meet inclusion criteria
- 72 Non-placebo-controlled clinical trials
- 1 Observational study
- 4 Systematic reviews or meta-analyses

12 RPCTs included in the meta-analysis
(**10** monotherapy RPCTs and **2** combination therapy RPCTs)

Analysis

Safe meta-analysis

Disproportionality analysis in the WHO pharmacovigilance database Vigibase®

14,237,423 ICSRs \geq 2010

1,810,862 anticancer drugs ICSRs (primary analysis population)

20,548 BRAF or MEK inhibitors ICSRs

1,698 CVAE reports with BRAF or MEK inhibitors (cases)

Disproportionality analysis