RESEARCH ARTICLE

# Efficacy and Safety of Selumetinib Compared with Current Therapies for Advanced Cancer: a Meta-analysis

**Chen-Tian Shen[&], Zhong-Ling Qiu[&], Quan-Yong Luo***

## Abstract

**Background and Aim: Selumetinib is a promising and interesting targeted therapy agent as it may reverse radioiodine uptake in patients with radioiodine-refractory differentiated thyroid cancer. We conduct this meta-analysis to compare the efficacy and safety of selumetinib with current therapies in patients with advanced cancer. Methods: An electronic search was conducted using PubMed/ Medicine, EMBASE and Cochrane library databases. Statistical analyses were carried out using either random-effects or fixed-effects models according to the heterogeneity of eligible studies. Results: Six eligible trials involved 601 patients were identified. Compared with current therapies, treatment schedules with selumetinib did not improve progression free survival (hazard ratio, 0.91; 95%CI 0.70–1.17, *P*= 0.448), but did identify better clinical benefits (odds ratio, 1.24; 95%CI 0.69–2.24, *P* = 0.472) and less disease progression (hazard ratio, 0.72; 95%CI 0.51–1.00, *P* = 0.052) though its impact was not statistically significant. Sub-group analysis resulted in significantly improved progression free survival (hazard ratio, 0.61; 95%CI 0.49–0.57, *P* = 0.00), clinical benefits (odds ratio, 3.04; 95%CI 1.60–5.77, *P* = 0.001) and reduced disease progression (hazard ratio, 0.35; 95%CI 0.18–0.67, *P* = 0.001) in patients administrated selumetinib. Dermatitis acneiform (risk ratio, 9.775; 95%CI 3.143–30.395, *P* = 0.00) and peripheral edema (risk ratio, 2.371; 95%CI 1.690–3.327, *P* = 0.00) are the most frequently observed adverse effects associated with selumetinib. Conclusions: Compared with current chemotherapy, selumetinib has modest clinical activity as monotherapy in patients with advanced cancer, but combinations of selumetinib with cytotoxic agents in patients with BRAF or KRAS mutations hold great promise for cancer treatment. Dermatitis acneiform and peripheral edema are the most frequently observed adverse effects in patients with selumetinib.**

**Keywords:** MEK1/2 inhibitor - selumetinib - advanced cancer - meta-analysis

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## Introduction

The mitogen-activated protein kinases (MAPKs) are important signal transducing enzymes, evolutionarily conserved, which respond to various extracellular stimuli and play critical roles in a vast number of fundamental cellular processes including growth, proliferation, differentiation, motility, stress response, survival, apoptosis and angiogenesis via a series of phosphorylation events and protein-protein interactions (Shaul et al., 2007; Raman et al., 2007; Pimienta et al., 2007; Krishna et al., 2008). MAPK activity is regulated through three-tiered cascades composed of MAPK, MAPK kinase (MAPKK, MKK or MEK) and MAPKK kinase or MEK kinase (MAPKKK or MEKK) (English et al., 1999). Four distinctly regulated groups of MAPKs have been identified and been named according to their MAPK module, namely extracellular signal-related kinases (ERK)-1/2, Jun amino-terminal kinases (JNK1/2/3), p38 proteins (p38a/b/g/d) and ERK5, all of which are activated by specific MAPKKs: MEK1/2 for ERK1/2, MKK3/6 for the p38 kinases, MKK4/7 (JNKK1/2) for the JNKs, and MEK5 for ERK5 (Robinson et al., 1997; Schaeffer et al., 1999; Chang et al., 2001).

MEK1 and MEK2, closely related, are dual specificity enzymes that phosphorylate threonine and tyrosine residues (in the activation sequence Thr-Glu-Tyr of ERK1/2) within the activation loop of their MAP kinase substrates (Pearson et al., 2001). Their key position within the Ras/Raf/MEK/ERK signal cascades (Wortzel et al., 2011), which is one of the most frequently dysregulated pathways involved in the process of human tumorigenesis (Peyssonnaux et al., 2001), provides a strong rationale for the development of small molecule inhibitors of MEK1/2 in the treatment modality of human cancer. Several MEK1/2 inhibitors have been identified, studied and have progressed to clinical trials since the first MEK inhibitor (PD098059) was described in the literature in 1995 (Dudley et al., 1995). MEK1/2 inhibitors have shown clinical benefits in the treatment of many types of malignancy and trametinib has been approved for use in patients with metastatic melanoma by the United States Food and Drug Administration (Wright and McCormack, 2013). Currently, thirteen MEK inhibitors (trametinib, selumetinib, PD-0325901, MEK162, among others.) have been tested clinically (Akinleye et al., 2013). Among them,

*Department of Nuclear Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, Chinan [&]Equal contributors *For correspondence: lqyn@sh163.net*

the MEK1/2 inhibitor, selumetinib is the most frequently studied drug that has demonstrated activity in preclinical models in a variety of tumors and recently a study (Ho et al., 2013) published in the New England Journal of Medicine made the authors interested in the new agent. Selumetinib (AZD6244, ARRY-142886, initially developed by Array BioPharma, Boulder, CO) is an orally available, potent, selective, allosteric, ATP-uncompetitive (they do not directly compete for the ATP–binding site) inhibitor of MEK1/2 (Yeh et al., 2007) and several randomized clinical trials have been conducted to evaluate the effectiveness and adverse effects of selumetinib in patients with advanced cancer. Most of these trials are characterized by a small sample size, with inadequate statistical power to exclude potentially clinically relevant differences in efficacy, and as a result, whether selumetinib should be the treatment of choice for patients with advanced cancer is still unknown. To our knowledge, to date there has been no meta-analysis with a greater statistical power conducted to compare treatment agents and detect differences.

In the current meta-analysis we attempted to analyze and combine the results of all eligible randomized trials to increase statistical power and investigate whether selumetinib is more effective than current chemotherapy in the treatment of patients with advanced cancer.

## Materials and Methods

*Literature search to identify related studies*

A search for human trials without language restrictions in the bibliographic databases PubMed/MEDLINE and EMBASE was conducted using the terms "selumetinib", "AZD6244" , "ARRY-142886" , "clinical trials" and "cancers" as well as text terms such as "efficacy" and "safety" to identify relevant information. We also carried out independent searches using the Cochrane library databases to ensure that no clinical trials were overlooked. The list of articles was supplemented through extensive crosschecking of the reference lists of all retrieved articles. Unpublished data and conference proceedings were not included.

*Study selection*

Two reviewers (ZL Qiu and CT Shen) independently assessed the eligibility of each article. After screening all titles and reading the abstracts, the full text of the selected articles was reviewed to determine their eligibility for inclusion in the study and any discrepancy between the reviewers was resolved by consensus. The criteria for inclusion of the clinical trials were: (1) phase II and III randomized controlled trials (RCTs); (2) random assignment of participants to selumetinib or control treatments (placebo or concurrent therapy using a chemotherapeutic or biological agent); (3) trials that recorded necessary data about therapy efficacy and safety and (4) patients with a diagnosis of advanced cancer. Exclusion criteria were: (1) pharmaceuticals used were not MEK1/2 inhibitors, (2) studies used animal or cell cultures and (3) letters, abstracts, reviews, case reports, editorials and comments. The quality of each clinical trial was assessed and calculated using the Jadad scale including randomization (0–2 scores), blinding method (0–2 scores), withdrawals and dropouts (0–1 scores) (Moher et al., 1998).

*Data extraction*

Data extraction was conducted independently by two investigators (CT Shen and ZL Qiu) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). For each relevant study, collected data included the following: (1) basic information of each eligible study such as year of publication, journal name, and author name; (2) characteristics of patients such as median age, gender composition, tumor type; (3) information of study designation such as number of enrolled subjects, group sample size, and treatment regimen; (4) results of treatment such as complete response (CR), partial response (PR), stable disease (SD), overall survival (OS), disease progression, and median progression-free survival (PFS). To resolve disagreements between reviewers, a third reviewer (QY Luo) assessed all discrepant items and the majority opinion was used to choose studies for analysis. To evaluate the toxicity of selumetinib, the authors also calculated the number of the following adverse effects (AEs) reported in the safety profile section of each study: dermatitis acneiform, peripheral edema, diarrhea, nausea, vomiting and fatigue. When available, all-grade (1–4) and high-grade (3–4) events provided in the studies were included in the analysis.

*Statistical analysis*

For each trial, the hazard ratio (HR) for PFS and disease progression, odds ratio (OR) for clinical benefits (the total of CR, PR and SD), and risk ratio (RR) for AEs were analyzed from the extracted data and 95% confidence intervals were derived. Heterogeneity analysis was performed by calculating the $I^2$ index, which was interpreted as low (25%), moderate (50%) and high heterogeneity (75%) (Higgins et al. 2003). It is reported that the $I^2$ index is an assessment not only of heterogeneity in a meta-analysis but also the extent of that heterogeneity, and as such it is considered a more appropriate procedure than Dixon's Q test in assessing whether there is true heterogeneity among studies in a meta-analysis (Berlin, 1995; Huedo-Medina et al., 2006). For the meta-analysis, both fixed-effects (weighted with inverse variance) and random-effects models were considered. A random-effects model was chosen when heterogeneity was > 50%, while a fixed-effects model was chosen when heterogeneity was < 50% (DerSimonian and Laird, 1986). In addition, if any eligible study reported zero events in the treatment or control arm, continuity corrections with 0.5 were adopted to calculate the incidence and the OR (Robins et al., 1986). Publication bias was assessed using a standard funnel plot, and funnel plot asymmetry was further tested using Begg's and Egger's regression method (Copas and Shi, 2000). Forest plots were sorted according to first author's name and year of publication to illustrate the HR, OR and RR. All statistical analyses were performed using Stata Version 12.0 software (Stata Corporation, College Station, TX).

**Table 1. Baseline Characteristics of Each Trial**

| Study | Year | Tumor type | Phase | Enrolled patients/n | Patients per arm/n | Regimens | Median age/years | M/F | mPFS/d | OS/m | DP/n | SD/n | PR/n |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bennouna et al. | 2010 | CRC | II | 69 | 34 | selumetinib 100 mg | 61.5 | 22/12 | 81 | - | 21 | 10 | 0 |
| | | | | | 35 | capecitabine 1250 mg/m$^2$ | 60 | 17/18 | 88 | - | 18 | 15 | 1 |
| Hainsworth et al. | 2010 | NSCLC | II | 84 | 40 | selumetinib 100 mg | 61.5 | 26/14 | 67 | - | 18 | 14 | 2 |
| | | | | | 44 | pemetrexed 500 mg/m$^2$ | 63.5 | 27/17 | 90 | - | 18 | 21 | 1 |
| Kirkwood et al. | 2011 | Melanoma | II | 200 | 104 | selumetinib 100 mg | 57.1 | 55/49 | - | - | 40 | 48 | 6 |
| | | | | | 96 | temozolomide 200 mg/m$^2$ | 57 | 65/31 | - | - | 43 | 36 | 9 |
| Bodoky et al. | 2012 | PC | II | 70 | 38 | selumetinib 100 mg | 65 | 24/14 | 63 | 5.4 | 32 | 12 | 2 |
| | | | | | 32 | capecitabine 1250 mg/m$^2$ | 62 | 11/21 | 68 | 5 | 28 | 9 | 3 |
| Jänne et al. | 2013 | NSCLC* | II | 87 | 44 | selumetinib 75 mg+docetaxel | 59.5 | 21/23 | 5.3m | 9.4 | 8 | 19 | 16 |
| | | | | | 43 | placebo+docetaxel | 59 | 20/23 | 2.1m | 5.2 | 18 | 20 | 0 |
| Robert et al. | 2013 | Melanoma# | II | 91 | 45 | selumetinib 75 mg+dacarbazine | 57 | 22/23 | 5.6m | 13.9 | 14 | 13 | 12 |
| | | | | | 46 | placebo+dacarbazine | 52 | 28/18 | 3m | 10.5 | 24 | 10 | 6 |

CRC, colorectal cancer; NSCLC non-small-cell lung cancer; PC, pancreatic cancer; d, day; m, month; M, male; F, female; mPFS, median progression-free survival; OS, overall survival ; DP, disease progression; SD, stable disease; PR, partial response; *indicates NSCLC with KRAS mutation; #indicates melanoma with BRAF mutation; "_" indicates a parameter that was not reported in the trial

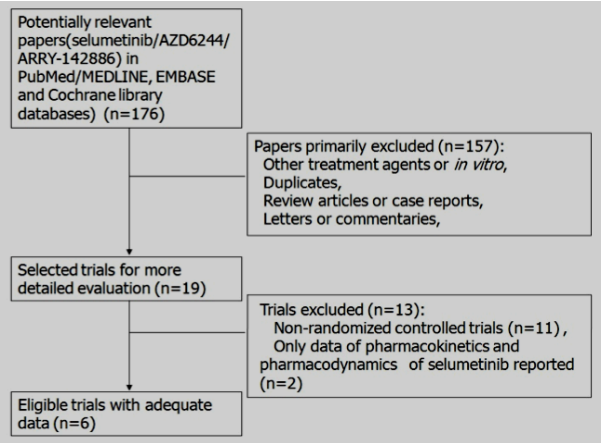


**Figure 1. Flow Chart Showing the Process of Study Selection**

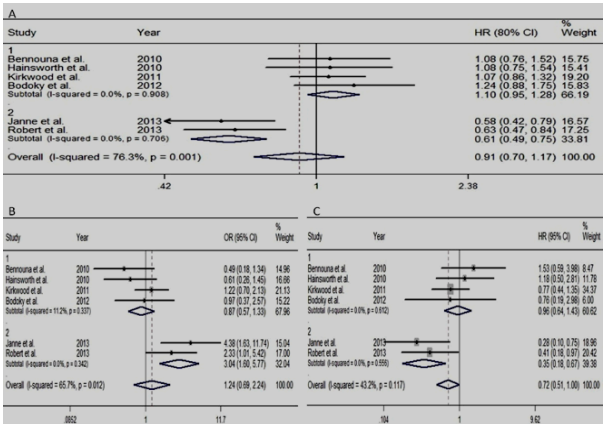


**Figure 2.** A: random-effects model of hazard ratio for progression-free survival and 80% confidence interval associated with selumetinib compared with current chemotherapies; B: random-effects model of odds ratio for clinical benefits and 95% confidence interval associated with selumetinib compared with current chemotherapies; C: fixed-effects model of hazard ratio for disease progression and 95% confidence interval associated with selumetinib compared with current chemotherapies. Dividing the study population according to specific mutations resulted in sub-group 1 (subjects who did not test the particular mutation) and sub-group 2 (subjects with BRAF or KRAS mutations)

## Results

*Study characteristics*

The current meta-analysis was carried out in accordance with the guidelines of PRISMA. The literature search identified 176 potentially relevant articles. After screening titles and abstracts, 157 irrelevant articles were excluded because they involved other treatment agents, duplicates, review articles, case reports, abstracts presented at meetings, letters or commentaries. Following a more detailed review, eleven articles were excluded because they are not RCTs. After reading the full text of the remaining eight studies, two papers were excluded as their purpose was to assessthe tolerability, pharmacokinetics and pharmacodynamics of selumetinib.Finally six clinical trials (Hainsworth et al., 2010; Bennouna et al., 2011; Kirkwood et al., 2012; Bodoky et al., 2012; Jänne et al., 2013; Robert et al., 2013) involving 601 patients matched our inclusion criteria. The process of study selection is shown in a flow chart (Figure 1).

The baseline characteristics of each trial are shown in Table 1. These six RCTs were published between 2010 and 2013 and all of them were phase II clinical trials. In all, there were 601 patients (median age: 52–65 years) with a male to female ratio of 338 to 263 who were diagnosed with cancer at four sites, namely colorectal cancer (CRC), non-small-cell lung cancer (NSCLC), melanoma, and pancreatic cancer (PC). Most of the subjects were confirmed with a high stage cancer and all of them were considered to require treatment but had failed to respond to previous chemotherapeutic regimens. The quality of the six included trials was high: two of them achieved Jadad scores of 5 and the others scored 3.

*Publication bias*

Several strategies were used in the study design to minimize the potential for publication bias. These were the extension of search strategy, strict inclusion criteria and the careful design of the analytic method (when analyzing the HR for PFS and disease progression, and the OR for clinical benefits, the eligible studies were divided into two groups according to the particular mutation of the tumors). Publication bias was not found according to the funnel plot (Begg's test, $P = 0.707$; Egger test, $P = 0.997$).

*Efficacy*

Progression-free survival: All of the eligible trials

**Table 2. Meta-analysis of All Grade AEs Comparing Selumetinib with Current Chemotherapies in Patients with Advanced Cancer**

| Toxicity/all grade | Trials/n | Selumetinib | Current chemotherapy | Heterogeneity | | RR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|
| | | | | *P*-value | $I^2$/% | | |
| Dermatitis acneiform | 5 | 135/261 | 14/257 | 0.006 | 72.6 | 9.775 (3.143-30.395) | 0.00 |
| Peripheral edema | 5 | 98/258 | 19/248 | | | 4.920 (2.926-8.274) | 0.00 |
| Gastrointestinal symptoms | | | | | | | |
| Diarrhea | 6 | 152/298 | 62/289 | 0.261 | 23.0 | 2.371 (1.690-3.327) | 0.00 |
| Nausea | 6 | 121/298 | 128/289 | 0.708 | 0.0 | 0.913 (0.676-1.234) | 0.554 |
| Vomiting | 6 | 92/298 | 85/289 | 0.27 | 21.7 | 1.044 (0.743-1.467) | 0.805 |
| Fatigue | 6 | 70/298 | 93/289 | 0.696 | 0.0 | 0.731 (0.513-1.041) | 0.082 |

RR, risk ratio; CI, confidence interval

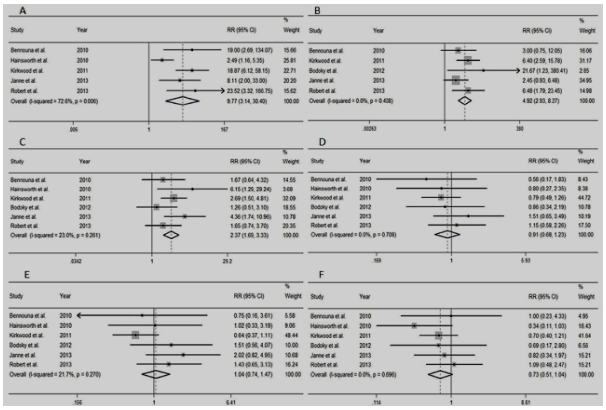

**Figure 3.** A: random-effects model of risk ratio for dermatitis acneiform associated with selumetinib compared with current chemotherapies; B, C, D, E, F illustrate fixed-effects models of risk ratios for peripheral edema, diarrhea, nausea, vomiting, and fatigue associated with selumetinib compared with current chemotherapies

reported PFS data with 80% confidence intervals, so the authors pooled the hazard ratios for PFS and derived the 80% confidence interval (in order to be consistent with the original articles) and the result did not show any significant difference between therapy schedules with or without selumetinib (HR, 0.91; 95%CI 0.70–1.17, $P$ = 0.448). However sub-group analysis resulted in significantly improved PFS (HR, 0.61; 95%CI 0.49–0.57, $P$ = 0.00) (Figure 2 A). Dividing the study population according to specific mutations resulted in sub-group 1 (subjects who did not test the particular mutation) and sub-group 2 (subjects with BRAF or KRAS mutations). There was significant heterogeneity between trials ($I^2$ = 76.3%), so the pooled HR for PFS was calculated using the random-effect model.

Clinical benefits (the total of CP, PR and SD): The pooled OR for clinical benefits showed a significant difference between therapy regimens with or without selumetinib (OR, 1.24; 95%CI 0.69–2.24, $P$ = 0.472). Sub-group analysis revealed that the clinical benefits of therapy regimens with selumetinib in patients with BRAF or KRAS mutations were much greater than current chemotherapy without selumetinib (OR, 3.04; 95%CI 1.60–5.77, $P$ = 0.001) (Figure 2 B). The heterogeneity test resulted in an $I^2$ = 65.7%, so the pooled OR for clinical benefits was performed using the random-effect model.

Disease progression:The pooled HR for disease progression showed significant differences between therapy regimens with or without selumetinib(HR, 0.72; 95%CI 0.51–1.00, $P$ = 0.052). Sub-group analysis revealed that disease progression in the therapy regimens with selumetinib was significantly reduced compared to the current chemotherapy without selumetinib (HR, 0.35; 95%CI 0.18–0.67, $P$ = 0.001) (Figure 2 C). The heterogeneity test resulted in a value of $I^2$ = 42.3%, so the pooled HR for disease progression was calculated using the fixed-effect model.

Safety: There was increased risk of all grade dermatitis acneiform (RR, 9.775; 95%CI 3.143–30.395, $P$ = 0.00), peripheral edema (RR, 4.920; 95%CI 2.926–8.274, $P$ = 0.00) and diarrhea (RR, 2.371; 95%CI 1.690–3.327, $P$ = 0.00) in the patients treated with selumetinib, while the risk of fatigue (RR, 0.731; 95%CI 0.513–1.041, $P$ = 0.082) was much less in those patients. For other AEs such as nausea and vomiting, equivalent frequencies were found between the subjects in the two regimens (Table 2 and Figure 3 A–F).

## Discussion

The MAP kinase signaling pathway has been one of the most studied signaling pathways in human solid tumors with the molecular rationale that the RAF/MEK/ERK1/2 signaling pathway plays an essential role in cell proliferation and survival. It has been hypothesized that inhibition of this pathway leads to tumor growth inhibition and regression (Almoguera et al., 1988; Smit et al., 1988; Messersmith et al., 2006; Wang et al., 2007), so until now plenty of small molecule compounds that may inhibit this pathway have been studied in vitro and in vivo (Frémin and Meloche, 2010).

Sorafenib was one of the first compounds aimed at targeting the RAF/MEK/ERK1/2 pathway, but its results were not as promising as expected (Flaherty et al., 2008; Flaherty et al., 2013). While MEK1/2 inhibitors have shown clinical benefits in the treatment of many types of malignancy, currently thirteen MEK inhibitors (trametinib, selumetinib, PD-0325901, and MEK162, among others) have been tested clinically and of these (Akinleye et al., 2013), selumetinib, which is a selective, non-ATP-competitive agent that blocks the MAP kinase-signaling cascade, is the most frequently studied drug. In addition to the cancer sites in the studies we analyzed in the current meta-analysis, there have been many other clinical studies estimating the clinical benefits of selumetinib in other types of malignancy including thyroid carcinoma (Ho et al.,

2013), ovarian cancer (Farley et al., 2013), biliary cancer (Bekaii-Saab et al., 2011), and hepatocellular carcinoma (O'Neil et al., 2011). Recently, a clinical study reported that selumetinib increased the uptake of iodine-124 in 12 of the 20 patients (4 of 9 patients with BRAF mutations and 5 of 5 patients with NRAS mutations) and all patients had decreases in serum thyroglobulin levels (mean reduction, 89%) with no observed toxic effects of grade 3 or higher attributable by the investigators to selumetinib (Ho et al., 2013). This result indicated a promising future for selumetinib use in patients with radioiodine-refractory thyroid cancer. Studies have shown that nearly 50% of cutaneous malignant melanomas harbor the BRAF mutation resulting in a constitutively active MAP kinase cascade (Davies et al., 2002; Curtin et al., 2005). This means that a high percentage of patients with melanoma have mutations that lead to constitutive activation of the MAP kinase signal pathway and unregulated cell proliferation. Based on these findings, melanoma is the most frequently studied malignancy used to estimate the efficacy of the MEK inhibitors. In one of the six eligible trials in the current meta-analysis (Robert et al., 2013), it was demonstrated that progression-free survival was significantly improved in the selumetinib plus dacarbazine group versus the placebo plus dacarbazine group (HR 0.63, 80% CI 0.47–0.84), with a median of 5.6 months (80% CI 4.9–5.9) versus 3.0 months (2.8–4.6), respectively. As a result, the authors hypothesized that selumetinib might be more effective and tolerable compared with the current therapies in patients with advanced cancer, especially in those patients with BRAF or RAS mutations.

Our systematic literature search identified six relevant RCTs, two (Jänne et al., 2013; Robert et al., 2013) of which compared the efficacy of the combination of selumetinib and a chemotherapeutic drug (docetaxel or dacarbazine) with the chemotherapeutic drug alone.The results of the current meta-analysis of the six eligible RCTs showed no significant difference between therapy regimens with or without selumetinib (HR, 0.91; 95%CI 0.70–1.17, $P = 0.448$), but sub-group analysis revealed that in the patients who harbored a specific mutation (BRAF or KRAS), treatment with the combination of selumetinib and a cytotoxic drug significantly improved PFS (HR, 0.61; 95%CI 0.49–0.57, $P = 0.00$).

Toxicity is particularly relevant in patients with advanced cancer. The results of our study demonstrated that there were more incidences of all grade dermatitis acneiform (RR, 9.775; 95%CI 3.143–30.395, $P = 0.00$), peripheral edema (RR, 4.920; 95%CI 2.926–8.274, $P = 0.00$) and diarrhea (RR, 2.371; 95%CI 1.690–3.327, $P = 0.00$) in the patients treated with selumetinib, while the risk of fatigue (RR, 0.731; 95%CI 0.513–1.041, $P = 0.082$) might show less. High grade AEs were not analyzed due to their low incidences and the most frequently reported grade 3/4 AEs observed in patients administrated with selumetinib were dermatitis acneiform and gastrointestinal symptoms which could be generally reversible and manageable.

Meta-analysis is considered to be a useful tool for analyzing rare and unintended effects of a treatment because it can synthesize the data, increase statistical power and improve estimates of any effects. However, several limitations had to be considered in the current meta-analysis. Firstly, four of the eligible trials lacked blinding, which might have resulted in an overestimate of the effects, although these trials were well randomized. Secondly, the differences in treatment schedules and malignancies lead to increased clinical heterogeneity, but it might improve generalizability due to the observed heterogeneity. Thirdly, the current meta-analysis was not based on individual patient data, another possible cause of an overestimate of the treatment effects. However, individual patient data-based analyses might include fewer studies if the authors did not agree to submit their full databases to the analyzing group. Finally, we performed subgroup-analysis according to specific mutations (BRAF and KRAS), but the limited data would potentially limit detection of the therapeutic effects.

In conclusion, our meta-analysis demonstrated that compared with current chemotherapy, selumetinib, a MEK1/2 inhibitor, has modest clinical activity as monotherapy in patients with advanced cancer (patients in whom the specific mutations were not identified), but combinations of selumetinib with cytotoxic agents in patients with the BRAF or KRAS mutation can significantly improve PFS, clinical benefits and reduce disease progression. Dermatitis acneiform and peripheral edema, both reversible and manageable, are the most frequently observed AEs in patients treated with selumetinib. Based on the findings in the current meta-analysis, the authors suggest that molecular testing (to identify the status of BRAF and RAS) can play a significant role in the selection of patients for treatment with selumetinib, and that combinations of selumetinib with cytotoxic or other biological agents show promise for the treatment of patients with advanced cancer.

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The author(s) declare that they have no competing interests.

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