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Original Article

The efficacy and safety of selumetinib in patients with cutaneous melanoma: a meta-analysis of three randomized controlled trials

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Abstract: Background: Selumetinib, a novel selective mitogen-activated protein kinases inhibitor, is generally thought to be beneficial to patients with melanoma. This meta-analysis aimed to investigate the efficacy and safety of selumetinib treatment comparing with other treatment agents in patients with cutaneous melanoma based on randomized controlled trials (RCTs). Methods: A meta-analysis was performed to analyze all available studies on the efficacy and safety of selumetinib in people with cutaneous melanoma. Results: Three RCTs that involved 374 participants were identified for evaluating the efficacy and safety of selumetinib for treating cutaneous melanoma. Results revealed that selumetinib treatment have better clinical benefits (the total of complete response, partial response, and stable disease) (odds ratio (OR)=1.58; 95% confidence interval (CI)=1.05-2.39, P=0.03), and reduce the risk of disease progression (OR=0.55; 95% CI=0.36-0.84, P<0.01), compared with other treatment agents. The most frequent adverse events were dermatitis (OR =17.75; 95% CI=2.37-132.72, P<0.01) and diarrhea (OR=4.05; 95% CI=2.56-6.40, P<0.001) in selumetinib treatment. However, selumetinib use was not associated with an improvement of progression-free survival (selumetinib vs. other agents: Hazard ratio (HR)=0.85; 95% CI=0.68-1.08, P=0.19) and overall survival (selumetinib vs. other agents: HR=1.18; 95% CI=0.91-1.53, P=0.20). Conclusion(s): Selumetinib used increased the risk of dermatitis and diarrhea. Selumetinib treatmenthave better clinical benefits and reduce disease progression. Furthermore, well-designed RCTs are needed to determine whether selumetinib provides a significant overall benefit for people with cutaneousmelanoma.

Keywords: Melanoma, selumetinib, mitogen-activated protein kinase, survival, meta-analysis, target therapy

Introduction

Cutaneous melanoma is one of the most common cancers worldwide and a highly aggressive type of cancer with an unfavorable prognosis [1]. It is estimated that almost 76100 new cases were diagnosed as melanoma, and nearly 10000 cases succumbed to this disease in the United States in 2014 [2]. In recalcitrant cancer, multiple modalities of anticancer treatment are recommended such as surgery, radiotherapy, and systemic therapy. With the understanding of the molecular pathway contributing to cancer development and progression, more novel drugs will be licensed to improve the survival of patients with advanced melanoma [3]. Most melanomas are driven by mutations that activate the Ras/Raf/MEK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) pathway, which play critical roles in regulating cell-cycle proliferation, differentiation, and survival [4, 5]. This pathway is a vital focus of new drug development for treating various cancers, including colorectal cancer, lung cancer, and melanoma [6]. The upregulation of this pathway was observed in variety of cancers when oncogenic mutations occurredin GNAO [7], GNA11 [8], KRAS [9], NRAS, HRAS, and BRAF [10]. The BRAF inhibitors could successfully suppress melanomas with BRAF (V600E) mutations [11]. Moreover, it has been reported in variousof studies that inhibiting MEK is a

potential target therapy for different types of cancers that depend on mitogen-activated protein kinases (MAPKs) pathway signals [12-14]. Trametinib, one of the MEK inhibitors, has been approved for clinical use by the United States Food and Drug Administration [15]. Other novel inhibitors of MEK1/2 are investigated among researchers worldwide.

As a novel non-ATP-competitive inhibitor of MEK1/2, selumetinib (AZD6244; ARRY-142886) has been widely investigated in human cancer cell lines [16], tumor xenograft models [17], and clinical study [18].

Some randomized controlled trials (RCTs) have been carried out to assess the efficacy and safety of selumetinib in patients with different types of cancers, including lung cancer, colorectal cancer, pancreatic cancer, and melanoma [18-23]. Whether selumetinib has a potential efficacy and safety in patients with cutaneous melanoma remains controversial. One study indicated that selumetinib did not have promising results in patients with cutaneous melanoma [22]. By contrast, Robert *et al.* suggested that selumetinib therapy has a significant benefit in terms of progression-free survival (PFS) [23].

In this study, we aimed to combine the current evidence of all eligible randomized trials to systematically evaluate the use of selumetinib versus current chemotherapy in the treatment of patients with cutaneous melanoma.

Methods

Eligibility criteria

Type of studies: RCTs were included for evaluating the efficacy and safety of selumetinib for treating cutaneous melanoma.

Type of participants: Patients diagnosed and histologically confirmed as cutaneous melanoma.

Type of interventions: Selumetinib and current chemotherapy were compared.

Type of outcomes: Primary outcome: Overall survival (OS). Secondary outcome: (1) PFS; (2) Adverse events: Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events; The adverse events include nausea, diarrhea, fatigue, constipation, stomatitis, vomiting; (3) Clinical benefits including the total of complete response (CR), partial response (PR) and stable disease (SD); (4) Disease progression.

Exclusion criteria

Studies were not RCT. Studies were not comparative studies that compared selumetinib treatment and other chemotherapy for treating cutaneous melanoma. Reviews, letters to the editors, and meeting abstracts were excluded.

Literature search

In this meta-analysis search, PubMed, EMBASE, Web of Science Knowledge, and the Cochrane Database were used, with the following search terms: “selumetinib”, “AZD6244”, “ARRY-142886”, and “melanoma”. In Pubmed, the search detail were “(((selumetinib) or AZD6244) or ARRY-142886) and melanoma”. The most recent search was conducted in 26th of June 2014, without language restriction in the selection of studies.

Study selection and data extraction

Two independent reviewers screened all available studies found through electronic database using a study selection form. The study selection process included two stages. First, titles and abstracts returned by the original search were screened. Studies that did not meet the inclusion criteria were excluded. Full text screening was required for potential studies to determine final decisions. If discrepancy existed, a discussion was conducted through author groups. Data were extracted by two independent reviewers with the use of a standard extraction sheet. The extraction data included: (1) Study characteristics (authors, publication year); (2) Study design features; (3) Study participants (e.g., eligibility criteria, baseline characteristics); (4) Study interventions (e.g., schedules, doses, and control interventions); and (5) Study outcomes (including survival outcomes, treatment response rate, and adverse events).

Assessing risk of bias

The risk of bias in each included study was evaluated by two independent reviewers (GL and

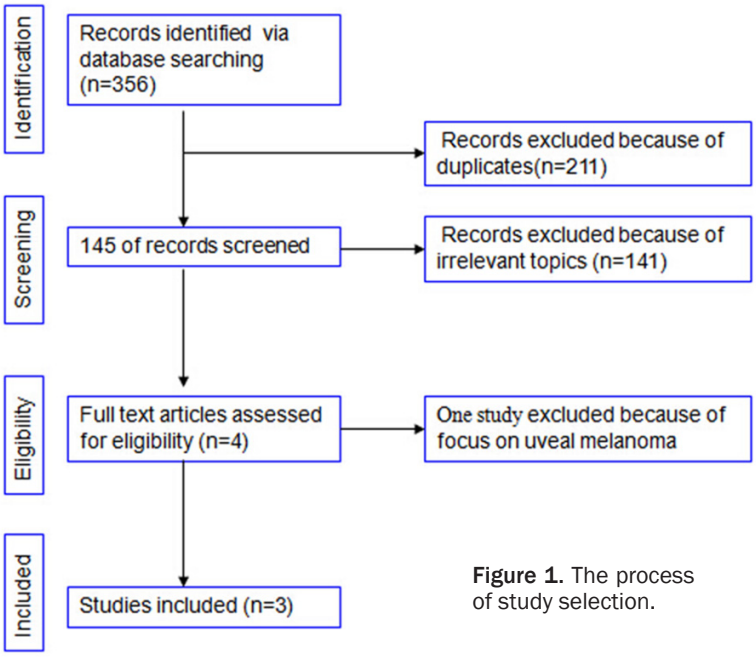


Figure 1. The process of study selection.

HS) using the Cochrane Collaboration's "risk of bias" tool [24], which was widely used for study quality assessment of RCTs.

Assessment of publication bias

Publication bias was assessment using funnel plot, Egger's test and Begg's test.

Statistical analysis

Data were analyzed with RevMan software (version 5.20). For survival outcomes, hazard ratio (HR) and its 95% confidence interval (CI) were applied. For dichotomous outcomes (adverse events and clinical benefits (the total of CR, PR, and SD), odds ratios (ORs)/Risk differences were calculated. Subgroup analyses were conducted according to specific mutations of the study population and adjuvant schedules. Sensitivity analyses were performed by considering the risk of bias of the studies or by excluding one study at each time. The heterogeneity of the included studies was analyzed using the Cochran Q test and the I^2 statistic [25]. P<0.1 or I^2>50% represents significant heterogeneity. If there was significant heterogeneity, random effects model was used for data analysis. Otherwise, we used fixed effects model. *P* values of less than 0.05 were considered statistically significant.

Results

Study characteristics

We conducted this meta-analysis according to the guidelines of PRISMA [26]. By electronic database search, we identified 356 potentially relevant articles. After a careful examination of titles and abstracts, four studies required full text screening. One study was excluded because it focused on uveal melanoma [27]. Finally, three RCTs [3, 22, 23] were included in our meta-analysis, which involved 190 patients in the selumetinib arm and 184 patients in the current therapy arm. The process of study selections is shown in **Figure 1**. The baseline characteristics of the included studies are listed in **Table 1**.

Assessing quality of studies

Risk of bias for each included RCT is displayed in **Figure 2A**, while a risk of bias across all RCTs is presented in **Figure 2B**. Risk of bias table is supported in Table S1.

Efficacy of selumetinib

Overall survival: Robert *et al.* reported that the combination of selumetinib and dacarbazine did not show significant improvement of OS [23]. Gupta *et al.* revealed that selumetinib plus docetaxel showed no significant improvement in PFS compared with docetaxel alone [3]. The study led by Kirkwood *et al.* described the variable of time to death [22]. The median survival time was 284 and 369 days for selumetinib treatment group and temozolomide treatment group, respectively. We considered the result partly equal to OS. As showed in **Figure 3A**, the HR and its 95% CI were measured using the fixed effects model (HR=1.18; 95% CI=0.91-1.53, P=0.20). This analysis indicated selumetinib use was not associated with a reduction risk of death compared with the control group.

Table 1. Basic characteristics of each included study

Study	Year	Case	Patients per arm	Regimens	Age	Median Os (M)	Median PFS (M)	Study phase	Treatment methods
Gupta A	2014	83	41	Selumetinib plus Docetaxel	62 (4)	9.5	4.23	II	Selumetinib P.O 75 mg orally twice daily + docetaxel IV 75 mg/m^2, on day 1 of a 21-day cycle up to a maximum of six cycles, until disease progression or unacceptable toxicity.
			42	Placebo plus Docetaxel	63 (4.75)	11.37	3.93		Placebo + docetaxel I.V. 75 mg/m^2, on day 1 of a 21-day cycle up to a maximum of six cycles, until disease progression or unacceptable toxicity.
Kirkwood JM	2012	200	104	Selumetinib	57.1 (16)	-	78	II	Selumetinib 100 mg free-base solution, twice daily in 28-day cycles.
			96	Temozolomide	57.0 (14)		80		Temozolomide (200 mg/m^2/d for 5 days, followed by 23 days off treatment).
Robert C	2013	91	45	Selumetinib plus dacarbazine	57 (5.25)	13.9	5.6	II	Selumetinib P.O (75 mg twice daily, in a 21-day cycle) and iv dacarbazine (1000 mg/m^2 on day 1 of a 21-day cycle.
			46	Placebo plus dacar bazine	52 (6.25)	10.5	3		I.V. dacarbazine (1000 mg/m^2 on day 1 of a 21-day cycle) + placebo.

P.O, per os; I.V., intravenous injection. M, month.

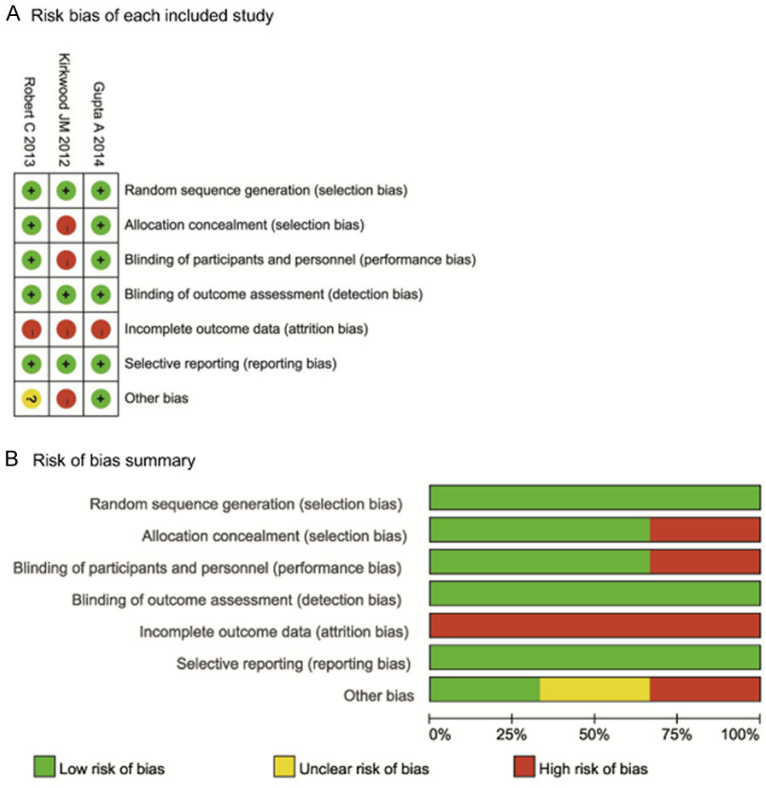


Figure 2. Risk of bias assessment: A. Risk of bias of each study. B. Risk of bias summary graph.

Progression-free survival: All included studies reported PFS [3, 22, 23]. Robert *et al.* suggested that the selumetinib plus dacarbazine group showed a significant clinical benefit in PFS compared with the placebo plus dacarbazine group [23]. By contrast, a study lead by Gupta *et al.* indicated that a combination of docetaxel with selumetinib did not significantly improve PFS compared with docetaxel alone [3]. Kirkwood *et al.* reported that no difference in PFS was observed in the selumetinib group compared with the temozolomide group [22]. The HR and its 95% CI was calculated using the fixed effects model (HR=0.85; 95% CI= 0.68-1.08, P=0.19) because of without significant heterogeneity (I^2=47%, P=0.15) among the 3 inclusion studies (**Figure 3B**). The result indicated that selumetinib treatment did not result in an improved PFS compared with other chemotherapy.

Overall clinical benefits (the total of CR, PR, and SD): The clinical benefits were evaluated with the combination of CR, PR and SD reported in all included studies [3, 22, 23]. Pooled analysis of data revealed that selumetinib treatment had favorable clinical bene-

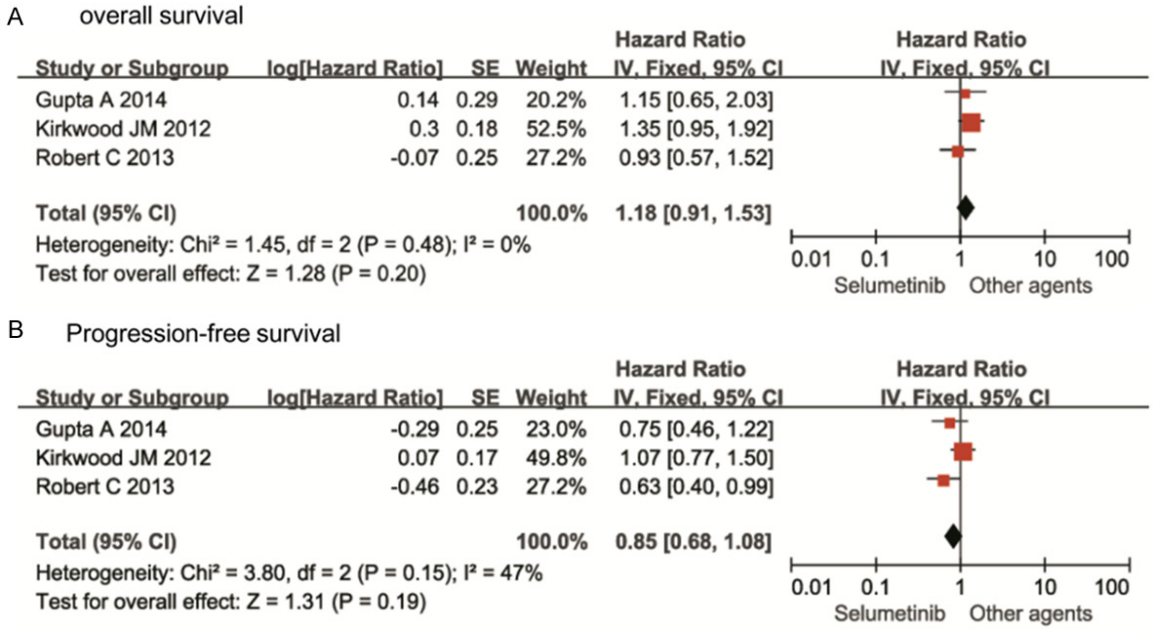


Figure 3. Meta-analysis of survival outcomes: A. Overall survival. B. Progression-free survival.

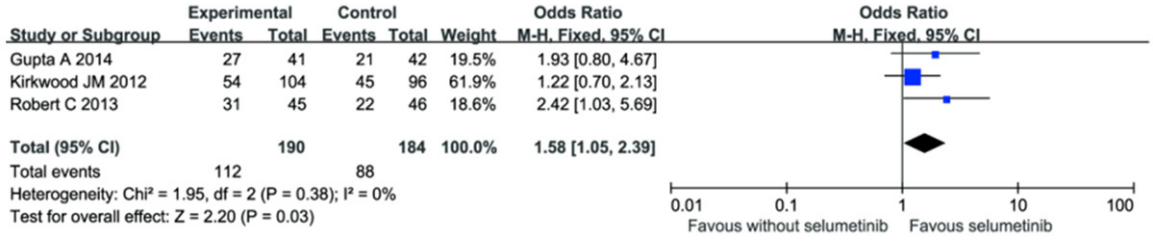


Figure 4. Meta-analysis of overall clinical effects (the total of complete response, partial response, and stable disease) between selumetinib and other agents.

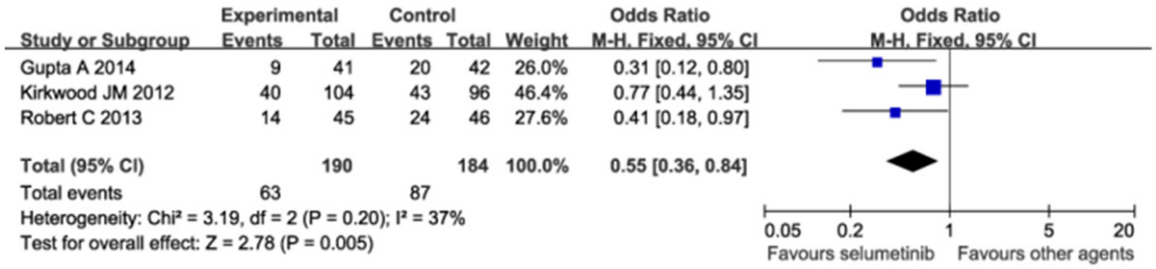


Figure 5. Meta-analysis of disease progression between selumetinib and other agents.

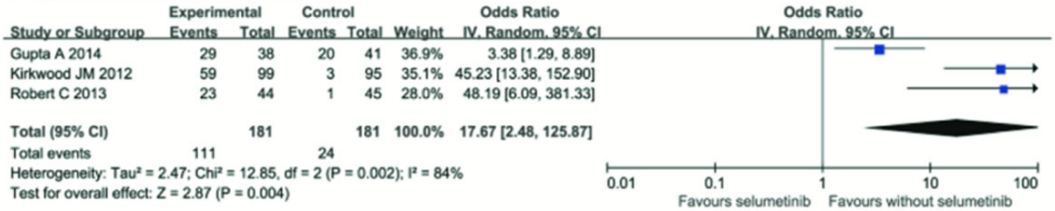
fits using a fixed effects model (OR=1.58; 95% CI=1.05-2.39, P=0.03, I^2=0) (**Figure 4**).

Disease progression: Pooled data of the three included studies [3, 22, 23] indicated that therapy regimens with selumetinib might reduce the risk of disease progression (OR=0.55; 95% CI=0.36-0.84, P=0.03, I^2=0) (**Figure 5**).

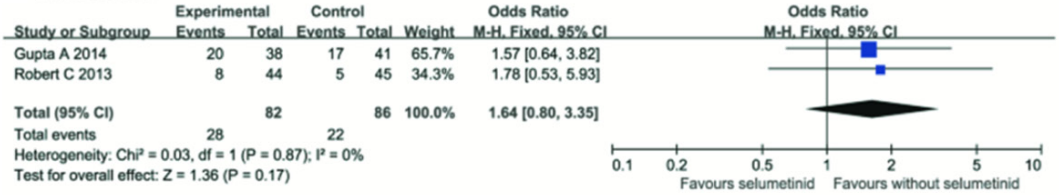
Safety of selumetinib

Adverse events were reported in all of the included studies [3, 22, 23]. The adverse events more frequently occurred in selumetinib group than in current chemotherapy group. The results indicated an increased risk of acneiform dermatitis (OR=17.75; 95% CI=2.37-

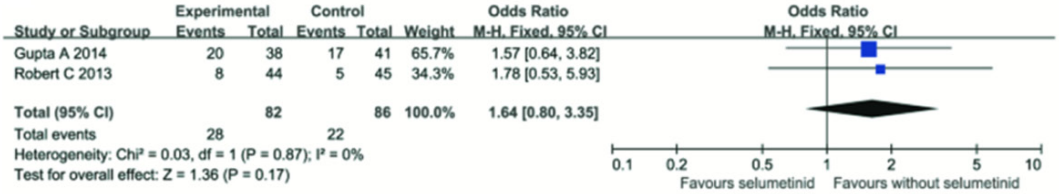
A acneiform dermatitis



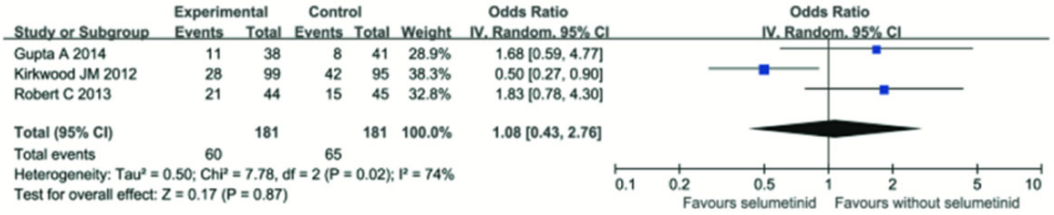
B mucositis



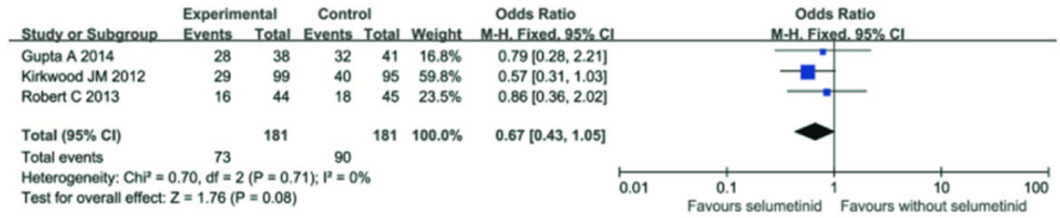
C diarrhea



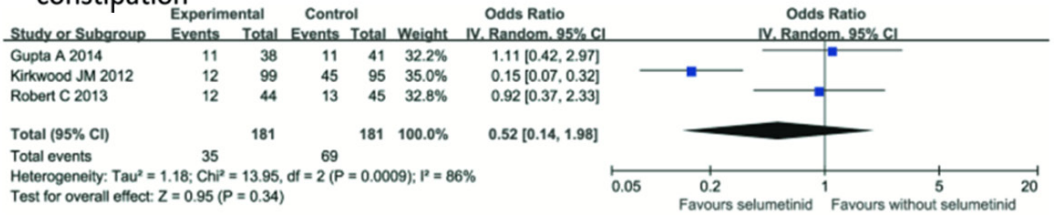
D vomiting



E fatigue



F constipation



G nausea

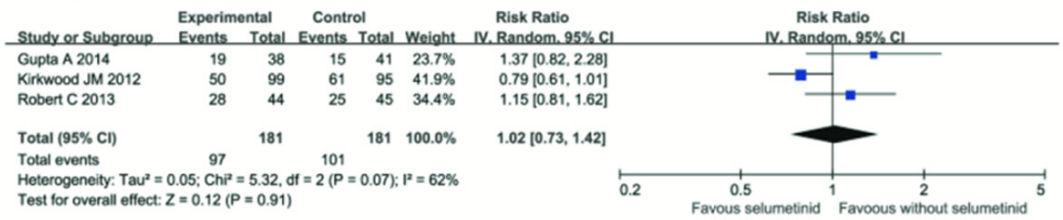


Figure 6. Meta analysis of the most generally adverse events in selumetinib treatment group compared with other agents treatment group.

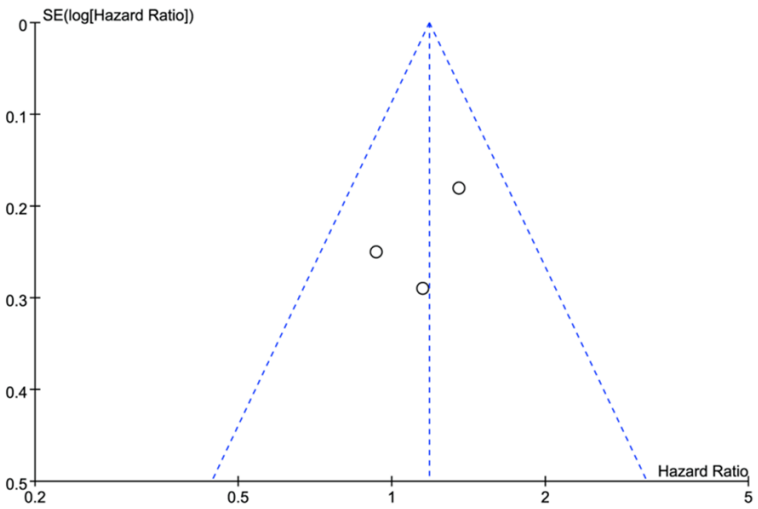


Figure 7. Funnel plot of overall survival for assessment of publication bias.

132.72, P=0.005) (**Figure 6A**), diarrhea (OR= 4.05; 95% CI=2.56-6.40, P<0.001) (**Figure 6C**).

For other adverse events such as nausea, mucositis, vomiting, fatigue, and constipation, equivalent frequencies were found between the subjects in the two groups (**Figure 6**).

Additional analysis

Publication bias was assessed using funnel plot for OS. The outcomes of all the included studies were within the 95% CIs (**Figure 7**). There was no publication bias according to the results from statistical tests (Begg's test *P*=0.60; Egger's test *P*=0.49). Sensitivity analysis was conducted by excluding the open-label study [22], and the hazard ratio for PFS benefit with selumetinib treatment was 0.68 (95% CI; 0.49-0.95), the test of interaction (P=0.02) was statistically significan (Figure S1A), which indicated that selumetinib treatment has an improved PFS. The other results are not influenced. However, sensitivity analysis was performed by excluding the study reported by Robert *et al.* [23]. There was no significantly promising result for PFS (Figure S1B). When excluding the study reported by Gupta *et al.* [3], there was also no significant improvement of PFS (Figure S1C). Subgroup analysis was conducted according to specific mutations of the study population. The patients who did not undergo particular mutation were regarded as subgroup 1. The availability of somatic mutation information in the studies and patients were summarized in Table S2. In patients with mutation, the HR was analyzed using the fixed effects model because of no significant heterogeneity for PFS (HR: 0.87; 95% CI=0.45-1.70, P=0.69) (Figure S2A) or for OS (HR: 1.20; 95% CI=0.69-2.10, P=0.51) (Figure S2B), respectively. No therapeutic benefits on PFS and OS were detected for selumetinib treatment.

Discussion

The MAP kinase signaling pathway is a critical signaling cascade for regulating major signal transduction. Constitutive activation of the Ras-Raf-Mek-ERK pathway has been associated with various human cancers, including melanoma, lung cancer, and pancreatic cancer [28]. Targeting-MEK inhibition effectively suppresses tumor growth in preclinical models and clinical trials. Sorafenib, a RAF/MEK/ERK1/2 pathway inhibitor, has been applied in cancer treatment and can prolong life of patients. Because therapy with the MEK1/2 inhibitors for patients with cancer can achieve better CR, an increasing number of MEK inhibitors are being investigated in clinical trials [12]. One of the most frequent studied compound is selumetinib, which is an oral, selective, and non-ATP-competitive inhibitor of MEK-1/2 [29]. This drug has been applied in clinical trial for various cancers and has shown some clinical benefits. Selumetinib therapy could reverse refractoriness to radioiodine in patients with thyroid cancerby increasing iodine uptake and retention [16]. Selumetinib also can achieve better treatment effects in patients with recurrent low-grade serous ovary carcinoma [30] and in patients with advanced pancreatic cancer [21]. Selumetinib showed potential efficacy and acceptable tolerability in patients with meta-

static biliary cancer [31]. Moreover, selumetinib resulted in CR in patients with BRAF-mutated melanoma [32]. Robert *et al.* reported that selumetinib plus dacarbazine could improve PFS than chemotherapy alone in mutant BRAF V600E melanoma [23]. However, in wild-type BRAF advanced melanoma, selumetinib combined with docetaxel showed no significant improvement of PFS than docetaxel alone [3]. It is reported that higher response rates were observed with selumetinib-containing regimens in patients who had tumors that harbored a BRAF mutation compared with patients who had wild-type BRAF [33].

Thus, it is inconclusive whether selumetinib showed advantages over other current agents in treatment of cutaneous melanoma. Our meta-analysis aimed to assess the efficacy and safety of selumetinib in patients with cutaneous melanoma. Our studies indicated that selumetinib treatment can significantly reduce the risk of disease progression (OR=0.55; 95% CI=0.36-0.84, P =0.03, I^2=0) (**Figure 5**). The results also indicated selumetinib use was not associated with a reduction risk of death compared with the control group (HR=1.18; 95% CI=0.91-1.53, P=0.20). Selumetinib use also did not have benefits on PFS (HR=0.85; 95% CI=0.68-1.08, P=0.19). In the sensitivity analysis, excluding the study reported by Kirkwood *et al.* [22], the results indicated selumetinib treatment can significantly improve PFS. The result was consistent with previous study [34]. However, sensitivity analysis was performed by excluding the study reported by Robert et al. [23] there was no significant promising result for PFS; When excluding the study reported by Gupta et al. [3], the result revealed no significant improvement of PFS. Furthermore, selumetinib may be beneficially associated with various outcomes when combined with other chemotherapy regimens, but does not appear to be beneficial as a monotherapy according to our result. The rational for these observations may be as follows: Combined treatment of selumetinib and other chemotherapyagents (docetaxel, temozolomide, or dacarbazine) results in enhanced anti-tumour efficacy, results in tumour regression and increased DNA damage, apotosis and cell death [35]. In a recently published 3 phase RCT reported that combination vemurafenib (a MEK inhibitor) with dacarbazine significantly improved survival in melanoma patients [10]. In another RCT also reported that ipilimumab plus sargramostim versus ipilimumab alone can achieve longer OS in advanced melanoma [36]. Combination treatments may be the practical direction that melanoma therapies are headed because most advanced melanomas with a BRAF/MEK backbone.

Moreover, our study suggested that there were no significant differences in PFS and OS between mutation melanoma group and wide-type melanoma group. The results also suggested that selumetinib treatment showed activity in melanoma with or without mutation.

Adverse events were reported in all of the included studies. Treatment-related adverse event rate is nearly 97% in patients treated with selumetinib, which was consistent with other MEK inhibitors [37]. Skin toxicity is the most frequent adverse event in selective MEK inhibitor treatment [37, 38]. The results in our study indicated the most frequently occurred adverse events were rash (111/181), diarrhea (109/181), and nausea (97/181) in the selumetinib group. With supportive management, most of the adverse events can be effectively treated, and some serious adverse events are required tominimize the dose of selumetinib or discontinue therapy. Limitations of the meta-analysis should be taken into account. First, although all the studies included were RCTs, one [22] of the included studies was not double blinding, which might induce an overestimation of outcomes. Second, different schedules and modalities of selumetinib were included in our analysis. Two studies evaluated selumetinib in combination with docetaxel or dacarbazine (versus these respective agents alone),while the third (Kirkwood et al.) [22] compared selumetinib as a monotherapy (compared to temozolomide alone). The different treatment methods might contribute to heterogeneity. As we all known, docetaxel, dacarbazine and temozolomide are commonly used for cutaneous melanoma and provide some benefits. And the aim of all the included studies was to evaluate the efficacy and safety of selumetinib comparison with other current chemotherapy agents in treatment of cutaneous melanoma. Grouping these trials together in a meta-analysis is feasible. However, it is better to evaluate selumetinib in a standard way comparing with the

same control treatment methods in different studies. Due to the limited number of studies, further studies are required to evaluate the role of selumetinib therapy for cutaneous melanoma. Third, the studies were heterogeneous in the patients' basic characteristics, co-morbidities, cancer status, and definition and measurement of outcomes. All of those factors might explain some heterogeneity of the results among the studies. Finally, all of the included studies are phase II studies, phase III or phase IV clinical trials are needed for clearer definition the roles of selumetinib in cutaneous melanoma.

Moreover, because of the inadequate number of eligible studies and subjects of studies, especially for subgroup analyses, the findings of this meta-analysis should be interpreted with caution.

In current evidence, selumetinib was not superior to other agents for cutaneous melanoma. Selumetinib used increased the risk of dermatitis and diarrhea and did not increase OS. Compared with other agents, selumetinib treatment has better total clinical benefits (the total of CR, PR, and SD), and a reduced disease progression. However, due to the limitations of the published trials, further studies are warranted with better design, including treatment schedules, placebo control, blinding, and outcome measurements.

Disclosure of conflict of interest

None.

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Table S1. Risk of bias table of each included studies

Gupta A 2014		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized 1:1 to receive docetaxel plus selumetinib or docetaxel plus placebo, stratifying for M status (M0, M1a or M1b versus M1c) and Performance Status (0 versus 1) using a variable block size".
Allocation concealment (selection bias)	Low risk	Quote: "double blind". Comment: Probably done.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double blind. Selumetinib 75 mg or matched placebo". Comment: Probably done.
Blinding of outcome assessment (detection bias)	Low risk	Obtained from medical records; Reviewer authors do not believe this will introduce bias.
Incomplete outcome data (attrition bias)	High risk	Quote: "Four patients (three in the selumetinib group and one in the placebo group) did not receive their allocated treatment and so were excluded from the safety and per-protocol (PP) analyses".
Selective reporting (reporting bias)	Low risk	All patients receiving any study medications were included in the safety analyses.
Other bias	Low risk	Stratifying for M status (M0, M1a or M1b versus M1c) and Performance Status (0 versus 1) using a variable block size.Baseline characteristics were well balanced between the two treatment arms, apart from the median sum of the target lesions
Kirkwood JM 2012		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized 1:1 to selumetinib (100 mg free-base solution, twice daily in 28-day cycles) or temozolomide (200 mg/m^2/d for 5 days, followed by 23 days off treatment).
Allocation concealment (selection bias)	High risk	Quote: "open-label study".
Blinding of participants and personnel (performance bias)	High risk	Quote: "open-label study"
Blinding of outcome assessment (detection bias)	Low risk	Obtained from medical records; Reviewer authors do not believe this will introduce bias.
Incomplete outcome data (attrition bias)	High risk	Of the 42 patients without confirmed mutation status, 24 did not have samples to analyze and 18 had no result due to assay failure.
Selective reporting (reporting bias)	Low risk	All patients completed the study and with reports of outcomes.
Other bias	High risk	In addition, more patients were BRAF mutant in the selumetinib group (43.3%) than in the temozolomide group (29.2%), and more patients in the selumetinib group had WHO performance status 1 or 2 than those receiving temozolomide (33.7% and 26.1%, respectively).
Robert C 2013		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomly assigned, in a 1:1 ratio (block size of four)
Allocation concealment (selection bias)	Low risk	Quote: "double-blind". "Treatment groups were assigned by means of an interactive voice response system at central locations (Nottingham, UK, and East Windsor, NJ, USA). The voice response system allocated randomisation numbers and drug pack codes. Patients, investigators, and the study team were masked to the treatment assigned".
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind", "patients, investigators, and the study team were masked to the treatment assigned".
Blinding of outcome assessment (detection bias)	Low risk	Obtained from medical records; Reviewer authors do not believe this will introduce bias.
Incomplete outcome data (attrition bias)	High risk	2 patients did not complete the study.
Selective reporting (reporting bias)	Low risk	Tumor response was based on investigator assessment of target and non-target lesions using CT or MRI at baseline, week 12, and then every 12 weeks, relative to date of randomization.
Other bias	Unclear risk	The author reviewer is not sure.

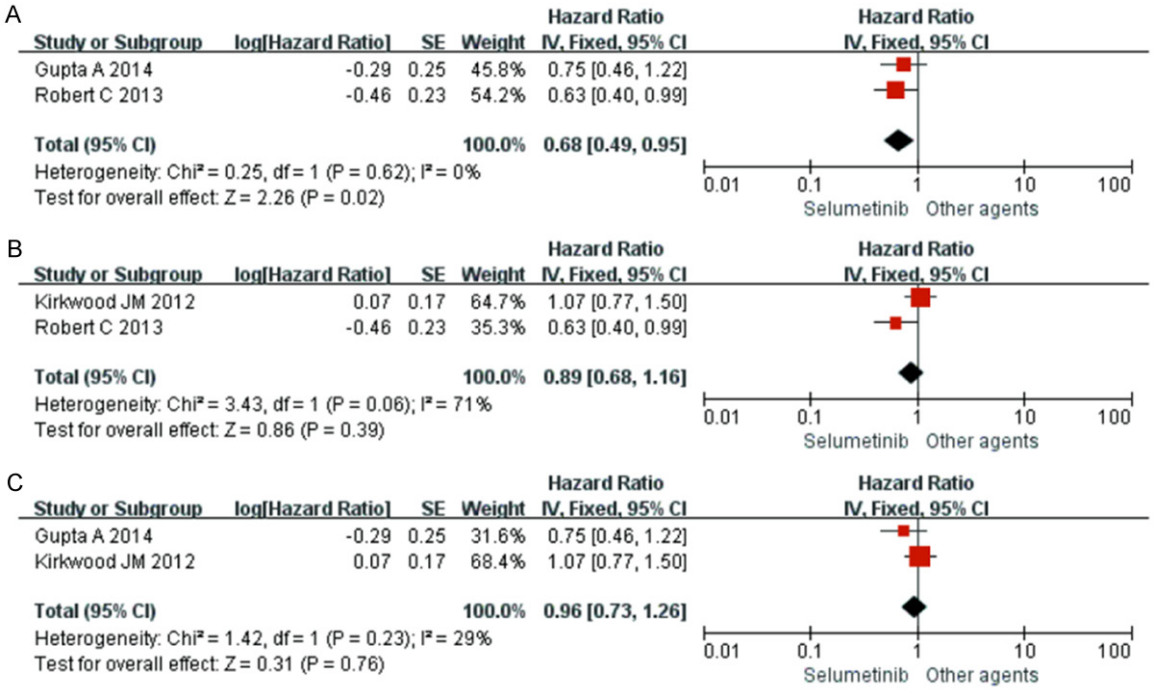

Figure S1. A leave-one-out sensitivity analyses by excluding one study at a time for progression-free survival.

Table S2. The somatic mutation information in the studies and patients for mutation analysis

Study	Somatic mutation	Cases (n)
Robert C	BRAF	BRAF: n=91
Kirkwood JM	BRAF or NRAS	BRAF: n=45; NRAS: n=10

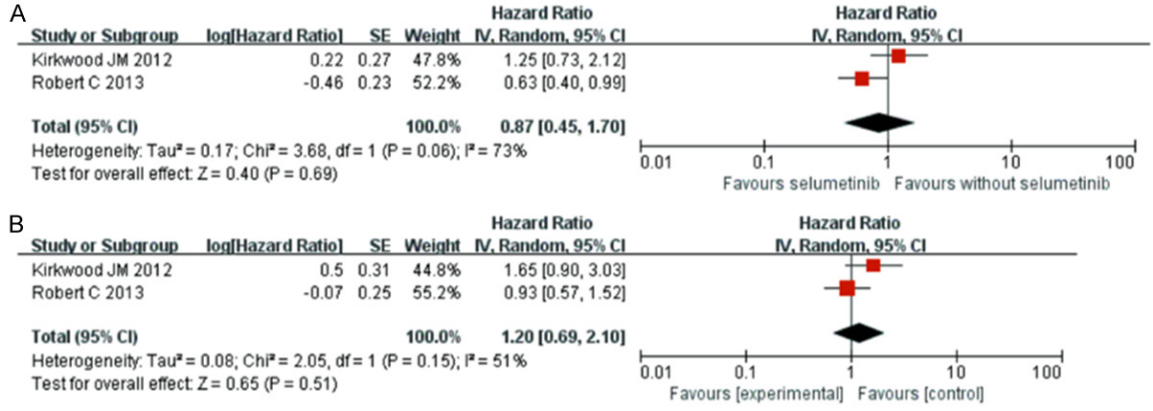

Figure S2. Meta-analysis of progression-free survival and overall survival in mutation melanoma.