Hindawi
Journal of Clinical Pharmacy and Therapeutics
Volume 2023, Article ID 9245663, 12 pages
https://doi.org/10.1155/2023/9245663

Research Article

A Systematic Review and Meta-Analysis: Safety and Efficacy of Cediranib in the Treatment of Cancer Patients

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Received 1 November 2022; Revised 16 June 2023; Accepted 1 August 2023; Published 22 August 2023

Academic Editor: Pranshu Sahgal

Objective. Tyrosine kinase inhibitors are exciting new anticancer strategies. As one of the most promising oral tyrosine kinase inhibitors, cediranib has been proven effective in treating various solid malignant tumors. This study aimed to evaluate the efficacy and safety of cediranib in cancer patients. *Methods*. A comprehensive literature review was conducted for phase II and phase III randomized controlled trials (RCTs) up to June 31, 2021, using databases from PubMed, Cochrane Library, Embase, and Web of Science. Relevant clinical trials reporting the efficacy and toxicity characteristics of cediranib in cancer patients were analyzed using Stata 15.1. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used to assess the strength of the evidence. *Results*. The systematic review yielded 14 eligible trials, comprising 4,387 patients with solid malignant tumors. The analysis results of RCTs showed that the cediranib-containing group had a significantly better PFS than the control group (HR: 0.75; 95% CI 0.69–0.82; $P < 0.001$), and the pooled OS of the cediranib-containing group was significantly higher than that of the control group (HR: 0.91; 95% CI 0.84–1.00; $P = 0.041$). The sensitivity analysis revealed that the pooled HR was stable and excluding a single study had no effect on the significance of the pooled HR. In addition, the meta-analysis passed Begg's and Egger's tests, indicating no publication bias. Regarding safety, the most common adverse events were diarrhea, nausea, hypertension, fatigue, sensory neuropathy, dyspnea, vomiting, headache, neutropenia, thrombocytopenia, and leukopenia. *Conclusion*. Cediranib treatment responds better than noncediranib therapy but can increase the risk of specific treatment-related toxicities.

1. Introduction

Irrespective of the level of human development, cancer is a significant cause of morbidity and mortality in every region of the world and threatens human health [1]. More than 18 million new cancer cases were diagnosed in 2018, with more than 9.5 million deaths [2]. Although most cancer patients experience effective treatment and diagnosis progression, the 5-year overall survival rate remains low, and other active treatment methods are required to improve the effectiveness of maintenance therapy [3]. An essential step in tumor growth and metastasis is the process of new blood vessel formation and angiogenesis. The VEGF binds to the VEGF receptor (VEGFR) on the cell surface, resulting in dimerization and passage through the cell phosphorylation of the internal tyrosine kinase region ultimately, which leads to the activation of the neovascularization cascade. Therefore, VEGF and VEGFR are essential targets for antitumor angiogenesis therapy and inhibiting vascular endothelial growth factor (VEGF) has become an essential strategy for cancer treatment. Tyrosine kinase inhibitors (TKIs) are molecules that bind to the intracellular ATP-binding catalytic site of the activated tyrosine kinase domain and block the latter, such as the vascular endothelial growth factor receptor (VEGFR), the epidermal growth factor receptor (EGFR), and the platelet-derived growth factor receptor (PDGFR), all of which play crucial roles in the pathophysiology of cancer [4]. Regarding pharmacokinetics (PK), cediranib demonstrated a linear relationship in the dose range of 0.5–60 mg, with the maximum plasma concentration (C_{max}) observed 1 to 8 hours after administration [5]. Patients typically have a terminal half-life of 12 to 36 hours,

with an average terminal half-life of 22 [6]. Cediranib belongs to the tyrosine kinase inhibitor that targets all three VEGFRs (VEGFR-1, VEGFR-2, and VEGFR-3) and c-Kit. It inhibits the VEGF signaling pathway in endothelial and cancer cells, resulting in antitumor activity in solid cancer patients. As a result, cediranib is regarded as a potentially effective drug added to standard chemotherapy [7]. In previous studies, cediranib is effective in the following cancers: malignant pleural mesothelioma [8], biliary tract cancer [9], cervical cancer [10], nonsmall cell lung cancer [11], colorectal cancer [12], renal cell carcinoma [13], breast cancer [14], and glioblastoma [15]. In addition, studies on the maintenance treatment of cediranib in recurrent ovarian cancer are ongoing (ClinicalTrials.gov: NCT03278717 and NCT03117933) [16, 17]. Furthermore, preclinical data show that antiangiogenic drugs may enhance the efficacy of PARP inhibitors [18], which is supported by two randomized phase II studies and a recent phase III trial. Combining antiangiogenic drugs with olaparib or olaparib resulted in more prolonged progression-free survival than PARP inhibitors alone [19–21]. In this paper, we aimed to review the current evidence on the role of cediranib in solid cancer and to conduct a meta-analysis in order to evaluate the efficacy and safety of cediranib in those patients.

2. Materials and Methods

2.1. Electronic Search. A systematic review and meta-analysis of cediranib were conducted for this study. A comprehensive search of PubMed, Embase, Cochrane Library, and Web of Science used medical subject heading (MeSH) terms and text words related to cediranib and neoplasms. The search was completed through June 31, 2021. Relevant articles and abstracts from retrieved articles were browsed for additional eligible studies.

2.2. Study Selection. The selection of literature was performed independently by two reviewers as part of the assessment of research eligibility. Any discrepancies were discussed and resolved by consensus between both reviewers. According to PICOS criteria, relevant clinical studies of cediranib maintenance therapy for patients with solid malignant tumors were included if they met all of the following eligibility criteria: (1) P (population): patients with solid malignant tumors were included in the study; (2) I (Intervention) and C (comparison): participants were randomly assigned to cediranib-containing or control treatment; (3) O (outcome): studies reported the progression-free survival (PFS), overall survival (OS), and adverse events; (4) S (study design): the trial was designed as a randomized controlled trial (RCT); and (5) articles that have been published in English. Studies would be excluded for the following reasons: (1) studies with unclear outcome indicators; (2) not RCTs but retrospective trials, observational studies, or case reports; and (3) conferences, abstracts, guidelines, letters, meta-analyses, and reviews. When an unpublished date on cediranib could not be obtained, efforts were made to contact the trial authors. Single-armed studies were excluded due to the lack of control groups. Studies in which progression-free survival was not a primary or secondary endpoint and trials conducted in a first-line setting were excluded.

2.3. Data Extraction. Two independent reviewers extracted the data from eligible primary studies. They converted them into a standard data extraction form, and if disagreement occurred, it was resolved by two authors for consensus. The following information was extracted from each trial: first author, publication year, country, and clinical trials, Gov number, study design, number of patients enrolled, participant's age, primary treatment received, intervention details, the dosage of cediranib, duration of maintenance, median follow-up, PFS, OS, and adverse events. We also extracted the logarithm of the hazard ratio (log (HR)) and its standard error from each eligible study for time-to-event data (PFS). To estimate the risk ratio (RR) for binary outcomes (such as adverse events), we extracted the number of participants in each eligible trial who experienced this event. Wherever available, the complete protocol of each trial was included to verify relevant information regarding study design and execution. The most recent or complete publication reporting the information of interest was considered for publications reporting results from the same trail. Adverse events were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (grade 1, mild; grade 2, moderate; grade 3, severe or medically significant; grade 4, life-threatening).

2.4. Assessment of Risk of Bias. We assessed the risk of bias independently and in duplicate using the Cochrane Risk of Bias 2.0 tool for RCTs. We used the tool to assess the risk of bias (ROB) in the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. We rated each domain as "some concerns," "low," or "high."

2.5. Grading the Certainty of Evidence for Major Outcomes. We assessed the certainty of the evidence for major outcomes based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. This approach incorporates five key domains: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision of the evidence, and (5) reporting bias. Two reviewers graded each domain for the major outcome and resolved differences by consensus discussion. We documented all decisions regarding up- or downgrading the certainty of evidence to ensure transparency.

2.6. Data Handling and Statistical Methods. The efficacy of cediranib in the treatment of solid malignant tumors was determined by calculating pooled PFS, OS, and hazard ratio (HR) with 95% confidence intervals (CI) based on data from all trials. Furthermore, in terms of safety, the binary data (adverse events) were calculated using the risk ratio (RR), with a 95% confidence interval (CI). For data analysis, Stata

15.1 software packages were utilized. $P < 0.05$ was considered statistically significant for heterogeneity, representing the percentage of total variation across studies. A fixed-effect model was used when substantial heterogeneity or $I^2 < 50\%$ ($P \geq 0.1$) was not observed. On the contrary, a random-effect model was adopted to obtain a more appropriate estimation of the average treatment effect in the case of between-study heterogeneity. A forest plot was used to display all the data analysis results. Moreover, sensitivity analyses were performed to assess the stability of the results by omitting individual studies sequentially, and publication bias was assessed using Begg's and Egger's tests. A P value <0.05 was considered statistically significant.

2.7. Patient and Public Involvement. Given that this systematic review will be carried out based on published studies, patients and members of the public will not be involved directly. Only data from published literature and/or the aforementioned sources will be used.

2.8. Ethics and Dissemination. This meta-analysis will be performed on published studies without involving any private and confidential patient data, so no approval is required from an ethics committee. The results will be reported by publishing them in a peer-reviewed journal or disseminated in the relevant conferences. No ethical issues will be raised.

3. Results

3.1. Search Results. One thousand three hundred and seven potentially relevant studies were obtained electronically from PubMed, Cochrane Library, Embase, and Web of Science. The inclusion and exclusion criteria for the excluded 1,293 studies were met by screening each record's titles, abstracts, and keywords. Three hundred and fifty four duplicates and 939 articles that did not meet the criteria were excluded. Finally, 14 studies were further assessed for eligibility, and the latest publication of each trial was adopted for the meta-analysis. The trial selection process was summarized in the PRISMA plot (Figure 1).

3.2. Study Characteristics. In total, 4,387 patients from fourteen RCTs were included in this meta-analysis, of whom 546 patients were with ovarian cancer, 62 patients were with breast cancer, 69 patients were with cervical cancer, 644 patients were with nonsmall cell lung cancer, 2454 patients were with colorectal cancer, 71 patients were with renal cell cancer, 124 patients were with biliary tract cancer, 325 patients were with glioblastoma, and 92 patients were with malignant pleural mesothelioma. The included trials included five phase III RCTs and nine phase II RCTs. All studies reported sufficient data on PFS and adverse events, and nine reported sufficient data on OS. Cediranib dosages varied across fourteen RCTs, with nine trials administering 20 mg once daily, while the other five trials gave participants 30 mg or 45 mg per day. The characteristics of patients in the fourteen articles are shown in Table 1.

3.3. Risk of Bias and Certainty of Evidence for Major Outcomes. Among the fourteen RCTs we included, the word "random" was mentioned in all articles, and specific random methods were mentioned in nine RCTs, such as a computer program. The seven RCTs described allocation concealment in great detail. The RCTs have complete outcome data, and none were selectively reported. A detailed risk of bias assessment is described in Figure 2. The GRADE assessment indicated a moderate quality for PFS and OS.

3.4. Progression-Free Survival. All studies reported the outcome of PFS. The combined HR for PFS was 0.75 (95% CI 0.69–0.82, $P < 0.001$; Figure 3), indicating that cediranib-containing treatment significantly improved PFS compared to the control therapy. The pooled HR was calculated using the fixed-effect model because there was significant heterogeneity among trials ($I^2 = 37.7\%$, $P = 0.083$).

3.5. Overall Survival. The pooled HR was calculated using a fixed-effect model since nine out of fourteen trials reported data on OS, which showed no significant between-study heterogeneity among trials (overall: I-squared = 0.0%, $P = 0.724$). In addition, patients receiving cediranib-containing therapy had a statistically significant improvement in OS (HR: 0.91; 95% CI 0.84–1.00; $P = 0.041$; Figure 4) compared to control therapy.

3.6. Safety. According to the reports, the incidence of diarrhea (RR = 1.96, 95% CI = 1.65-2.33, $P < 0.001$) and fatigue (RR = 1.14, 95% CI = 1.03-1.25, $P = 0.008$) in the cediranib-containing group was higher than that in the control group. The incidence of tertiary and above adverse events was higher (Table 2). The following aspects were included in the analysis of the most common adverse events: hypertension, fatigue, sensory neuropathy, dyspnea, anorexia, vomiting, headache, neutropenia, thrombocytopenia, and leukopenia. Furthermore, we discovered that the incidence of hypertension (RR = 2.73, 95% CI = 2.00–2.71, $P < 0.001$), anorexia (RR = 1.27, 95% CI = 1.16–1.40, $P < 0.001$), stomatitis (RR = 1.54, 95% CI = 1.36–1.74, $P < 0.001$), vomiting (RR = 1.17, 95% CI = 1.06–1.30, $P = 0.002$), constipation (RR = 0.87, 95% CI = 0.76–0.98, $P = 0.023$), hand-foot syndrome (RR = 2.17, 95% CI = 1.31–3.58, $P = 0.002$), headache (RR = 2.78, 95% CI = 1.69–4.58, $P < 0.001$), abdominal pain (RR = 1.24, 95% CI = 1.08–1.43, $P = 0.003$), dysphonia (RR = 5.43, 95% CI = 1.25–23.61, $P = 0.024$), neutropenia (RR = 1.30, 95% CI = 1.20–1.41, $P < 0.001$), and thrombocytopenia (RR = 1.53, 95% CI = 1.37–1.70, $P < 0.001$) in the cediranib-containing group was higher compared to that of the control group.

Furthermore, there was no difference in the risk of occurrence of these adverse events in the cediranib-containing group and the control group for nausea, anemia, sensory neuropathy, dyspnea, leukopenia, epistaxis, and venous thromboembolism (Table 3).

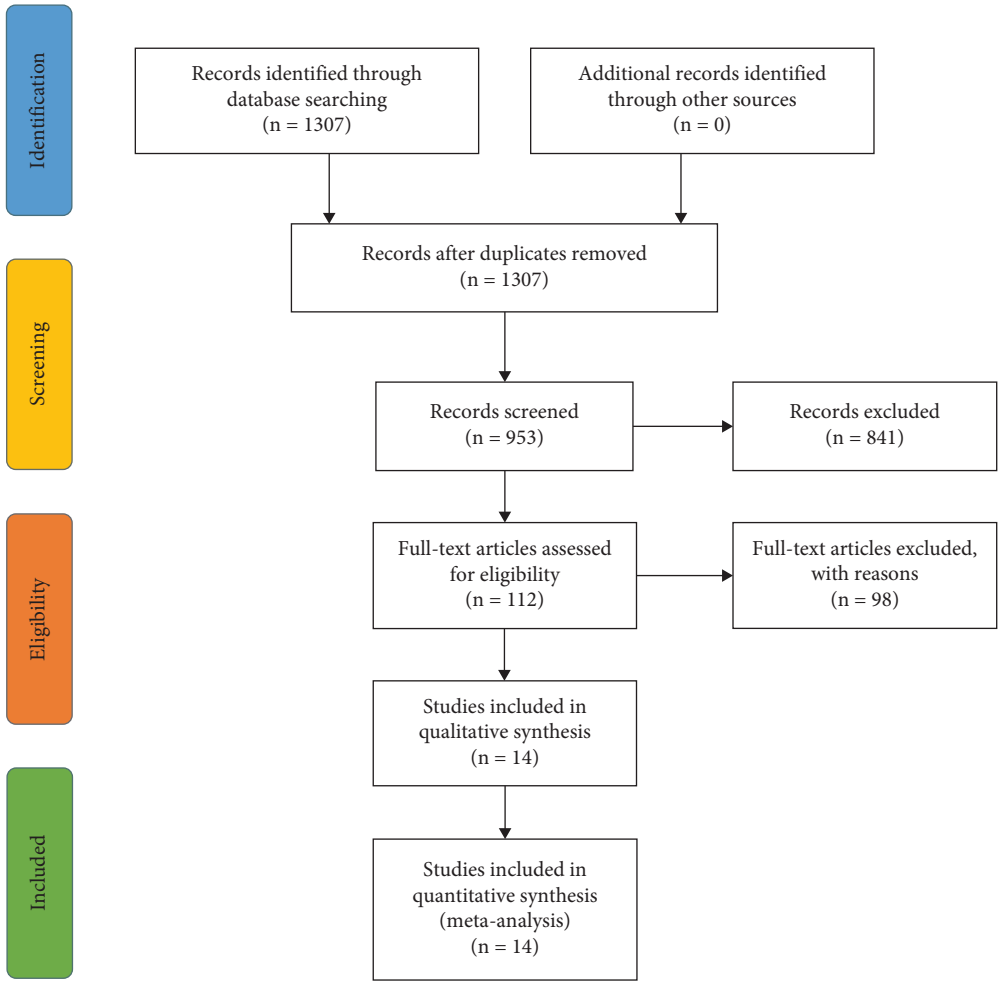


Figure 1: PRISMA flowchart of the selection process for trials included in the meta-analysis.

3.7. Sensitivity Analysis. We conducted a sensitivity analysis to evaluate the stability and reliability of the pooled HR (for PFS and OS) and RR (for all-grade adverse events). As shown in Figure 5, the horizontal box plot of the leave-one-out method confirmed a study (Schmoll, 2012) that affects the aggregate HR of PFS. Before removing this article, the combined HR for PFS was 0.75 (95% CI 0.65–0.87, $P < 0.001$), and after removing it, PFS was 0.75 (95% CI 0.69–0.82, $P < 0.001$). However, the horizontal box plot of the leave-one-out method confirmed that no single study had a qualitative influence on the pooled HR of OS. Simultaneously, we performed a sensitivity analysis for all-grade adverse events, and after excluding each study in turn, the overall RR value remained unchanged.

3.8. Publication Bias. This meta-analysis performed a funnel chart analysis on the outcome indicators (PFS and OS) and included adverse events with subgroups ≥10. We utilized Begg's adjusted rank correlation test and Egger's test to assess the publication bias of works of literature. The Z-value (continuity corrected) of Begg's adjusted rank correlation test was 1.77 ($P = 0.077$) on PFS (Figure 6(a)), and Egger's test ($P > |t| = 0.128$) was used to detect publication bias (Figure 6(b)). In addition, Begg's test ($\Pr > |z| = 0.175$; Figure 6(c)) and Egger's test ($P > |t| = 0.141$; Figure 6(d)) were used to detect the publication bias of OS and found no publication bias. The publication bias results for adverse events with subgroups ≥10 showed that the funnel charts of these outcome indicators were symmetrical. Therefore, the present results were statistically steady and robust.

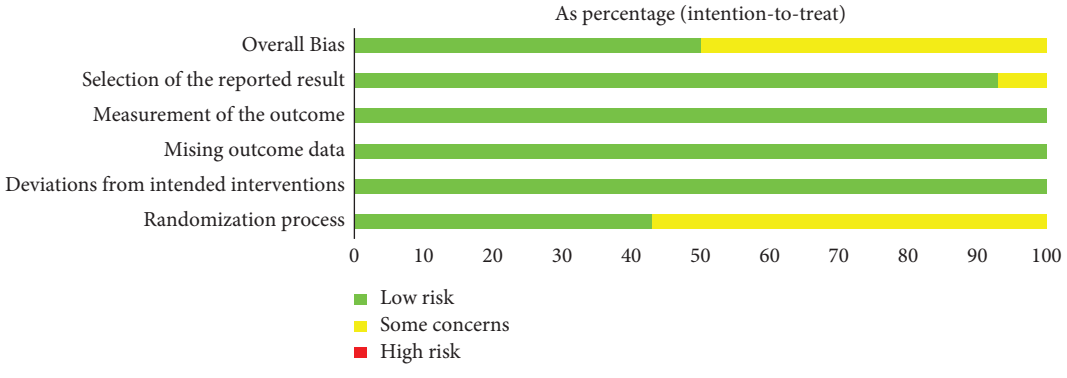
4. Discussion

Cediranib is an oral, potent, small molecule antitumor drug developed by Astra Zeneca in the United States. Cediranib is an effective ATP-competitive VEGF signaling inhibitor that can inhibit in vivo and in vitro and prevent VEGF-induced angiogenesis vivo [23]. It can also inhibit tumor cell growth by inhibiting lymphangiogenesis, which VEGFR-3 mediates [24]. Previously, many researchers such as Chen et al. in 2021 were concerned about the efficacy and safety of Cediranib in treating malignant tumors. The combination of cediranib and lomustine showed the highest incidence of grade 3–4 adverse events [25]. The combination of antiangiogenesis

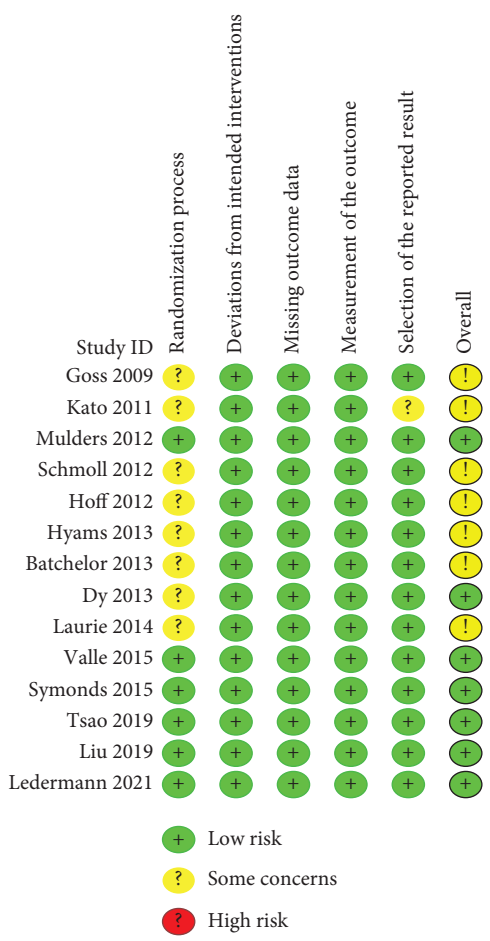
Table 1: Baseline characteristics of included studies in the meta-analysis.

First author, year	Phase	Underlying malignancy	Treatment arm	Control arm	Patient enrolled	Age (years), median (range)	Median PFS (m)	Median OS (m)
Goss 2009	II	NSCLC	Cediranib 30 mg once daily plus PC	Placebo plus PC	251	Intervention: 60 (36–77) Control: 58 (39–81)	0.77	—
Kato 2011	II	CRC	Cediranib 20 mg once daily plus mFOLFOX6	Placebo plus mFOLFOX6	172	Intervention: 64 (33–79) Control: 64 (36–80)	0.70	—
Hoff 2012	III	CRC	Cediranib 20 mg once daily plus FOLFOX/CAPOX	Placebo plus FOLFOX/ CAPOX	860	Intervention: 58 (22–83) Control: 59 (22–82)	0.84	0.94
Mulders 2012	II	RCC	Cediranib 45 mg once daily	Placebo	71	Intervention: 60 (46–75) Control: 61 (45–79)	0.45	—
Schmoll 2012	III	CRC	Cediranib 20 mg once daily plus mFOLFOX6	Bevacizumab plus mFOLFOX6	1422	Intervention: 59 (18–83) Control: 60 (22–88)	1.10	0.95
Dy 2013	II	NSCLC	Cediranib 30 mg once daily plus GC	GC	87	Intervention: 65 (46–81) Control: 64 (45–82)	0.69	0.66
Hyams 2013	II	BC	Cediranib 45 mg once daily plus fulvestrant	Placebo plus fulvestrant	62	59 (18–83)	0.867	—
Batchelor 2013	III	GB	Cediranib 20 mg once daily plus lomustine	Placebo plus lomustine	325	Intervention: 54 Control: 54	0.76	1.15
Laurie 2014	III	NSCLC	Cediranib 20 mg once daily plus PC	Placebo plus PC	306	Intervention: 63 (23–85) Control: 62 (36–77)	0.91	0.94
Symonds 2015	II	CC	Cediranib 20 mg once daily plus PC	Placebo plus PC	69	Intervention: 44 (37–60) Control: 44 (34–53)	0.58	—
Valle 2015	II	BTC	Cediranib 20 mg once daily plus GP	Placebo plus GP	124	Intervention: 68 (60–73) Control: 64.5 (60–73)	0.93	0.86
Tsao 2019	II	MPM	Cediranib plus PP	Placebo plus PP	92	Intervention: 72 (46–82) Control: 72 (51–85)	0.77	0.88
Liu 2019	II	OC	Cediranib 30 mg once daily plus olaparib	Olaparib	90	Intervention: 58 (53–67) Control: 58 (52–63)	0.5	0.64
Lederman 2021	III	OC	Cediranib 20 mg once daily plus PC	Placebo plus PC	456	Intervention: 62 (54–68) Control: 62 (53–67)	0.56	0.86

Abbreviations: NSCLC: nonsmall cell lung cancer; CRC: colorectal cancer; RCC: renal cell carcinoma; BC: breast cancer; GB: glioblastoma; CC: cervical cancer; BTC: biliary tract cancer; MPM: malignant pleural mesothelioma; OC: ovarian cancer; PC: paclitaxel-carboplatin; mFOLFOX6: modified FOLFOX6; FOLFOX/CAPOX: fluorouracil, leucovorin, and oxaliplatin/capecitabine and oxaliplatin; GC: gemcitabine-carboplatin; GP: gemcitabine-cisplatin; PP: pemetrexed-platinum; m: months.



(a)



(b)

Figure 2: Continued.

Cediranib-containing therapy compared to Control for solid malignant tumors

Patient or population: patients with solid malignant tumors
Settings:
Intervention: Cediranib-containing therapy
Comparison: Control

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Cediranib-containing therapy	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
PFS HR Follow-up: mean 37 months	Study population		HR 0.75 (0.69 to 0.82)	0 (13 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	-2147483648 per 1000 (-2147483648 to -2147483648)				
OS HR Follow-up: mean 43	Study population		HR 0.91 (0.84 to 1)	0 (9 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	-2147483648 per 1000 (-2147483648 to -2147483648)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HR:** Hazard ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

(c)

Figure 2: (a) Risk of bias graph: review authors' judgments on each risk of bias item presented as percentages across all included studies. (b) Risk of bias summary: review authors' judgments on each risk of bias item for each included study. (c) Certainty of evidence for major outcomes.

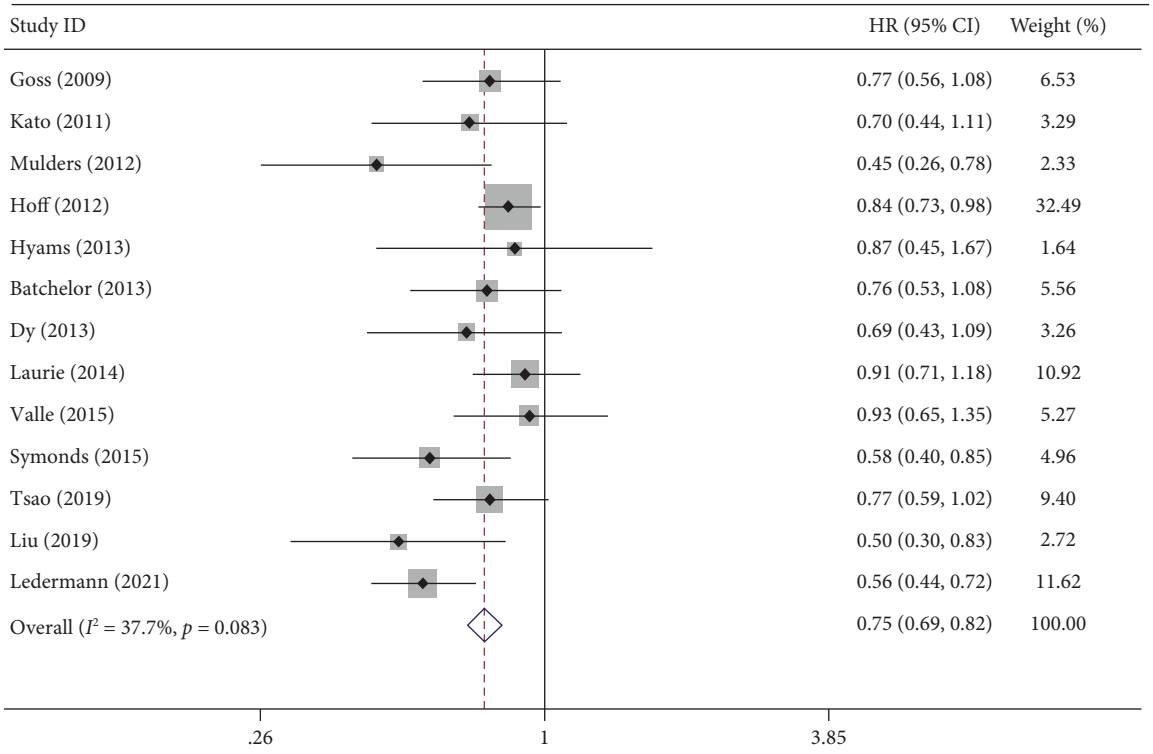


Figure 3: Forest plots of pooled HRs for PFS by the fixed-effect model. HR, hazard ratio; PFS, progression-free survival.

and PARP inhibitors provided a significant PFS benefit for women newly diagnosed with advanced ovarian cancer who tested positive for homologous recombination defects, indicating a new treatment option [26]. Currently, phase II and phase III clinical trials to evaluate the role of cediranib in solid malignant tumors are underway. Cediranib has an excellent clinical effect but exploring the best combination of chemotherapy and other targets is more important. Research on the combination of cediranib and PARP inhibitors has gradually increased. PARP inhibitors can reduce VEGF-induced angiogenesis while increasing VEGF2 phosphorylation, indicating that using PARP inhibitors in combination with antiangiogenic drugs has a synergistic effect [27]. Our previous publication revealed the efficacy and safety of olaparib in the treatment of platinum-sensitive recurrent ovarian cancer [28]. Furthermore, the efficacy of cediranib and olaparib combined maintenance therapy for recurrent ovarian cancer after platinum therapy is still being investigated [14]. The research found that cediranib may have antitumor activity in metastatic castration-resistant

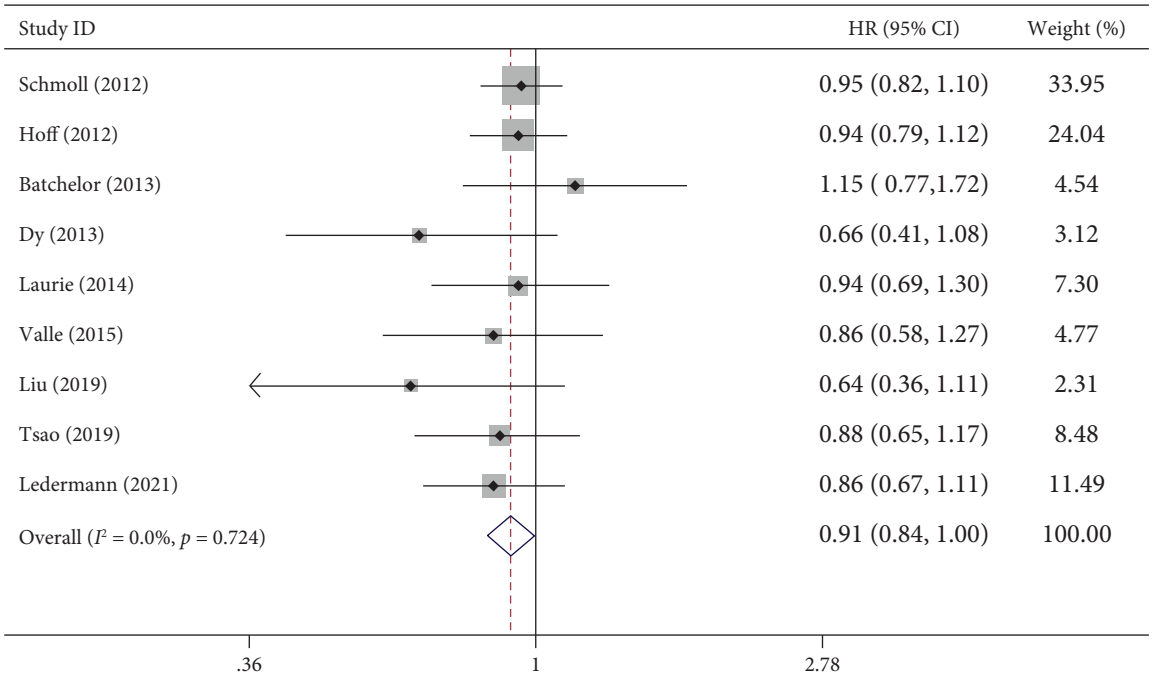


Figure 4: Forest plots of pooled HRs for OS by fixed-effect model. HR, hazard ratio; OS, overall survival.

Table 2: Grade ≥3 adverse events.

	Studies	Cediranib- containing therapy	Control	RR (95% CI)	P value	I^2 (%)	
Fatigue	12	271 of 2228	116 of 1754	1.80 (1.46–2.23)	<0.001	0.0	Fixed
Diarrhea	12	311 of 2228	80 of 1783	3.11 (2.46–3.95)	<0.001	0.0	Fixed
Hypertension	10	207 of 2122	47 of 1675	3.06 (2.22–4.24)	<0.001	43.4	Fixed
Neutropenia	10	503 of 2063	289 of 1625	1.37 (1.21–1.56)	<0.001	23.8	Fixed
Thrombocytopenia	8	229 of 1973	86 of 1532	1.80 (1.43–2.27)	<0.001	0.0	Fixed
Vomiting	7	69 of 1163	40 of 816	1.13 (0.77–1.66)	0.524	0.0	Fixed
Nausea	6	37 of 663	16 of 458	1.35 (0.76–2.39)	0.300	0.0	Fixed
Anemia	6	82 of 392	82 of 372	0.96 (0.75–1.23)	0.741	49.3	Fixed
Anorexia	5	24 of 416	10 of 420	2.37 (1.17–4.79)	0.016	0.0	Fixed
Leukopenia	4	62 of 275	25 of 190	1.63 (1.09–2.43)	0.017	0.0	Fixed
Sensory neuropathy	3	63 of 914	76 of 915	0.83 (0.60–1.14)	0.252	22.6	Fixed
Abdominal pain	3	6 of 136	6 of 143	1.02 (0.37–2.83)	0.967	0.0	Fixed
Stomatitis	2	7 of 158	0 of 158	8,11 (1.01–65.31)	0.049	0.0	Fixed
Hand-foot syndrome	2	23 of 626	5 of 481	3.44 (1.31–9.03)	0.012	0.0	Fixed
Venous thromboembolism	2	14 of 455	14 of 429	2.64 (0.71–9.75)	0.146	0.0	Fixed

prostate cancer (mCRPC) cells [29]. Meanwhile, cediranib is also being tested in a large-scale clinical trial, and it is expected to improve the treatment of solid malignant tumors in the future. As the most promising oral tyrosine kinase inhibitor, cediranib has undergone systematic clinical evaluation as both a single agent and in combination therapy in various malignant tumors. Until now, cediranib has shown a stable response in ovarian, nonsmall cell lung cancer, and so on [9, 14]. We systematically evaluated the efficacy and safety of cediranib in cancer patients for the first time. Several new RCTs of cediranib in ovarian cancer and malignant pleural mesothelioma have recently been completed, and thus the efficacy and safety of cediranib should be evaluated. As a result, we systematized the available information in order to conduct this meta-analysis on the role of cediranib in cancer treatment. This meta-analysis examined nine types of tumor, including ovarian cancer [30, 31], breast cancer [12], cervical cancer [8], nonsmall cell lung cancer [9, 32, 33], colorectal cancer [10, 34, 35], renal cell carcinoma [11], biliary tract cancer [7], glioblastoma [13], and malignant pleural mesothelioma [6]. We evaluated the survival data of 4,387 cancer patients treated with cediranib, and 14 different studies were systematically included.

In summary, the results indicated that the cediranib-containing group had a significantly better PFS than the control group (HR: 0.75; 95% CI = 0.69–0.82; $P < 0.001$), and the pooled OS of the cediranib-containing group was significantly

Table 3: Adverse and safety profile.

	Studies	Cediranib- containing therapy	Control	RR (95% CI)	P value	I^2 (%)	
Fatigue	13	1213 of 2255	821 of 1781	1.14 (1.03–1.25)	0.008	58.1	Random
Diarrhea	13	1547 of 2259	747 of 1814	1.96 (1.65–2.33)	<0.001	77.2	Random
Hypertension	12	981 of 2197	337 of 1752	2.73 (2.00–2.71)	<0.001	79.8	Random
Nausea	11	1146 of 2010	850 of 1627	1.05 (0.99–1.12)	0.084	0.0	Fixed
Neutropenia	10	920 of 2049	550 of 1613	1.30 (1.20–1.41)	<0.001	30.1	Fixed
Thrombocytopenia	10	715 of 2049	346 of 1613	1.53 (1.37–1.70)	<0.001	49.0	Fixed
Anorexia	8	637 of 1665	450 of 1524	1.27 (1.16–1.40)	<0.001	39.1	Fixed
Stomatitis	8	513 of 1656	307 of 1480	1.54 (1.36–1.74)	<0.001	10.9	Fixed
Vomiting	8	588 of 1584	448 of 1448	1.17 (1.06–1.30)	0.002	27.8	Fixed
Sensory neuropathy	7	701 of 1617	643 of 1478	1.03 (0.95–1.2)	0.442	0.0	Fixed
Constipation	7	343 of 1441	357 of 1226	0.87 (0.76–0.98)	0.023	46.9	Fixed
Anemia	7	202 of 515	207 of 436	0.96 (0.85–1.07)	0.447	38.1	Fixed
Leukopenia	5	117 of 319	86 of 236	1.17 (0.97–1.40)	0.095	0.0	Fixed
Hand-foot syndrome	4	176 of 835	75 of 692	2.17 (1.31–3.58)	0.002	52.8	Random
Headache	4	59 of 160	15 of 130	2.78 (1.69–4.58)	<0.001	35.9	Fixed
Abdominal pain	4	343 of 1299	245 of 1159	1.24 (1.08–1.43)	0.003	0.0	Fixed
Dyspnea	3	148 of 309	126 of 311	1.17 (0.99–1.38)	0.072	10.0	Fixed
Venous thromboembolism	3	25 of 500	10 of 285	1.66 (0.75–3.68)	0.207	23.0	Fixed
Dysphonia	3	74 of 262	13 of 229	5.43 (1.25–23.61)	0.024	73.9	Random
Epistaxis	3	191 of 808	181 of 809	1.38 (0.68–2.81)	0.369	60.4	Random

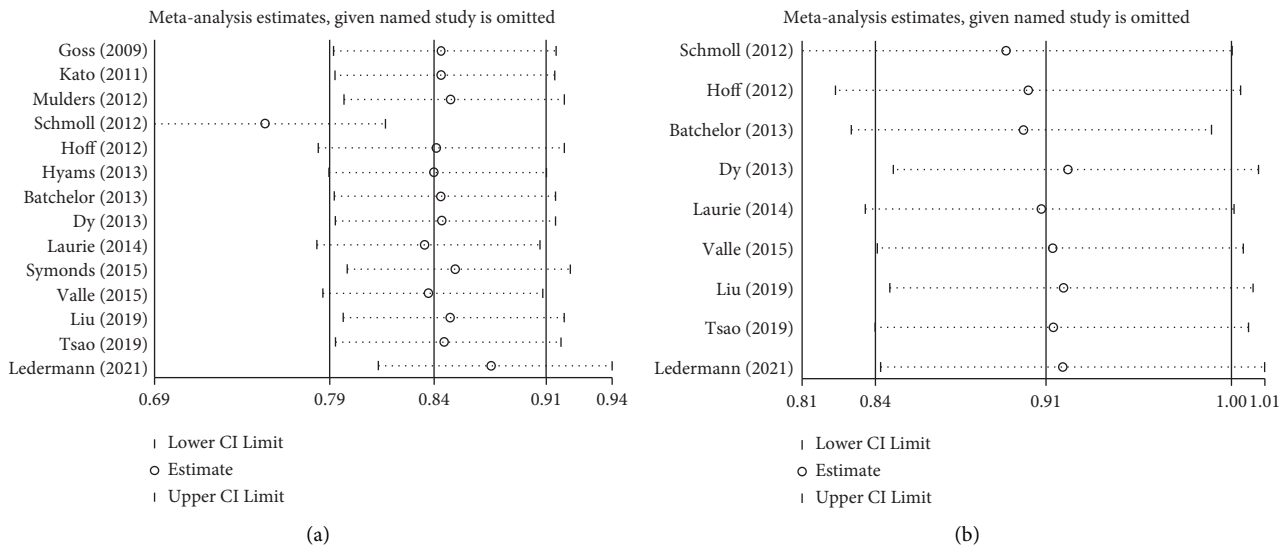


Figure 5: Leave-one-out sensitivity analysis of efficacy with cediranib-containing therapy vs. control therapy. (a) Progression-free survival; (b) overall survival.

higher than that of the control group (RR: 0.91; 95% CI = 0.84–1.00; $P = 0.041$). Moreover, the toxicity of cediranib is similar to that of the other VEGFR inhibitors. Toxic reactions are the most common reason for treatment discontinuation. During cediranib treatment, the most common toxic reactions were diarrhea, fatigue, hypertension, anorexia, stomatitis, vomiting, constipation, hand-foot syndrome, headache, abdominal pain, dysphonia, neutropenia, and thrombocytopenia. Therefore, more research is needed to determine the most beneficial population and the best treatment plan, while reducing adverse reactions and overcoming resistance, which can maximize the prognosis of patients and reduce the potential negative impact on life.

Despite the clinical potential of cediranib therapy, several limitations should be considered in our meta-analysis. First, there were potential differences among the studies included, such as drug doses, different types of malignancies, race, age, and even study quality, making interpreting a meta-analysis more difficult. Second, not all OS data and AEs have been reported, or OS was not the primary endpoint for most studies, which may lead to immature data for OS and AEs. Third, the exclusion of non-English articles may have influenced our meta-analysis. Although we conducted a comprehensive search, some data will inevitably be lost. Finally, due to the limited number of included studies, this study did not perform the subgroup analysis, which may lead to differences in the

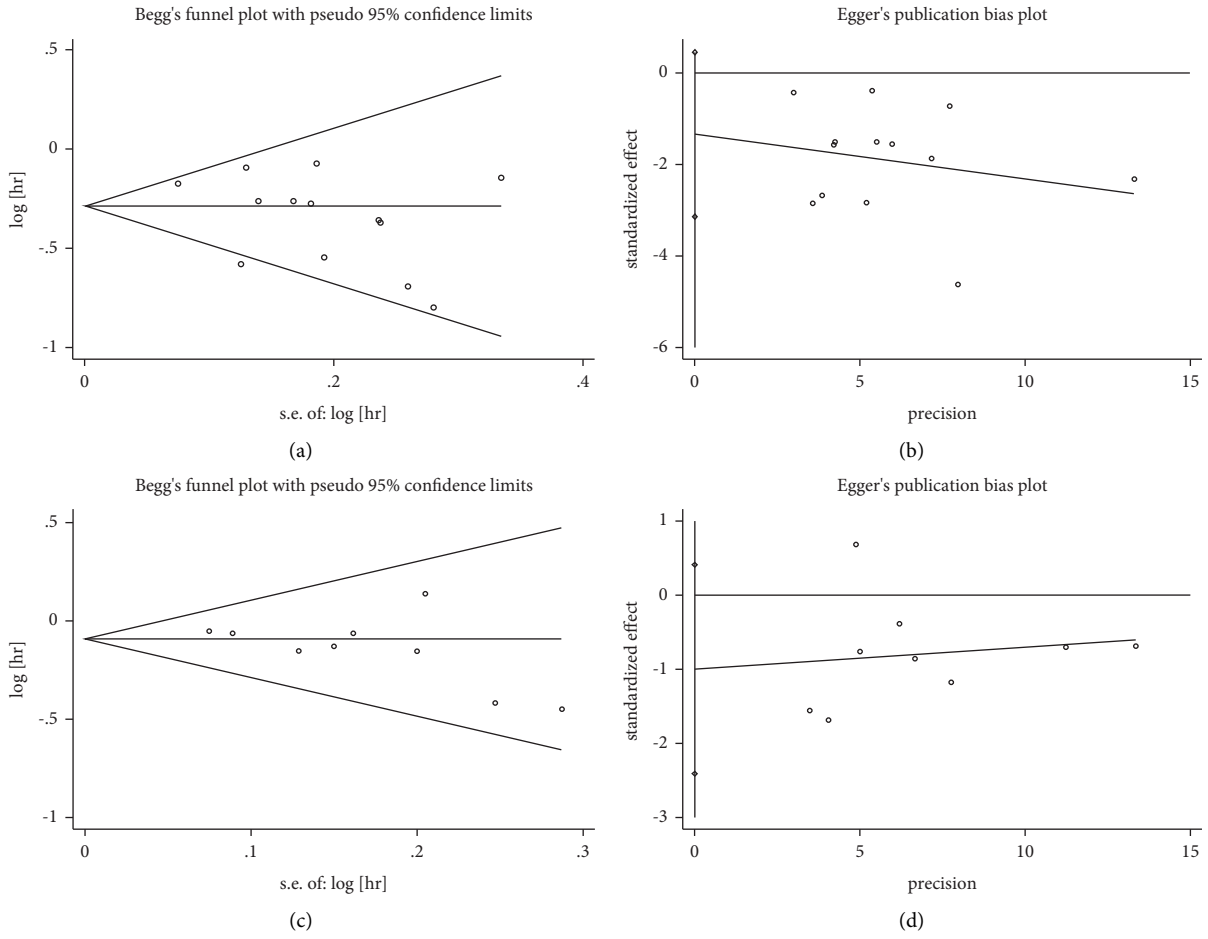


Figure 6: Publication bias assessment. (a) Begg's funnel plot of progression-free survival; (b) Egger's funnel plot of progression-free survival; (c) Begg's funnel plot of overall survival; and (d) Egger's funnel plot of overall survival.

antitumor effects of cediranib on different malignancies. As a result of the limitations of this meta-analysis, more comprehensive perspectives and large-scale sample studies are required to assess cediranib's efficacy and safety.

In conclusion, our meta-analysis demonstrates that cediranib treatment has a better treatment response than noncediranib therapy. Even though cediranib is associated with an increased risk of specific treatment-related toxicities such as diarrhea and fatigue, cediranib significantly improved the quality of life and patient outcomes in multiple clinical trials, providing a new potential therapeutic option for cancer patients. Trials on cediranib, the most promising oral anti-angiogenic tyrosine kinase inhibitor, are currently in progress. In the future, the ongoing randomized, double-masked phase II/III clinical trials will help to understand better the role of cediranib in the treatment of solid malignant tumors, and toxicities associated with its use should be given more attention in order to provide stricter monitoring and management and continuously improve the prognosis of patients.

Data Availability

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Yan Wang and Qi-Ming Wang designed the study; Yan Wang performed the study and wrote the paper; Yan Wang and Yan Cai assessed the studies included in this review and collected the data; Yan Wang and Yan Cai analyzed the data; and Qi-Ming Wang reviewed the manuscript. All authors contributed to the data analysis, drafting, and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Acknowledgments

This study was funded by the Ningbo Health Branding Subject Fund (Grant no. PPXK2018-06).

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