

Safety of combining vascular endothelial growth factor receptor tyrosine-kinase inhibitors with chemotherapy in patients with advanced non-small-cell lung cancer

A PRISMA-compliant meta-analysis

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Abstract

Background: Vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs) have been developed for targeted therapies in non-small-cell lung cancer (NSCLC); moreover, some drug-related toxic reactions among cancer patients have been reported. A meta-analysis of randomized controlled trials (RCTs) to definite the incidence and the risk of grade ≥ 3 adverse events (AEs), serious and fatal AEs (SAEs and FAEs), with VEGFR-TKIs in advanced/metastatic NSCLC patients was performed.

Methods: A comprehensive literature search was conducted for the clinical trials published up to December 2017. Qualified studies allotted patients with advanced/metastatic NSCLC to receive either chemotherapy alone or in combination with VEGFR-TKIs. Data were extracted by 2 authors.

Results: Eighteen RCTs of VEGFR-TKIs plus chemotherapy, involving 8461 advanced NSCLC patients were included. The proportion of patients with grade ≥ 3 AEs was increased with the addition of VEGFR-TKIs (relative risk, 1.35; 95% confidence interval [CI] 1.19–1.52; incidence, 68.1% vs 50.1%; $P < .001$). The most common grade ≥ 3 AEs was neutropenia (24.9% vs 15.4%, $P < .001$). Addition of VEGFR-TKIs was also related to the increased risk of SAEs (relative risk, 1.34; 95% CI 1.14–1.56; incidence, 37.8% vs 27.9%; $P < .001$) and FAEs (relative risk, 2.16, 95% CI 1.47–3.19; incidence, 3.4% vs 1.8%). Subgroup analysis suggested there was no difference in the rates of SAEs and FAEs in the second-line settings. No evidence of bias was found between the literatures. The study was registered with PROSPERO (CRD42018099654).

Conclusions: In comparison with chemotherapy alone, the addition of VEGFR-TKIs in advanced NSCLC patients was related to the increased risk of grades ≥ 3 AEs, SAEs, and FAEs, especially in the first-line settings. Physicians should be aware of some specific grade ≥ 3 adverse effect, especially haematologic adverse events, and it is also necessary to monitor cancer patients receiving VEGFR-TKIs.

Abbreviations: AEs = adverse events, CI = confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, FAEs = fatal adverse events, NSCLC = non-small cell lung cancer, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, RCTs = randomized controlled trials, RR = relative risk, SAEs = serious adverse events, VEGFR-TKIs = vascular endothelial growth factor receptor-tyrosine kinase inhibitors.

Keywords: fatal adverse events, grade ≥ 3 adverse events, NSCLC, serious adverse events, VEGFR-TKIs

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1. Introduction

It can be said that lung cancer is so common diagnosed malignant tumors throughout the world. Approximately 85% of lung cancer patients are infected with non-small-cell lung cancer (NSCLC).^[1] Of them, 65% to 75% patients had locally advanced or metastatic disease.^[2] At present, not only traditional chemotherapy, but also targeted therapy has been used to treat patients with NSCLC. Most people could benefit from targeted therapy with epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR-TKIs), but will develop resistance and subsequent disease progression. KRAS mutations^[3] and other reasons^[4] reportedly were associated with resistance to EGFR-TKIs therapy. Inhibitors targeting KRAS,^[5] especially other important oncogenic signaling pathways, might be the options for patients with NSCLC.

Vascular endothelial growth factor receptor (VEGFR) is an important target for NSCLC.^[6] Several kinds of VEGFR-TKIs-targeted treatment of NSCLC have been developed by scientists, such as sorafenib, vandetanib, cediranib, and sunitinib. Although TKI may not have typical side effects on patients like other cytotoxic chemotherapeutic drugs, some drug-related toxicities have been found in cancer patients. Therefore, the concerns about the serious consequences or fatal adverse events (FAEs) with these target agents have been arisen.

In a recent meta-analysis, Hong et al^[7] demonstrated that the risk of death in NSCLC patients increased significantly (odds ratio: 2.37, $P = .01$) by using VEGFR-TKIs. Wang et al^[8] carried out a pooled analysis of the risk of grade ≥ 3 AEs of VEGFR-TKIs in advanced NSCLC patients. Both these meta-analyses-enrolled patients received VEGFR-TKIs or in combination with other drugs. A meta-analysis performed by Gu et al^[9] assessed the overall risk of severe AEs related to anti-VEGFR agents. Besides VEGFR-TKIs, VEGF antibody-based agents were also included in this meta-analysis. Grade ≥ 3 toxicity and the treatment-related deaths were comprehensively analyzed in a meta-analysis carried out by Li et al.^[10]

To our best knowledge, there is little systematic review and meta-analysis to summarize the incidence and risk of grade ≥ 3 toxicity, SAEs, and FAEs related to VEGFR-TKIs in combination with traditional chemotherapy, compared with traditional chemotherapy alone. Consequently, we performed this up-date meta-analysis of randomized controlled trial (RCTs). Additionally, the specific category of grade ≥ 3 AEs reported in these RCTs was simultaneously extracted.

2. Materials and methods

2.1. Study design

We conducted the meta-analysis according to the preferred reporting items for Systematic Reviews and Meta-Analysis.^[11] The project was prospectively registered in PROSPERO database, number CRD42018099654.

2.2. Search strategy and selection criteria

An extensive search was carried out in the following databases: PubMed, Embase, Web of Science, and the Cochrane library. The following keywords were searched: “non-small cell lung neoplasms,” “NSCLC,” “lung cancer,” “lung Carcinoma,” “sorafenib,” “BAY43-9006,” “nexavar,” “sunitinib,” “SU11248,” “sutent,” “pazopanib,” “GW786034,” “votrient,”

“axitinib,” “AG-013736,” “regorafenib,” “cediranib,” “AZD2171,” “vandetanib,” “caprelsa,” “ZD6474,” “lapatinib,” “apatinib,” “lenvatinib,” “cabozantinib,” “tivozanib,” “AV-951,” “Linifanib,” “ABT-869,” “angiogenesis inhibitor,” “VEGFR-TKIs,” and “randomized controlled trial.” References in the primary studies and relevant review articles were also viewed to find more publications. Only prospective RCTs published in English were searched.

Clinical trials that met the following condition were enrolled: patients with advanced NSCLC; subjects received chemotherapy or in combination with VEGFR-TKIs; reported the endpoints of interest; phase II or III RCTs comparing VEGFR-TKIs plus chemotherapy versus chemotherapy alone.

2.3. Data extraction and study validity assessment

Two investigators extracted data independently. The following messages were recorded: the name of the first author, the year of publication, study period, treatment line, treatment arms and VEGFRs dosage, number of patients included, median age, and the events of grade ≥ 3 AEs, SAEs, and FAEs.

The National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) criteria, version 3 or 4.0 was used.^[12] The primary endpoint of this research was the incidence and relative risk of FAEs. The National Cancer Institute’s General Terminology Standard for Adverse Events defines the concept of FAEs as death from exposure to experimental drugs during clinical trials. We did not include FAEs related to disease progression. Secondary endpoints included grade ≥ 3 AEs and SAEs. The definition of SAEs is AEs causing death, life-threatening situation, hospitalization or prolongation of hospitalization, disability or permanent injury, congenital anomalies, or birth defects.^[13]

The quality evaluation of each study was based on the Cochrane Collaboration guidelines and “Risk of bias” tool.^[14] Disagreements between investigators were resolved by consensus.

2.4. Statistical analysis

The Cochrane Review Manager Version 5.3 and Stata/SE version 14.0 software (Stata, College Station, TX) were used to perform the statistical analysis. Data were summarized using relative risk (RR) with its 95% confidence interval (CI). The total incidence and RRs were counted by making the use of random-effects or fixed-effects models, relying on the heterogeneity of contained studies. The χ^2 -based Q statistic test was applied for the evaluation of the between-study heterogeneity, which was deemed to be significant when $P_{\text{heterogeneity}} < .05$ or $I^2 > 50\%$.^[15] A 2-tailed P value $< .05$ was deemed to statistical significance. An estimate of potential publication bias was carried out making use of Begg and Egger tests.^[16,17]

3. Results

3.1. Trial characteristics and patients

As shown in Figure 1, 18 RCTs involving 8461 NSCLC patients were included for analysis,^[18-35] with 10 studies reporting the summary grade ≥ 3 AEs,^[22-26,31-35] 10 studies reporting SAEs,^[22-25,29-31,33-35] and 10 trials reporting treatment-related deaths.^[18-20,22-24,27,30,32-34] Their characteristics are listed in Table 1.

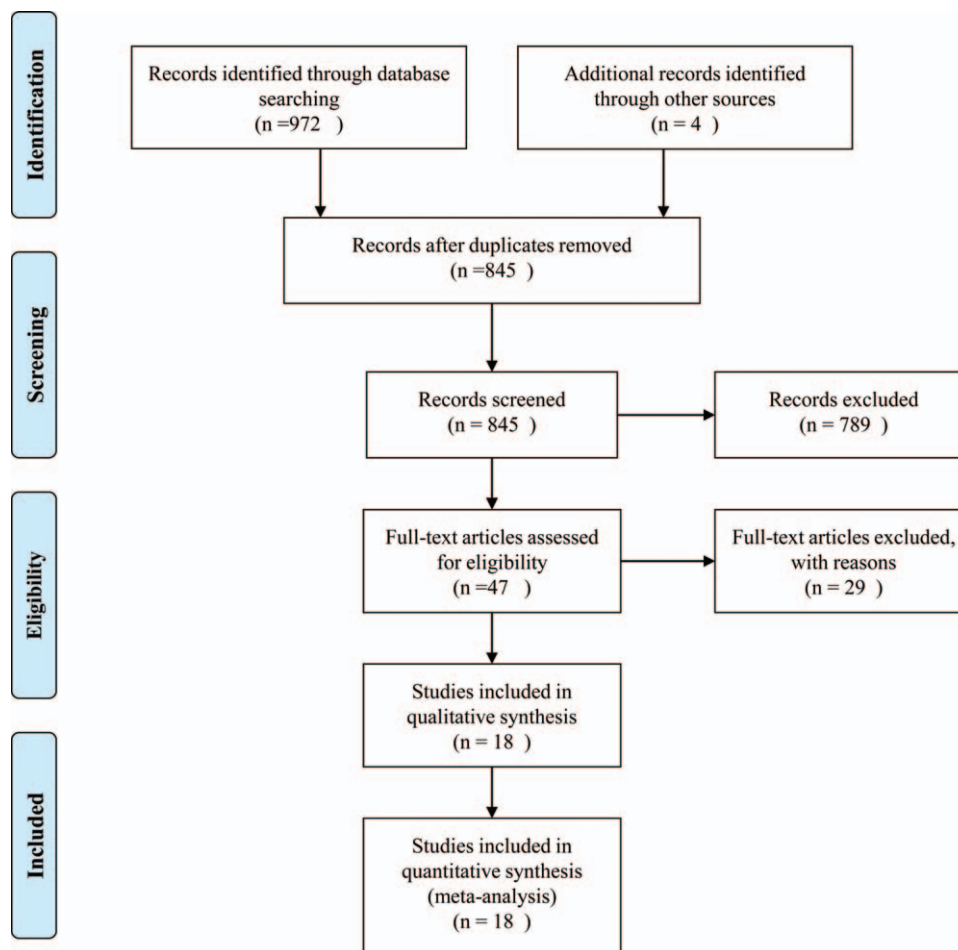


Figure 1. Selection process for the randomized controlled trials included in the meta-analysis.

3.2. Risk of bias

The quality of the trial was generally good and the risk of bias was low (Fig. 2). Of the studies enrolled, 7 trials were considered to be with an excellent quality without bias. The most common problem is that there is no expression of randomization process and allocation concealment (selection bias), and the lack of blinding in the studies by Bellani et al,^[28] Dy et al,^[26] Heist et al,^[32] and Scagliotti et al^[27] (performance bias and detection bias).

3.3. Grade ≥ 3 AEs

A total of 3007 patients from 10 treatment arms receiving VEGFR-TKIs could be used for analysis of summary incidence of grade ≥ 3 toxicity. Using a random-effects model, the total incidence of grade ≥ 3 AEs was determined to be 68.1% (95% CI 59.5%–76.7%) in VEGFR-TKIs group, compared with 50.1% (95% CI 38.2%–61.9%) in chemotherapy group.

A meta-analysis of RR for grade ≥ 3 AEs associated with VEGFR-TKIs was carried out. The pooled results indicated that the risk of grade ≥ 3 AEs was significantly increased with the application of VEGFR-TKIs (RR=1.35, 95% CI 1.19–1.52, $P < .001$). As shown in Figure 3, subgroup analysis showed the increased grade ≥ 3 toxicity was still significant in both first-line (RR=1.40, 95% CI 1.17–1.69, $P < .001$) and second-line settings (RR=1.23, 95% CI 1.04–1.46, $P = .02$).

Specific grade ≥ 3 AEs reported in ≥ 5 studies or with a morbidity of $>5\%$ were assessed for further analysis. Neutropenia (24.9%, 95% CI 18.0%–31.7% vs 15.4%, 95% CI 10.3%–20.4%; $P < .001$) was the most common AE. As shown in Table 2, except for gastrointestinal events (nausea, vomiting, and constipation, decreased appetite), thromboembolic events, dyspnea, and peripheral neuropathy, other severe AEs showed significantly difference compared with control group. However, the risk of grade ≥ 3 anemia with VEGFR-TKIs was significantly lower than that in control group.

3.4. SAEs

A total of 6225 patients (3122 VEGFR-TKIs, 3103 controls) from 10 RCTs were available for the analysis of SAEs. The total incidence of SAEs was 37.8% (95% CI 30.2%–45.2%) in treatment group and 27.9% (95% CI 19.9%–35.9%) in control group by using a random-effects model.

The risk of SAEs was significantly higher in the TKI combination therapy group, using a random model (RR=1.34, 95% CI 1.14–1.56; $P < .001$). It was of interest to note the increased risk of SAEs was significant in the first-line treatment (RR 1.52, 95% CI 1.36–1.71, $P < .001$, $I^2 = 12\%$), but not in the second-line settings (RR=1.01, 95% CI 0.90–1.13, $P = .91$, $I^2 = 7\%$, Fig. 4).

Table 1
Characteristics of included randomized controlled trials.

First author, year (ref)	Study design	Treatment line	Treatment arms	Number for analysis	Median age, y	Median PFS, mo	Median OS, mo
Heymach et al, 2007 ^[18]	Phase II	Second line	Vandetanib 100 mg + docetaxel	42	61 (30–76)	4.7	13.1
			Vandetanib 300 mg + docetaxel	44	60 (29–82)	4.2	7.9
Heymach et al, 2008 ^[19]	Phase II	First line	Placebo + docetaxel	41	58 (41–78)	4.0	13.4
			Vandetanib 300 mg + carboplatin/ paclitaxel	56	60 (36–79)	6.0	10.2
			Placebo + carboplatin/paclitaxel	52	59 (42–83)	5.8	12.6
Goss et al, 2010 ^[20]	Phase II	First line	Cediranib 30 mg/day + paclitaxel/carboplatin	126	60 (36–77)	5.6	NM
Herbst et al, 2010 ^[21]	Phase II	Second line	Placebo + paclitaxel/carboplatin	123	58 (39–81)	5.0	
			Vandetanib 100 mg/day + docetaxel	689	59 (28–82)	4.0	10.6
Scagliotti et al, 2010 ^[22]	Phase III	First line	Placebo + docetaxel	690	59 (20–82)	3.2	10.0
			Sorafenib 400 mg twice a day + carboplatin/paclitaxel	463	62 (34–86)	4.6	10.7
de Boer et al, 2011 ^[23]	Phase III	Second line	Placebo + carboplatin/paclitaxel	459	63 (34–82)	5.4	10.6
			Vandetanib 100 mg/day + pemetrexed	260	60 (28–82)	4.4	10.5
Paz-Ares et al, 2012 ^[24]	Phase III	First line	Placebo + pemetrexed	273	60 (35–83)	3.0	9.2
			Sorafenib 400 mg twice a day + gemcitabine/cisplatin	385	59 (28–81)	6.0	12.4
Scagliotti et al, 2012 ^[25]	Phase III	First line	Placebo + gemcitabine/cisplatin	384	58 (22–77)	5.5	12.5
			Motesanib 125 mg/day + paclitaxel/carboplatin	533	60 (23–87)	5.6	13.0
Dy et al, 2013 ^[26]	Phase II	First line	Placebo + paclitaxel/carboplatin	539	60 (21–84)	5.4	11.0
			Cediranib 30 mg/day + gemcitabine/carboplatin	58	65 (46–81)	6.3	12
Scagliotti et al, 2013 ^[27]	Phase II	First line	Gemcitabine/carboplatin	29	64 (45–82)	4.5	9.9
			Pazopanib 800 mg/day + pemetrexed	61	62 (40–75)	6.2	NM
Belani et al, 2014 ^[28]	Phase II	First line	Cisplatin + pemetrexed	34	64 (36–74)	5.7	
			Axitinib 5 mg bid + pemetrexed/cisplatin	55	62 (30–77)	8.0	17.0
Gridelli et al, 2014 ^[29]	Phase II	First line	Pemetrexed/cisplatin	55	59 (42–76)	7.1	15.9
			Vandetanib 100 mg/day + gemcitabine	61	75 (70–82)	6.1	8.7
Laurie et al, 2014 ^[30]	Phase III	First line	Placebo + gemcitabine	63	75 (70–84)	5.6	10.2
			Cediranib 20 mg/day + paclitaxel/carboplatin	151	63 (23–85)	5.5	12.2
Novello et al, 2014 ^[31]	Phase III	First line	Placebo + carboplatin/paclitaxel	153	62 (36–77)	5.5	12.1
			Motesanib 125 mg/day + carboplatin/paclitaxel	181	62 (31–79)	4.9	11.1
Heist et al, 2014 ^[32]	Phase II	Second line	Placebo + carboplatin/paclitaxel	173	59.5 (32–81)	5.1	10.7
			Pemetrexed + sunitinib 37.5 mg daily	39	63 (38–84)	3.7	6.7
Reck et al, 2014 ^[33]	Phase III	Second line	Pemetrexed	42		4.9	10.5
			Nintedanib 200 mg twice daily + docetaxel	652	60 (53–67)	3.4 2.7	10.9
Ramalingam et al, 2015 ^[34]	Phase II	First line	Placebo + docetaxel	655	60 (54–66)		7.9
			Linifanib 7.5 mg + carboplatin/paclitaxel	42	61.5 (35–79)	8.3	11.4
Hanna et al, 2016 ^[35]	Phase III	Second-line	Linifanib 12.5 mg carboplatin/paclitaxel	47	60 (43–79)	7.3	13.0
			Placebo + carboplatin/paclitaxel	47	61 (44–79)	5.4	11.3
			Nintedanib 200 mg twice daily + pemetrexed	347	60 (21–84)	4.4	12.0
			Placebo + pemetrexed	357	59 (26–86)	3.6	12.7

NM = not mentioned, OS = overall survival, PFS = progression-free survival.

3.5. FAEs

Ten trials were included for the analysis of FAEs. No FAEs occurred in 1 RCT.^[18] There are 78 among 2108 patients who received VEGFR-TKIs and 33 in 1989 control patients experienced FAEs. Again, a random-effects model was applied. The incidence of FAEs was 3.4% (95% CI 1.9%–4.9%) in VEGFR-TKIs group, and 1.8% (95% CI 0.0%–3.3%) in chemotherapy group.

This pooled result of RR indicated that the risk of FAEs was significantly increased by adding VEGFR-TKIs (RR = 2.16, 95% CI 1.47–3.19, $P < .001$; Fig. 5). Subgroup analysis suggested a significant increase of risk in first-line (RR = 3.64, 95% CI 1.88–7.07, $P < .001$, $I^2 = 0\%$), but not in the second-line settings (RR = 1.52, 95% CI 0.93–2.48, $P = .09$, $I^2 = 16.9\%$), which was the same as the results of SAEs.

3.6. Sensitive analysis

Sensitivity analysis was performed to test the reliability and stability of pooled RRs by sequential omission of individual

studies, to interpret heterogeneity in grade ≥ 3 AEs. The consequence showed that the significance estimate of pooled RRs was not influenced by deleting any single study (Table 3).^[22–26,31–35]

3.7. Risk of bias across studies

No public bias was found between studies that reported SAEs by either the Begg or Egger tests, except for grade ≥ 3 AEs and FAEs. However, public bias almost disappeared stratified by line of chemotherapy (Table 4).

4. Discussion

Targeted therapies for cancer treatment are positive and negative, like coins. Patients often overestimate the benefits of treatment and ignore the side effects.^[36] Thus, in the decision-making process of oncology clinic, the discussion of possible side effects should play an important role.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Belani, 2014	+	+	-	-	-	+	+
de Boer, 2011	+	+	+	+	+	+	+
Dy, 2013	?	?	-	-	+	+	+
Goss, 2010	+	+	+	+	+	+	+
Gridelli, 2014	+	+	+	+	+	+	+
Hanna, 2016	+	?	+	+	+	+	+
Heist, 2014	+	+	-	-	+	+	+
Herbst, 2010	+	+	+	+	+	+	+
Heymach, 2007	?	?	?	-	+	+	+
Heymach, 2008	?	?	?	-	+	+	+
Laurie, 2014	+	?	+	+	+	+	+
Novello, 2014	+	?	+	+	+	+	+
Paz-Ares, 2012	+	+	+	+	+	+	+
Ramalingam, 2015	?	?	+	+	-	+	+
Reck, 2014	+	+	+	+	+	+	+
Scagliotti, 2010	?	?	+	+	+	+	+
Scagliotti, 2012	+	+	+	+	+	+	+
Scagliotti, 2013	?	?	-	-	+	+	+

Figure 2. Risk of bias assessment.

There have been some meta-analyses estimating toxicities with VEGFR inhibitors. However, specific meta-analysis assessing the SAEs and/or FAEs associated with VEGFR-TKIs in advanced NSCLC was very little. Additionally, it was worth to mention

that only grade ≥ 3 AEs were mostly reported in these meta-analyses. Another important endpoint, SAEs, which can cause treatment interruption or discontinuation, even can cause hospitalizations, disabilities and deaths, should be a significant part of shared decision-making.^[37] As far as we know, limited data are particularly focused on the SAEs related to VEGFR-TKIs in NSCLC. We therefore carried out this meta-analysis of RCTs to assess not only the incidence and RR of FAEs, but also grade ≥ 3 toxicities and SAEs of VEGFR-TKIs in advanced NSCLC patients.

First, this meta-analysis showed the risk of grade ≥ 3 toxicities was significantly increased compared with traditional chemotherapy agents (RR: 1.35, 95% CI 1.19–1.52, $P < .001$). A subgroup analysis was carried out to explain the heterogeneity. The result suggested the incidence of grade ≥ 3 AEs was higher in VEGFR-TKIs group, either in first- or in the second-line treatment, which was consistent with the result of the previous study.^[10]

Compared with cytotoxic chemotherapy, VEGFR-TKIs were historically deemed to have obviously nonoverlapping toxicities. Whereas, meta-analysis have exposed that TKIs were related to the addition of the risk of neutropenia,^[38] thrombocytopenia,^[38] cutaneous toxicities,^[39–42] hypertension,^[43–46] fatigue,^[47] hemorrhage,^[48] and arterial thrombotic event.^[49] According to the current reported experimental results, some toxicities are indeed overlapping and additive (neutropenia, leukocytopenia, thrombocytopenia, rash, fatigue, diarrhea, hypertension, anorexia, mucositis, and hemorrhage events). Although the risk of neutropenia, thrombocytopenia, and leukocytopenia was higher with VEGFR-TKIs, high-grade anemia was not increased with VEGFR-TKIs in the previously reported meta-analyses.^[38,50,51] Our results also indicated there is no addition of the danger of severe anemia with VEGFR-TKIs (RR: 0.75, 95% CI 0.57–0.98, $P = .04$), and showed that VEGFR-TKIs may have a certain protective effect on anemia.^[52]

Importantly, this meta-analysis showed VEGFR-TKIs combining with traditional chemotherapy are associated with increased rates of SAEs and FAEs in patients with advanced NSCLC. We surprisingly found that both of these associations were not statistically significant in the second-line settings (Figs. 3 and 4). The risk of SAEs associated with VEGFR-TKIs had only been reported in 2 meta-analyses.^[53,37] Both of these 2 studies were not related about NSCLC. Our study is the first meta-analysis to report on SAEs with VEGFR-TKIs in advanced NSCLC patients. The pooled incidence of FAEs in patients receiving VEGFR-TKIs was 3.4% in this meta-analysis, nearly twice as high as for those patients in placebo/control groups at 1.8%. The risk of FAEs related to VEGFR-TKIs in cancer patients had been reported in 5 meta-analysis.^[54,55,7,56,57] Subgroup analysis stratified by line of chemotherapy was not performed in any one of these studies, except one conducted by Li et al.^[10] They found treatment-related deaths were significantly higher with the addition of VEGFR-TKIs to chemotherapy in advanced NSCLC patients (odds ratio 2.37, 95% CI 1.58–3.56; $P < .0001$), and this increase was also significant in the second-line treatment (odds ratio 1.74, $P = .03$). In their second-line subgroup analysis, deaths data from RCT performed by Herbst et al.^[21] was also included. In that RCT, 5 deaths in patients receiving vandetanib plus docetaxel were not definitely attributed to treatment protocol, which was therefore dropped in our study. In the first treatment line, VEGFR-TKIs were combined with platinum doublet

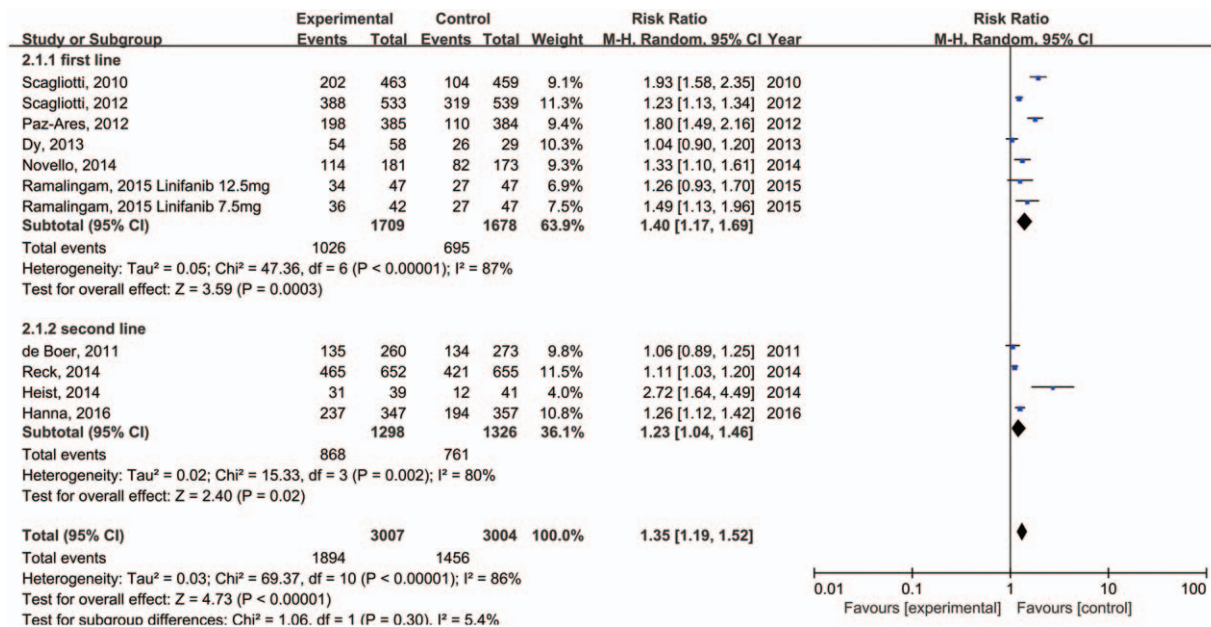


Figure 3. Forest plot and pooled risk ratio for grade ≥3 adverse events.

chemotherapy. That might have led to serious toxicity reactions (SAEs, RR 1.52, $P < .001$; FAEs, RR 3.64, $P < .001$), and may be the reason of the higher incidence of SAEs and FAEs in the first-line setting.

However, this meta-analysis has some limitations. First, this is a meta-analysis based on the study level. Second, patients treated with different VEGFR-TKIs were included, and the clinical heterogeneity might be increased among the trials,

although subgroup analysis according to the treatment line was carried out. Additionally, heterogeneity can be found in the analysis of grade ≥3 AEs. Therefore, the random-effects model was applied to adjust for the heterogeneity. We also conducted a subgroup and sensitivity analysis for this endpoint. Ultimately, publication bias is likely to occur, even though no evidence of published bias has been found through Begg or Egger tests.

Table 2
Incidence and RR of specific severe adverse events in randomized controlled trials.

Specific adverse outcome (grade ≥3)	No. of studies (n)	No. of patients		RR (95% CI)	P	I ² (%)
		VEGFR-TKIs, events/total	Controls, events/total			
Neutropenia	14	573/3140	402/3071	1.34 (1.20–1.49)	<.001	41.5
Rash	8	91/1384	13/1348	6.28 (3.66–10.78)	<.001	17.0
Fatigue	14	230/2938	164/2873	1.35 (1.11–1.63)	.002	5.9
Diarrhea	16	232/4148	81/4077	2.75 (2.16–3.52)	<.001	41.0
Thrombocytopenia	10	134/1994	49/1946	2.63 (1.92–3.60)	<.001	34.6
Dyspnea	10	116/2260	133/2239	0.87 (0.68–1.10)	.24	0
Leukocytopenia	4	133/1482	100/1465	1.31 (1.02–1.67)	.03	44.1
Hypertension	13	123/3087	25/3008	4.32 (2.89–6.47)	<.001	0
Thromboembolic events*	8	77/2179	76/2207	1.03 (0.76–1.39)	.87	0
Anemia	12	89/2959	110/2899	0.75 (0.57–0.98)	.04	34.6
Anorexia	7	53/2103	29/2134	1.81 (1.17–2.82)	.008	25.9
Decreased appetite	5	22/1296	17/1274	1.24 (0.67–2.30)	.50	0
peripheral neuropathy	5	29/1154	25/1171	1.18 (0.70–1.99)	.54	0
Nausea	13	55/3400	45/3368	1.15 (0.78–1.68)	.49	0
Vomiting	13	56/3847	52/3866	1.07 (0.74–1.55)	.72	16.6
Mucositis	5	20/1964	2/1961	5.68 (1.85–17.44)	.002	0
Hemorrhage events†	8	29/2413	9/2409	2.99 (1.46–6.10)	.003	0
Constipation	8	7/2289	8/2304	0.83 (0.34–2.04)	.68	0

CI = confidence interval, RR = relative risk, VEGFR-TKIs = vascular endothelial growth factor receptor-tyrosine kinase inhibitors.

* Thromboembolic events include arterial thromboembolic events, venous thromboembolic events, and pulmonary embolism.

† Hemorrhage events include hemoptysis, pulmonary hemorrhage, gastrointestinal hemorrhage, and nose hemorrhage.

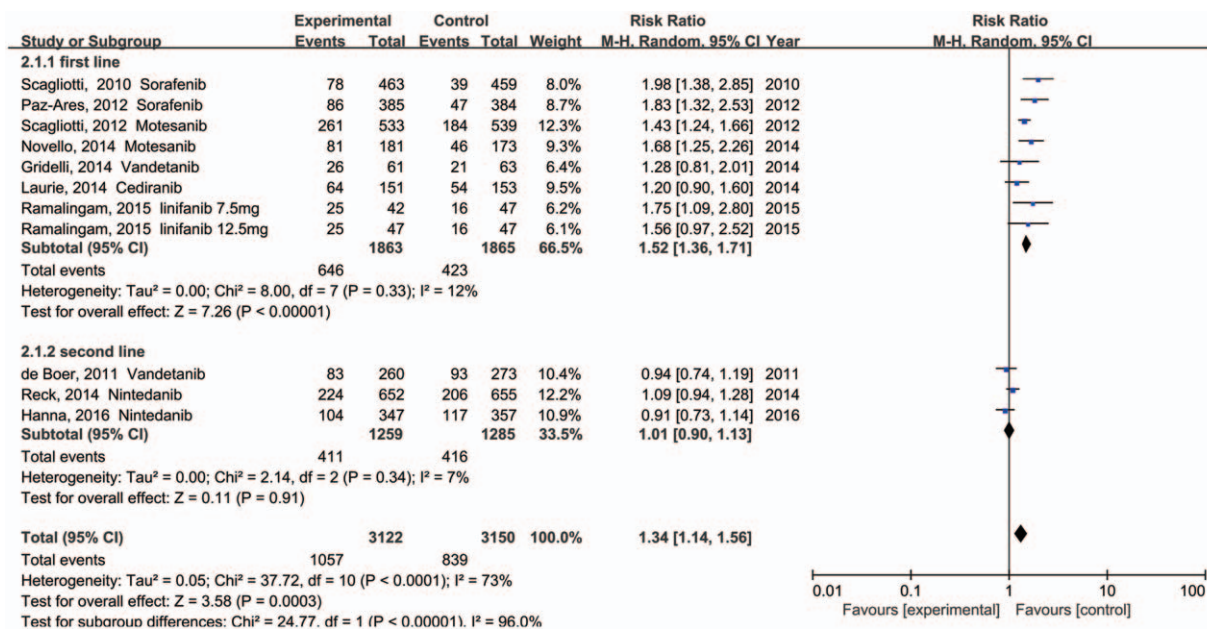


Figure 4. Forest plot and pooled risk ratio for serious adverse events.

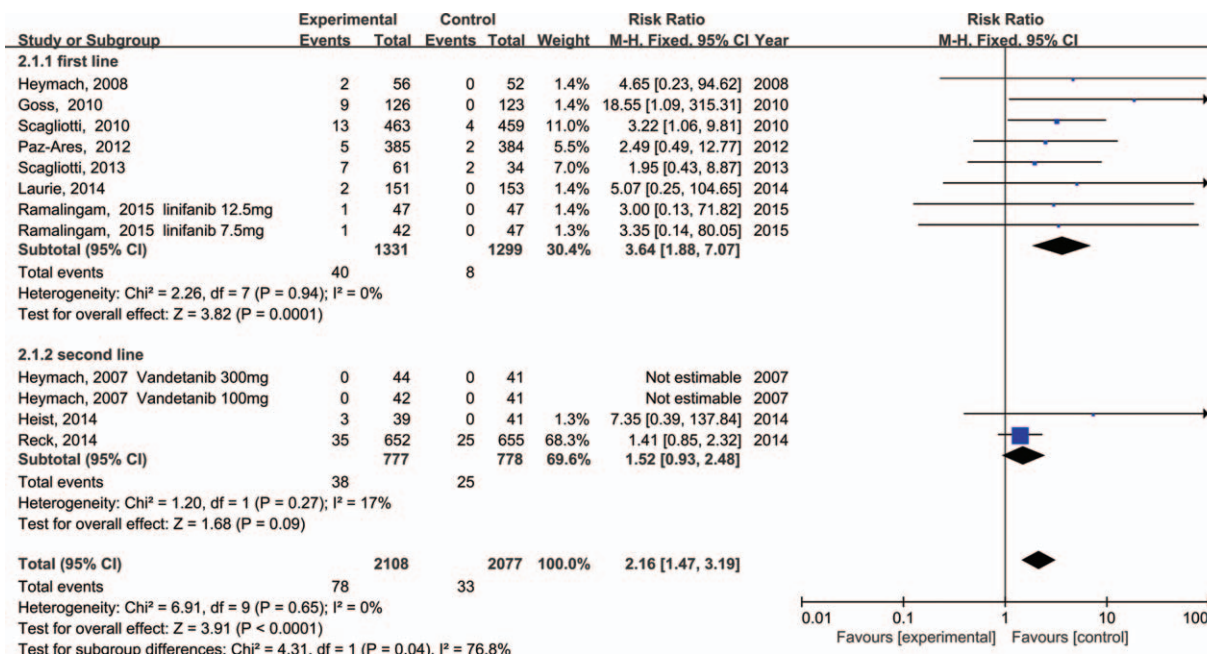


Figure 5. Forest plot and pooled risk ratio for fatal adverse events.

5. Conclusions

This is a comprehensive meta-analysis that specifically evaluated the grade ≥3, serious and fatal toxicities of adding VEGFR-TKIs to chemotherapies in advanced NSCLC patients, and also the most reported specific grade ≥3 AEs. Our results show that the

addition of VEGFR-TKIs to chemotherapies in NSCLC significantly increases grade ≥3 toxicity, SAEs, and FAEs compared with traditional chemotherapy alone, especially in the first treatment line. Monitoring AEs, especially haematologic AEs during VEGFR-TKIs therapy, is recommended.

Table 3**Sensitivity analysis of grade ≥ 3 AEs associated with VEGFR-TKIs versus control.**

First author, year	Remove	RR (95% CI)	P (%)
Scagliotti et al, 2010 ^[22]	✓	1.29 (1.15–1.43)	80
de Boer et al, 2011 ^[23]	✓	1.38 (1.21–1.58)	87
Scagliotti et al, 2012 ^[25]	✓	1.37 (1.18–1.59)	87
Paz-Ares et al, 2012 ^[24]	✓	1.30 (1.16–1.45)	82
Dy et al, 2013 ^[26]	✓	1.39 (1.22–1.58)	85
Novello et al, 2014 ^[31]	✓	1.35 (1.18–1.54)	87
Heist et al, 2014 ^[32]	✓	1.30 (1.16–1.47)	85
Reck et al, 2014 ^[33]	✓	1.39 (1.20–1.60)	85
Ramalingam et al, 2015 7.5 mg ^[34]	✓	1.34 (1.17–1.52)	87
Ramalingam et al, 2015 12.5 mg ^[34]	✓	1.35 (1.19–1.54)	87
Hanna et al, 2016 ^[35]	✓	1.36 (1.18–1.57)	87

AEs = adverse events, CI = confidence interval, RR = relative risk, VEGFR-TKIs = vascular endothelial growth factor receptor-tyrosine kinase inhibitors.

Table 4**Public bias Begg and Egger test (P value).**

Endpoint	Total studies	Begg test		Total studies	Egger test	
		First line	Second line		First line	Second line
Grade ≥ 3 AEs	0.04	0.55	0.31	0.04	0.29	0.25
SAEs	0.28	0.54	1.00	0.25	0.38	0.20
FAEs	1.00	0.71	1.00	0.003	0.22	NA

AEs = adverse events, FAEs = fatal adverse events, NA = not available, SAEs = serious adverse events.

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