

# Risk of rash associated with vandetanib treatment in non-small-cell lung cancer patients

## A meta-analysis of 9 randomized controlled trials

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### Abstract

**Background:** Vandetanib is a promising anticancer target agent for treating advanced carcinomas, such as non-small-cell lung cancer (NSCLC) and breast cancer. Rash is a frequently reported adverse event of vandetanib. We conducted this meta-analysis to determine the incidence rate and overall risks of all-grade and high-grade rash with vandetanib in NSCLC patients.

**Methods:** PubMed, Embase, Web of Science, American Society of Clinical Oncology, and Cochrane Library were systematically searched to identify studies with vandetanib and rash in NSCLC patients. Data were extracted to calculate the pooled incidence of all-grade and high-grade (grade  $\geq 3$ ) rash caused by vandetanib treatment.

**Results:** Nine randomized controlled trials involving 4893 patients met the inclusion criteria and were included in this meta-analysis. The overall incidence of all-grade and high-grade rash caused by vandetanib treatment was 46% (95% CI: 37.1%, 54.8%), and 3.2% (95% CI: 1.4%, 5.1%), respectively. The risk ratios (RR) of all-grade and high-grade rash for vandetanib treatment versus control treatment were 2.35 (95% CI: 1.20, 4.61;  $P < .001$ ) and 4.68 (95% CI 1.42, 15.37;  $P < .001$ ), respectively. Subgroup analysis suggested that the increased risk of all-grade rash was clear across all subgroups, including first-line/second-line therapy, phase 2/phase 3 trial, sample size  $</>200$ , a dosage of 100 or 300 mg, and monotherapy/combination therapy. However, for the high-grade rash, vandetanib did not increase the risk of rash when it was used in first-line therapy, or in a phase II trial, or in a trial with sample size  $<200$ .

**Conclusions:** This study suggests that vandetanib was associated with a significantly increased risk of rash. Therefore, early recognition and appropriate monitoring should be taken when NSCLC patients were treated with vandetanib.

**Abbreviations:** CI = confidence interval, EGF = epidermal growth factor, EGFR = epidermal growth factor receptor, NSCLC = non-small-cell lung cancer, RCTs = randomized controlled trials, RR = risk ratios.

**Keywords:** chemotherapeutics, non-small-cell lung cancer, rash, vandetanib

### 1. Introduction

It is reported that lung cancer is responsible for more deaths than a combination of those caused by colorectal cancer, breast cancer, and prostate cancer.<sup>[1]</sup> Non-small-cell lung cancer

(NSCLC) is the main origin of cancer-related death, and 85% or more patients are diagnosed with NSCLC at an advanced stage.<sup>[2]</sup> Chemotherapy plus radiotherapy has been reported to be one of the most effective treatment options against NSCLC in the previous study.<sup>[3]</sup> Platinum-based doublets are used as the first-line therapy for NSCLC.<sup>[4]</sup> Docetaxel, pemetrexed, gefitinib, and erlotinib are approved for the second-line treatment of advanced NSCLC.<sup>[5]</sup> However, platinum and other chemotherapeutic agents have systemic toxic side effects. Therefore, developing a drug with high efficacy and low toxicity is eagerly needed. Vandetanib (ZD6474, Caprelsa), is a newly developed drug with a prescribed oral dose of once daily. It is a potent, active, low molecular weight inhibitor of kinase insert domain-containing receptor and tyrosine kinase activity.<sup>[5]</sup> ZD6474 blocks in vivo phosphorylation and signaling of the RET/PTC3 and RET/MEN2B oncoproteins and is an inhibitor of epidermal growth factor (EGF)-activated EGF-receptor/RET chimeric receptor.<sup>[6]</sup> The multiple roles of vandetanib contribute to exhibit a positive effect in terms of anti-NSCLC activity. Moreover, vandetanib has also been reported to be associated with the adverse events of rash, hypertension, fatigue, diarrhea, acne, headache, nausea, decreased appetite, and abdominal pain. Other selective tyrosine kinase inhibitors targeting the EGF or vascular endothelial growth factor pathways, such as bevacizumab, erlotinib, sorafenib, cetuximab, and gefitinib, have also been reported to be associated with significant rash.

Currently, there are many studies reporting vandetanib for the treatment of advanced NSCLC, but their results are not

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YL and MQ participated in the design of the study and performed the statistical analysis. SH and LS carried out search strategies and inclusion criteria. JZ and YL took part in data extraction and quality assessment. QL conceived of the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

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consistent, especially for the adverse event of rash. Thus, we conducted this meta-analysis of randomized controlled trials (RCTs) to assess the overall risks of all-grade and high-grade rash during the vandetanib treatment in NSCLC patients.

## 2. Data and methods

### 2.1. Search strategies and inclusion criteria

A literature search was performed in electronic databases, including PubMed, Embase, Web of Science, American Society of Clinical Oncology, and Cochrane Library. This search was conducted from the inception to September 5, 2016. The following search terms were used: (“N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine”[Supplementary Concept] OR “N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine”[All Fields] OR “vandetanib”[All Fields]) AND (“carcinoma, non-small-cell lung”[MeSH Terms] OR (“carcinoma”[All Fields] AND “non-small-cell”[All Fields] AND “lung”[All Fields]) OR (“non-small-cell lung carcinoma”[All Fields] OR (“non”[All Fields] AND “small”[All Fields] AND “cell”[All Fields] AND “lung”[All Fields] AND “cancer”[All Fields]) OR “non small cell lung cancer”[All Fields] AND (“exanthema”[MeSH Terms] OR “exanthema”[All Fields] OR “rash”[All Fields])). Our search was limited to human subjects, and no language restriction was imposed. We also manually searched the references of included studies and reviews until no potential trials could be found.

The following selection criteria were applied: study design: RCT; population: adult patients diagnosed with advanced NSCLC; intervention: vandetanib alone or vandetanib in combination with chemotherapy; and outcome measures: incidence of all-grade and high-grade rash. The rash was graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.

### 2.2. Data extraction and quality assessment

Data extraction was performed by 2 reviewers independently. The following information was extracted: the first author, publication year, study designation, number of patients in each group, stage of patients, age, smoking habit, therapy line, and Jadad scale. Any discrepancy was discussed with another author until a consensus was reached.

Quality assessment of the trials was performed using Jadad scores, which assess trials according to the following items: whether the trial reported an appropriate randomization method (score 0–2); whether the trials reported an appropriate blinding method (score 0–2); and whether the trial reported withdrawals and dropouts (score 0–1).<sup>[7]</sup>

### 2.3. Statistical analysis

Our study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.<sup>[8]</sup> For dichotomous outcomes, they were expressed with relative risk (RR), with a 95% confidence interval (CI). A random-effects model or fixed-effects model was applied to pool the results according to the heterogeneity.<sup>[9]</sup> Heterogeneity across studies was tested using the  $I^2$  statistic.<sup>[10]</sup> We used the  $I^2$  statistic to test the heterogeneity among the included studies, in which the value of  $I^2 < 25%$  was considered to be no, 25% to 50% to be low, 50% to 75% to be moderate, and  $> 75%$  to be high. When significant heterogeneity

was found, sensitivity analysis was performed to explore the potential sources for heterogeneity by sequentially excluding each study in each turn. We also conducted subgroup analysis based on therapy line, sample size, phase of clinical trials, treatment programs, and vandetanib dose.  $P < .05$  was considered significant. All data and statistical analyses were combined and performed using RevMan 5.3.0 (The Cochrane Collaboration, Oxford, UK).

## 3. Results

### 3.1. Search results

The initial search yielded 512 publications, and 274 of them were deleted because of duplicate records. After reviewing titles and abstracts and full-text information, 219 and 10 articles were removed, respectively. Then the remaining 10 articles<sup>[11–19]</sup> with a total of 4893 patients met the inclusion criteria and were included in this meta-analysis (Fig. 1).

### 3.2. Characteristics of included studies

The main characteristics of included studies are presented in Table 1. All these trials were RCTs and published in English full-text between 2007 and 2013. The sample sizes of these RCTs varied from 117 to 1379. Among the RCTs, 5<sup>[13,16–19]</sup> used vandetanib as monotherapy, whereas the remaining 4<sup>[11,12,14,15]</sup> used in combination with chemotherapy. The dosage of vandetanib among these studies varied. In 5 trials,<sup>[12,13,16–18]</sup> the dosage of vandetanib was 300 mg/day, in 5 trials<sup>[14,15,19]</sup> was 100 mg/day; in the remaining 1 trial,<sup>[11]</sup> both 100 and 300 mg/day was used.

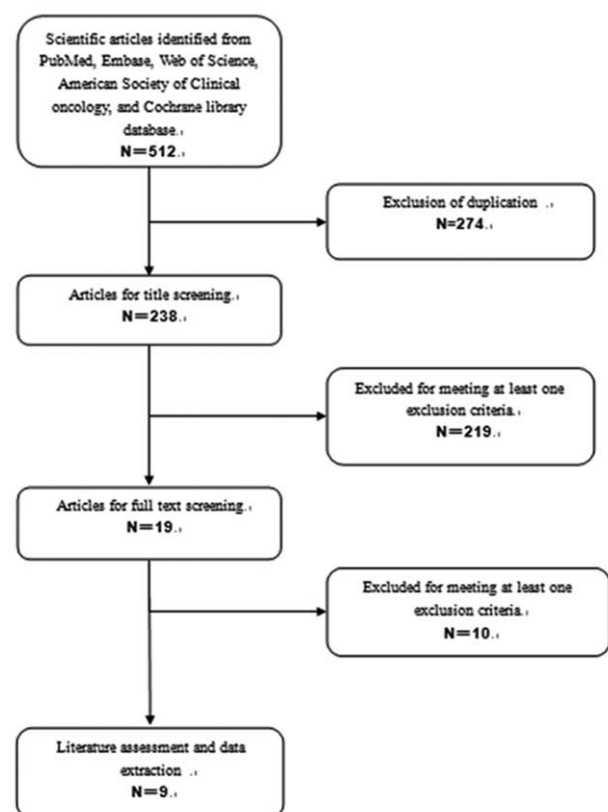


Figure 1. Eligibility of studies for inclusion in meta-analysis.

**Table 1**  
Baseline characteristics of patients in the trials included in the meta-analysis.

Study	Year	Trial phase	Arms	No. of patients	Median age, y	Smoking, %	Therapy-line	Jadad score
Heymach <sup>[11]</sup>	2007	2	Vand (100 mg) + Doc	42	60	83	Second-line	3
			Van (300 mg) + Doc	44	58	91		
			Placebo + Doc	41	58	90		
Heymach <sup>[12]</sup>	2008	2	Vand (300 mg)	74	60	75	First-line	3
			Vand (300 mg) + TC	56	60	77		
			TC	52	59	79		
Natale <sup>[13]</sup>	2009	2	Vand (300 mg)	120	61	86	Second-line	3
			Gef	114	63	91		
Herbst <sup>[14]</sup>	2010	3	Vand (100 mg) + Doc	689	59	77	Second-line	5
			Placebo + Doc	690	59	75		
De Boer <sup>[15]</sup>	2011	3	Van (100 mg) + Pem	260	60	78	Second-line	4
			Placebo + Pem	278	60	81		
Natale <sup>[16]</sup>	2011	3	Vand (300 mg)	623	61	79	Second-line	3
			Erl	614	61	77		
Lee <sup>[17]</sup>	2012	3	Vand (300 mg)	619	60	48	Second-line	3
			Placebo	303	60	46		
Ahn <sup>[18]</sup>	2013	2	Vand (300 mg)	75	61	63	Second-line	4
			Placebo	42	60.5	67		
Aisner <sup>[19]</sup>	2013	2	Vand (100 mg)	77	63.5	93	Second-line	5
			Placebo	81	63	94		

Doc = docetaxel, Erl = erlotinib, Gef = gefitinib, Pem = pemetrexed, TC = paclitaxel + carboplatin, Vand = vandetanib.

The mean Jadad score was 3.7 points. Five trials<sup>[11–13,16,17]</sup> were scored 3 points, 2<sup>[15,18]</sup> were 4 points, and 2<sup>[14,19]</sup> were 5 points. These scores suggested that all these RCTs were of high quality.

**3.3. Total incidences of all-grade and high-grade rash**

All the studies reported the data on all-grade rash.<sup>[11–19]</sup> The incidence of rash among these studies ranged from 27.6% to 77.3%, with the lowest incidence observed in the trial conducted by Natale RB,<sup>[13]</sup> and the highest incidence noted in the trial conducted by Ahn JS.<sup>[18]</sup> The pooled results using a random-effects model showed that the incidence of all-grade rash was 46% (95% CI: 37.1%, 54.8%).

All studies reported the data on high-grade rash.<sup>[11–19]</sup> The incidence of high-grade rash varied remarkably from 1.6% to 20.8%, with the lowest incidence observed in the trial conducted by Lee JS,<sup>[17]</sup> and the highest incidence noted in the trial conducted by Natale RB.<sup>[16]</sup> The pooled estimates showed the incidence of high-grade rash was 3.2% (95% CI: 1.4%, 5.1%).

**3.4. Risk ratio of all-grade and high-grade rash**

All the studies reported the data on all-grade rash.<sup>[11–19]</sup> Pooled results demonstrated that, vandetanib was associated with a significantly higher risk of all-grade rash than control treatment (risk ratios [RR]=2.35; 95% CI: 1.20, 4.61; *P* < .001) (Fig. 2). There was significant heterogeneity among the included studies (*P* = .01; *I*<sup>2</sup> = 97%).

All studies reported the data on high-grade rash.<sup>[11–19]</sup> Pooled results showed that patients treated with a significantly higher risk of rash than those treated with control therapy (RR=4.68; 95% CI: 1.42, 15.37; *P* < .001) (Fig. 3). There was significant heterogeneity among the included studies (*P* = .01; *I*<sup>2</sup> = 93%).

**3.5. Subgroup analysis for all-grade and high-grade rash**

We also conducted subgroup analysis based on therapy line (first-line vs second-line), sample size (≥200 vs <200), phase of clinical trials (phase II vs phase III), treatment programs (monotherapy vs combination therapy), and vandetanib dose (100 vs 300 mg). The

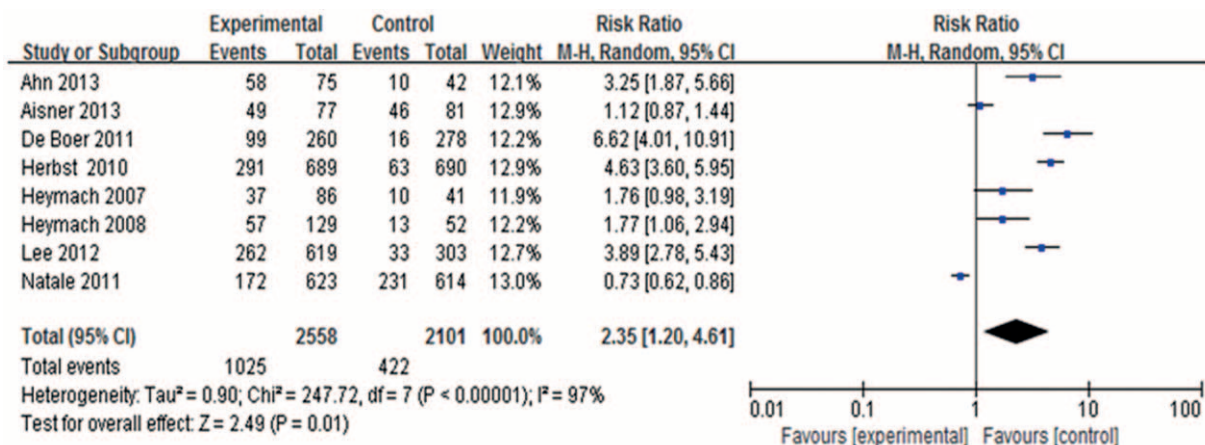


Figure 2. Forest plot of the relative risk of all-grade rash.

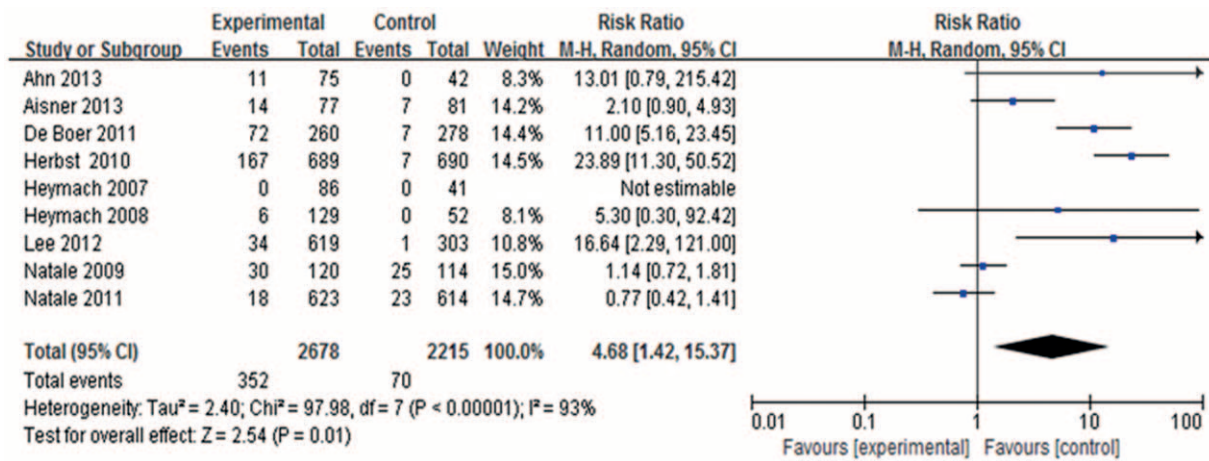


Figure 3. Forest plot of the relative risk of high-grade rash.

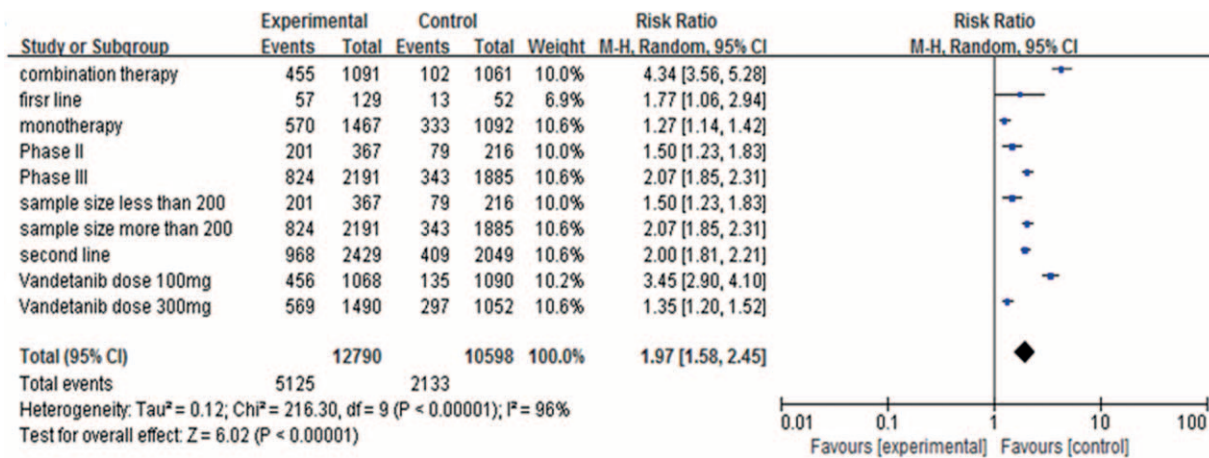


Figure 4. Forest plot of the subgroup analyzed for all-grade rash.

pooled results in the subgroup of all-grade rash did not alter substantially, which suggested that vandetanib was associated with a significantly higher risk of all-grade rash than control treatment (Fig. 4). Whereas, in the subgroup analysis of high-grade rash, the pooled results showed that vandetanib did not

induce a significantly higher risk of high-grade rash when it was used as first-line treatment (RR=5.30, 95% CI: 0.30–92.42) or in phase 2 trial (RR=1.29, 95% CI: 0.86–1.94), or in the study with sample size <200 (RR=1.29, 95% CI: 0.86–1.94) (Fig. 5). The pooled results were summarized in Table 2.

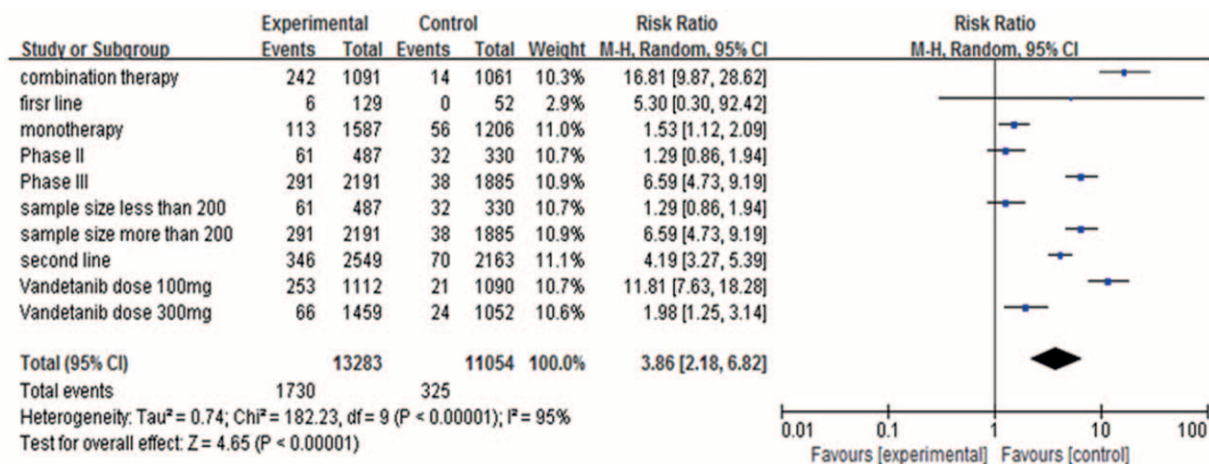


Figure 5. Forest plot of the subgroup analyzed for high-grade (grade ≥3) rash.

**Table 2****Subgroup analysis for all-grade and high-grade rash.**

Subgroup	All-grade rash		High-grade rash	
	RR	95% CIs	RR	95% CIs
Monotherapy	1.27	1.14–1.42	1.53	1.12–2.09
Combination therapy	4.34	3.56–5.28	16.81	9.87–28.62
First-line	1.77	1.06–1.42	5.30	0.30–92.42
Second-line	2.00	1.81–2.21	4.19	3.27–5.39
Phase 2	1.50	1.23–1.83	1.29	0.86–1.94
Phase 3	2.07	1.85–231	6.59	4.73–9.19
Sample size (<200)	1.50	1.23–1.83	1.29	0.86–1.94
Sample size (≥200)	2.07	1.85–231	6.59	4.73–9.19
Vandetanib dosage (100 mg)	3.45	2.90–4.10	11.81	7.63–18.28
Vandetanib dosage (300 mg)	1.35	1.20–1.52	1.98	1.25–3.14

**Table 3****Sensitivity analyses in all-grade rash.**

First author	Year	Remove	RR	I <sup>2</sup>	Z
Aisner	2013	✓	2.63	97%	2.36
Ahn	2013	✓	2.25	98%	2.18
Lee	2012	✓	2.19	97%	2.12
Natale	2011	✓	2.80	94%	3.51
De Boer	2011	✓	2.04	97%	2.02
Herbst	2010	✓	2.12	96%	2.24
Heymach	2008	✓	2.45	96%	2.36
Heymach	2007	✓	2.45	98%	2.38
Nine RCTs			2.35	97%	2.49

RCTs = randomized controlled trials

**3.6. Sensitivity analysis for all-grade and high-grade rash**

As there was significant heterogeneity among the included studies, we conducted sensitivity analysis to explore the potential sources of heterogeneity. When we excluded the trial conducted by Natale RB,<sup>[16]</sup> the RR value of all-grade rash changed from 2.35 to 2.80 (Table 3); however, the heterogeneity still existed ( $I^2=94%$ ). When we deleted the trial of De Boer,<sup>[15]</sup> the value turned to be 2.04, but the heterogeneity did not disappear ( $I^2=97%$ ). Further exclusion of any single study changed the pooled estimates slightly (ranging from 2.04 to 2.80), but the heterogeneity was still present.

Sensitivity analysis for high-grade rash showed that when we excluded 1 trial at a time, the RR value had a moderate change, which ranged from 3.17 to 6.41 (Table 4); however, the heterogeneity was still observed among the remaining studies.

**3.7. Publication bias**

The funnel plot show that there was no significant publication bias for all grades and high grade (grade ≥3) rash among the included studies (for all-grade: Egger test,  $P=.331$ ; Begg test,  $P=.35$ ; for high-grade: Egger test,  $P=.243$ ; Begg test,  $P=.223$ ).

**4. Discussion**

The objective of this meta-analysis is to assess the overall risks of all-grade and high-grade rash in NSCLC patients who were treated with vandetanib. Our study demonstrated that patients treated with vandetanib had a significantly increased risk of all-grade and high-grade rash. Subgroup analysis showed that the association between vandetanib and all-grade rash was observed in all the subgroup, no matter vandetanib was used in first- or

**Table 4****Sensitivity analyses in high-grade (grade ≥3) rash.**

First author	Year	Remove	RR	I <sup>2</sup>	Z
Aisner	2013	✓	5.35	97%	2.29
Ahn	2013	✓	4.22	97%	2.16
Lee	2012	✓	3.96	97%	2.07
Natale	2011	✓	6.41	92%	2.75
De Boer	2011	✓	3.96	96%	2.11
Herbst	2010	✓	3.17	97%	2.27
Natale	2009	✓	6.12	97%	2.03
Heymach	2008	✓	4.60	97%	2.27
Heymach	2007	✓	4.65	96%	2.40
Nine RCTs			4.68	93%	2.54

RCTs = randomized controlled trials

second-line therapy, as monotherapy or combination therapy, with a dosage of 100 or 300 mg, in phase II or III trial, or in the trial with sample size less or more than 200. However, for the high-grade rash, vandetanib did not increase the risk of rash when it was used in first-line therapy or in a phase II trial or in a trial with sample size <200. Therefore, appropriate monitoring should be taken when NSCLC patients were treated with vandetanib.

There has been 1 recently published meta-analysis,<sup>[20]</sup> which assessed the risk of rash in NSCLC patients who were treated with vandetanib. In that study, the authors included 4 RCTs that reported the vandetanib alone or combined with chemotherapy in NSCLC patients. They found that patients treated with vandetanib had a higher risk of all-grade rash than those without vandetanib (RR=1.39, 95% CI: 0.89, 2.17,  $P=.15$ ). However the difference did not reach statistical significance.<sup>[20]</sup> Our meta-analysis expands on the early meta-analysis to provide better evidence for the risk of rash in NSCLC patients treated with vandetanib. First, our study has an enlarged sample size in the data analysis, which gives greater power to assess the rash risk of vandetanib. Second, in this meta-analysis, we conducted subgroup analysis to examine the influence of various factors to the overall estimates, such as therapy line (first vs second), sample size ( $\geq 200$  vs <200), phase of clinical trials (phase II vs phase III), treatment programs (monotherapy vs combination therapy), and vandetanib dose (100 vs 300 mg). However, the authors of the previous study did not perform subgroup analyses. Third, all of the included studies were regarded as high quality (Jadad score >3). The high quality of the included studies and the in-depth analysis of the outcomes improved our statistical power to provide more reliable and credible results.

In this meta-analysis, we found that vandetanib-based therapy significantly increased risks of all-grade and high-grade rash in NSCLC patients. Our results were consistent with findings of the included studies. However, in the trial conducted by Natale et al,<sup>[16]</sup> they reported reverse results. In that trial, 1240 patients with advanced NSCLC were randomly assigned to receive vandetanib ( $n=623$ ), or erlotinib ( $n=617$ ).<sup>[16]</sup> Patients treated with vandetanib experienced a lower incidence of all-grade rash than those treated with erlotinib (28% vs 38%, respectively).<sup>[16]</sup> In addition, the incidence of high-grade rash was also higher in the erlotinib group than that in the vandetanib group (4% vs 3%, respectively).<sup>[16]</sup> As the result of the Natale et al<sup>[16]</sup> was significantly different with that of other studies, we conducted sensitivity analysis by deleting this trial. However, the overall combined RR did not change substantially, which indicated the robustness of our result.

For the high-grade rash, our subgroup analysis suggested that vandetanib did not increase the risk of rash when it was used in first-line therapy or in a phase II trial or in a trial with sample size <200. We thought these results might be the result of a type II error as there was very small number of cases that developed high-grade rash in the vandetanib and control groups. Given the high-grade rash was found in 349 of 2578 patients in vandetanib group and 70 of 2215 patients in control group, the power to detect a significant difference ( $\alpha=0.05$ ) in incidence of high-grade rash was decreased. Thus, future large-scale, well-conducted RCTs are needed to confirm our findings.

The etiology of the rash to vandetanib is unclear, but it is more likely a result of vandetanib inhibition of EGFR, as this has been described for other EGFR inhibitors (EGFRI), such as erlotinib, cetuximab, and panitumumab.<sup>[21]</sup> EGFR is crucial for the normal physiological activities of the epidermis, and in the skin, EGFR is predominately localized to undifferentiated, actively proliferating

basal and suprabasal keratinocytes.<sup>[22,23]</sup> The formation of the characteristics EGFRI rash is believed to be the result of direct EGFR inhibition and induction of an inflammatory response secondary to follicular obstruction.<sup>[24]</sup>

There are several potential limitations in this meta-analysis that should be taken into account. First, there was substantial heterogeneity among the included studies. However, several factors varied greatly between the studies, including characteristics of population (gender, age, and ethnicity), dosage of vandetanib, line of therapy, duration of follow-up, and control treatment. These factors contributed to the heterogeneity and had a potential impact on the pooled estimates. Second, among the 9 RCTs, several studies had a relatively small sample size. Studies with small sample size would be more likely to result in an overestimation of the treatment effect than large trials. Third, despite there was no publication bias among the included studies, we could not exclude the possibility that the trials with negative results or non-English language studies were not included in this meta-analysis, which might bias our results.

In conclusion, the current evidence suggests that vandetanib is associated with significantly increased risk of developing rash in advanced NSCLC patients who are treated with vandetanib. Although the severity of rash is mild to moderate in most cases, patients are treated for extended periods of time, which may negatively affect quality of their life. Thus, these patients should be given appropriate monitoring and treatment of skin adverse events in a reactive fashion. This may improve patients' quality of life and adherence to therapy. Considering the limitations in this study, more large-scale, well-designed RCTs are needed to confirm our findings.

## References

- [1] Khan I, Morris S, Hackshaw A, et al. Cost-effectiveness of first-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy. *BMJ Open* 2015;5:e006733.
- [2] Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest* 2003;123(1 suppl):21S-49S.
- [3] Chong CR, Wirth LJ, Nishino M, et al. Chemotherapy for locally advanced and metastatic pulmonary carcinoid tumors. *Lung Cancer* 2014;86:241-6.
- [4] Bareschino MA, Schettino C, Rossi A, et al. Treatment of advanced non small cell lung cancer. *J Thorac Dis* 2011;3:122-33.
- [5] Wedge SR, Ogilvie DJ, Dukes M, et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res* 2002;62:4645-55.
- [6] Carlomagno F, Vitagliano D, Guida T, et al. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res* 2002;62:7284-90.
- [7] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-2.
- [8] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
- [9] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
- [10] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- [11] Heymach JV, Johnson BE, Prager D, et al. Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non-small-cell lung cancer. *J Clin Oncol* 2007;25:4270-7.
- [12] Heymach JV, Paz-Ares L, De Braud F, et al. Randomized phase II study of vandetanib alone or with paclitaxel and carboplatin as first-line treatment for advanced non-small-cell lung cancer. *J Clin Oncol* 2008;26:5407-15.
- [13] Natale RB, Bodkin D, Govindan R, et al. Vandetanib versus gefitinib in patients with advanced non-small-cell lung cancer: results from a two-part, double-blind, randomized phase ii study. *J Clin Oncol* 2009;27:2523-9.

- [14] Herbst RS, Sun Y, Eberhardt WE, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. *Lancet Oncol* 2010;11:619–26.
- [15] de Boer RH, Arrieta O, Yang CH, et al. Vandetanib plus pemetrexed for the second-line treatment of advanced non-small-cell lung cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2011;29:1067–74.
- [16] Natale RB, Thongprasert S, Greco FA, et al. Phase III trial of vandetanib compared with erlotinib in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol* 2011;29:1059–66.
- [17] Lee JS, Hirsh V, Park K, et al. Vandetanib versus placebo in patients with advanced non-small-cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: a randomized, double-blind phase III trial (ZEPHYR). *J Clin Oncol* 2012;30:1114–21.
- [18] Ahn JS, Lee KH, Sun JM, et al. A randomized, phase II study of vandetanib maintenance for advanced or metastatic non-small-cell lung cancer following first-line platinum-doublet chemotherapy. *Lung Cancer* 2013;82:455–60.
- [19] Aisner J, Manola JB, Dakhil SR, et al. Vandetanib plus chemotherapy for induction followed by vandetanib or placebo as maintenance for patients with advanced non-small-cell lung cancer: a randomized phase 2 PrECOG study (PrE0501). *J Thorac Oncol* 2013;8:1075–83.
- [20] Mengjun Li CT, Jieyu He. Meta-analysis of vandetanib in the treatment of advanced non-small-cell lung cancer. *Cancer Pharm* 2012;2:385–91.
- [21] Morabito A, Piccirillo MC, Costanzo R, et al. Vandetanib: an overview of its clinical development in NSCLC and other tumors. *Drugs Today (Barc)* 2010;46:683–98.
- [22] Fuchs E, Raghavan S. Getting under the skin of epidermal morphogenesis. *Nat Rev Genet* 2002;3:199–209.
- [23] Nanney LB, Stoscheck CM, King LEJr, et al. Immunolocalization of epidermal growth factor receptors in normal developing human skin. *J Invest Dermatol* 1990;94:742–8.
- [24] Pérez-Soler R, Delord JP, Halpern A, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. *Oncologist* 2005;10:345–56.