ORIGINAL RESEARCH

A systematic review and meta-analysis of the risk of diarrhea associated with vandetanib treatment in carcinoma patients

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Background and purpose: Vandetanib is a promising anticancer targeted agent for treating advanced carcinomas, such as non-small-cell lung cancer, small-cell lung cancer, breast cancer, malignant glioma, hepatocellular cancer, and unresectable, locally advanced, or metastatic medullary thyroid cancer. However, diarrhea is a frequently reported adverse event. The incidence of vandetanib-associated diarrhea varies extensively in different study populations and has not been carefully estimated. This systematic review and meta-analysis of clinical trials aims to figure out the overall risks of all-grade and high-grade diarrhea during vandetanib treatment and get a better understanding of its prediction and management.

Materials and methods: A comprehensive search was performed in EMBASE, PubMed, and Cochrane Library for clinical trials studying vandetanib and diarrhea prior to April 2015. Eligible articles were selected according to the inclusion criteria. Data were extracted to calculate the summary incidence of all-grade and high-grade diarrhea caused by vandetanib treatment.

Results: Thirteen clinical trials that involved 3,264 patients were included in this meta-analysis. The overall incidences of all-grade and high-grade diarrhea caused by vandetanib treatment were 52.1% (95% confidence interval [CI], 48.3%–55.8%) and 5.6% (95% CI, 4.4%–76.7%), respectively. The risk ratios of the all-grade and high-grade diarrhea for vandetanib arm versus control arm were 1.932 (95% CI, 1.746–2.138; $P < 0.001$) and 3.190 (95% CI, 2.061–4.938; $P < 0.001$), respectively. Studies with small-cell lung cancer demonstrated the highest incidence of all-grade diarrhea (78.85%) and high-grade diarrhea (17.31%), whereas the lowest incidences of all-grade (42.11%) and high-grade (2.67%) diarrhea are seen in patients with hepatocellular carcinoma and non-small-cell lung cancer, respectively.

Conclusion: Our findings demonstrate that the administration of vandetanib leads to a significantly increased risk of diarrhea, which varies in different carcinoma patients. Early recognition and timely management may be key factors to avoid dose reduction, drug interruption, and drug discontinuation, which is significant to maximize the treatment benefits.

Keywords: vandetanib treatment, diarrhea, carcinoma

Introduction

Malignant tumor is the leading cause of death worldwide. Most cancer patients who are diagnosed at advanced stage are not candidates for surgical curative resection and are only amenable to palliative treatment. Traditional chemotherapy is a main treatment. However, the tumor response to traditional chemotherapy is not usually satisfactory. Nowadays, a large number of clinical studies have demonstrated that a newly developing therapy, molecular-targeted therapy, exerts a positive influence on advanced tumors, which shows considerable promise.

Vandetanib (ZD6474, Caprelsa; AstraZeneca plc, London, UK) is a once-daily oral anticancer agent that selectively targets the vascular endothelial growth factor receptor (VEGFR)-2 and -3, epidermal growth factor receptor (EGFR), and rearranged during transfection.[1,2] The activity of competing the ATP binding sites of these receptors makes vandetanib a good agent inhibiting tumor cell proliferation, tumor progression, and angiogenesis.[3]

The mechanism and effect of vanditanib have been searched out by many prior studies. To our knowledge, VEGFR and EGFR are well-known pivotal drivers in tumor carcinogenesis, which actively contribute to the pathogenesis and progression of many different kinds of cancers. Furthermore, the VEGFR and EGFR pathways are shown to be relevant. Since EGFR regulates the production of VEGF, resistance of EGFR inhibitors, such as erlotinib and gefitinib, is thought to be associated with the increase of VEGF, which means targeting both VEGFR and EGFR simultaneously may be more effective than using the inhibitors of either pathway.[4] EGFR and VEGFR are clinical validated targets in non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), thyroid cancer, breast cancer, malignant glioma, and hepatocellular cancer, which are common worldwide malignant tumors threatening people's health. As an inhibitor of both VEGFR and EGFR, vandetanib has been shown to have clinically meaningful benefits in these cancers in previous clinical trials.

Besides, vandetanib has been reported to have the inhibiting effect on rearranged during transfection. And the gain-of-function mutation in the rearranged during transfection protooncogenes is the key driver in the development of hereditary medullary thyroid cancer (MTC).[5,6] Therefore, it is well demonstrated that vandetanib shows a particularly powerful efficacy in the treatment of MTC[7] and is currently approved for use in clinical practice. In April 2011, the US Food and Drug Administration approved it for the treatment of unresectable, locally advanced, or metastatic MTC.[8] According to several Phase I trials, the daily tolerable dose of vandetanib is 300 mg or less, with the regimen of giving once daily.

However, several adverse events are commonly reported during the application of vandetanib, including diarrhea, rash,[9] nausea, hypertension,[10] headache, and corrected QT interval prolongation.[8] Among these adverse events, diarrhea and other gastrointestinal diseases are most frequently detected, which is consistent to the activity of inhibiting EGFR by vandetanib. Similar to other tyrosine kinase inhibitor of the VEGFR and EGFR, patients receiving vandetanib treatment experience higher incidence of diarrhea than patients receiving placebo only. In several clinical trials, the diarrhea is so severe that it leads to dose reduction, interruption, or drug discontinuation, and causes a lower quality of life. So far, the total incidence of diarrhea in patients receiving vandetanib treatment is still unclear. According to the previous clinical trials, the incidences of all-grade and high-grade diarrhea vary enormously from 42.11% to 78.85% and from 2.67% to 17.31%, respectively, which is probably due to the various sample sizes, tumor types, or patient sources.

The aim of this paper is to figure out the overall risks of all-grade and high-grade diarrhea during vandetanib treatment and get a better understanding of its prediction and management.

Materials and methods
Literature sources
A literature search was performed in the databases, including EMBASE, PubMed, and Cochrane Library, using the searching terms "vandetanib" and "diarrhea". The related articles function was used to extend the search. The last search date was April 25, 2015. Two authors independently screened the titles and abstracts to determine potential eligibility for this meta-analysis. When discrepancies occurred, consensus was achieved after further discussion.

Inclusion and exclusion criteria and data extraction
All available randomized controlled trials and observational comparative studies that compared vandetanib with placebo or other tyrosine kinase inhibitor were included. The language was restricted to English. Editorials comments, letters to editor, review studies, case reports, conference abstracts, and experimental animal studies were excluded. Since traditional chemotherapy may increase the risk of diarrhea, studies that combined vandetanib with other traditional chemotherapy in the treatment arm were excluded. Besides, because of the different dose levels, Phase I trials were also excluded. To conclude, the inclusion criteria include 1) application of vandetanib 300 mg/d as a single agent in the treatment arm; 2) prospective Phase II and III clinical trials conducted in patients with cancers; and 3) full texts and data of diarrhea available. Two authors independently extracted the following data from the selected articles: first authors, year of publication, trial design, number of patients in the vandetanib arm, number of patients in the control arm, underlying cancer, and number of patients suffering all-grade or high-grade

diarrhea. We contacted the authors of the original articles for further clarification if relevant information was unclear. In order to accurately select articles that met the inclusion criteria, two authors independently did the searching work and evaluated each article.

Outcome measure

The primary outcome of this meta-analysis was the total incidence of all-grade and high-grade diarrhea in patients receiving vandetanib treatment. Subgroup analysis was conducted by distinguishing among the patients of different tumor types. The secondary outcome of this meta-analysis was the comparison of the incidence of all-grade and high-grade diarrhea between patients in the vandetanib group and the control group.

Diarrheas were classified according to the National Cancer Institute (Bethesda MD, USA) Common Toxicity Criteria Version 2 or Common Terminology Criteria for Adverse Events Version 3 (Table 1).[11]

Statistical analysis

This meta-analysis was performed using Version 12 of the Stata program (StataCorp LP. College Station, TX, USA). The proportions of patients with all-grade and high-grade diarrheas for each clinical trial were calculated, and the 95% confidence interval (CI) was derived. For studies that performed a comparison between the vandetanib group and control group, the relative risks of all-grade and high-grade diarrheas among patients in the vandetanib group were also calculated. Two-side hypothesis was used with $\alpha = 0.5$. Statistically significant difference was set at a P-value ≤ 0.05. The heterogeneity of each study was evaluated by a visual inspection of forest plots and an inconsistency (I^2) statistic. I^2 values $>50\%$ or P-value <0.05 indicated heterogeneity. When the heterogeneity exists, random-effects model was applied. Otherwise, the fixed-effects model was considered.

Table 1 US National Cancer Institute grading for diarrhea

Grade 1	Increase of fewer than four stools per day over baseline
Grade 2	Increase of four to six stools per day over baseline, intravenous fluids <24 hours
Grade 3	Increase of seven or more stools per day over baseline Incontinence Intravenous fluids ≥24 hours Hospitalization indicated Limits self-care activities of daily living
Grade 4	Life-threatening consequences Urgent intervention indicated
Grade 5	Death

Results

Overview of searching results

A total of 59 reports on clinical use of vandetanib were yielded by the comprehensive search, of which 35 articles were selected based on their titles, abstracts, and article types. After the full publication review of 29 potentially eligible articles, the 13 studies that fulfilled the inclusion criteria were finally selected and analyzed (Figure 1).[12–24]

Characteristics of included studies

The characteristics of the studies included in the meta-analysis are presented in Table 2. A total of 3,264 patients (1,964 in the vandetanib arm and 1,300 in the control arm) from 13 studies were included. Among the 13 studies, three were randomized-controlled Phase III studies,[13,16,18] seven were randomized-controlled Phase II studies,[12,15,17,18,20–22] one was nonrandomized-controlled Phase II study,[24] and the remaining two were single arm Phase II studies.[14,19]

Comparisons between patients receiving vandetanib and placebo were performed in six clinical trials,[12,13,15–17,23] while five trials were just included for the analysis of the use of vandetanib.[14,19,21,22,24] The remaining two trials compared the use of vandetanib, erlotinib,[18] and gefitinib,[20] respectively.

Two studies included patients having 100 or 300 mg/d in the vandetanib arm.[17,24] But, as is mentioned in the inclusion criteria, only data about the dose of 300 mg/d were extracted in this meta-analysis. One study included patients having vandetanib only, vandetanib combined with PC (P, paclitaxel 200 mg/m²; C, carboplatin 6 mg/mL*min), and placebo with PC.[22] Since PC belongs to traditional chemotherapy agents, only data of the vandetanib arm were applied in the analysis.

In these 13 included trials, the associated underlying malignant neoplasms were NSCLC (six trials[12,16,18,20–22]), thyroid carcinoma (three trials[13,15,19]), malignant glioma (one trial[14]), hepatocellular carcinoma (one trial[17]), SCLC (one trial[23]), and metastatic breast cancer (one trial[24]).

Primary outcomes

The total incidences of all-grade and high-grade diarrhea

For the incidence analysis, we considered only arms receiving vandetanib 300 mg as a single agent. All-grade diarrhea was reported in all the 13 studies, with 1,964 patients treated by 300 mg vandetanib, and its incidence ranged from 42.11% in a randomized-controlled Phase II study of patients of hepatocellular carcinoma[17] to 78.85% in another randomized-controlled Phase II study of patients of SCLC.[23] Since the meta-analysis revealed no evidence of heterogeneity of the
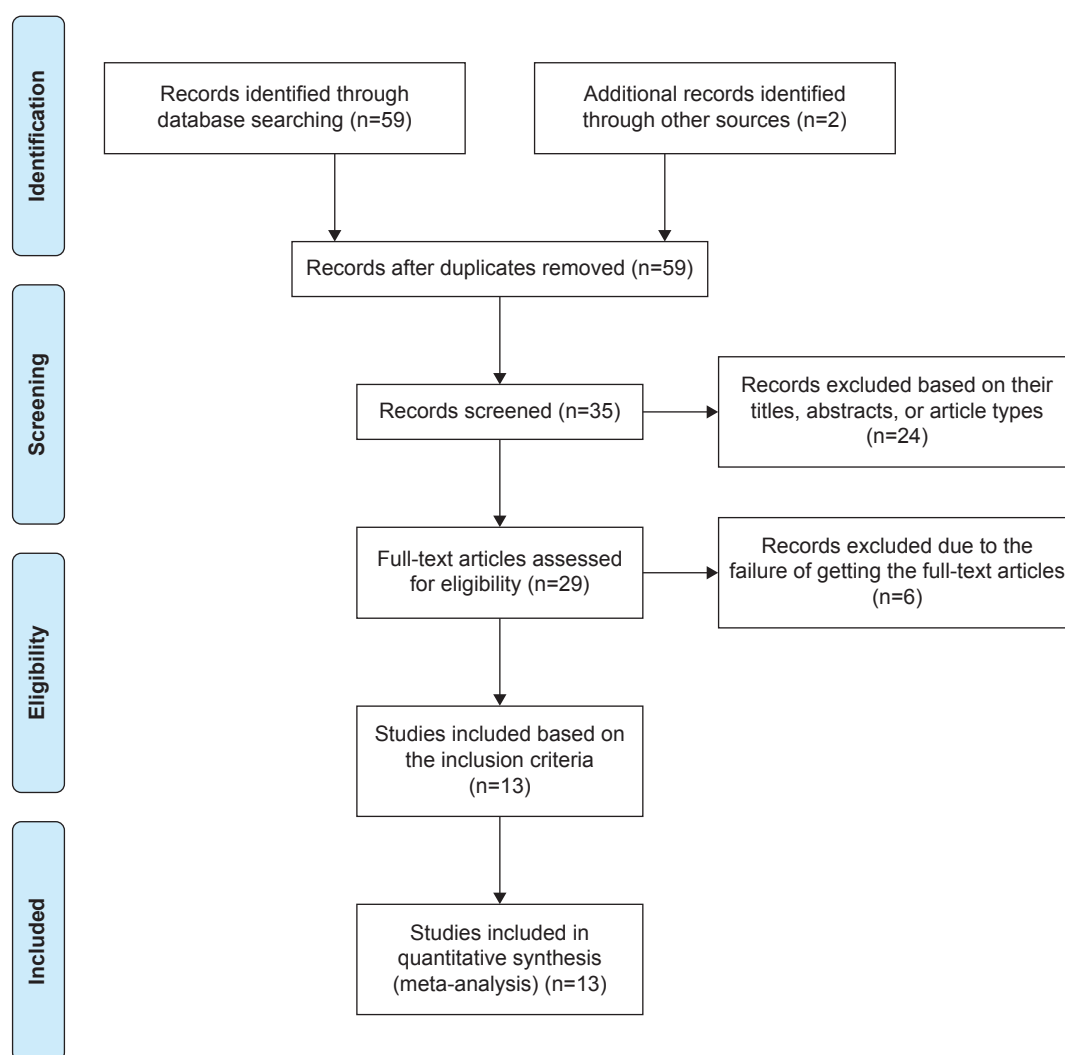
Figure 1 Identification of included studies in this systematic review and meta-analysis.

included studies (heterogeneity test, I^2=18.7%, P=0.255), the fixed-effects model was applied. The calculated summary incidence of all-grade diarrhea was calculated to be 52.1% (95% CI, 48.3%–55.8%) (Figure 2).

High-grade diarrhea was associated with serious morbidity and prone to dose reduction, drug interruption, and drug discontinuation. Among the 13 studies, only eleven had available data for high-grade diarrhea, which include 1,881 patients treated by 300 mg vandetanib. The incidence of high-grade diarrhea varied remarkably from 2.67% to 17.31%, with the lowest incidence observed in a randomized-controlled Phase II study of patients of NSCLC,[12] and the highest incidence noted in a randomized-controlled Phase II study of patients of SCLC.[23] Using the fixed-effects model (heterogeneity test, I^2=35.8%, P=0.113), the meta-analysis revealed that the overall incidence of high-grade diarrhea was 5.6% (95% CI, 4.4%–6.7%) (Figure 3).
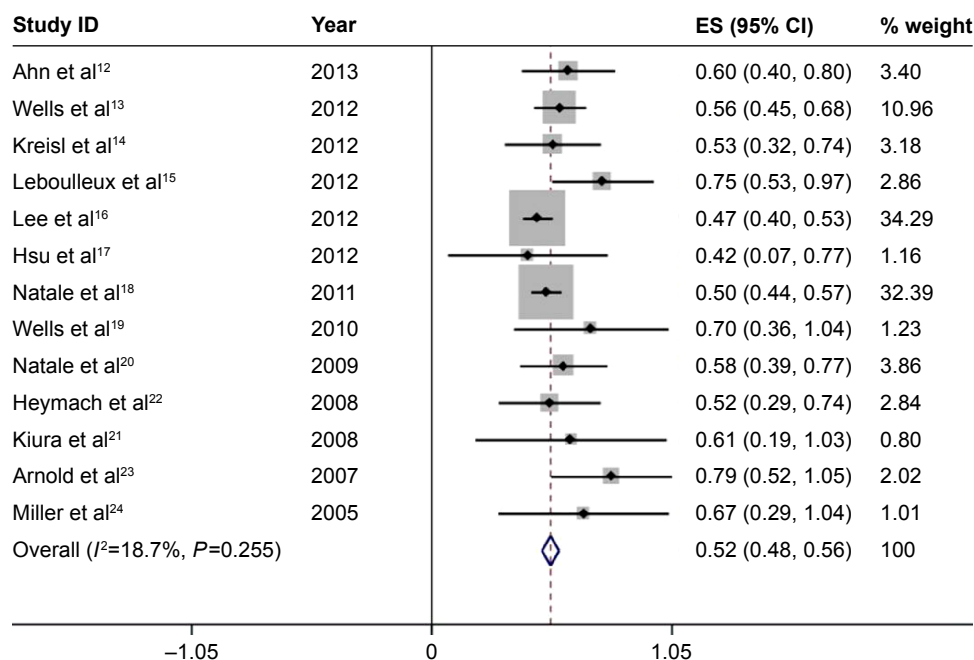
Incidences of all-grade and high-grade diarrhea of different tumor types

We further calculated the incidences of all-grade and high-grade diarrhea based on different tumor types to explore the relationship between diarrhea and tumor types. For a total of 1,472 patients receiving vandetanib with NSCLC, the pooled incidence of all-grade and high-grade diarrhea was 49.6% (95% CI, 45.3%–53.8%) (Figure S1) and 4.9% (95% CI, 3.7%–6.2%) (Figure S2), respectively. For studies associated with thyroid carcinoma, 333 patients in total were involved to receive vandetanib treatment, yielding a total incidence of all-grade diarrhea of 61.0% (95% CI, 51.2%–70.7%) (Figure S3), and an incidence of high-grade diarrhea of 10.5% (95% CI, 6.6%–14.4%) (Figure S4). Only one trial was conducted in other types of tumor, respectively. And the two trials associated with malignant glioma and hepatocellular carcinoma only had

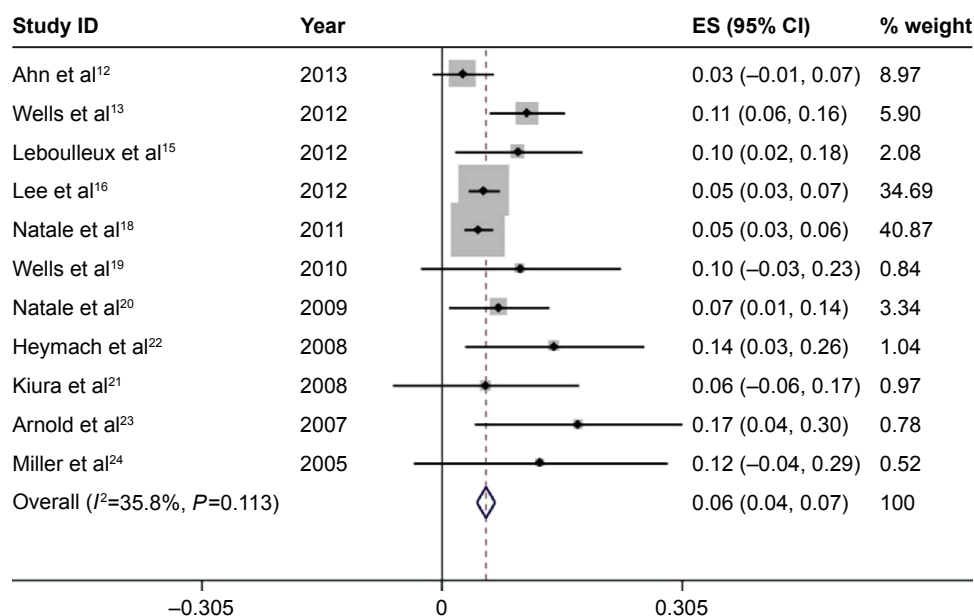**Table 2** Characteristics of studies included in the meta-analysis

First author	Year	Trial design	Vandetanib arm	Control arm	Population of vandetanib arm	Population of control arm	Underlying cancer
Ahn et al[12]	2013	Randomized Phase II study	Vandetanib 300 mg	Placebo	75	42	Advanced or metastatic NSCLC
Wells et al[13]	2012	Randomized Phase III study	Vandetanib 300 mg	Placebo	231	100	Medullary thyroid cancer
Kreisl et al[14]	2012	Single arm Phase II study	Vandetanib 300 mg		64		Recurrent malignant glioma
Leboulleux et al[15]	2012	Randomized Phase II study	Vandetanib 300 mg	Placebo	72	73	Differentiated thyroid cancer
Lee et al[16]	2012	Randomized Phase III study	Vandetanib 300 mg	Placebo	617	307	Advanced NSCLC
Hsu et al[17]	2012	Randomized Phase II study	Vandetanib 300 mg	Placebo	19	23	Inoperable HCC
Natale et al[18]	2011	Randomized Phase III study	Vandetanib 300 mg	Erlotinib 150 mg	623	617	Advanced NSCLC
Wells et al[19]	2010	Single arm Phase II study	Vandetanib 300 mg		30		Medullary thyroid cancer
Natale et al[20]	2009	Randomized Phase II study	Vandetanib 300 mg	Gefitinib 250 mg	83	85	Advanced NSCLC
Heymach et al[22]	2008	Randomized Phase II study	Vandetanib 300 mg		56		NSCLC
Kiura et al[21]	2008	Randomized Phase II study	Vandetanib 300 mg		18		NSCLC
Arnold et al[23]	2007	Randomized, Phase II study	Vandetanib 300 mg	Placebo	52	53	SCLC
Miller et al[24]	2005	Nonrandomized Phase II study	Vandetanib 300 mg		24		Metastatic breast cancer

Abbreviations: HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung carcinoma; SCLC, small-cell lung carcinoma.

Figure 2 Forest plot of the total incidence of all-grade diarrhea of patients with carcinomas receiving vandetanib.
Notes: The size of the gray square corresponded to the weight of the study in the meta-analysis. The horizontal line represented the 95% confidence interval (CI), and the vertical dotted line showed the total incidence of all-grade diarrhea. Since heterogeneity test indicated no heterogeneity, the total incidence of all-grade diarrhea was calculated using the fixed-effects model.
Abbreviation: ES, effect size.

Study ID	Year		ES (95% CI)	% weight
Ahn et al[12]	2013		0.03 (−0.01, 0.07)	8.97
Wells et al[13]	2012		0.11 (0.06, 0.16)	5.90
Leboulleux et al[15]	2012		0.10 (0.02, 0.18)	2.08
Lee et al[16]	2012		0.05 (0.03, 0.07)	34.69
Natale et al[18]	2011		0.05 (0.03, 0.06)	40.87
Wells et al[19]	2010		0.10 (−0.03, 0.23)	0.84
Natale et al[20]	2009		0.07 (0.01, 0.14)	3.34
Heymach et al[22]	2008		0.14 (0.03, 0.26)	1.04
Kiura et al[21]	2008		0.06 (−0.06, 0.17)	0.97
Arnold et al[23]	2007		0.17 (0.04, 0.30)	0.78
Miller et al[24]	2005		0.12 (−0.04, 0.29)	0.52
Overall (I^2=35.8%, P=0.113)			0.06 (0.04, 0.07)	100

−0.305   0   0.305

Figure 3 Forest plot of the total incidence of high-grade diarrhea of patients with carcinomas receiving vandetanib.
Notes: The size of the gray square corresponded to the weight of the study in the meta-analysis. The horizontal line represented the 95% confidence interval (CI) and the vertical dotted line showed the total incidence of high-grade diarrhea. Since heterogeneity test indicated no heterogeneity, the total incidence of high-grade diarrhea was calculated using the fixed-effects model.
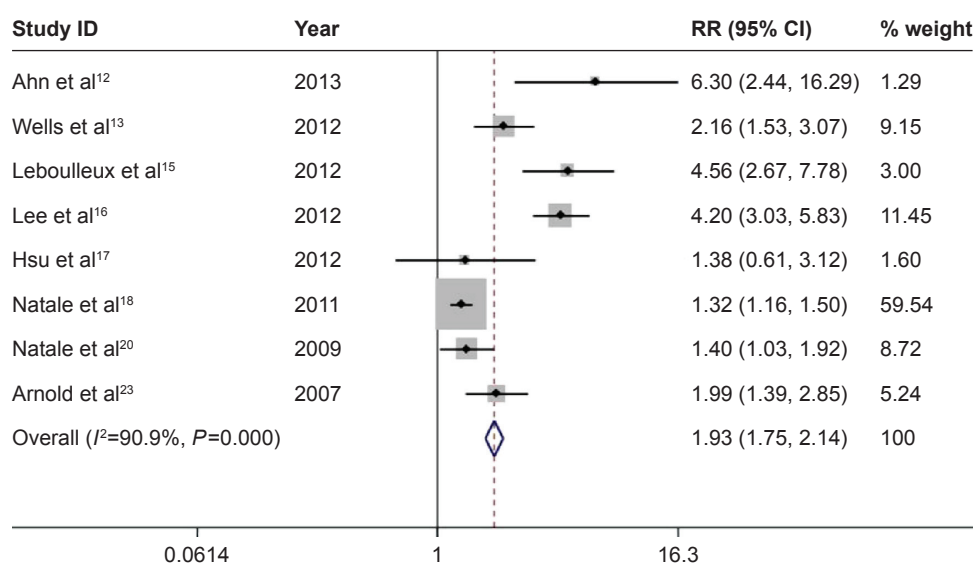**Abbreviation:** ES, effect size.

available data for all-grade diarrhea. According to the provided data, the overall incidences of all-grade diarrhea of malignant glioma, hepatocellular carcinoma, SCLC, and metastatic breast cancer were 53% (95% CI, 32%–74%), 42% (95% CI, 7%–77%), 79% (95% CI, 52%–105%), and 67% (95% CI, 29%–104%), respectively, while high-grade diarrhea was seen in 17% (95% CI, 4%–30%) and 12% (95% CI, −4%–29%) in trials associated with SCLC and metastatic breast cancer, respectively.

Secondary outcomes
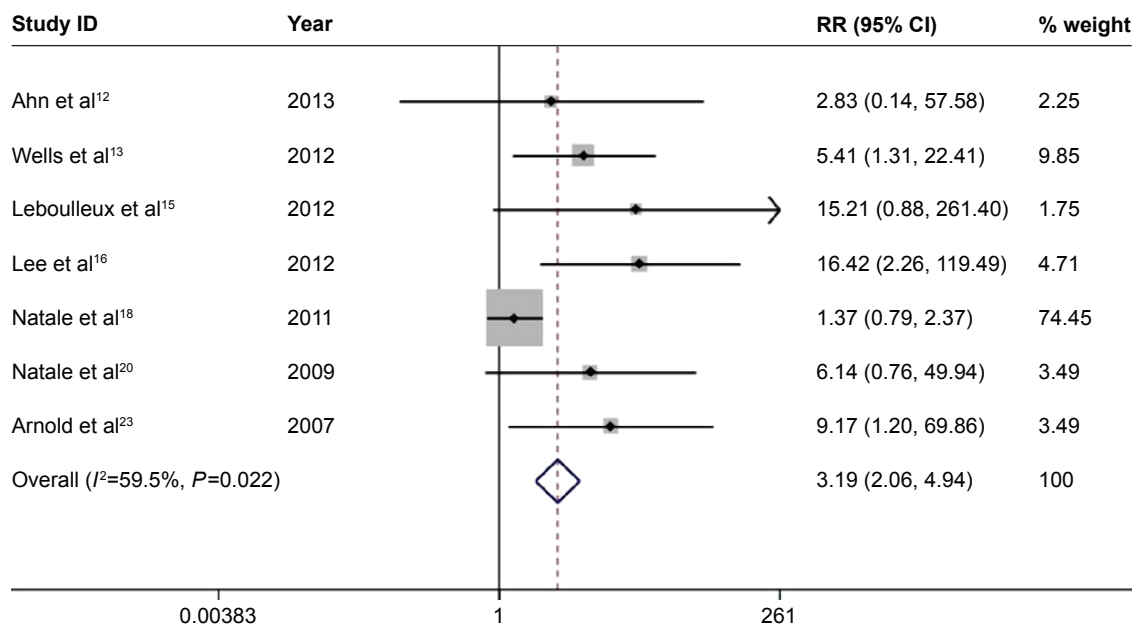### Risk ratios of all-grade and high-grade diarrhea
There are eight comparative clinical trials in total, which include six trials using placebo as controls, one using erlotinib, and one using gefitinib. Subjects in the vandetanib arm were at a significantly higher risk for all-grade diarrhea than subjects in the control arm (relative risk =1.932; 95% CI, 1.746–2.138; $P<0.001$) (Figure 4), with the use of the random-effects model (heterogeneity test, I^2=90.9%,

Study ID	Year		RR (95% CI)	% weight
Ahn et al[12]	2013		6.30 (2.44, 16.29)	1.29
Wells et al[13]	2012		2.16 (1.53, 3.07)	9.15
Leboulleux et al[15]	2012		4.56 (2.67, 7.78)	3.00
Lee et al[16]	2012		4.20 (3.03, 5.83)	11.45
Hsu et al[17]	2012		1.38 (0.61, 3.12)	1.60
Natale et al[18]	2011		1.32 (1.16, 1.50)	59.54
Natale et al[20]	2009		1.40 (1.03, 1.92)	8.72
Arnold et al[23]	2007		1.99 (1.39, 2.85)	5.24
Overall (I^2=90.9%, P=0.000)			1.93 (1.75, 2.14)	100

0.0614   1   16.3

Figure 4 Forest plot of the relative risk (RR) of all-grade diarrhea events.
Notes: The size of the gray square corresponded to the weight of the study in the meta-analysis. The horizontal line represented the 95% confidence interval (CI) and the vertical dotted line showed the total RR of all-grade diarrhea.

Study ID	Year		RR (95% CI)	% weight
Ahn et al[12]	2013		2.83 (0.14, 57.58)	2.25
Wells et al[13]	2012		5.41 (1.31, 22.41)	9.85
Leboulleux et al[15]	2012		15.21 (0.88, 261.40)	1.75
Lee et al[16]	2012		16.42 (2.26, 119.49)	4.71
Natale et al[18]	2011		1.37 (0.79, 2.37)	74.45
Natale et al[20]	2009		6.14 (0.76, 49.94)	3.49
Arnold et al[23]	2007		9.17 (1.20, 69.86)	3.49
Overall (I^2=59.5%, P=0.022)			3.19 (2.06, 4.94)	100

0.00383   1   261

Figure 5 Forest plot of the relative risk (RR) of high-grade diarrhea events.
Notes: The size of the gray square corresponded to the weight of the study in the meta-analysis. The horizontal line represented the 95% confidence interval (CI) and the vertical dotted line showed the total RR of high-grade diarrhea.

$P<0.001$). Seven out of these eight clinical trials provide data of high-grade diarrhea. Subjects in the vandetanib group were at a notably greater risk for high-grade diarrhea than subjects in the control arm (relative risk =3.190; 95% CI, 2.061–4.938, $P<0.001$) (Figure 5), with the application of the random-effects model (heterogeneity test, I^2=59.5%, P=0.022).

Discussion

Vandetanib is a promising anticancer targeted agent in NSCLC, SCLC, thyroid cancer, breast cancer, malignant glioma, and hepatocellular carcinoma. And it is the first oral medicine with demonstrated antineoplastic role in MTC, which has been approved by the US Food and Drug Administration for the treatment of unresectable, locally advanced, or metastatic MTC. To our knowledge, diarrhea is one of the most common adverse events when patients receive vandetanib treatment. However, the understanding of diarrhea caused by vandetanib is still limited. Our meta-analysis summarized all the clinical trials regarding vandetanib-associated diarrhea in carcinoma patients. Based on the available data, our results revealed that vandetanib caused a significantly increased risk of diarrhea. The overall incidences of all-grade and high-grade diarrhea are 52.1% and 5.6%, respectively.

In fact, many studies demonstrated that diarrhea was the most common reported adverse event of treatment with targeted agents in carcinoma patients.[25] Though the mechanism remained poorly understood, diarrhea caused by vandetanib treatment is most likely attributed to its anti-EGFR activity. EGFR is frequently expressed on normal epithelium-originated cells, such as skin, gastrointestinal mucosa, and liver. It plays a crucial role in cells proliferation and growth. This may explain why diarrhea, rash, and oral mucositis are frequently observed in patients treated with EGFR inhibitors. As is mentioned in the study of Uribe et al,[26] EGF inhibits the Ca_2^+-dependent Cl^- secretion in T84 human colonic epithelial cells. In other words, anti-EGFR agents counteract this effect and thus lead to excessive secretion of Cl^- in the gastrointestinal tract, which secondarily causes diarrhea. This is believed to be the most probable etiology of diarrhea caused by vandetanib treatment. Besides, some studies indicated that multiple factors might contribute to the EGFR inhibitor-associated diarrhea, such as quickened intestinal peristalsis, alteration of intestinal micro flora,[27] and colonic crypt impairment, which resulted in decreased absorption of water.

Considering that different tumor types may result in different incidences of diarrhea, we analyzed the incidences based on different tumor types. As is shown in the results, patients with SCLC treated with vandetanib demonstrated the highest incidence of all-grade diarrhea (78.85%) and high-grade diarrhea (17.31%), whereas the lowest incidences of all-grade (42.11%) and high-grade diarrhea (2.67%) were seen in patients with hepatocellular carcinoma and NSCLC, respectively. Compared with other meta-analyses, the incidence of diarrhea caused by vandetanib is similar to that of other anti-EGFR agents.

Because of the potential for long-term application of vandetanib in patients with cancers, it is important for doctors and patients to have a good understanding of the severity of diarrhea. Diarrhea is impactful on a patient's quality of life, and may lead to water and electrolyte imbalance, renal insufficiency, corrected QT interval prolongation, or other severe consequences. It should be carefully evaluated and early intervention should be taken. Essentially, meticulous pretreatment education is of great importance. Patients should be informed what diarrhea is, the incidence and the severity of the high-grade diarrhea, when to contact the health care team, and how to manage diarrhea if it is not so severe. Once diarrhea occurs, it can be treated at home first. Patients should be instructed to drink enough water to avoid dehydration. At the same time, antidiarrhea agents should be applied at the onset of diarrhea. Loperamide still has a prominent role in the treatment of EGFR inhibitor-associated diarrhea. It is recommended to begin at a dose of 4 mg at the onset, and then 2 mg every four hours until the diarrhea ceases.[28] Moreover, loperamide is not recommended to use over 20 mg every day in adults. Besides, diphenoxylate/atropine and codeine can also be considered to control the diarrhea. If diarrhea gets worse after 48 hours, hospitalization is needed. Doctors should perform a careful physical examination and assess the dehydration severity.[29] Close attention should be paid to electrolyte and electrocardiogram results. Through the above managements, early identification and timely management can be reached to help prevent aggravation, dose reduction, and vandetanib interruption, which is helpful to achieve the maximum benefits from the treatment.[30]

However, if grade 2 diarrhea continues for >2 days, or grade 3/4 diarrhea occurs, vandetanib treatment must be interrupted or the dose must be reduced. Meanwhile, the antidiarrhea agents should still be put into use. If severe diarrhea persists >2 weeks, vandetanib treatment should be permanently discontinued until diarrhea ceases and resumed at a lower dose. If still the diarrhea continues after the cessation of vandetanib, fecal and bloody laboratory examinations for pathogens are strongly suggested.

As in previous studies, rash resulting from EGFR tyrosine kinase inhibitor was a probable predictor of benefit and the severity of rash correlated with clinical benefit. The development of diarrhea caused by vandetanib may also be linked to better clinical responses. It has been suggested that diarrhea may serve as a positive prognostic indicator in several previous studies. Early in the study of Cohen et al,[31] diarrhea was found to have a clear relationship with more favorable overall survival in patients with recurrent and metastatic squamous cell carcinoma of the head and neck who underwent erlotinib, lapatinib, or gefitinib treatment. Later in the studies of Zheng et al,[32] Zhang et al,[33] and Bettinger et al,[34] it has been proved that diarrhea caused by sorafenib was a positive independent predictor of better progression-free survival and overall survival in patients with metastatic renal cell carcinoma or advanced hepatocellular carcinoma. Until now, no study has shown the association between diarrhea caused by vandetanib and clinical responses. Therefore, a further prospective experiment is needed. If the diarrhea caused by vandetanib really predicts a positive result, clinical doctors could have a better command of the outcome of disease.

Limitations

There are several limitations in our study. First, the included studies are heterogeneous in tumor types, which may influence the pooled estimates of the total incidence of diarrhea. Second, there are potential biases from preferential publication and selective reporting. Third, no data in our study imply the relationship of diarrhea severity and clinical responses. Finally, no risk factors could be found in the included studies, so we cannot predict which kind of patients should be closely taken care of.

Conclusion

Our study provides evidences that vandetanib treatment leads to a significantly increased incidence of diarrhea. However, whether the increased severity is associated with a preferable clinical response is still unclear. Further exploration is needed to examine the underlying association. Early recognition and management of diarrhea should be emphasized since it might be a vital factor for the success of the anticarcinoma treatment.

Disclosure

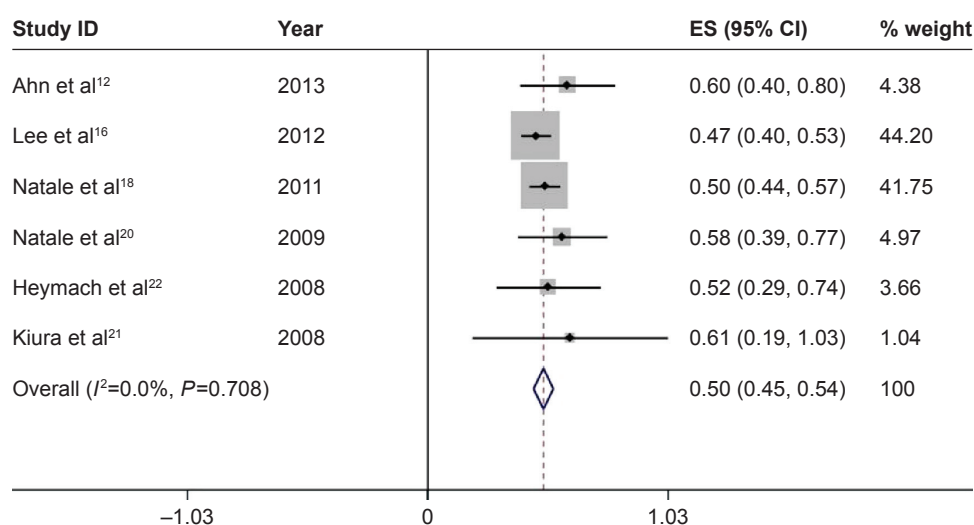The authors report no conflicts of interest in this work.

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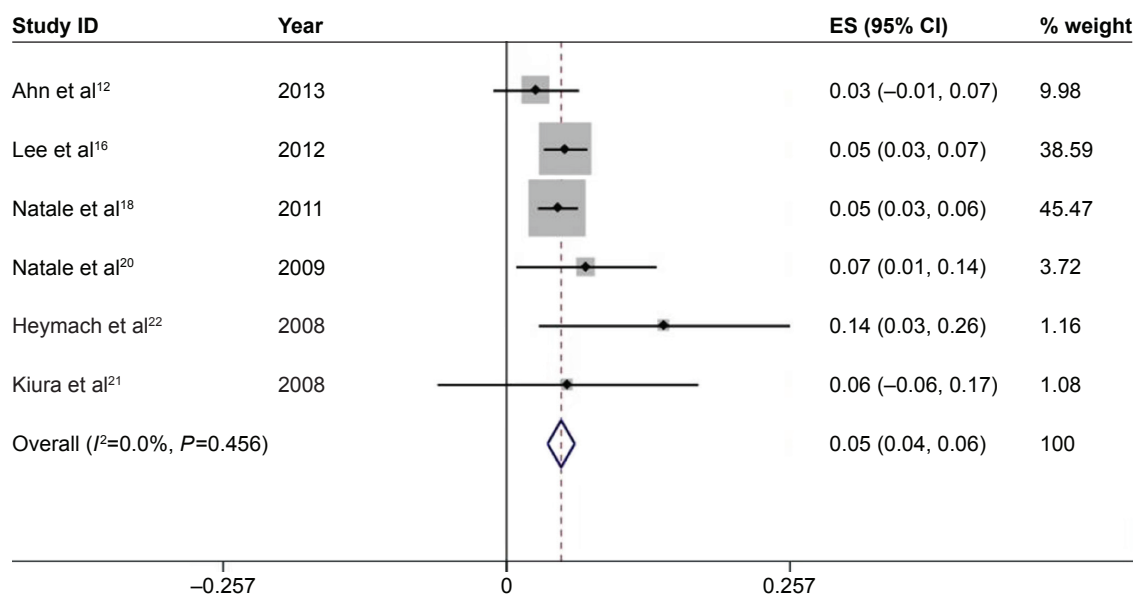
Supplementary materials

Study ID	Year		ES (95% CI)	% weight
Ahn et al[12]	2013		0.60 (0.40, 0.80)	4.38
Lee et al[16]	2012		0.47 (0.40, 0.53)	44.20
Natale et al[18]	2011		0.50 (0.44, 0.57)	41.75
Natale et al[20]	2009		0.58 (0.39, 0.77)	4.97
Heymach et al[22]	2008		0.52 (0.29, 0.74)	3.66
Kiura et al[21]	2008		0.61 (0.19, 1.03)	1.04
Overall (I^2=0.0%, P=0.708)			0.50 (0.45, 0.54)	100

−1.03   0   1.03

Figure S1 Forest plot of the total incidence of all-grade diarrhea of patients with non-small-cell lung cancer receiving vandetanib.
Notes: The size of the gray square corresponded to the weight of the study in the meta-analysis. The horizontal line represented the 95% confidence interval (CI) and the vertical dotted line showed the total incidence of all-grade diarrhea. Since heterogeneity test indicated no heterogeneity, the total incidence of all-grade diarrhea was calculated using the fixed-effects model.
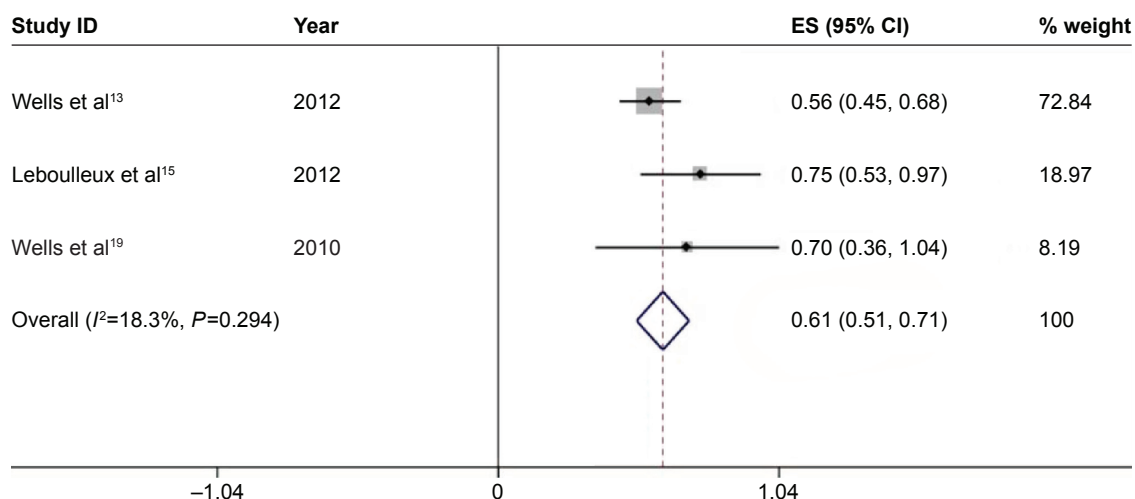**Abbreviation:** ES, effect size.

Study ID	Year		ES (95% CI)	% weight
Ahn et al[12]	2013		0.03 (−0.01, 0.07)	9.98
Lee et al[16]	2012		0.05 (0.03, 0.07)	38.59
Natale et al[18]	2011		0.05 (0.03, 0.06)	45.47
Natale et al[20]	2009		0.07 (0.01, 0.14)	3.72
Heymach et al[22]	2008		0.14 (0.03, 0.26)	1.16
Kiura et al[21]	2008		0.06 (−0.06, 0.17)	1.08
Overall (I^2=0.0%, P=0.456)			0.05 (0.04, 0.06)	100

−0.257   0   0.257

Figure S2 Forest plot of the total incidence of high-grade diarrhea of patients with non-small-cell lung cancer receiving vandetanib.
Notes: The size of the gray square corresponded to the weight of the study in the meta-analysis. The horizontal line represented the 95% confidence interval (CI) and the vertical dotted line showed the total incidence of high-grade diarrhea. Since heterogeneity test indicated no heterogeneity, the total incidence of high-grade diarrhea was calculated using the fixed-effects model.
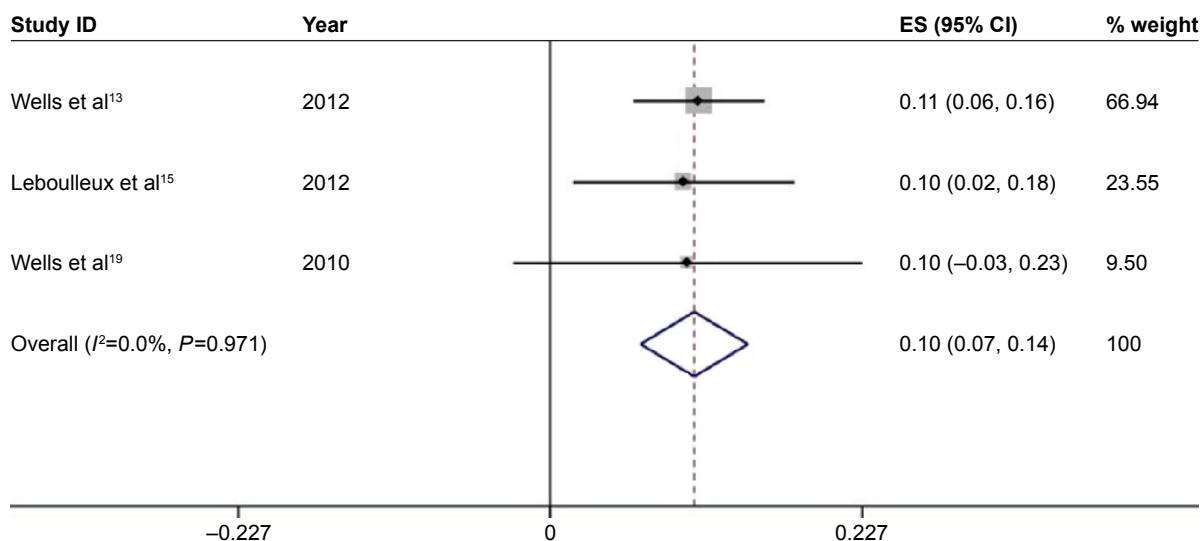**Abbreviation:** ES, effect size.

Study ID	Year		ES (95% CI)	% weight
Wells et al[13]	2012		0.56 (0.45, 0.68)	72.84
Leboulleux et al[15]	2012		0.75 (0.53, 0.97)	18.97
Wells et al[19]	2010		0.70 (0.36, 1.04)	8.19
Overall (I^2=18.3%, P=0.294)			0.61 (0.51, 0.71)	100

−1.04   0   1.04

Figure S3 Forest plot of the total incidence of all-grade diarrhea of patients with thyroid cancer receiving vandetanib.
Notes: The size of the gray square corresponded to the weight of the study in the meta-analysis. The horizontal line represented the 95% confidence interval (CI) and the vertical dotted line showed the total incidence of all-grade diarrhea. Since heterogeneity test indicated no heterogeneity, the total incidence of all-grade diarrhea was calculated using the fixed-effects model.
Abbreviation: ES, effect size.

Study ID	Year		ES (95% CI)	% weight
Wells et al[13]	2012		0.11 (0.06, 0.16)	66.94
Leboulleux et al[15]	2012		0.10 (0.02, 0.18)	23.55
Wells et al[19]	2010		0.10 (−0.03, 0.23)	9.50
Overall (I^2=0.0%, P=0.971)			0.10 (0.07, 0.14)	100

−0.227   0   0.227

Figure S4 Forest plot of the total incidence of high-grade diarrhea of patients with thyroid cancer receiving vandetanib.
Notes: The size of the gray square corresponded to the weight of the study in the meta-analysis. The horizontal line represented the 95% confidence interval (CI) and the vertical dotted line showed the total incidence of high-grade diarrhea. Since heterogeneity test indicated no heterogeneity, the total incidence of high-grade diarrhea was calculated using the fixed-effects model.
Abbreviation: ES, effect size.