

RESEARCH COMMUNICATION

Efficacy and Safety of Vandetanib, a Dual VEGFR and EGFR Inhibitor, in Advanced Non-Small-Cell Lung Cancer: a Systematic Review and Meta-Analysis

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Abstract

Background: Vandetanib, an oral inhibitor of vascular endothelial growth factor receptor and epidermal growth factor receptor signaling, has attracted wide interest in treatment of advanced non-small-cell lung cancer (NSCLC). We aimed to assess its efficacy and safety via a systematic review and meta-analysis. **Methods:** Trials comparing vandetanib-based therapy and non-vandetanib therapy for advanced NSCLC were identified. Endpoints evaluated were progression-free survival (PFS), overall survival (OS), objective tumor response rate (ORR), and toxicity. **Results:** Seven trials including 4,492 patients were included in the analysis. As compared with placebo, vandetanib yielded a clear benefit for ORR (odds ratio (OR) = 2.04; 95% CI, 1.60-2.61; P < 0.001), and a clinically and statistically significant 25% improvement in PFS (hazard ratio (HR) = 0.75; 95% CI, 0.66-0.85; P < 0.001). However, these benefits did not translate into a significant improvement in OS (HR = 0.95; 95% CI, 0.88-1.04; P = 0.291). Subgroup analyses showed that vandetanib 100mg/d was associated with greater antitumor activity than 300mg/d when given in combination with chemotherapy. In addition, the pooled results demonstrated no statistically significant difference between vandetanib and single-targeted agents in PFS, ORR or OS. Vandetanib was associated with more frequent adverse events. **Conclusions:** Vandetanib, as compared with placebo, significantly increases ORR and PFS, but does not improve OS in the treatment of advanced NSCLC. As compared with single-targeted agent, vandetanib does not provide any efficacy advantage. Furthermore grade 3 or greater toxicity proved greater in the vandetanib arm.

Keywords: vandetanib - non-small-cell-lung-cancer - multi-targeted therapy - epidermal growth factor receptor - vascular endothelial growth factor receptor - meta-analysis

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Introduction

Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer, and is the leading cause of cancer-related death worldwide (Jemal et al., 2009). Most patients are diagnosed with NSCLC at an advanced stage which is only amenable to palliative therapy.

With the notion that a “chemotherapy efficacy plateau” has been achieved with traditional cytotoxic chemotherapy, molecular-targeted drugs which selectively target the signaling pathways contributing to the development and progression of NSCLC have entered the therapeutic arena in recent years. Vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) are clinically validated therapeutic

targets in NSCLC. The addition of bevacizumab, a monoclonal antibody against VEGF, to paclitaxel and carboplatin provided clinical benefit in previously untreated non-squamous advanced NSCLC (Sandler et al., 2006). And the small-molecule EGFR inhibitors, gefitinib and erlotinib, has both demonstrated antitumor activity in the treatment of advanced NSCLC. (Shepherd et al., 2005; Kim et al., 2008; Maemondo et al., 2010) Despite all of these improvements, the benefits associated with these agents are modest and serve to stress the need for novel therapeutic approaches. Moreover, EGFR is known to regulate the production of VEGF and other proangiogenic factors, (Ciardiello et al., 2006) and increased VEGF expression has been associated with resistance to EGFR inhibition in a human tumor xenograft model of NSCLC. (Naumov et al., 2009) Given well-established and the

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potential crosstalk role of VEGFR and EGFR signaling pathways in angiogenesis and tumor growth, a logical strategy for improving anti-tumor efficacy, without increasing toxicity, is combined inhibition of both EGFR and VEGFR signaling by using one single multi-targeted agent.

Vandetanib is a once-daily, orally available anticancer drug that inhibits VEGFR and EGFR dependent signaling, as well as the RET (rearranged during transfection) receptor tyrosine kinase, which is an important growth driver in certain types of thyroid cancer (Carlomagno et al., 2002; Wedge et al., 2002; Herbst et al., 2007). Simultaneous inhibition of the VEGFR and EGFR signaling pathways with vandetanib may offer the potential greater anti-tumor efficacy for advanced NSCLC than inhibitors of either pathway alone. Several clinical trials have evaluated vandetanib for the treatment of advanced NSCLC. Although some of these trials have suggested benefit, others have shown no effect, leading to uncertainty about the presence and magnitude of any anticancer effects of vandetanib for advanced NSCLC and difficulties for clinicians in interpretation of the results.

To synthesize the available clinical trial evidence and to improve definition of the likely effects of vandetanib for advanced NSCLC patients, we performed a systematic review and meta analysis of randomized controlled trials to evaluate the role of vandetanib on objective tumor response rate, progression-free survival, overall survival and adverse events in patients with advanced NSCLC.

Materials and Methods

Search strategy and selection criteria

For inclusion in this meta-analysis, randomized controlled trials were required to have compared vandetanib-based therapy with non-vandetanib therapy in the treatment of patients with stage III B or stage IV NSCLC. Relevant studies were identified by searching three electronic databases (PubMed, Embase and the Cochrane Center Register of Controlled Trials) up to July 2011, using the search term of “vandetanib”, “non-small-cell lung cancer”, and “NSCLC”. We also manually searched the American Society of Clinical Oncology Annual Scientific Meeting (ASCO) from 2004 to 2011. In addition, reference lists of the selected trials and relevant reviews were examined for other eligible trials. Moreover, we also searched in <http://www.ClinicalTrials.gov> websites for the information of prospective and ongoing trials. No language restriction was applied.

Data extraction and quality assessment

Using a standardized data recording form, Qin and Li extracted the following information from each eligible study independently: publication details, patient characteristics (age, sex, WHO performance status), interventions, dose of vandetanib and outcome measures. The quality of included trials was assessed by Qin and Li according to quantitative 5 point Jadad scale (Jadad et al., 1996). And disagreements were adjudicated by a third reviewer after referring to the original articles. End points of interest included objective tumor response rate,

progression-free survival, overall survival and adverse events.

Statistical analysis

All eligible trials were separated into two groups according to the control used (placebo and single-targeted agent) to analyze the efficacy and safety. For time to event data, the log HRs and their variances were estimated using the methods proposed by Parmar et al. (1998) from confidence intervals (CIs) of HRs extracted from each trial before data pooling. The summary HRs and their 95% CIs were estimated using a general variance-based method. Among the studies used, there were two three-arm trials (Heymach et al., 2007; 2008). For the trial (Heymach et al., 2007) which compared different dosages of vandetanib plus docetaxel with placebo plus docetaxel, we combined groups to create a single pair-wise comparison by incorporating the effect size and its variance of vandetanib 100 mg/d plus docetaxel versus placebo plus docetaxel with those of vandetanib 300 mg/d pair-wise comparison (Borenstein et al., 2009). Another three-arm trial (Heymach et al., 2008) included one pair-wise comparison of vandetanib arm with chemotherapy arm, and data from that comparison was not included in this meta-analysis. The methods reported by Mantel and Haenszel were induced to calculate the pooled OR of ORR and AEs (Deeks et al.). ORR included complete response and partial response. And AEs were analyzed as the WHO grade 3 or greater toxicity. An OR >1 indicated a higher tumor response rate and more toxicity in the vandetanib arm.

The heterogeneity between trials was assessed by test and I² statistic (Higgins et al., 2003). The pooled HRs and ORs were estimated by fix-effect model. However, when the trials were heterogeneous with each other (I² of heterogeneity > 25%), the random-effect model was employed to recalculate the pooled efficacy and safety. This model could yield wider CIs underlying effect varied among included trials, and provide a more conservative statistical claim (DerSimonian et al. 1986). In our study, we undertook subgroup analyses according to the varying dosage of vandetanib. All the reported P values were two-side and P values less than 0.05 were regarded as statistically significant. Statistical analyses were carried out using STATA 11.0.

Results

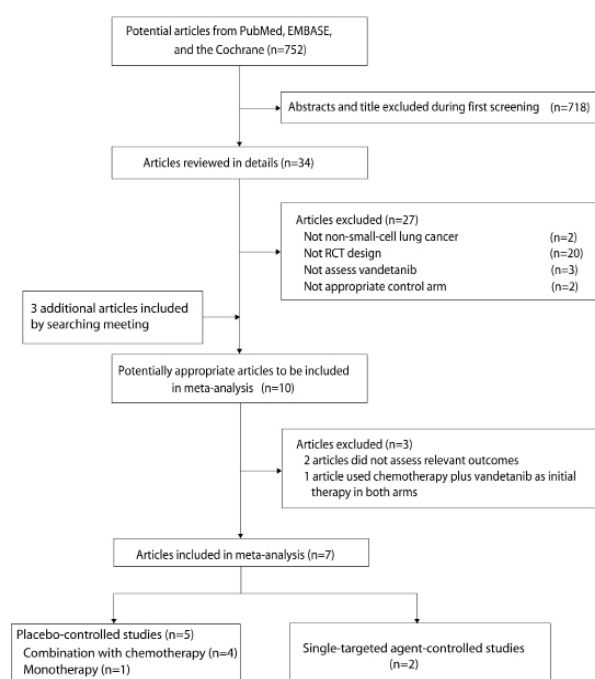
Characteristics of the inclusive trials

We identified 7 trials (Heymach et al., 2007; 2008; Natale et al., 2009; 2011; Herbst et al., 2010; Lee et al., 2010; de Boer et al., 2011) including 4,492 patients using the strategy summarized in Figure 1. Five (Heymach et al., 2007; 2008; Herbst et al., 2010; Lee et al., 2010; de Boer et al., 2011) of the 7 trials were placebo-controlled studies which assessed the effect of vandetanib as monotherapy or in combination with chemotherapy. The other 2 trials (Natale et al., 2009; 2011) compared vandetanib with a single-targeted agent (erlotinib or gefitinib) which inhibits only EGFR signaling pathway. Among the 5 placebo-controlled trials, two (Herbst et al., 2010; de Boer et al.,

Table 1. Characteristics of Included Trials

Trials	Authors and Year	Number of Patients	Therapy of Treatment And Control Arm	Male (%)	Median Age (years)	Stage IV (%)	WHO PS=2 (%)	Jadad Score
6474IL/0006 ¹³	Heymach et al. (2007)	127	A	21(50) 25(57) 27(66)	61 60 58	28(67) 35(80) 28(68)	0(0) 0(0) 0(0)	4
6474IL/0007 ¹⁴	Heymach et al.(2008)	108	B	39(70) 37(71)	60 59	49(88) 47(90)	0(0) 0(0)	4
ZODIAC ¹⁹	Herbst et al.(2010)	1391	C	497(72) 473(68)	59 59	598(86) 590(85)	6(0.9) 2(0.3)	5
ZEPHYR ²⁰	Lee et al.(2010)	924	D	NR NR	NR NR	NR NR	NR NR	3
ZEAL ²¹	de Boer et al.(2011)	534	E	159(62) 171(62)	60 60	219(86) 232(83)	18(7) 13(5)	4
6474IL/0003 ²²	Natale et al.(2009)	168	F	48(58) 52(61)	63 61	69(83) 63(74)	0(0) 0(0)	4
ZEST ²³	Natale et al.(2009)	1240	H	381(61) 393(64)	61 61	517(83) 519(84)	65(10) 77(13)	4

NR, not reported; PD, disease progression; PT, prohibitive toxicity; AUC, area under concentration/time curve; A, Vandetanib 100mg once-daily + Docetaxel 75mg/m² on d1 every 21 days until PD or PT, Vandetanib 300mg once-daily + Docetaxel 75mg/m² intravenous infusion on d1 every 21 days until PD or PT, Placebo+Docetaxel 75mg/m² on d1 every 21 days until PD or PT; B, Vandetanib 300mg once-daily until PD or PT + Paclitaxel 200mg/m² plus Carboplatin AUC6 for maximum 6 cycles of 21 d, Placebo + Paclitaxel 200mg/m² plus Carboplatin AUC6 for maximum 6 cycles of 21 d; C, Vandetanib 100mg/d until PD or PT + Docetaxel 75mg/m² for maximum 6 cycles of 21 d, Placebo+ Docetaxel 75mg/m² for maximum 6 cycles of 21 d; D, Vandetanib 300 mg/d until PD or PT, Placebo, F, Vandetanib 100mg/d until PD or PT + Pemetrexed 500mg/m² for maximum 6 cycles of 21 d, Placebo + Pemetrexed 500mg/m² for maximum 6 cycles of 21 d; G, Vandetanib 300mg once-daily until PD or PT, Gefitinib 250mg once-daily until PD or PT; H, Vandetanib 300 mg/d until PD or PT, Erlotinib 150 mg/d until PD or PT

**Figure 1. Identification Process for Eligible Studies**

2011) assessed vandetanib at 100mg/d while another two(Heymach et al., 2008; Lee et al., 2010) assessed vandetanib at 300mg/d and one(Heymach et al., 2007) was three-arm trial which involved both doses of vandetanib. Vandetanib was administered as 300mg/d in the 2 trials (Natale et al., 2009; 2011) with single-targeted agent as control. The characteristics of each study are listed in Table 1.

Among these 7 eligible trials, one trial(Herbst et al., 2010) had Jadad score of 5, five trials(Heymach et al.,

2007; Heymach et al., 2008; Natale et al., 2009; de Boer et al., 2011; Natale et al., 2011) were given score of 4, and one trial(Lee et al., 2010) was assessed as score of 3. However, the trial(Lee et al., 2010) with Jadad score of 3 was published in abstract format and did not provided the detail information about randomization or blind.

Vandetanib versus placebo

Vandetanib was compared with placebo in 5 randomized trials(Heymach et al., 2007; Heymach et al., 2008; Herbst et al., 2010; Lee et al., 2010; de Boer et al., 2011) including 3,084 patients. Four trials(Heymach et al., 2007; Heymach et al., 2008; Herbst et al., 2010; de Boer et al., 2011) assessed vandetanib in combination with chemotherapy while one trial(Lee et al., 2010) evaluated vandetanib as monotherapy.

Vandetanib was associated with a statistically significant improvement in ORR as compared with placebo (OR = 2.04; 95% CI, 1.60-2.61; P < 0.001) with no evidence of heterogeneity (p for heterogeneity = 0.532; I² = 0%) (Figure 1). The absolute benefit was 5%, which corresponded to an increase in the tumor response rate from 8% with placebo to 13% with vandetanib (Figure 1). Furthermore, the subgroup analyses were conducted according to the dose used. The results of subgroup analyses showed statistically significant benefits on ORR of vandetanib at both 100mg/d (OR = 2.07; 95% CI, 1.59-2.70; P < 0.001) and 300mg/d (OR = 1.90; 95% CI, 1.03-3.49; P = 0.039) (Figure 1). However, when the subgroup analysis of vandetanib 300mg/d was restricted to trials evaluating vandetanib in combination of chemotherapy, there was no statistical difference in the overall response rate between the vandetanib group and placebo group (OR = 1.48; 95% CI, 0.74-2.95; P = 0.268).

A clinically and statistically significant 25%

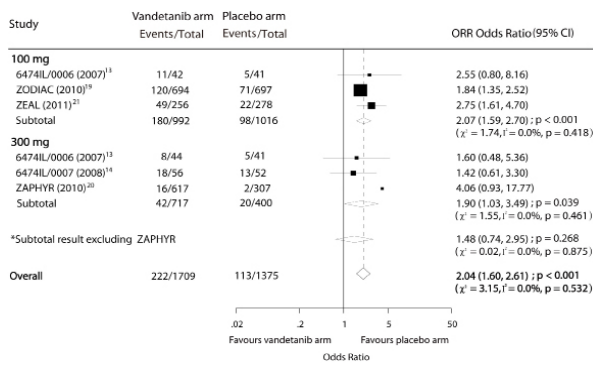


Figure 1. Comparison of Objective Tumor Response Rate Between Vandetanib and Placebo

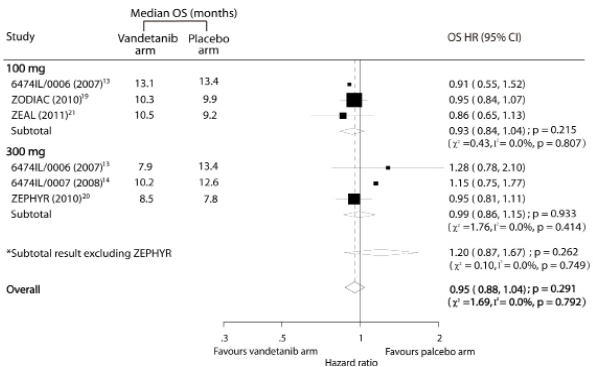


Figure 3. Comparison of Overall Survival Between Vandetanib and Placebo

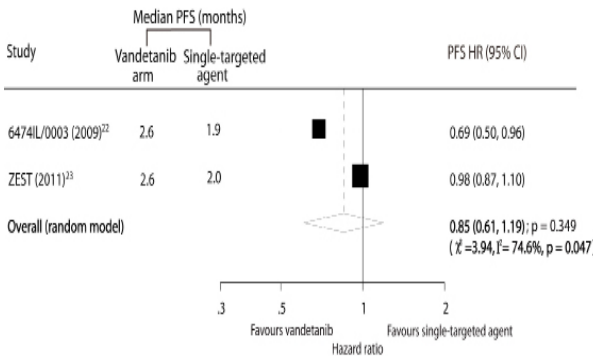


Figure 5. Comparison of Progression-free Survival Between Vandetanib and Single- Targeted Agent

improvement in PFS was attributable to vandetanib compared with placebo (HR = 0.75; 95% CI, 0.66-0.85; P < 0.001) (Figure 2). There might be some heterogeneity in the hazard ratios for PFS among the individual trials (P = 0.140; I² = 42.2%). Vandetanib at 100mg/d showed a 20% decrease in the hazard for disease progression (HR = 0.80; 95% CI, 0.72-0.89; P < 0.001) (Figure 2) with no evidence of heterogeneity (P = 0.545; I² = 0%). Vandetanib at 300mg/d seemed to demonstrate greater benefits in PFS (HR = 0.66; 95% CI, 0.57-0.76; P < 0.001) (Figure 2) with no evidence of heterogeneity (P = 0.446; I² = 0%). However, all of the trials of vandetanib at 100mg/d were add-on design, while the subgroup analysis of vandetanib at 300mg/d included the ZEPHYR study(Lee et al., 2010)—a trial that specifically compared vandetanib as monotherapy with placebo. A sensitivity analysis excluding the ZEPHYR trial showed that combination of vandetanib at 300mg/d and chemotherapy did not result in an statistically significant improvement in PFS compared

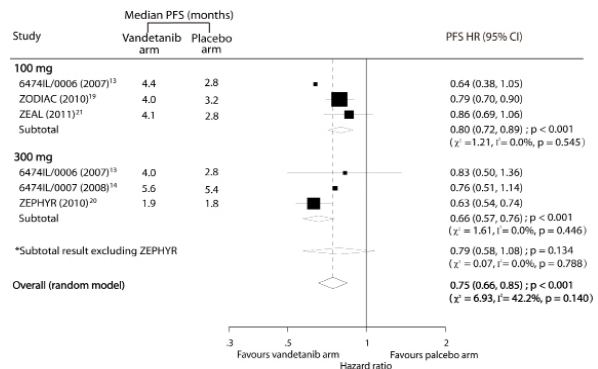


Figure 2. Comparison of Progression-free Survival Between Vandetanib and Placebo

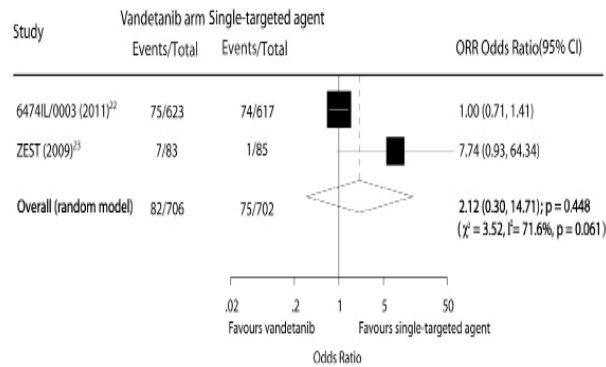


Figure 4. Comparison of Objective Tumor Response Rate Between Vandetanib and Single-targeted Agent

with chemotherapy alone (HR = 0.79; 95% CI, 0.58- 1.08; P = 0.134).

Vandetanib was associated with 5% improvement in overall survival as compared with placebo, but this difference was not statistically significant (HR = 0.95; 95% CI, 0.88-1.04; P = 0.291; Figure 3). No evidence of heterogeneity was observed between individual studies (P = 0.792; I² = 0%). Subgroup analyses showed that the effect on OS was slightly greater for vandetanib at 100mg/d (HR = 0.93; 95% CI, 0.84 -1.04; P = 0.215) than 300 mg/d (HR = 0.99; 95% CI, 0.86-1.15; P = 0.933). However, the results of both subgroups also failed to reach statistical significance. After excluding the ZEPHYR study(Lee et al., 2010), the combined HR for OS comparing vandetanib 300mg/d plus chemotherapy vs placebo plus chemotherapy was 1.20 (95% CI, 0.87-1.67). As expected, vandetanib as monotherapy or in combination with chemotherapy, compared with placebo arm, had a statistically significant increase in the risk of rash, diarrhea, hypertension and neutropenia. Similar low rates of grade 3 or greater hemoptysis were reported with vandetanib and placebo arms. Besides, there was no significant difference in the frequency of cough, dyspnea, pulmonary embolism, nausea, vomiting, constipation, fatigue, anorexia, asthenia (Supplementary Figure 2).

Vandetanib versus single-targeted agent

Two trials (Natale et al., 2009; Natale et al., 2011) including 1408 patients compared vandetanib at 300mg/d with a single-targeted agent. The single-targeted agents in our meta-analysis only included anti-EGFR TKIs (gefitinib and erlotinib).

The pooled analysis demonstrated that the tumor

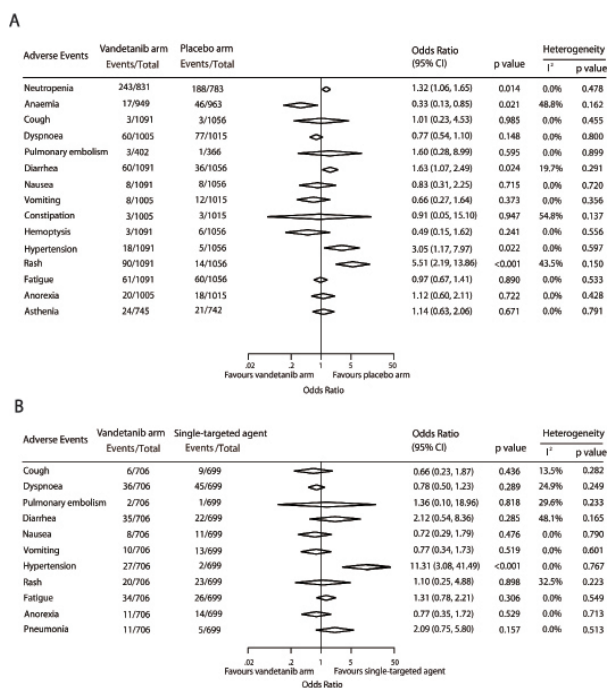


Figure 5. Summary of Toxicities Grade 3 or Greater

response rate of the vandetanib arm and single-targeted agent arm were 12% and 11%, respectively. And there was no significant difference between the two arm (OR = 2.12; 95% CI, 0.30-14.71; P = 0.448; Figure 4).

PFS was not significantly different between vandetanib and single-targeted agents (HR = 0.85; 95% CI, 0.61-1.19; P = 0.349; Figure 5). There might be substantial heterogeneity in the HRs for PFS from the individual trials (P = 0.047; I² = 74.6%), and we incorporated it into random-effects model.

Both of the two trials (Natale et al., 2009; Natale et al., 2011) had compared the effect on OS between vandetanib and single-targeted agent. However, assessment of the effect of vandetanib on OS may be confounded due to the two-part crossover design of the 6474IL/0003 trial (Natale et al., 2009). Therefore, data on OS was available for analysis from only one trial investigating vandetanib as compared with single-targeted agent, which found no difference in OS between vandetanib and erlotinib.

Compared with single-targeted agent, vandetanib was associated with a significant increase in the OR for grade 3 or greater hypertension. However, the risk of grade 3 or greater rash and diarrhea was comparable between vandetanib and anti-EGFR TKIs. No statistically significant difference was also found between the two arms for cough, dyspnoea, pulmonary-embolism, nausea, vomiting, fatigue and anorexia, pneumonia (Figure 5).

Discussion

This meta-analysis showed that vandetanib, as compared with placebo, was associated with a clinically substantial and statistically significant improvement in progression-free survival and advantages of tumor response rate, but no improvement in overall survival and higher rates of adverse events. As compared with single-targeted agent, vandetanib did not demonstrate any

efficacy advantage.

Our data showed that vandetanib determined a statistically significant increase in ORR and PFS as compared with placebo. Most of inclusive placebo-controlled trials were add-on design which might underestimate the treatment effect of vandetanib. Despite this, we still found a significant improvement in PFS. The data of the study by Heymach et al. (Heymach et al., 2007) suggested that the antitumor activity of vandetanib may be higher in patients receiving the lower dose. In our study, the result of subgroup analysis for vandetanib 300mg/d was influenced by the ZEPHYR trial (Lee et al., 2010) and physicians should carefully interpret these results when they apply it in clinical practice. It is thought that EGFR TKIs induce G1 cell cycle arrest and thereby reduce the efficacy of cell cycle-dependent cytotoxic agents. As shown in four randomized phase III studies, (Giaccone et al., 2004; Herbst et al., 2004; Herbst et al., 2005; Gatzemeier et al., 2007) the addition of EGFR TKIs to chemotherapy does not improve outcome in unselected patients with NSCLC. And it has been theorized that, the level of EGFR inhibition at higher doses of vandetanib is sufficiently high to antagonize chemotherapy, which may explain the inefficacy for ORR and PFS of high dose vandetanib when in combination of chemotherapy.

Despite the increase in ORR and PFS in the subgroup of vandetanib, these benefits did not translate in a significant improvement in overall survival as compared with placebo. None of the trials included in our analyses revealed improvement in overall survival, and pooled HR analyses revealed only a positive trend without reaching statistical significance. Hence, solid recommendation of vandetanib for advanced NSCLC could not be given until overall survival trend will be translated in statistical significant advantages.

Our meta-analysis suggested vandetanib did not yielded any efficacy advantage compared with single-targeted agent in unselected patients with NSCLC. However, correlative studies of tumor and circulating biomarker have been conducted and suggest that circulating VEGF levels, EGFR gene copy number (FISH+) and EGFR mutation status (EGFR MT) may be potential biomarkers. (Kiura et al., 2008; Hanrahan et al., 2009; Johnson et al., 2010) One can speculate whether improved results could be obtained by a more selective targeting of patients with specific biomarkers predictive of drug sensitivity. However, because of insufficient data, we were unable to make firm conclusion and confirmation must await investigation in future studies.

Our results confirmed that vandetanib as monotherapy or in combination with chemotherapy, compared with placebo arm, was associated with a significant increase in the risk of rash, diarrhea and hypertension, which were typically associated with anti-EGFR (rash, diarrhea) and anti-VEGFR (hypertension) therapies. (Herbst 2006; Ricciardi et al., 2009) Hypertension was the only adverse event which was significantly frequent in the vandetanib arm compared with the anti-EGFR TKIs arm. The incidence of grade 3 or greater hypertension of vandetanib (3.82%) was similar to that previously reported for bevacizumab in advanced NSCLC. Specially, no major

haemoptysis occurred in patients receiving vandetanib, suggesting that vandetanib, unlike bevacizumab, can be administered safely to all histological NSCLC subtypes. QTc prolongations seemed to be a typically adverse event of vandetanib, however, most adverse events were mild (grade 1 or 2) and asymptomatic, which resolved after dose interruption /reduction. Despite the increase of adverse events, vandetanib seemed not decrease the time to deterioration of symptoms (TDS) of NSCLC patients. We were unable to statistically pool results about TDS because the relevant results were reported infrequently and inconsistently. However, where differences in TDS did exist, they were in favor of vandetanib group.

Several limitations of this meta-analysis should be acknowledged. First, the analysis was not based on individual patient data, which might provide further insight for efficacy of vandetanib (Stewart et al., 1993). Second, because the results of vandetanib compared with single-targeted agents in this meta-analysis were based on the trials of anti-EGFR therapy, they are not necessarily applicable to those compared with anti-VEGFR therapies. Finally, we did not test formally for publication bias because we had few studies (Ioannidis et al., 2007), but we cannot exclude the possibility of publication bias.

In conclusions, Whilst we can be confident in the benefits on PFS and ORR of vandetanib compared with placebo, its inefficacy for OS and increased toxicity must not be ignored. And the lack of any efficacy advantage compared with single-targeted agents also argues against a routine practice of vandetanib for advanced NSCLC in all patients. Additional research is urgently needed to further identify molecular biomarkers which can define groups of patients potentially benefiting from vandetanib.

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