Int J Clin Exp Med 2016;9(8):16157-16163
www.ijcem.com /ISSN:1940-5901/IJCEM0028541

Original Article

Does the age affect the efficacy of anti-VEGF agents in advanced non-small-cell lung cancer? A meta-analysis

Xin Wan[1], Jun Wang[1], Xiao-Hui Cao[2], Chao-En Bao[2], Qing-Xiang Zhou[2], Yong-Feng Yang[2]

[1]*Department of Radiation Oncology, Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China;*
[2]*Department of Radiation Oncology, Third Hospital of Hebei Medical University, Shijiazhuang 050051, China*

Received March 17, 2016; Accepted June 12, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Purpose: This meta-analysis aimed to assess whether the age would affect the efficacy of anti-vascular endothelial growth factor (VEGF) agents in advanced non-small-cell lung cancer (NSCLC). Methods: Electronic databases, including PubMed, Web of Science and the Cochrane Central Register of Controlled trials were searched to identify relevant studies. Eligible studies included prospective randomized controlled trials (RCTs) evaluating therapies with or without anti-VEGF agents in elderly patients with advanced NSCLC. Hazard ratios (HRs) were used to estimate overall survival (OS) and progression-free survival (PFS). Sub-group analysis and publication bias were also evaluated. Results: Ten trials involving a total of 3,163 elderly patients with advanced NSCLC were included. The addition of anti-VEGF agents to therapies in elderly patients significantly improve PFS (HR 0.88, 95% CI: 0.88-1.00, *P*=0.048), but not for OS (HR 0.99, 95% CI: 0.90-1.10, *P*=0.91) when compared to controls. On subgroup analysis, similar results were found based on treatment line. No publication bias was detected by Begg's and Egger's tests for OS. Conclusions: Among elderly patients with advanced NSCLC, the use of anti-VEGF agents offers an improved PFS, but not for overall survival benefit. With present evidence, we are still unable to clearly set the role of anti-VEGF agents in the treatment of advanced NSCLC in this setting.

Keywords: Non-small-cell lung cancer, elderly, efficacy, anti-VEGF agents, meta-analysis

Introduction

Lung cancer is a leading cause of cancer-related mortality accounting for almost 1.4 million deaths annually, worldwide [1]. Approximately eighty-five percent of all cases of lung cancer have non-small cell lung cancer (NSCLC). The data of Surveillance Epidemiology and End Results (SEER) showed that approximately 53% of lung cancer cases were older than 70 years, and approximately 15% of cases are diagnosed in patients aged more than 80 years [2]. Therefore, the elderly represent a large subgroup of patients affected by advanced NSCLC in our clinical practice. However, there are many challenges involved in the treatment of an elderly population with advanced NSCLC. Old age is commonly associated with several comorbidities, decreased organ function and functional status, which lead to limited life expectancy and reduced tolerance of cancer treatments [3]. Undertreatment is an additional risk for older individuals. Only 35% of patients with regional disease and 27% with metastatic disease received guideline-recommended treatment among patients aged ≥65 years [4]. Furthermore, elderly patients are underrepresented in clinical trials, and treatment decisions are based on results of trials conducted in younger individuals [5-7]. Therefore, the optimal treatment for NSCLC in elderly patients remains undetermined.

During the past decades, the emergence of molecularly targeted agents has provided another strategy for the treatment of elderly patients with advanced NSCLC [8-10], and anti-angiogenesis therapies represent the most promising therapeutic approach being developed [11-14]. Until now, two anti-angiogenesis agents by through inhibiting VEGF signal pathway bevacizumab and nintedanib has been approved for the treatment of advanced NSCLC patients [15, 16]. Nonetheless, there is limited

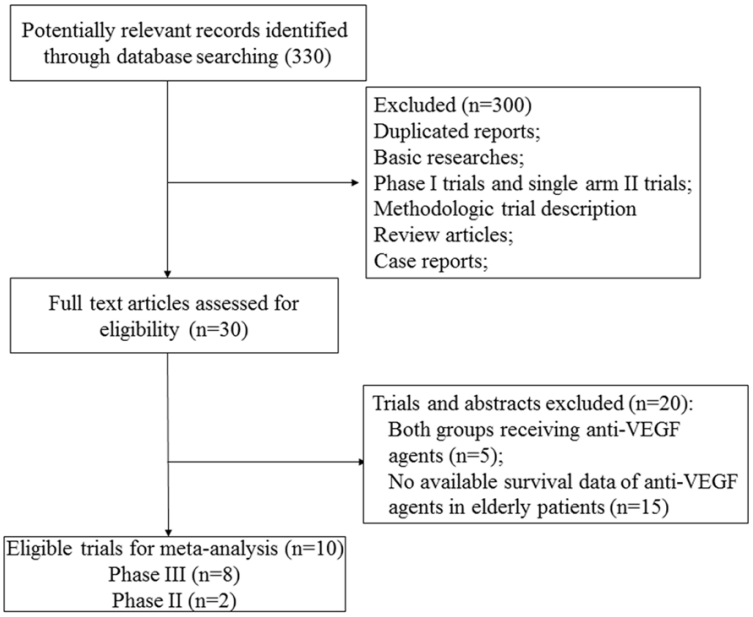

Figure 1. Studies eligible for inclusion in the meta-analysis.

data regarding the role of anti-VEGF agents in NSCLC patients aged ≥65 years old, whether anti-VEGF agents would benefit elderly patients with advanced NSCLC remains unknown. Thus, we conduct this meta-analysis of all available randomized controlled trials (RCTs) to determine the overall efficacy of anti-VEGF agents in this sub-group patient.

Material and methods

Literature search and inclusion criteria

The Pubmed, Embase, and Cochrane Library electronic databases were search to identify relevant studies of anti-VEGF agents in advanced non-small-cell lung cancer (published before December 31, 2015). The following search terms were used: "bevacizumab", "aflibercept", "anti-VEGF agents", "sorafenib", "sunitinib", "sutent", "vandetanib", "axitinib", "pazopanib", "regorafenib", "apatinib", "ramucirumab", "nintedanib", "angiogenesis inhibitors", "clinical trials", "lung cancer", and "lung neoplasm". The search was limited to human studies and randomized controlled trials (RCTs). No language restriction was imposed. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences that took place between Jan 2004 and Jun 2015.

Phase 1 trials and single-group phase 2 trials were omitted from analysis because of lack of controls. Trials that met the following inclusion criteria were included: (1) Study design, RCT; (2) population, patients were pathologically confirmed of non-small-cell lung cancer; (3) intervention, therapy with or without anti-VEGF agents; (4) outcome measure, the study had sufficient survival data (overall survival and progression-free survival) of elderly patients (≥65) for extraction. If duplicate data were presented in several studies, only the most informative or complete article were included.

Data extraction and clinical end point

Two authors independently extracted the following data according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [17] and any discrepancy between the reviewers was resolved by consensus. For each study, the following data was extracted: first author, year of publication, trial phase, the number of elderly patients, treatment regimen, primary endpoints, and median follow-up. A standardized Excel file was used for data extraction. The quality of reports of clinical trials was assessed and calculated using the 5-item Jadad scale including randomization, double-blinding, and withdrawals as previously described [18]. The quality scale ranges from 0 to 5 points. A higher score indicates better quality. Articles with more than 3 points were considered to have high quality.

Data analysis

We assessed the overall efficacy of adding anti-VEGF agents to therapies in the treatment of elderly patients with advanced NSCLC based on data from the included trials. PFS and OS were treated as time-to-event variables, and thus were expressed as hazard ratios (HRs) with 95% CIs for each study. Between-study heterogeneity was estimated using the

Table 1. Clinical characteristic of included trials for analysis

Author/year	Phase	Line of treatment	No. of elderly patients	Age	Treatment regimens	Median follow-up (m)	Jadad score
Garon E.B. et al/2014	III	Second-line	455	≥70	Ramucirumab 10 mg/kg+DOC Placebo+DOC	9.5	5
Reck M. et al/2014	III	Second-line	414	≥65	Nintedanib 200 mg qd po+DOC Placebo+DOC	7.1	5
Gridelli C. et al/2014	II	First-line	124	≥70	Vandetanib 100 mg qd po+Gem Placebo+Gem	NR	5
Doebele R.C. et al/2014	II	First-line	68	≥65	Ramucirumab 10 mg/kg+Pemetrexed Pemetrexed	NR	3
Scagliotti G.V. et al/2012	III	Second-line	354	≥65	Sunitinib 37.5 mg qd po+erlotinib Placebo+erlotinib	21.3	5
Scagliotti G.V. et al/2012	III	First-line	370	≥65	Motesanib 125 mg qd po+PTX+CBP Placebo+PTX+CBP	NR	5
Herbst R.S. et al/2011	III	Second-line	327	≥65	Bev 15 mg/kg+erlotinib Placebo+erlotinib	19	5
Scagligotti G. et al/2010	III	first-line	381	≥65	Sorafenib 400 mg bid po+CBP+PTX CBP+PTX	NR	3
Reck M et al/2009	III	First -line	304	≥65	Bev 7.5 mg/kg+DDP+Gem Bev 15 mg/kg+DDP+Gem Placebo+DDP+Gem	NR	5
Sandler A. et al/2006	III	First -line	366	≥65	Bev 15 mg/kg+CBP+PTX CBP+PTX	19	3

Abbreviations: DOC, Docetaxel; Gem, Gemcitabine; PTX, Paclitaxel; CBP, Carboplatin; RT, Radiotherapy; Bev, Bevacizumab; DDP, Cisplatin; NR, Not reported.

χ^2-based Q statistic [19]. The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials.

I^2 values of 25%, approximately 50%, approximately 75%, and approximately 100% indicated no, low, moderate, and high heterogeneity, respectively. A fixed-effects model (Mantel-Haenszel method) was used, whereas a random effects model (DerSimonian-Larid method) [20] was used when significant heterogeneity existed (I^2>50%). A sub-group analysis was conducted according to treatment line. The presence of publication bias was evaluated by using the Begg and Egger tests [21]. All *p*-values were two-sided. All *CI*s had a two-sided probability coverage of 95%. Statistical analysis was calculated using Version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ).

Results

Identification of eligible trials

The initial search of the Pubmed, Embase, and Cochrane Library electronic databases yielded a total of 330 potentially relevant studies. Of these, 30 were excluded for duplicate records, and 280 were excluded after reviewing the title or abstract, leaving 30 articles for full-text review. In the review, 20 trials were excluded for the following reasons shown in **Figure 1**. Finally, ten published RCTs with sub-group analysis assessing the efficacy of anti-VEGF agents in elderly patients were included [16, 22-30]. The main characteristics of the ten trials were presented in **Table 1**. A total of 3,709 patients were available for the meta-analysis. Seven trials were performed in first-line settings, and four in second-line. The quality of each included study was roughly assessed according to Jadad scale, the median Jadad score of the included studies was 5 (rang: 3-5).

Overall survival

Seven trials reported OS data of elderly patients. Since between study heterogeneity was not observed, a fixed-effect model was used for OS (I^2=0%, *P*=0.95). No significant differences were observed with respect to OS (HR 0.99, 95% CI: 0.90-1.10, *P*=0.91, **Figure 2**) between the anti-VEGF agents and controls. We then performed sub-group analysis according to treatment line, and found that the use of anti-VEGF agents as first-line (HR 0.95, 95% CI:

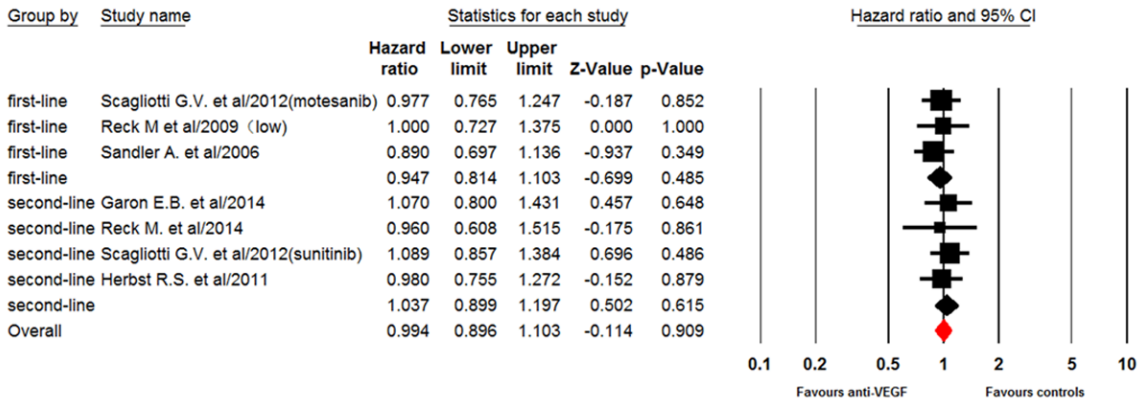

Figure 2. Fixed-effects Model of Hazard Ratio (95% CI) of OS Associated with therapies with or without anti-VEGF agents.

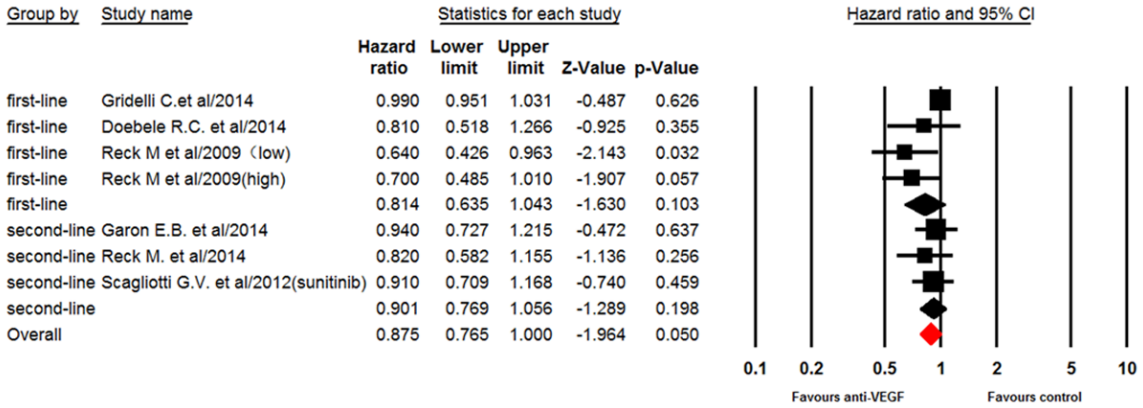

Figure 3. Random-effects Model of Hazard Ratio (95% CI) of PFS Associated with therapies with or without anti-VEGF agents.

0.81-1.10, *P*=0.49) or second-line therapies (HR 1.04, 95% CI: 0.90-1.20, *P*=0.62) did not improve OS in comparison with controls.

Progression-free survival

Six trials with seven comparisons reported PFS data. The pooled hazard ratio for PFS demonstrated that anti-VEGF agents significantly improve PFS giving HR 0.88 (95% CI: 0.88-1.00, *P*=0.05, **Figure 3**), compared with controls. There was moderate heterogeneity between trials (I^2=46.32%, *P*=0.083), and the pooled HR for PFS was performed by using random-effects model. A sub-group analysis was performed on the treatment line and found that anti-VEGF agents as first-line (HR 0.98, 95% CI: 0.94-1.02, *P*=0.33) or second-line therapies (HR 0.90, 95% CI: 0.77-1.06, *P*=0.20) had a tendency to improve PFS in elderly patients with advanced NSCLC.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The Begg's funnel plots did not reveal any evidence of obvious asymmetry (*P*=0.88 for OS and *P*=0.07 for PFS, respectively). Then, Egger's test still did not suggest any evidence of publication bias for OS (*P*=0.99) but not for PFS (*P*=0.008). The difference in the results obtained from the two methods may be due to a greater statistical power of the regression methods [31].

Discussion

The angiogenesis pathways, playing a critical role in the growth and metastasis of tumors, have been targeted as a promising therapeutic options in NSCLC [9]. The results from latest investigations have showed that the addition of

angiogenesis inhibitors to therapies in advanced NSCLC significantly improve PFS and OS [13, 14]. However, the elderly patients with advanced NSCLC are traditionally underrepresented in clinical trials. The median age across treatment arms in recent major phase III trials was 59 to 63 years, which is considerably younger than the median age of 71 years at diagnosis [6]. Therefore, the applicability of these data to the overall patient population deserves critical appraisal in the absence of trials dedicated specifically to the elderly. Preplanned and unplanned subset analysis of registration trial data is becoming increasingly common as a substitute measure to provide valuable information to guide the use of targeted agents in the elderly.

Our study includes a total of 3,136 patients from 10 randomized controlled trials. According to the current results, regimens containing anti-VEGF agents has substantial improvements for PFS outcomes in elderly patients when compared to controls (P=0.048). In contrast, benefits in OS is not statistically significant. Similar results were also observed in sub-group analysis according to treatment line. Based on our results, we could conclude that the addition of anti-VEGF agents to treatment therapies could improve PFS in unselected elderly patients with advanced NSCLC, but it does not translate into survival benefit. However, the administration of targeted agents in unselected patients with precisely confirmed targets is not reasonable. Thus, further studies are still needed to identify patients who will most likely benefit from specific anti-angiogenesis therapy. Additionally, we still could not clearly set the role of each anti-angiogenesis agent in the treatment of elderly patients with advanced NSCLC due to limited RCTs included for analysis.

The present meta-analysis has several limitations needed to be considered. First, this analysis is based on published data; and individual patient information is not available. Therefore, confounding variables at patient level, such as comorbidities and prior exposure to treatment therapies, could not be incorporated into the analysis. Second, we include patients treated with different anti-angiogenesis agents. While each of these molecules inhibits VEGF signal pathway, these drugs have different potencies, and have inhibitory properties against a range of non-overlapping targeted receptors. Given the limited sample size of patients treated with any single anti-VEGF agents, we decide to include patients treated with all of these drugs in this class with adequate data on survival of elderly patients with NSCLC, which would increase the clinical heterogeneity among included trials. Furthermore, our study could not answer that which anti-VEGF agent would be the best choice. Finally, in the meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published. The present study detects no publication bias using Begg and Egger tests for OS but not for PFS.

Conclusion

In conclusion, therapies containing anti-VEGF agents is superior to those without these agents in terms of PFS in unselected elder patients with advanced NSCLC. However, no significant survival benefit is observed. Further studies are recommended to identify patients who could derive greater benefits from specific anti-VEGF agents.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yong-Feng Yang, Department of Radiation Oncology, Third Hospital of Hebei Medical University, No. 139, Ziqiang Road, Shijiazhuang 050051, Hebei Province, China. Tel: +86-0311-88602563; E-mail: yongfengyang2016@tom.com

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.

[2] Azzoli CG, Baker S Jr, Temin S, Pao W, Aliff T, Brahmer J, Johnson DH, Laskin JL, Masters G, Milton D, Nordquist L, Pfister DG, Piantadosi S, Schiller JH, Smith R, Smith TJ, Strawn JR, Trent D, Giaccone G; American Society of Clinical Oncology. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2009; 27: 6251-6266.

[3] Yancik R, Ganz PA, Varricchio CG, Conley B. Perspectives on comorbidity and cancer in older patients: approaches to expand the knowledge base. J Clin Oncol 2001; 19: 1147-1151.

[4] Wang S, Wong ML, Hamilton N, Davoren JB, Jahan TM, Walter LC. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. J Clin Oncol 2012; 30: 1447-1455.
[5] Giuliani J, Bonetti A. Second-Line Treatment in Elderly Patients With Advanced Non-Small-Cell Lung Cancer. Clin Lung Cancer 2016; 17: e25-7.
[6] Langer CJ. Clinical evidence on the undertreatment of older and poor performance patients who have advanced non-small-cell lung cancer: is there a role for targeted therapy in these cohorts? Clin Lung Cancer 2011; 12: 272-279.
[7] Meoni G, Cecere FL, Lucherini E, Di Costanzo F. Medical treatment of advanced non-small cell lung cancer in elderly patients: a review of the role of chemotherapy and targeted agents. J Geriatr Oncol 2013; 4: 282-290.
[8] Gajra A, Akbar SA, Din NU. Management of Lung Cancer in the Elderly. Clinics in Geriatric Medicine 2016; 32: 81-95.
[9] Antonelli G, Libra M, Panebianco V, Russo AE, Vitale FV, Colina P, D'Angelo A, Rossello R, Ferraù F. Molecular-targeted therapy for elderly patients with advanced non-small cell lung cancer. Oncol Lett 2016; 11: 3-8.
[10] Li N, Yang L, Ou W, Zhang L, Zhang SL, Wang SY. Meta-Analysis of EGFR Tyrosine Kinase Inhibitors Compared with Chemotherapy as Second-Line Treatment in Pretreated Advanced Non-Small Cell Lung Cancer. PLoS One 2014; 9: e102777.
[11] Qi WX, Wang Q, Jiang YL, Sun YJ, Tang LN, He AN, Min DL, Lin F, Shen Z, Yao Y. Overall survival benefits for combining targeted therapy as second-line treatment for advanced non-small-cell-lung cancer: a meta-analysis of published data. PLoS One 2013; 8: e55637.
[12] Wang WL, Tang ZH, Xie TT, Xiao BK, Zhang XY, Guo DH, Wang DX, Pei F, Si HY, Zhu M. Efficacy and safety of sorafenib for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials. Asian Pac J Cancer Prev 2014; 15: 5691-5696.
[13] Liang W, Wu X, Hong S, Zhang Y, Kang S, Fang W, Qin T, Huang Y, Zhao H, Zhang L. Multitargeted antiangiogenic tyrosine kinase inhibitors in advanced non-small cell lung cancer: meta-analyses of 20 randomized controlled trials and subgroup analyses. PLoS One 2014; 9: e109757.
[14] Hong S, Tan M, Wang S, Luo S, Chen Y, Zhang L. Efficacy and safety of angiogenesis inhibitors in advanced non-small cell lung cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2015; 141: 909-21.
[15] Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RF 3rd, Gaudreault J, Damico LA, Holmgren E, Kabbinavar F. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004; 22: 2184-2191.
[16] Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M, von Pawel J, Gottfried M, Bondarenko I, Liao M, Gann CN, Barrueco J, Gaschler-Markefski B, Novello S; LUME-Lung 1 Study Group. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol 2014; 15: 143-55.
[17] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
[18] Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998; 352: 609-613.
[19] Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 2005; 28: 123-137.
[20] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control clin trials 1986; 7: 177-188.
[21] Vandenbroucke JP. Bias in meta-analysis detected by a simple, graphical test. Expert's views are still needed. BMJ 1998; 316: 469-470; author reply 470-461.
[22] Doebele RC, Spigel D, Tehfe M, Thomas S, Reck M, Verma S, Eakle J, Bustin F, Goldschmidt J Jr, Cao D, Alexandris E, Yurasov S, Camidge DR, Bonomi P. Phase 2, randomized, open-label study of ramucirumab in combination with first-line pemetrexed and platinum chemotherapy in patients with nonsquamous, advanced/metastatic non-small cell lung cancer. Cancer 2015; 121: 883-892.
[23] Gridelli C, Novello S, Zilembo N, Luciani A, Favaretto AG, De Marinis F, Genestreti G, Crinò L, Grossi F, Caffo O, Ferraù F, Cruciani G, Brandes AA, Galetta D, Barni S, Fasola G, Cerea G, Ferrari S, Iannacone C, Ciardiello F. Phase II randomized study of vandetanib plus gemcitabine or gemcitabine plus placebo as first-line treatment of advanced non-small-cell lung cancer in elderly patients. J Thorac Oncol 2014; 9: 733-737.
[24] Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, Gorbunova V, Kowalyszyn RD, Pikiel J, Czyzewicz G, Orlov SV, Lewanski CR, Thomas M, Bidoli P, Dakhil S, Gans S, Kim JH, Grigorescu A, Karaseva N,

Reck M, Cappuzzo F, Alexandris E, Sashegyi A, Yurasov S, Pérol M. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014; 384: 665-673.

[25] Scagliotti GV, Vynnychenko I, Park K, Ichinose Y, Kubota K, Blackhall F, Pirker R, Galiulin R, Ciuleanu TE, Sydorenko O, Dediu M, Papai-Szekely Z, Banaclocha NM, McCoy S, Yao B, Hei YJ, Galimi F, Spigel DR. International, randomized, placebo-controlled, double-blind phase III study of motesanib plus carboplatin/paclitaxel in patients with advanced nonsquamous non-small-cell lung cancer: MONET1. J Clin Oncol 2012; 30: 2829-2836.

[26] Scagliotti GV, Krzakowski M, Szczesna A, Strausz J, Makhson A, Reck M, Wierzbicki RF, Albert I, Thomas M, Miziara JE, Papai ZS, Karaseva N, Thongprasert S, Portulas ED, von Pawel J, Zhang K, Selaru P, Tye L, Chao RC, Govindan R. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non-small-cell lung cancer: a phase III trial. J Clin Oncol 2012; 30: 2070-2078.

[27] Herbst RS, Ansari R, Bustin F, Flynn P, Hart L, Otterson GA, Vlahovic G, Soh CH, O'Connor P, Hainsworth J. Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial. Lancet 2011; 377: 1846-1854.

[28] Scagliotti G, Novello S, von Pawel J, Reck M, Pereira JR, Thomas M, Abrão Miziara JE, Balint B, De Marinis F, Keller A, Arén O, Csollak M, Albert I, Barrios CH, Grossi F, Krzakowski M, Cupit L, Cihon F, Dimatteo S, Hanna N. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. J Clin Oncol 2010; 28: 1835-1842.

[29] Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009; 27: 1227-1234.

[30] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355: 2542-2550.

[31] Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000; 53: 1119-1129.