

The impact of histological types on the efficacy of angiogenesis inhibitors in the treatment of advanced NSCLC: a meta-analysis of randomized controlled trials

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Purpose: We aimed at assessing the overall efficacy of angiogenesis inhibitor (AI)-containing regimens in the treatment of advanced non-small-cell lung cancer (NSCLC) according to histological types.

Methods: Studies from PubMed and Web of Science, and abstracts presented at American Society of Clinical Oncology (ASCO) meeting up to October 31, 2014 were searched to identify relevant studies. Eligible studies included prospective randomized controlled trials (RCTs) evaluating AIs in advanced NSCLC with survival data according to patients' histologies. The endpoints were overall survival (OS) and progression-free survival (PFS). Statistical analyses were conducted by using either random effects or fixed effect models according to the heterogeneity of included studies.

Results: A total of 10,035 patients with advanced NSCLC from 13 RCTs were identified for analysis. The pooled results demonstrated that AI-containing regimens significantly improved the PFS (HR, 0.84, 95% confidence interval (CI): 0.78–0.91, $P < 0.001$) and OS (HR, 0.92, 95% CI: 0.85–0.99, $P = 0.017$) in lung adenocarcinoma when compared to non-AI-containing regimens. Additionally, there was a significantly improved PFS (HR, 0.87, 95% CI: 0.77–0.98, $P = 0.027$) for AI-containing regimens in squamous cell lung carcinoma, but it did not translated into OS benefit (HR, 1.02, 95% CI: 0.92–1.15, $P = 0.68$). For NSCLC patients with other histological types, the use of AIs did not significantly improve PFS (HR, 0.90, 95% CI: 0.75–1.09, $P = 0.27$) and OS (HR, 0.90, 95% CI: 0.76–1.08, $P = 0.19$).

Conclusion: The findings of this study suggest that the addition of AIs to the treatment therapies for patients with lung adenocarcinoma offers improved survival benefits. Prospective clinical trials investigating the role of AIs in this setting are recommended.

Keywords: non-small-cell lung cancer, histological types, randomized controlled trials, angiogenesis inhibitors, meta-analysis

Introduction

Lung cancer is the leading cause of cancer-related mortality, with an estimated 1.4 million deaths each year.¹ Non-small-cell lung cancer (NSCLC) accounts for 85% of the cases. Most of the NSCLC patients have advanced disease at diagnosis. For these patients, platinum-based doublet therapy is the standard of care.² Regardless of the emergence of new cytotoxic agents, chemotherapy provides only marginal benefit in overall survival (OS). Clearly, novel therapeutic approaches to improve outcomes for patients with NSCLC are urgently needed.³

Angiogenesis, the process of new blood vessel formation, is critical for tumor progression, invasion, and metastasis in solid tumors.^{4–6} The vascular endothelial

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growth factor (VEGF) pathway has been the most well studied.⁷ Currently, bevacizumab is the only approved antiangiogenic agent for NSCLC patients when added to first-line carboplatin/paclitaxel chemotherapy.^{8–10} More recently, many new antiangiogenic agents targeting platelet-derived growth factor (PDGF) and fibroblast growth factor pathways are under clinical evaluation in NSCLC.^{11–17} In fact, a recent meta-analysis has demonstrated that the use of angiogenesis inhibitors (AIs) significantly improved OS and progression-free survival (PFS) in comparison with non-AI-containing therapies.¹⁸ However, NSCLC contains several different histological subtypes, and the biological behavior of each cell type appears to be different, which might affect the efficacy of AIs in different histological types. As a result, we performed this meta-analysis based on histologies to identify patients who will most likely benefit from AI-combining therapies.

Materials and methods

Selection of studies

We searched PubMed (data from January 2000 to October 2014), Embase (data from January 2000 to October 2014), and the Cochrane Library electronic databases. The search criteria included only randomized controlled trials (RCTs) published in the English language, and the keywords “bevacizumab”, “avastin”, “aflibercept”, “VEGFR-TKIs”, “sorafenib”, “nexavar”, “sunitinib”, “sutent”, “SU1248”, “vandetanib”, “caprelsa”, “ZD6474”, “axitinib”, “pazopanib”, “votrient”, “GW786034”, “regorafenib”, “apatinib”, “ramucirumab”, “nintedanib”, “BIBF1120”, “thalidomide”, “lenalidomide”, “motesanib”, “angiogenesis inhibitors”, “randomized”, and “non-small-cell lung cancer”. 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 January 2004 and June 2014. Each publication was reviewed and in case of duplicate publication only the most complete, recent, and updated report of the clinical trial was included in the meta-analysis.

Data extraction and clinical end point

Data extraction was conducted independently by two investigators according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (see checklist [Table S1](#))¹⁹ and any discrepancy between the reviewers was resolved by consensus. For each study, the following information was extracted: first author’s name, year of publication, trial phase, number of enrolled patients, treatment arms, age, primary end points, and median follow-up.

Phase I trials and single-group Phase II trials were omitted from analysis because of lack of controls. Trials that met the following criteria were included in our analysis: 1) prospective RCTs comparing AI-containing regimen to AI-free regimens as any line treatments in advanced NSCLC; 2) trials involving patients who were pathologically confirmed to have NSCLC; and 3) trials having sufficient survival data according to histological types for extraction. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included. The quality of reports of clinical trials was assessed and calculated using the 5-item Jadad scale including randomization, double-blinding, and withdrawals as described previously.²⁰

Data analysis

The analysis was undertaken on an intention-to-treat basis: patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. The outcomes used were 1) OS, defined as the time from random assignment to death from any cause, censoring patients who had not died at the date last known alive; 2) PFS, defined as the time from random assignment to first documented progression.

Statistical analysis of the overall hazard ratio (HR) for OS and PFS was calculated using Version 2 of the Comprehensive Meta analysis program (Biostat, Englewood, NJ, USA). A statistical test with a *P*-value less than 0.05 was considered significant. HR >1 reflected more deaths or progression in AI-containing regimens group, and vice versa. Between-study heterogeneity was estimated using the χ^2 -based *Q* statistic.²¹ The *I*² statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. Heterogeneity was considered statistically significant when $P_{\text{heterogeneity}} < 0.05$ or $I^2 > 50\%$. If heterogeneity existed, data were analyzed using a random effects model. In the absence of heterogeneity, a fixed-effects model was used. The presence of publication bias was evaluated by using the Begg and Egger tests.²² All *P*-values were two sided. All confidence intervals (CIs) had a two-sided probability coverage of 95%.

Results

Search results

A total of 320 potentially relevant studies were retrieved electronically, 307 of which were excluded for the reasons shown in Figure 1. Thirteen published RCTs with subgroup analysis assessing the efficacy of AIs in NSCLC according to different histologies were included in the

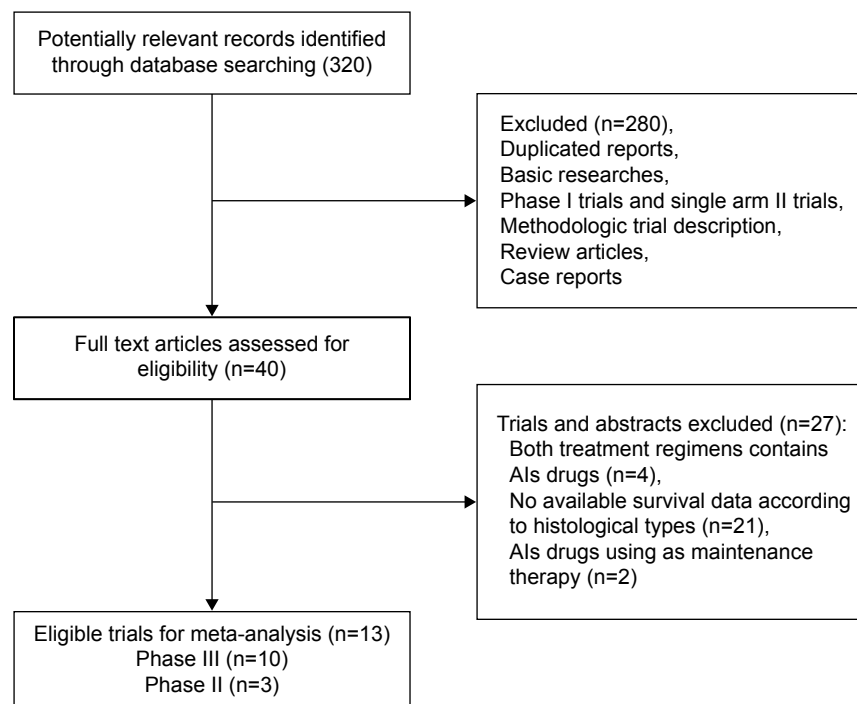


Figure 1 Studies eligible for inclusion in the meta-analysis.

meta-analysis.^{15,23–34} The baseline characteristics of each trial are listed in Table 1. A total of 10,035 patients were available. Six trials were performed in first-line settings, and seven in second-line. According to the inclusion criteria of each trial, patients were required to have adequate renal, hepatic, and hematologic function. The quality of each study was roughly assessed according to the Jadad scale. Ten trials had Jadad score of 5,^{15,24,25,27–32,34} and three trials had Jadad score of 3.^{23,26,33}

Overall survival

For patients with lung adenocarcinoma, seven of the 13 trials with a total of 4,457 patients reported OS data. The pooled results demonstrated that the use of AIs significantly improve OS in comparison with non-AI-containing therapies (HR, 0.92, 95% CI: 0.85–0.99, $P=0.017$, Figure 2 and Table 2) using a fixed-effects model ($I^2=0\%$). A total of 1,796 squamous cell cancer (SCC) patients from nine trials reported OS data, and the pooled results found that AI-containing regimens did not improve OS in comparison with non-AI-containing regimens (HR, 1.02, 95% CI: 0.92–1.15, $P=0.68$, Figure 2 and Table 2) using a fixed-effects model ($I^2=24.3\%$). Additionally, a nonsignificantly improved OS was observed in NSCLC patients with other histologies who were treated with AI-containing therapies (HR, 0.90, 95% CI: 0.76–1.08, $P=0.19$, Figure 2 and Table 2). We then performed subgroup

analysis according to treatment line. Our results showed that the use of AIs as second-line therapy in adenocarcinoma significantly improved OS (HR, 0.93, 95% CI: 0.86–1.00, $P=0.05$), while only one trial using AIs as first-line therapy in adenocarcinoma was included for analysis, and a tendency to improve OS was also observed (HR, 0.88, 95% CI: 0.75–1.03, $P=0.11$). For SCC patients, the use of AIs as second-line therapy seemed to improve OS (HR, 0.97, 95% CI: 0.86–1.10, $P=0.66$). However, the use of AIs as first-line therapy in these patients tended to decrease OS (HR, 1.25, 95% CI: 0.97–1.60, $P=0.08$).

Progression-free survival

A total of 3,692 lung adenocarcinoma and 1,354 SCC patients were included for analysis. The pooled HR for PFS demonstrated that AI-containing therapies significantly improve PFS in lung adenocarcinoma (HR, 0.84, 95% CI: 0.78–0.91, $P<0.001$, Figure 3 and Table 2) and SCC (HR, 0.87, 95% CI: 0.77–0.98, $P=0.027$, Figure 2 and Table 2), compared with non-AIs containing therapy. There was moderate heterogeneity between trials ($I^2=43.9\%$ and 46.2%), and the pooled HR for PFS was performed by using fixed-effects model. For patients with other histologies, the pooled results did not significantly improve PFS when compared to non-AI-containing regimens (HR, 0.90; 95% CI: 0.75–1.09, $P=0.27$, Figure 2 and Table 2).

Table 1 Baseline characteristic of included 13 trials for analysis

Study	Total patients	Treatment line	Histologies			Treatment regimens	Primary endpoint	Median follow-up (mo)	Jadad score
			Adenocarcinoma	Squamous	Others				
Heymach et al ²⁵	108	First line	59	26	23	Vandetanib 300 mg qd po + PTX + CBP Placebo + PTX + CBP	PFS	NR	5
Natale et al ²⁷	168	Second line	98	38	32	Vandetanib 300 mg qd po gefitinib 250 mg qd po	PFS	NR	5
Reck et al ²⁹	1,043	First line	876	0	167	Bev 7.5 mg/kg + DDP + GEM Bev 15 mg/kg + DDP + GEM	PFS	NR	5
Herbst et al ³⁴	1,391	Second line	829	344	218	Placebo + DDP + GEM Vandetanib 100 mg qd po + Doc Placebo + Doc	PFS	12.8	5
Hoang et al ²⁶	546	First line	202	191	153	Thalidomide 200 mg qd + OS PTX + CBP + RT PTX + CBP + RT	OS	61.8	3
Scagliotti et al ¹⁴	926	First line	534	223	169	Sorafenib 400 mg bid po + CBP + PTX Placebo + PTX + CBP	OS	NR	5
de Boer et al ²⁴	534	Second line	336	114	84	Vandetanib 100 mg qd po + pemetrexed Placebo + pemetrexed	PFS	NR	5
Herbst et al ³³	636	Second line	477	28	131	Bev 15 mg/kg + erlotinib Erlotinib 150 mg qd po	OS	19	3
Natale et al ²⁸	1,240	Second line	741	272	227	Vandetanib 300 mg qd po + erlotinib Placebo + erlotinib	PFS	NR	5
Scagliotti et al ³¹	960	Second line	506	270	184	Sunitinib 17.5 mg qd po + erlotinib Placebo + erlotinib qd po	OS	21.3	5
Scagliotti et al ³²	1,090	First line	890	0	200	Motesanib 125 mg qd po + CBP + PTX Placebo + CBP + PTX	OS	11	5
Garon et al ¹⁵	1,253	Second line	912	328	13	Ramucirumab 10 mg/kg + Doc Placebo + Doc	OS	9.5	5
Doebele et al ²³	140	First line	122	0	18	Ramucirumab + Pemetrexed + platinum Pemetrexed + platinum	PFS	NR	3

Abbreviations: PTX, paclitaxel; CBP, carboplatin; DDP, cisplatin; GEM, gemcitabine; Doc, docetaxel; RT, radiotherapy; Bev, bevacizumab; PFS, progression-free survival; OS, overall survival; NR, not reported.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. Begg's funnel plots did not reveal any evidence of obvious asymmetry for PFS (adenocarcinoma: $P=0.46$, SCC: $P=0.13$, and other histologies: $P=0.80$, respectively) and OS (adenocarcinoma: $P=0.76$, SCC: $P=0.12$, and other histologies: $P=0.06$). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias for PFS (adenocarcinoma: $P=0.27$, SCC:

$P=0.13$, and other histologies: $P=0.56$, respectively) and OS (adenocarcinoma: $P=0.94$ and SCC: $P=0.33$ respectively), but not for OS in patients with other histologies ($P=0.02$). The difference in the results obtained from the two methods might be due to a greater statistical power of the regression methods.³⁵

Discussion

NSCLC includes various histological types; SCC and adenocarcinoma are the most common. There are several differences

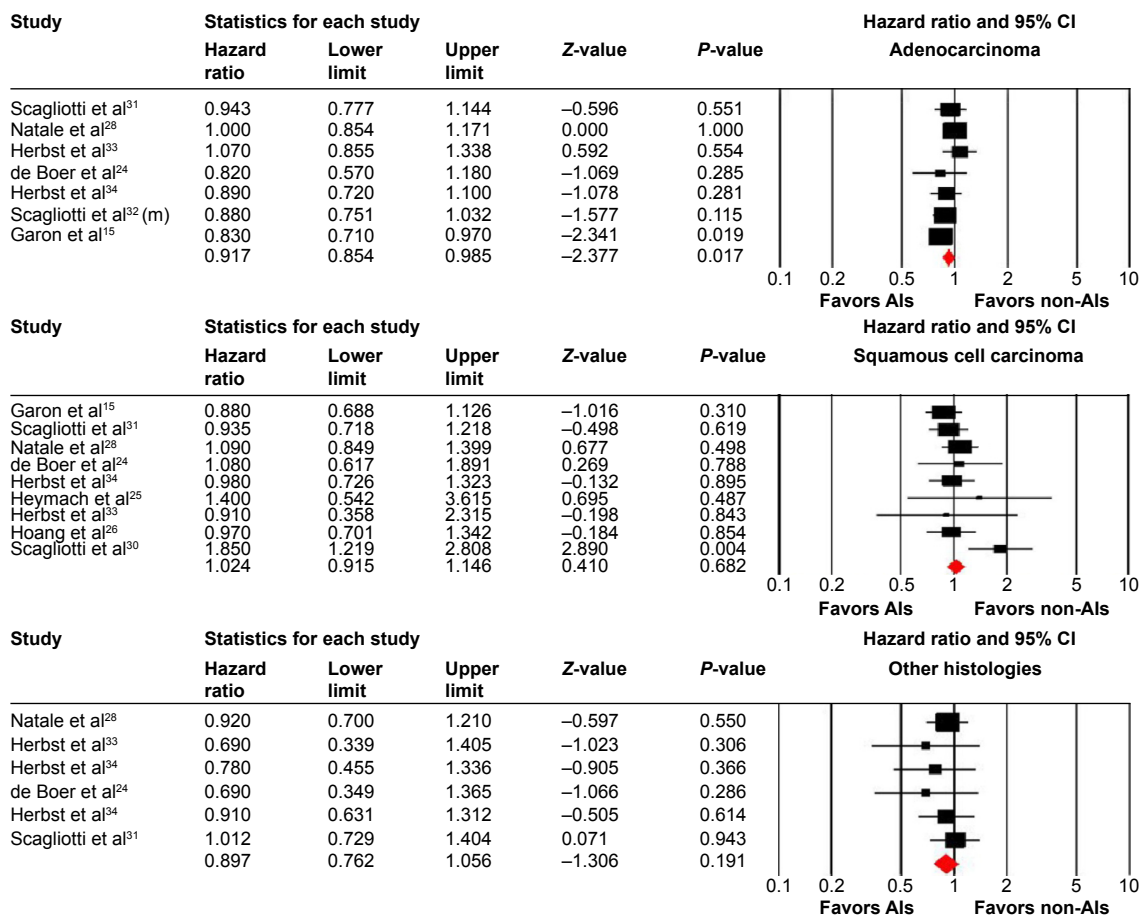


Figure 2 Fixed-effects model of HR (95% CI) of OS associated with AI-containing regimens versus non-AI-containing regimens.

Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; AIs, angiogenesis inhibitors.

in the clinical behavior of the histological types. Adenocarcinoma has a relatively higher possibility of developing distant metastases without local progression in NSCLC patients treated with definitive radiotherapy. A Japanese randomized Phase III trial of adjuvant chemotherapy with uracil-tegafur for completely resected pathological stage I NSCLC showed a survival benefit for patients with adenocarcinoma; however,

Table 2 Comparison of primary outcomes for therapies with or without angiogenesis inhibitors according to histologies

Groups	Trials (n)	Patients (n)	I ² (%)	HR (95%)	P
SCC					
OS	9	1,796	24.3	1.02 (0.92–1.15)	0.68
PFS	6	1,354	46.2	0.87 (0.77–0.98)	0.027
Adenocarcinoma					
OS	7	4,457	0	0.92 (0.85–0.99)	0.017
PFS	8	3,692	43.9	0.84 (0.78–0.91)	<0.001
Others					
OS	5	860	0	0.90 (0.76–1.08)	0.19
PFS	4	594	0	0.90 (0.75–1.09)	0.27

Note: I² ≥ 50% suggests high heterogeneity across studies.

Abbreviations: SCC, squamous-cell carcinoma; OS, overall survival; PFS, progression-free survival; HR, hazard ratio.

there was no benefit for patients with SCC.^{36,37} Similarly, a Phase III trial in regionally advanced, unresectable NSCLC to test whether chemotherapy followed by radiotherapy resulted in survival superior to either hyperfractionated radiotherapy alone or standard radiotherapy alone revealed a survival benefit in patients with nonsquamous cell carcinoma, whereas no benefit was recognized in those with SCC. These data suggest that the histological subtype is a very important factor to establish the treatment strategy for NSCLC. We thus performed this meta-analysis according to histologies identify patients who will most likely benefit from AI-combining therapies.

To the best of our knowledge, this study is the first meta-analysis with a focus on investigating the impact of histological types on the efficacy of AIs in advanced NSCLC. This study includes 13 RCTs incorporating 10,035 patients. The pooled results confirm that AI-containing regimens significantly improve PFS and OS in patients with lung adenocarcinoma compared to non-AI-containing regimens. For patients with squamous cell lung carcinoma, the use of AIs significantly improves PFS, but not OS. Additionally,

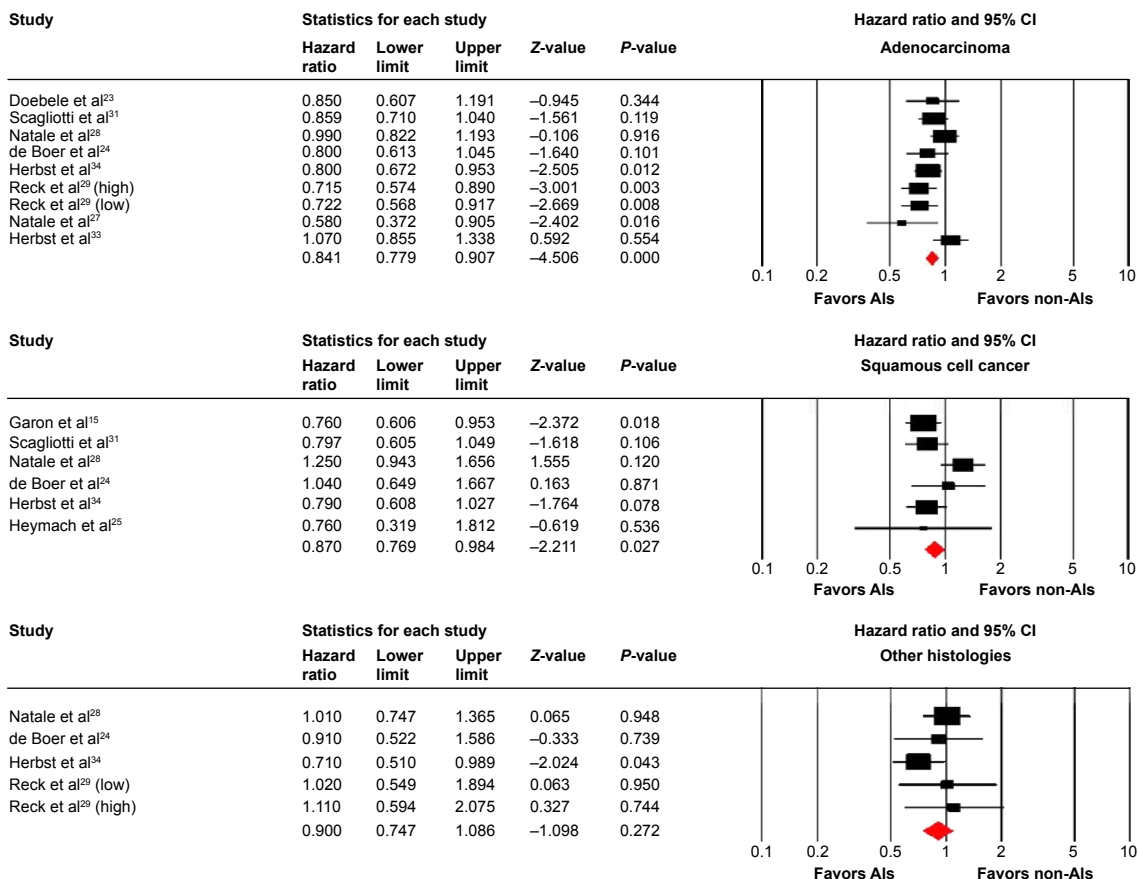


Figure 3 Fixed-effects model of HR (95% CI) of PFS associated with AI-containing regimens versus non-AI-containing regimens. **Abbreviations:** HR, hazard ratio; CI, confidence interval; OS, overall survival; AIs, angiogenesis inhibitors; PFS, progression-free survival.

there is a tendency to improve OS and PFS in patients with other histologies receiving AI-containing regimens. Therefore, the current findings suggest that, in patients with lung adenocarcinoma, AI-containing regimens could be a preferable treatment option over standard chemotherapy alone, although this recommendation cannot be conclusive because the overall comparisons are not based on randomization. Furthermore, the efficacy of AIs in patients with other histological types still needs to be assessed due to limited patients included in this study.

Our analysis has some obvious limitations. First, all included studies are conducted at major academic institutions among patients with adequate major organ function; thus, the results may not entirely apply to the general patient population in the community or patients with organ dysfunction. Second, we included patients receiving different antiangiogenesis agents for analysis. While each of these molecules inhibits angiogenesis, these drugs have different potencies, and have inhibitory properties against a range of nonoverlapping targeted receptors. Given the limited sample size of patients treated with any single AI,

we decide to include patients treated with all of these drugs in this class with adequate data on survival of patients with NSCLC according to histologies, which would increase the clinical heterogeneity among included trials. Third, the toxicity profile is another important factor for choosing treatment options. However, it is not possible to perform an analysis to deal with such a concern because reports of adverse events from each subgroup are not available. Finally, in the meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published and trials with null results tend not to be published. Our research detects no publication bias for OS, but not for PFS.

Conclusion

In conclusion, this is the first meta-analysis specifically assessing the role of AIs in advanced NSCLC according to histological types. The results of our study suggest that the addition of AIs to the treatment therapies for patients with lung adenocarcinoma offers an improved survival benefit when compared to non-AI-containing regimens. Prospective

clinical trials investigating the role of AIs in this setting are recommended.

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Disclosure

The authors report no conflicts of interest in this work.

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