ORIGINAL RESEARCH

Efficacy of targeted agents in the treatment of elderly patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis

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Purpose: The efficacy of targeted agents (TAs) in the treatment of elderly patients with advanced non-small-cell lung cancer (NSCLC) remains controversial. We aimed to assess the efficacy of TAs in the treatment of advanced NSCLC in this setting.

Materials and methods: Relevant trials were identified by searching electronic databases and conference meetings. Prospective randomized controlled trials assessing chemotherapies with or without TAs in elderly patients with advanced NSCLC were included. Outcomes of interest included overall survival (OS) and progression-free survival (PFS) in elderly patients with advanced NSCLC.

Results: A total of 4,093 elderly patients from 17 randomized controlled trials were included for analysis. The addition of TAs to chemotherapy significantly improved PFS (hazard ratio [HR] 0.85, 95% confidence interval [CI]: 0.75–0.96, $P=0.01$) when compared to chemotherapy alone. There was also a tendency to improve OS in the combination groups (HR 0.92, 95% CI: 0.85–1.01, $P=0.064$). Subgroup analysis based on treatment line indicated that TAs plus chemotherapy as first-line chemotherapy in elderly patients with advanced NSCLC significantly improved PFS (HR 0.80, 95% CI: 0.68–0.95, $P=0.01$) and OS (HR 0.91, 95% CI: 0.83–0.99, $P=0.037$), while the use of TA-containing regimens as second-line therapy in these patients did not significantly improve PFS (HR 0.91, 95% CI: 0.75–1.10, $P=0.33$) and OS (HR 1.04, 95% CI: 0.81–1.33, $P=0.77$) in comparison with chemotherapy alone. No publication bias was detected by Begg's and Egger's tests for OS.

Conclusion: The findings of this study suggest that the addition of TAs to first-line chemotherapy in elderly patients with advanced NSCLC offers an improved PFS and OS. Further trials are recommended to clearly investigate the efficacy of adding specific TAs to first-line chemotherapy for advanced NSCLC in this setting.

Keywords: non-small-cell lung cancer, elderly, targeted agents, randomized controlled trials, meta-analysis

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, accounting for almost 1.4 million deaths each year.[1] Approximately 85% of these patients have non-small-cell lung cancer (NSCLC) and more than two-thirds are older than 65 years.[2] Demographics that are shifting toward an older population suggest that oncologists will be seeing more elderly patients with lung cancer in years to come.[3,4] However, there are many challenges involved in the treatment of an elderly population with advanced NSCLC. Many of these patients have more comorbidities and tend to be less tolerant to toxic medical treatments than their younger counterparts.[5] Moreover, only 35% of patients with regional disease and 27% with metastatic

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disease received guideline-recommended treatment among patients aged ≥65 years.[6] Therefore, the optimal treatment for NSCLC in elderly patients remains unknown.

In current practice, there is a significant underrepresentation of elderly patients in most clinical trials on lung cancer.[7–9] However, previous clinical trials have shown that systematic chemotherapy would benefit elderly patients if they were carefully selected.[10,11] Subsequently, two meta-analyses also demonstrated that doublet combination chemotherapy was superior to a single third-generation cytotoxic agent for the treatment of elderly patients with advanced NSCLC.[12,13] Although these data have provided the rationale to treat fit elderly patients with standard chemotherapy regimens, a large number of elderly patients are still undertreated.

In recent decades, the emergence of molecularly targeted agents (TAs) has provided a novel treatment option for elderly patients with advanced NSCLC.[8,14–16] Several drugs designed to interfere with specific aberrant biological pathways in NSCLC, including angiogenesis inhibitors targeting vascular endothelial growth factors (VEGFs) pathway (anti-VEGF monoclonal antibody including bevacizumab[17] and ramucirumab[18]) and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (including erlotinib[19] and gefitinib[20,21]), have been approved for use in advanced NSCLC due to their potential survival benefits. In addition, other TAs are at varying stages of clinical development, such as anti-EGFR monoclonal antibodies (cetuximab and necitumumab), immune modulator (thalidomide), and small multikinase inhibitor targeting VEGF receptor/platelet-derived growth factor receptor/FLT-3/c-KIT (sorafenib, motesanib, nintedanib, and vandetanib). Although the trials that established the efficacy of these agents allow the enrollment of patients older than 70 years, the elderly patients constitute the minority. Additionally, the elderly patients in these clinical trials are not entirely representative of the overall elderly patient population due to the stringent enrollment criteria on organ function and performance status. As a result, the applicability of the data of these trials to the overall patient population needs to be cautious due to the lack of trials dedicated specifically to the elderly population. Thus, we perform this meta-analysis of all available randomized controlled trials (RCTs) to determine the overall efficacy of TAs in NSCLC patients aged ≥65 years.

Materials and methods
Selection of studies
The PubMed, Embase, and Cochrane Library electronic databases were search to identify relevant studies of TAs in advanced NSCLC (published before September 31, 2015). The search was limited to human studies and RCTs. No language restriction was imposed. The keywords are "bevacizumab", "avastin", "aflibercept", "VEGFR-TKIs", "sorafenib", "nexavar", "sunitinib", "sutent", "SU1248", "vandetanib", "caprelsa", "ZD6474", "axitinib", "pazopanib", "votrient", "GW786034", "regorafenib", "apatinib", "ramucirumab", "nintedanib", "BIBF1120", "thalidomide", "lenalidomide", "angiogenesis inhibitors", "cetuximab", "panitumumab", "erlotinib", "gefitinib", "afatinib", "randomized", and "non-small-cell lung cancer". In addition, we searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences for relevant trials (from January 2004 to June 2015). If duplicate data were presented in several studies, only the most informative or complete articles 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,[22] and any discrepancy between the reviewers was resolved by consensus. The following data were extracted: first author, year of publication, trial phase, number of elderly patients, treatment arms, age, primary end points, and median follow-up. A standardized Excel file was used for data extraction. Trials that met the following inclusion criteria were included: 1) study design, RCT; 2) population, patients were pathologically confirmed of NSCLC; 3) intervention, comparing chemotherapies with or without TAs; and 4) outcome measure, the study had sufficient survival data of elderly patients (≥65 years) for extraction. We used the Jadad score to assess the quality of clinical trials, which was calculated by using the five-item Jadad scale, including randomization, double-blinding, and withdrawals, as described previously.[23]

Data analysis
We assessed the overall efficacy of adding TAs to therapies in the treatment of elderly patients with advanced NSCLC. The outcomes used were 1) overall survival (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 and 2) progression-free survival (PFS), defined as the time from random assignment to first documented progression. PFS and OS were treated as time-to-event variables and thus were expressed as hazard ratios (HRs) with 95% confidence intervals [CI] for each study. Between-study heterogeneity was estimated

using the chi-square (χ^2)-based Q statistic.[24] The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. I^2 values of 25%, ~50%, ~75%, and ~100% indicated no, low, moderate, and high heterogeneities, respectively. We pooled the analysis according to the heterogeneity among the included trials. To investigate the sources of heterogeneity, we also conducted predefined subgroup analysis according to treatment line. Additionally, we used the Begg's and Egger's tests to assess the publication bias.[25]

Results

Search results

The initial search of the PubMed, Embase, and Cochrane Library electronic databases yielded a total of 450 potentially relevant studies. Of these, 433 were excluded for the reasons shown in Figure 1. Sixteen published RCTs with subgroup analysis assessing the efficacy of TAs in elderly patients were included in the meta-analysis. One additional RCT investigating the efficacy of vandetanib in elderly patients with NSCLC was included.[26] Finally, a total of 17 trials were included for analysis. The main characteristics of each trial are presented in Table 1. A total of 4,093 patients were available. Fourteen trials were performed in first-line settings,[17,18,26–37] and three in second-line settings.[38–40] Thirteen trials were randomized Phase III trials,[17,27–36,38,39–40] and three were randomized Phase II trials.[18,26,37] The quality of each included study was roughly assessed according to Jadad scale, and six trials had Jadad score of 5, and eleven trials had Jadad score of 3.

Overall survival

Eleven trials with 13 comparisons reported OS data of elderly patients. The pooled results demonstrated that the

addition of TAs to chemotherapy had a tendency to improve OS in comparison with chemotherapy alone (HR 0.92, 95% CI: 0.85–1.01, P=0.064, Figure 2) using a fixed-effects model. We then performed subgroup analysis according to treatment line and found that trials using TA-containing regimens as first-line therapy (HR 0.91, 95% CI: 0.83–0.99, P=0.037) significantly improved OS when comparing chemotherapy alone but not for second-line therapies (HR 1.04, 95% CI: 0.81–1.33, P=0.77). We then performed subgroup analysis according to specific TAs and found that the use of anti-EGFR agents significantly improved OS (HR 0.87, 95% CI: 0.77–0.98, P=0.024) but not for anti-VEGF agents (HR 0.97, 95% CI: 0.86–1.10, P=0.65).

Progression-free survival

Ten trials with 12 comparisons reported PFS data. The pooled HR for PFS demonstrated that the addition of TAs to chemotherapies significantly improved PFS giving HR 0.85 (95% CI: 0.75–0.96, P=0.01, Figure 3), compared with chemotherapy alone. There was significant heterogeneity between trials (I^2=47.3%, P=0.035), and the pooled HR for PFS was performed by using random-effects model. We performed subgroup analysis according to treatment line and found that the addition of TAs to chemotherapy significantly improved PFS as first-line therapy (HR 0.80, 95% CI: 0.68–0.95, P=0.01) in elderly patients with advanced NSCLC but not for second-line therapy (HR 0.91, 95% CI: 0.75–1.10, P=0.33). Additionally, we performed subgroup analysis according to specific TAs and found that the use of anti-VEGF agents significantly improved PFS (HR 0.81, 95% CI: 0.69–0.96, P=0.012) and a marginally significant PFS benefits for anti-EGFR agents (HR 0.89, 95% CI: 0.79–1.01, P=0.06).

Publication bias

We performed Begg's funnel plot and Egger's test to assess the publication bias of literatures. The Begg's funnel plots revealed no evidence of publication bias (P=0.63 for OS and P=0.15 for PFS). Additionally, Egger's test still did not suggest any evidence of publication bias for OS (P=0.83) but it did detect potential publication bias for PFS (P=0.003). The differences in the results obtained from the two methods might be due to a greater statistical power of the regression methods.[41]

Discussion

During the past few decades, the introduction of biological agents targeting specific signal pathways related to tumor growth and survival, including EGFR and the VEGF signaling
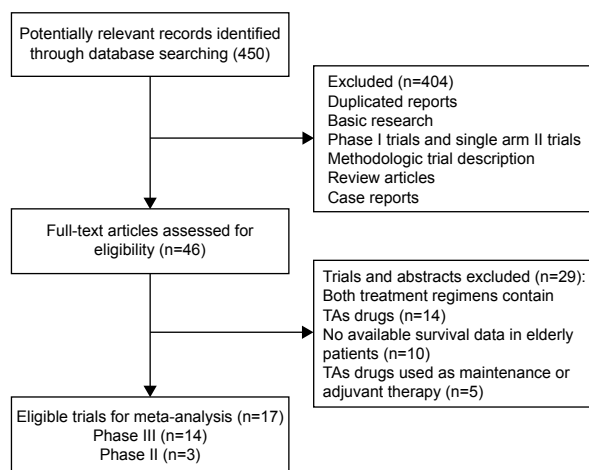

Figure 1 Studies eligible for inclusion in the meta-analysis.
Abbreviation: TA, targeted agent.

Table 1 Baseline characteristic of included 17 trials for analysis

Author/year	Phase	Line of treatment	No of elderly patients	Age	Targets	Treatment regimens	Primary end point	Jadad score
Zhou et al[32] (2015)	III	First line	53	≥65	VEGF	Bev + PTX + CBP Placebo + PTX + CBP	PFS	5
Doebele et al[18] (2015)	II	First line	66	≥65	VEGFR-2	Ramucirumab + pemetrexed + platinum Pemetrexed + platinum	PFS	3
Thatcher et al[35] (2015)	III	First line	421	≥65	EGFR	Necitumumab + Gem + DDP Gem + DDP	OS	3
Soria et al[40] (2015)	III	Second line	77	≥65	EGFR	Gefitinib + pemetrexed + DDP Pemetrexed + DDP	PFS	3
Paz-Ares et al[34] (2015)	III	First line	115	≥65	EGFR	Necitumumab + pemetrexed + DDP Pemetrexed + DDP	OS	3
Garon et al[39] (2014)	III	Second line	252	≥70	VEGFR-2	Ramucirumab + Doc Placebo + Doc	OS	5
Reck et al[38] (2014)	III	Second line	158	≥65	VEGFR-1, -2, -3; PDGFR; FGFR-1, -2, -3; Flt-3	Nintedanib + Doc Placebo + Doc	PFS	5
Gridelli et al[26] (2014)	II	First line	124	≥70	VEGFR-2, -3; EGFR	Vandetanib + Gem Placebo + Gem	PFS	5
Wu et al[36] (2013)	III	First line	102	≥65	EGFR	Erlotinib + Gem + platinum Gem + platinum	PFS	3
Scagliotti et al[31] (2012)	III	First line	370	≥65	VEGFR-1, -2, -3; PDGFR; Flt-3; c-kid	Motesanib + PTX + CBP Placebo + PTX + CBP	OS	5
Hoang et al[27] (2012)	III	First line	546	≥65	Antiangiogenic agents	Thalidomide + PTX + CBP + RT PTX + CBP + RT	OS	3
Niho et al[37] (2012)	II	First line	67	≥65	VEGF	Bevacizumab + PTX + CBP PTX + CBP	PFS	3
Scagliotti et al[30] (2010)	III	First line	381	≥65	b-Raf, VEGFR-2, -3; PDGFR; Flt-3; c-kid	Sorafenib + CBP + PTX CBP + PTX	OS	3
Lynch et al[28] (2010)	III	First line	340	≥65	EGFR	Cetuximab + taxane + CBP Taxane + CBP	PFS	3
Reck et al[29] (2009)	III	First line	304	≥65	VEGF	Bev 7.5 mg/kg + DDP + Gem Bev 15 mg/kg + DDP + Gem Placebo + DDP + Gem	PFS	5
Pirker et al[33] (2009)	III	First line	351	≥65	EGFR	Cetuximab + vinorelbine + DDP Vinorelbine + DDP	OS	3
Sandler et al[17] (2006)	III	First line	366	≥65	VEGF	Bev 15 mg/kg + CBP + PTX CBP + PTX	OS	3

Abbreviations: VEGF, vascular endothelial growth factor; Bev, bevacizumab; PTX, paclitaxel; CBP, carboplatin; PFS, progression-free survival; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; Gem, gemcitabine; DDP, cisplatin; OS, overall survival; Doc, docetaxel; RT, radiotherapy.

cascade, represents the most promising option to improve survival outcome for patients with advanced NSCLC.[42,43] However, there are limited data specifically focusing on the efficacy of TAs in elderly patients with advanced NSCLC. We therefore conducted this meta-analysis of RCTs with preplanned and unplanned subset analysis of elderly patients (≥65 years) to investigate the overall efficacy of TAs in the treatment of advanced NSCLC in this setting.

To our best knowledge, this is the first meta-analysis to assess the efficacy of adding TAs to chemotherapy in elderly patients with advanced NSCLC. Our study, including 4,026

patients from 17 RCTs, demonstrates that the addition of TAs to chemotherapy in elderly patients with advanced NSCLC significantly improves PFS, and there is also a tendency to improve OS in the combination groups. Subgroup analysis according to treatment line shows that the addition of TAs to first-line chemotherapy significantly improves PFS and OS, while no significant survival benefits have been observed in TAs plus second-line chemotherapy. Based on our results, we could conclude that the combination of TAs plus chemotherapy could be recommended as first-line treatment for elderly patients with advanced NSCLC, but
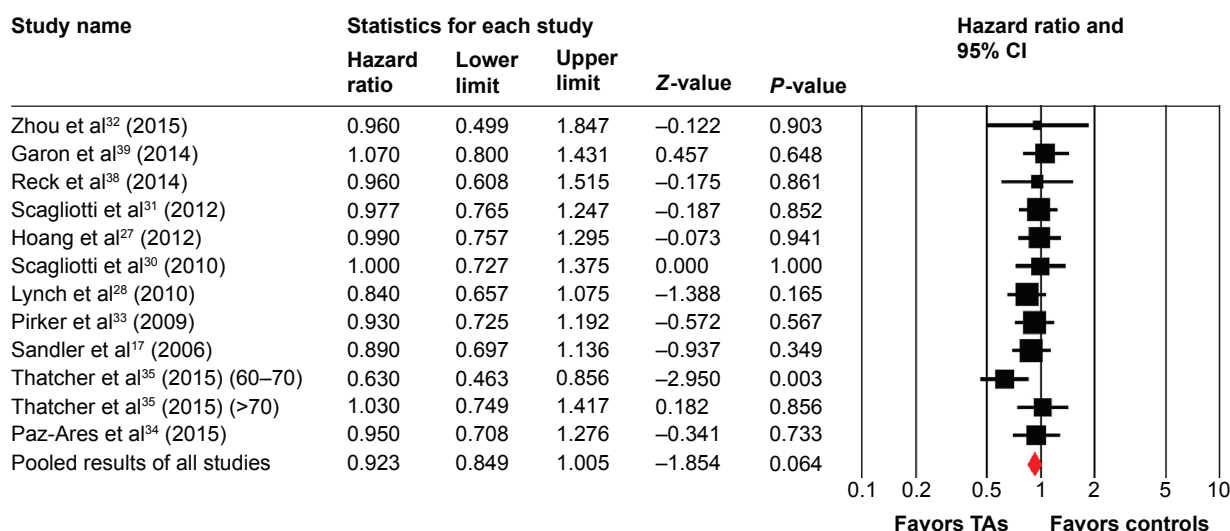
Study name	Statistics for each study					Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	Z-value	P-value	
Zhou et al[32] (2015)	0.960	0.499	1.847	−0.122	0.903	
Garon et al[39] (2014)	1.070	0.800	1.431	0.457	0.648	
Reck et al[38] (2014)	0.960	0.608	1.515	−0.175	0.861	
Scagliotti et al[31] (2012)	0.977	0.765	1.247	−0.187	0.852	
Hoang et al[27] (2012)	0.990	0.757	1.295	−0.073	0.941	
Scagliotti et al[30] (2010)	1.000	0.727	1.375	0.000	1.000	
Lynch et al[28] (2010)	0.840	0.657	1.075	−1.388	0.165	
Pirker et al[33] (2009)	0.930	0.725	1.192	−0.572	0.567	
Sandler et al[17] (2006)	0.890	0.697	1.136	−0.937	0.349	
Thatcher et al[35] (2015) (60–70)	0.630	0.463	0.856	−2.950	0.003	
Thatcher et al[35] (2015) (>70)	1.030	0.749	1.417	0.182	0.856	
Paz-Ares et al[34] (2015)	0.950	0.708	1.276	−0.341	0.733	
Pooled results of all studies	0.923	0.849	1.005	−1.854	0.064	

0.1   0.2   0.5   1   2   5   10

Favors TAs   Favors controls

Figure 2 Fixed-effects model of hazard ratio (95% CI) of OS associated with chemotherapy with or without TAs.
Notes: Thatcher et al,[35] divided older patients into two groups (60–70 and >70) within their study, as both groups consist of patients with NSCLC treated with targeted agents. Thus, the efficacy of targeted agents in these two groups are different so they are displayed separately.
Abbreviations: CI, confidence interval; OS, overall survival; TA, targeted agent.

more evidence is still required to identify patients who will most likely benefit for the specific TAs plus chemotherapy. Due to only three RCTs assessing the efficacy of TAs plus second-line chemotherapy in elderly patients for analysis, we acknowledge that data are immature to make an exact conclusion about the role of TAs in this setting, and more evidence is still needed to clearly set the role of adding TAs to second-line chemotherapy for elderly patients with advanced NSCLC. Additionally, we performed subgroup analysis according to specific TAs and found that the use of anti-EGFR agents in elderly patients with advanced NSCLC significantly improved PFS and OS, while anti-VEGF agents marginally improved PFS, but not for OS in these patients.

Further studies are still needed to identify patients who will most likely benefit from the appropriate TAs in elderly patients with advanced NSCLC.

Several limitations exist in this analysis. First, this meta-analysis considers only published literature, and lack of individual patient data prevents us from adjusting the treatment effect according to disease and patient variables. Second, elderly patients treated with different TAs were included for analysis, which would increase the clinical heterogeneity. Furthermore, our study could not answer which TA would be the best choice. Finally, publication bias is an important issue because trials with positive results are more likely to be published than trials with null results. Our research detects
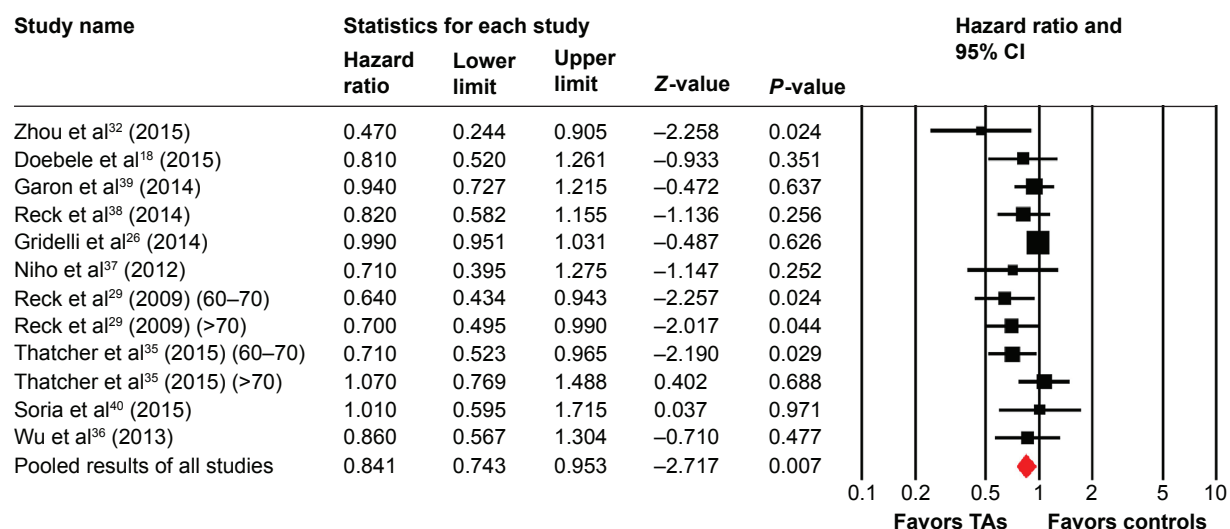
Study name	Statistics for each study					Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	Z-value	P-value	
Zhou et al[32] (2015)	0.470	0.244	0.905	−2.258	0.024	
Doebele et al[18] (2015)	0.810	0.520	1.261	−0.933	0.351	
Garon et al[39] (2014)	0.940	0.727	1.215	−0.472	0.637	
Reck et al[38] (2014)	0.820	0.582	1.155	−1.136	0.256	
Gridelli et al[26] (2014)	0.990	0.951	1.031	−0.487	0.626	
Niho et al[37] (2012)	0.710	0.395	1.275	−1.147	0.252	
Reck et al[29] (2009) (60–70)	0.640	0.434	0.943	−2.257	0.024	
Reck et al[29] (2009) (>70)	0.700	0.495	0.990	−2.017	0.044	
Thatcher et al[35] (2015) (60–70)	0.710	0.523	0.965	−2.190	0.029	
Thatcher et al[35] (2015) (>70)	1.070	0.769	1.488	0.402	0.688	
Soria et al[40] (2015)	1.010	0.595	1.715	0.037	0.971	
Wu et al[36] (2013)	0.860	0.567	1.304	−0.710	0.477	
Pooled results of all studies	0.841	0.743	0.953	−2.717	0.007	

0.1   0.2   0.5   1   2   5   10

Favors TAs   Favors controls

Figure 3 Random-effects model of hazard ratio (95% CI) of PFS associated with chemotherapy with or without TAs.
Abbreviations: CI, confidence interval; PFS, progression-free survival; TA, targeted agent.

no publication bias using Begg's and Egger's tests for OS but not for PFS.

Conclusion

This is the first meta-analysis specifically assessing the efficacy of adding TAs to chemotherapy in elderly patients with advanced NSCLC. The results of our study suggest that the addition of TAs to first-line chemotherapy in elderly patients with NSCLC offers an improved PFS and OS, when compared to chemotherapy alone. With present available data from randomized clinical trials, we could not clearly set the role of TAs in the second-line treatment for elderly patients with advanced NSCLC. Further studies are recommended to assess the efficacy of adding TAs to second-line chemotherapy for advanced NSCLC in this setting.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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