ORIGINAL RESEARCH

The role of maintenance therapy in the treatment of elderly non-small-cell lung cancer patients: a meta-analysis of randomized controlled trials

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Purpose: Maintenance therapy is an effective treatment strategy for advanced non-small-cell lung cancer (NSCLC). We aim to investigate whether age would affect the efficacy of maintenance therapy in the treatment of advanced NSCLC.

Materials and methods: Relevant trials were identified by searching electronic databases and conference meetings. Prospective randomized controlled trials assessing maintenance therapy 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 2,724 patients from 5 randomized controlled trials were included for analysis, with 897 patients aged ≥65 years and 1,577 patients aged <65 years. Single-agent maintenance therapy in elderly patients significantly improved PFS (hazard ratio [HR] 0.65, 95% CI: 0.43–0.98, $p=0.04$) and OS (HR 0.81, 95% CI: 0.68–0.97, $p=0.024$) when compared with placebo. In addition, doublet maintenance therapy significantly improved PFS (HR 0.81, 95% CI: 0.68–0.97, $p=0.024$) in comparison with single-agent maintenance therapy. However, doublet maintenance did not improve OS in comparison with single-agent maintenance therapy (HR 1.05, 95% CI: 0.60–1.83, $p=0.86$).

Conclusions: The findings of this study suggest that single-agent maintenance therapy in elderly patients with advanced NSCLC offers an improved PFS and OS when compared with placebo. Further trials are recommended to clearly investigate the efficacy of combination maintenance therapy for advanced NSCLC in this setting.

Keywords: non-small-cell lung cancer, maintenance therapy, elderly, meta-analysis, lung neoplasm, older, systematic review

Introduction

Lung cancer remains the highest incidence of all cancers and the leading cancer-related death worldwide.[1] Histopathologically, the majority of lung cancer (about 85%) are classified as non-small-cell lung cancer (NSCLC).[2] Most patients with NSCLC (~80%) are diagnosed with locally advanced or metastatic disease.[3] Currently, platinum-based doublet chemotherapy is the standard of care for first-line therapy.[4–6] However, outcomes of advanced NSCLC is disappointing, with 5-year overall survival (OS) <5%. Clearly, novel anti-cancer agents or treatment strategies are needed to improve the survival of these patients.

In order to sustain a reduced tumor size and relieve tumor-related symptoms, maintenance therapy has emerged as a novel therapeutic strategy for advanced NSCLC.[7–9] Maintenance therapy can be classified into 2 types: switch maintenance therapy and continuous maintenance therapy. Continuation maintenance is defined as keeping ongoing

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administration 1 or more drugs (combination maintenance) used in first-line regimen; while switch maintenance generally introduces an additional agent immediately after completion of 4 to 6 cycles of first-line chemotherapy. Several published meta-analyses have demonstrated that maintenance therapy with either a continuation or a switch strategy significantly increased progression-free survival (PFS) and OS in comparison with controls, but more incidences of toxicities are observed in maintenance therapy group.[10–15] Based on these published data, maintenance therapy has been recommended by the US Food and Drug Administration in advanced NSCLC after first-line chemotherapy.[16] However, to our best knowledge, the role of maintenance therapy in the treatment of elderly NSCLC remains undetermined. As a result, we conducted this systematic review and meta-analysis to assess the overall efficacy of maintenance therapy in this patient population with advanced NSCLC.

Materials and methods
Study design
We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines 2009.[17]

Search strategy
We conducted a comprehensive literature search of public databases, including PubMed, EMBASE, and the Cochrane library (up to April 30, 2017). Relevant search keywords included the followings: "non-small-cell lung cancer," "maintenance therapy," and "randomized controlled trials (RCTs)." No language restriction was administered. We also conducted a manual search of conference proceedings. All results were input into Endnote X7 reference software (Thomson Reuters, Stamford, CT, USA) for duplication exclusion and further reference management.

Study selection
Clinical trials that met the following criteria were included: 1) prospective Phase II or III trials involving NSCLC patients; 2) patients received maintenance therapy; and 3) available survival data regarding elderly NSCLC patients. 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.

Data extraction
Two independent investigators conducted the data abstraction, and any discrepancy between the reviewers was resolved

by consensus. The following information was extracted for each study: first author's name, year of publication, trial phase, number of enrolled subjects, treatment arms, median age, median PFS, and OS.

Outcome measures
A formal meta-analysis was conducted using Comprehensive Meta-Analysis software (Version 2.0; Biostat, Englewood, NJ, USA). The outcome data were pooled and reported as hazard ratio (HR). The primary outcome of interest was OS and secondary outcomes PFS in elderly patients with advanced NSCLC.

Statistical analysis
All statistical analyses were performed by using Version 2 of the Comprehensive Meta-Analysis program. Between-study heterogeneity was estimated using the χ^2-based Q statistic.[18] The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. If heterogeneity existed, data were analyzed using a random-effects model based on DerSimonian and Laird method. In the absence of heterogeneity, a fixed-effects model was used based on Mantel-Haenszel Method. HR >1 reflected more deaths or progression in maintenance regimens group, and vice versa. A statistical test with a p-value <0.05 was considered significant. Study quality was assessed by using the Jadad 5-item scale that included the randomization, double blinding, and withdrawals; the final score was reported between 0 and 5.[19]

Results
Search results
We initially found 210 relevant citations of maintenance therapy in NSCLC patients. After excluding review articles, Phase I studies, case reports, editorial, letters, commentaries, meta-analyses and systematic review (Figure 1), we selected 7 prospective RCTs,[20–26] and 2 studies with update results of previously published trials (PARAMOUNT[22] and AVAPERL[21]). Finally, a total of 5 trials were included for analysis in the present study. A total of 2,724 patients from 5 RCTs were included for analysis, with 897 patients aged $\geq$65 years and 1,577 patients aged $<$65 years. Table 1 listed the baseline characteristics of patients and studies. The quality of each included study was roughly assessed according to Jadad scale, and 4 of the 5 RCTs were double-blind placebo-controlled trials, thus had Jadad score of 5. Another Phase III trial was an open-label controlled trial that had a Jadad score of 3.
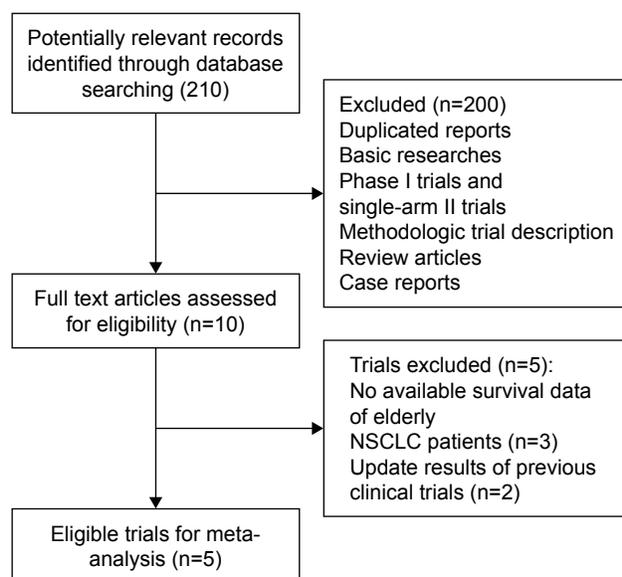
Figure 1 Studies eligible for inclusion in the meta-analysis.
Abbreviation: NSCLC, non-small cell lung cancer.

Single-agent maintenance therapy in elderly patients

Two trials reported PFS data of single-agent maintenance therapy in elderly patients. The pooled HR for PFS demonstrated that the single-agent maintenance therapy in elderly patients significantly improved PFS giving HR 0.65 (95% CI: 0.43–0.98, p=0.04, Figure 2), in comparison with placebo. There was moderate heterogeneity between trials (I^2=68.0%, p=0.077), and the pooled HR for PFS was performed by using random-effects model. Three trials reported OS data of single-agent maintenance therapy in this patient population. The pooled HR for OS showed that the single-agent maintenance therapy significantly improved OS

giving HR 0.81 (95% CI: 0.68–0.97, p=0.024, Figure 2), in comparison with placebo.

Combination maintenance therapy in elderly patients

Two included trials comparing combination versus single-agent maintenance therapy reported survival data of elderly patients. The pooled HR for PFS demonstrated that combination maintenance therapy in elderly patients significantly improved PFS giving HR 0.67 (95% CI: 0.53–0.85, p=0.01, Figure 3), in comparison with singe agent maintenance therapy. However, no survival benefit was observed in combination maintenance in elderly patients (HR 1.05, 95% CI: 0.60–1.83, p=0.86).

Publication bias

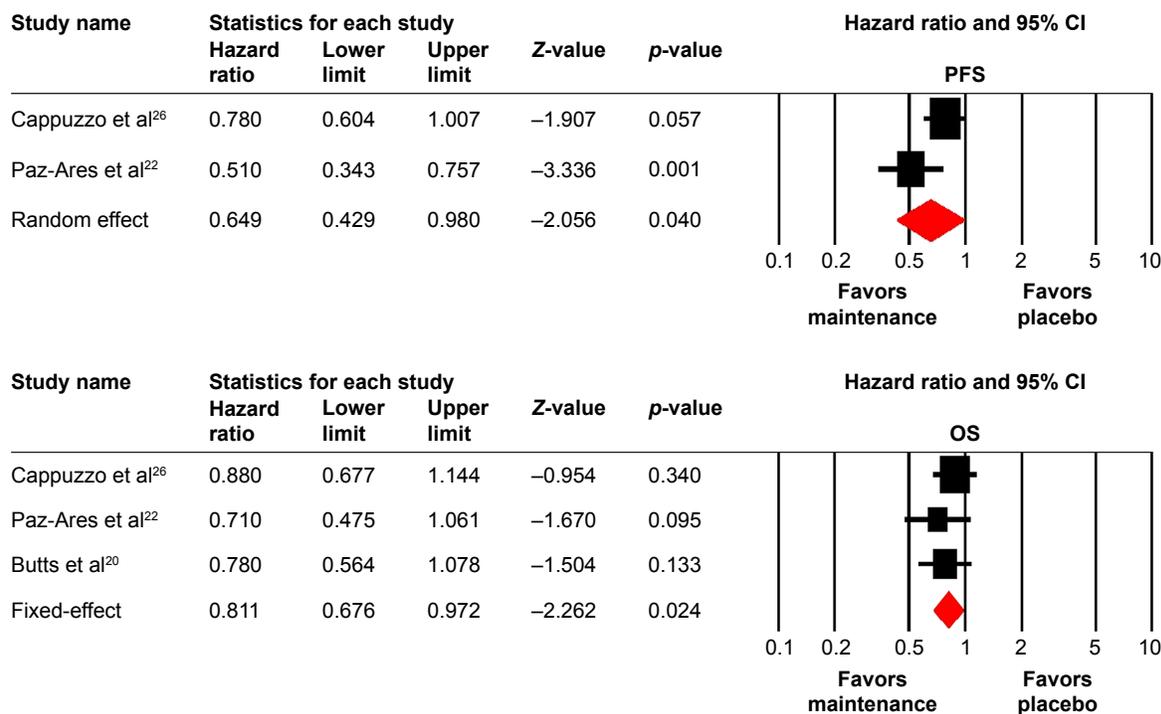We did not perform publication bias analysis due to limited RCTs in the present study.

Discussion

Until now, platinum-based doublet chemotherapy represented the gold standard in the treatment of advanced NSCLC, but with modest improvement in OS. Previous studies had demonstrated that prolongation of platinum-containing chemotherapy yielded no survival benefit and exposed patients to a higher risk of severe side effects. A meta-analysis conducted by Rossi et al[27] also confirmed that 4 courses of platinum-based treatment were the optimal duration of first-line chemotherapy. During the past decades, maintenance therapy for patients who achieved at least stable disease after first-line treatment has been extensively investigated to improve outcomes of advanced NSCLC patients. In fact, 5 meta-analyses[13,15,28–30] have been conducted to pool the overall

Table 1 Baseline characteristics of 5 included trials

Study/year	Phase	No of elderly patients	Cut-off of age	First-line therapy	Maintenance arm	Type of maintenance	Primary endpoint	Jadad score
Cappuzzo et al[26]	III	296	≥65	Platinum-doublet chemotherapy	Erlotinib Placebo	EGFR-targeted therapy/ switch maintenance	PFS	5
Barlesi et al[24]	III	72	≥65	Platinum-doublet chemotherapy + bevacizumab	Bevacizumab + pemetrexed Bevacizumab	AI-targeted therapy/ continuous maintenance	PFS	3
Johnson et al[23]	III	184	≥65	Platinum-doublet chemotherapy + bevacizumab	Bevacizumab + erlotinib Bevacizumab + placebo	AI-targeted therapy/ continuous maintenance	PFS	5
Paz-Ares et al[22]	III	189	≥65	Platinum-doublet chemotherapy	Pemetrexed Placebo	Cytotoxic agents/ continuous maintenance	OS	5
Butts et al[20]	III	156	≥65	Chemoradiotherapy	Tecemotide Placebo	Immunotherapy/switch continuous maintenance	OS	5

Abbreviations: AI, aromatase inhibitor; EGFR, epidermal growth factor receptor; PFS, progression-free survival; OS, overall survival.

Study name	Statistics for each study					Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	Z-value	p-value	PFS
Cappuzzo et al[26]	0.780	0.604	1.007	−1.907	0.057	
Paz-Ares et al[22]	0.510	0.343	0.757	−3.336	0.001	
Random effect	0.649	0.429	0.980	−2.056	0.040	

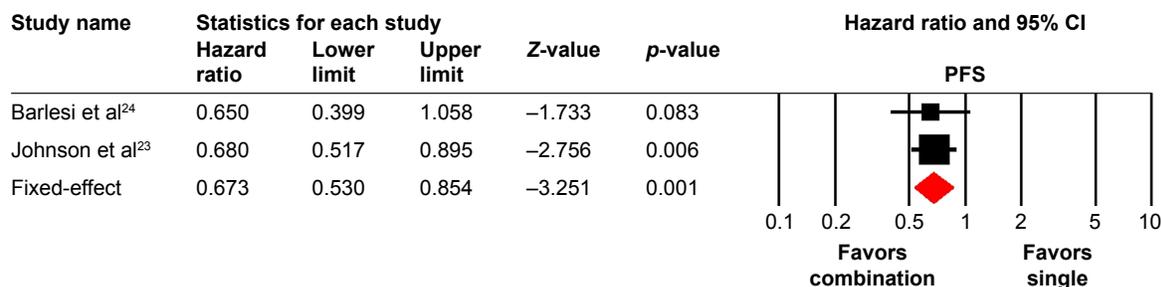| Study name	Statistics for each study					Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	Z-value	p-value	OS
Cappuzzo et al[26]	0.880	0.677	1.144	−0.954	0.340	
Paz-Ares et al[22]	0.710	0.475	1.061	−1.670	0.095	
Butts et al[20]	0.780	0.564	1.078	−1.504	0.133	
Fixed-effect	0.811	0.676	0.972	−2.262	0.024	

Figure 2 Pooled hazard ratio (95% CI) associated with maintenance therapy versus placebo in elderly NSCLC patients.
Abbreviations: NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival.

results of randomized trials assessing maintenance therapy in advanced NSCLC patients. All these meta-analyses show that maintenance therapy exposes patients to an increased risk of toxicity. Regarding effectiveness, single agent maintenance strategies demonstrate an improvement in PFS and OS in comparison with placebo. Additionally, combined maintenance therapy significantly improves PFS but not OS when compared with single agent maintenance. However, to our best knowledge, these are no systematic review and meta-analysis to comprehensively assess the role of maintenance therapy in the treatment of elderly NSCLC patients.

Our study included a total of 897 patients aged ≥65 years for analysis. The pooled results demonstrated that single-agent maintenance therapy in elderly NSCLC patients significantly improved PFS (HR 0.65) and OS (HR 0.81) in

comparison with placebo. In addition, doublet maintenance therapy significantly improved PFS (HR 0.81), but not OS (HR 1.05) in comparison with single-agent maintenance therapy. One possible explanation for this finding is that age may limit the aggressive maintenance treatment for elderly patients with advanced NSCLC, and elderly patients might have a slightly worse tolerance to combined maintenance therapy. Although we could not assess the toxicities of maintenance therapy in the present study, several previous studies have demonstrated an increased risk of toxicity with maintenance therapy in patients >65 years. In 1 study, patients who received pemetrexed maintenance therapy were more likely to have grade 3/4 toxicity (19% versus 10%), with the most common grade 3 toxicity being anemia and neutropenia.[31]

Study name	Statistics for each study					Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	Z-value	p-value	PFS
Barlesi et al[24]	0.650	0.399	1.058	−1.733	0.083	
Johnson et al[23]	0.680	0.517	0.895	−2.756	0.006	
Fixed-effect	0.673	0.530	0.854	−3.251	0.001	

Figure 3 Fixed-effects model of hazard ratio (95% CI) of PFS associated with combined versus single-agent therapy in elderly NSCLC patients.
Abbreviations: NSCLC, non-small cell lung cancer; PFS, progression-free survival.

Limitations

Several limitations exist in this analysis. First, this meta-analysis only considers published literature, and a meta-analysis of individual level data might define more clearly treatment benefits in specific subgroups. For instance, elderly patients are more likely to have comorbid conditions, and we are unable to investigate whether the survival benefit is similar in elderly patients with or without comorbid conditions. Second, none of the included trials report the toxicities of maintenance therapy in elderly patients. Thus, we could not answer whether the use of maintenance therapy in this patient population would increase the toxicities in comparison with controls. Third, there is still no general agreement on the definition of the elderly population. In the present study, all the included trials define elderly patients as >65 years. Finally, switch and continuous maintenance therapies are combined in the meta-analysis, which might increase the heterogeneity among included trials. In addition, our study includes different drugs with different mechanisms for analysis, which might be another source of heterogeneity. Although significant clinical heterogeneity of the meta-analysis could make the interpretation of a meta-analysis more problematic, but clinical heterogeneity might improve the generalizability of the observed heterogeneity.

Conclusion

In conclusion, this is the first meta-analysis specifically assessing the efficacy of maintenance therapy in the treatment of elderly patients with advanced NSCLC. The results of our study suggest that single-agent maintenance offers an improved PFS and OS in elderly NSCLC patients who have not progressed (ie, complete response, partial response, or stable disease) after at least 4 cycles of platinum-based chemotherapy. Further studies are recommended to investigate the efficacy and toxicities of combined maintenance therapy in the treatment of elderly NSCLC patients.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69–90.
2. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med*. 2008;359(13):1367–1380.
3. Shepherd FA. Screening, diagnosis, and staging of lung cancer. *Curr Opin Oncol*. 1993;5(2):310–322.
4. Schiller JH, Harrington D, Belani CP, et al; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346(2):92–98.
5. Georgoulias V, Ardavanis A, Agelidou A, et al. Docetaxel versus docetaxel plus cisplatin as front-line treatment of patients with advanced non-small-cell lung cancer: a randomized, multicenter phase III trial. *J Clin Oncol*. 2004;22(13):2602–2609.
6. Rino Y, Yukawa N, Sato T, et al. Phase II study on the combination of irinotecan plus cisplatin as a second-line therapy in patients with advanced or recurrent gastric cancer. *Mol Clin Oncol*. 2013;1(4):749–752.
7. Genestreti G, Di Battista M, Cavallo G, et al. Maintenance therapy in non-small cell lung cancer. *Expert Rev Anticancer Ther*. 2015;15(7):839–846.
8. Schmid-Bindert G. Maintenance therapy in non-small-cell lung cancer. *Transl Lung Cancer Res*. 2012;1(2):105–110.
9. Gridelli C, de Marinis F, Di Maio M, et al. Maintenance treatment of advanced non-small-cell lung cancer: results of an international expert panel meeting of the Italian association of thoracic oncology. *Lung Cancer*. 2012;76(3):269–279.
10. Cai H, Lin Y, Li W, Li X. Maintenance treatment with different strategies in advanced non-small-cell lung cancer: a systematic review and meta-analysis. *Clin Lung Cancer*. 2013;14(4):333–341.
11. Behera M, Owonikoko TK, Chen Z, et al. Single agent maintenance therapy for advanced stage non-small cell lung cancer: a meta-analysis. *Lung Cancer*. 2012;77(2):331–338.
12. Petrelli F, Borgonovo K, Cabiddu M, Barni S. Erlotinib as maintenance therapy in patients with advanced non-small cell lung cancer: a pooled analysis of three randomized trials. *Anticancer Drugs*. 2011;22(10):1010–1019.
13. Wang Q, Huang H, Zeng X, Ma Y, Zhao X, Huang M. Single-agent maintenance therapy for advanced non-small cell lung cancer (NSCLC): a systematic review and Bayesian network meta-analysis of 26 randomized controlled trials. *PeerJ*. 2016;4:e2550.
14. Hu X, Pu K, Feng X, et al. Role of gemcitabine and pemetrexed as maintenance therapy in advanced NSCLC: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2016;11(3):e0149247.
15. Zhang C, Huang C, Wang J, Wang X, Li K. Maintenance or consolidation therapy for non-small-cell lung cancer: a meta-analysis involving 5841 subjects. *Clin Lung Cancer*. 2015;16(5):e15–e23.
16. Lee JE, Chung CU. Update on the evidence regarding maintenance therapy. *Tuberc Respir Dis*. 2014;76(1):1–7.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
18. Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. *Genet Epidemiol*. 2005;28(2):123–137.
19. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet*. 1998;352(9128):609–613.
20. Butts C, Socinski MA, Mitchell PL, et al; START trial team. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014;15(1):59–68.
21. Barlesi F, Scherpereel A, Gorbunova V, et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. *Ann Oncol*. 2014;25(5):1044–1052.
22. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013;31(23):2895–2902.
23. Johnson BE, Kabbinavar F, Fehrenbacher L, et al. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2013;31(31):3926–3934.

24. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). *J Clin Oncol*. 2013;31(24):3004–3011.

25. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. 2012;13(3):247–255.

26. Cappuzzo F, Ciuleanu T, Stelmakh L, et al; SATURN investigators. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol*. 2010;11(6):521–529.

27. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. *J Clin Oncol*. 2012;30(14):1692–1698.

28. Lu S, Yu Y, Chen Z, Ye X, Li Z, Niu X. Maintenance therapy improves survival outcomes in patients with advanced non-small cell lung cancer: a meta-analysis of 14 studies. *Lung*. 2015;193(5):805–814.

29. Yuan DM, Wei SZ, Lu YL, et al. Single-agent maintenance therapy in non-small cell lung cancer: a systematic review and meta-analysis. *Chin Med J (Engl)*. 2012;125(17):3143–3149.

30. Rossi A, Garassino MC, Cinquini M, et al. Maintenance or consolidation therapy in small-cell lung cancer: a systematic review and meta-analysis. *Lung Cancer*. 2010;70(2):119–128.

31. Gridelli C, de Marinis F, Thomas M, et al. Final efficacy and safety results of pemetrexed continuation maintenance therapy in the elderly from the PARAMOUNT phase III study. *J Thorac Oncol*. 2014;9(7):991–997.