Original Article

Erlotinib in wild type epidermal growth factor receptor non-small cell lung cancer: A systematic review

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Abstract:

BACKGROUND: Targeting epidermal growth factor receptors (EGFR) is an innovative approach to managing non-small cell lung cancer (NSCLC) which harbors EGFR mutation. However, the efficacy of these agents like erlotinib in patients without the mutation is not known.

METHODS: This systematic review included Phase III randomized clinical trials that compared single agent erlotinib to other management options in the setting of NSCLC with reported outcome data on patients with EGFR wild type (EGFRWT) tumors. Outcome data include overall survival (OS), progression free survival (PFS) and response rate (RR). Random effects meta-analysis was used to pool outcomes across studies.

RESULTS: Three studies met the inclusion criteria. These studies included a total of 2044 patients with outcome data on 674 patients with EGFRWT tumors (33%). Meta-analysis revealed a statistically significant improvement in OS with erlotinib (hazard ratio of 0.780; 95% confidence interval: 0.654-0.930, $P = 0.006$). Data were not available to perform PFS or RR analysis. The quality of this evidence is considered to be moderate to high.

CONCLUSION: Our study revealed a significant benefit of erlotinib in patient with EGFRWT tumors compared with other approaches. These findings add another therapeutic option to patients generally considered difficult to treat.

Key words:

Epidermal growth factor, erlotinib, non-small cell lung cancer

Lung cancer is the leading cause of cancer death world-wide with more than 1.376 million patients die from this disease annually.[1] Non-small cell lung cancer (NSCLC) constitutes 85% of all lung cancers, with a dismal 5 year survival of 15% of all diagnosed patients. Although the cure for advanced NSCLC remains elusive, recent advances in molecular field coupled with the development of targeted therapies marked a step forward in the management of this disease. Personalized medicine in lung cancer is heavily dependent on histological subtypes and other molecular features of the tumors. Targeting epidermal growth factor receptors (EGFR) is an important treatment modality for many solid tumors including NSCLC.

Targeted therapy for EGFR in lung cancer preceded the full understanding of the mechanism of action and the identification of predictive markers. Gefitinib and erlotinib, tyrosine kinase inhibitors (TKIs), were approved and clinically used widely before the unraveling of the EGFR mutation story.[2-4] Therefore, patients with NSCLC were empirically treated with these agents both in practice and in multiple clinical trials that enrolled thousands of patients studying these agents in various settings such as randomized versus placebo or versus chemotherapy as a single agent or in combinations.[5,6]

After identifying the EGFR mutation, evaluation of EGFR mutation was initially carried out on tumor specimen from previously treated patients with TKIs to assess its predictive value in term of response and patient outcome.[7-9]

EGFR mutation was found to be a strong predictive marker for tumor response and progression free survival (PFS). Then subsequent studies were developed using EGFR mutation as pre-requisite for patient selection and inclusion criteria.[10,11] However, excited about the impressive impact of EGFR mutation, patients with EGFRWT tumors were deemed to be not suitable for TKIs therapy without proper study or evaluation. Clinical practice guidelines excluded these patients from TKI therapy as a matter of fact.[12-14]

EGFRWT patients constitute 80-90% of all NSCLC and 60-85% of adenocarcinoma, which means more than half a million patients annually world-wide. These patients are deprived of these treatment options leaving them to the classic chemotherapy, which is more toxic and has limited benefits.

Our hypothesis is that patients with EGFR wild type (EGFRWT) tumors may benefit from TKIs, especially erlotinib as much as any other known

therapies given in the salvage setting. Our study aims at studying the outcome of patients with advanced NSCLC with EGFRWT tumors who received erlotinib in randomized trials comparing it to other salvage treatment modality.

Methods

The research question

Is erlotinib comparable with other management options in patients with EGFRWT NSCLC?

Protocol

Inclusion criteria

We included all Phase III randomized clinical trials that met the following criteria using the PICO Acronym.

P – Patients: Adult patients (>18 years of age) with metastatic NSCLC.

I – Intervention: Used erlotinib as a single agent in any line of therapy.

C – Comparator: Any chemotherapy regimen or placebo.

O – Outcome: Response rate (RR), overall survival (OS), Progression Free Survival (PFS).

Study design

randomized control trial that reported outcomes separately for patients with EGFRWT NSCLC.

Exclusion

We excluded any study using other concurrent cancer therapy with erlotinib; studies that did not have EGFRWT data or Phase II randomized studies.

Data Sources and Search Strategies

A comprehensive search of several databases from each database's earliest inception to May 2012, adults, any language was conducted. The databases included Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane database of systematic reviews and Scopus. The search strategy was designed and conducted by an experienced reference librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for lung cancer, erlotinib and EGFR as well as to limit to randomized controlled trials.

Data items

Data were obtained from review of the selected published manuscripts. Trials characteristics are presented in Table 1 including: Study label, diagnosis, line of therapy, number of patients, inclusion and exclusion criteria, intervention, patient number in each intervention arm, comparison and outcomes.

Risk of bias of individual studies

We used the Cochrane risk of bias tool to evaluate the quality of the studies. This tool assesses bias based on the adequacy of randomization and allocation concealment, blinding methods and loss to follow-up. We also considered whether the trials were halted prematurely, a characteristic that can exaggerate the effect size. Quality would be also weakened if EGFR testing was carried out in a retrospective fashion without a proper *a priori* planned stratification, which would

Table 1: Characteristics of the trials included in the systemic review

Study label	Diagnosis	Line of therapy	No. of patients	Inclusion criteria	Exclusion criteria	Intervention, number	Comparison	Outcome 1 (primary)	Outcome 2	Outcome 3
Tsao 2005 (BR21)	NSCLC	Second and third line	731	Adult, NSCLC, metastatic, progressive after at least 1 line of therapy, who has molecular studies, PS=0-3, adequate organ function (renal, hepatic and hematology)	Other malignancies, symptomatic brain mets, comorbidities (cardiac, GI, eye disease)	Erlotinib 150 mg/day, 488	Placebo, 243	OS	RR	
Cappuzzo 2010	NSCLC	Maintenance	889	Adult, NSCLC, measurable, advanced or metastatic, stable or responsive to first line therapy, PS=0-1, adequate organ function (renal, hepatic and hematology	Other malignancies, previous exposure to anti EGFR, uncontrolled brain mets	Erlotinib 150 mg/daily, 438 pts	Placebo, 451	PFS	OS, TTP, PFS in EGFR neg., TTD of symptoms and QOL	RR
Ciuleanu 2012 (TITAN)	NSCLC	Second line	424	Adult, NSCLC, measurable, advanced or metastatic failed first line chemotherapy PS=0-2, adequate organ function (renal, hepatic and hematology)	Other malignancies, Previous exposure to EGFR or pemetrexed, previous antineoplastic therapy other than platinum based regimen, uncontrolled brain mets, spinal cord compression	Erlotinib 150 mg/day, *N*=203	Chemotherapy (standard dose of docetaxel or pemetrexed, *N*=221	OS	PFS-TTP	RR

NSCLC = Non-small cell lung cancer, PS = Performance status, GI = Gastro Intestinal, EGFR = Epidermal growth factor receptors, PFS = Progression free survival, OS = Overall survival, RR = Response rate, QOL = Quality of life, TTP = Time to progression, TTD = Time to death

Table 2: Quality of studies included in the systemic review

Study label	Blinded group	Allocation concealment	Stopped for the benefit	Reported baseline imbalances	No. EGFRWT/ total erlotinib	No. EGFRWT/ total received comparator	Source of study funding
Tsao 2005 (BR21)	Double blinded points and physician	Yes	No	None	93/488	44/243	NCI-Canada, OSI Pharma
Cappuzzo 2010	All points, physicians monitors, sponsor	Yes	No	None	199/438	189/451	Hoffman La Roche
Ciuleanu 2012 (TITAN)	None	Yes	No	None	75/203	74/221	Hoffman La Roche

EGFR = Epidermal growth factor receptors wild type, NCI = National cancer institute

lead to spurious subgroup effect conclusions and imbalance between groups.

Statistical analysis

The outcomes of interest are OS, PFS and RR. The OS is calculated from enrolment in study until death and PFS from enrolment in study until progression of disease to patient death. RR is calculated by adding complete response and partial response.

We pooled hazard ratios (HR) across studies using the random effects model incorporating within-study and between- study heterogeneity. Heterogeneity was evaluated using the I2 statistic with values >50% consistent with substantial heterogeneity.[15,16]

Results

Three studies were identified that meet inclusion criteria. Tables 1 and 2 summarize characteristics and quality of these studies. A study by Tsao *et al*. sponsored by the Canadian National Cancer Institute and OSI Pharmaceutical included 731 patients with NSCLC. Patients were randomized into 2:1 to erlotinib versus placebo in the second and third line of therapy. It included all non-small cell histology and EGFR testing was not pre-requisite for enrolment in the study. Authors reported OS and RR, but PFS was not reported. An EGFR testing was performed on archival tissue. EGFRWT was identified in 93/488 of treatment arm and 44/243 of the control arm.[8]

The second study by Cappuzzo *et al*. (sponsored by Hoffman-La Roche) including 889 patients with NSCLC in the maintenance setting. The study included patients with stable responsive disease after 1st line therapy. OS, PFS and RR were reported. EGFRWT tumor were identified in 199/438 and 189/451 in the erlotinib arm as placebo.[17]

The third study by Ciuleanu *et al*. randomized 424 patients with NSCLC who failed first line therapy to erlotinib (203) or chemotherapy (221 pts) including docetaxel or pemetrexed. EGFRWT was identified in 75/203 in erlotinib arm and 74/221 in the chemotherapy arm.[18]

A study by Lilenbaum *et al*. was identified by using erlotinib versus chemotherapy in patients with NSCLC and poor performance status. The study was not included as it was Phase II study in special population and had very small number of EGFRWT (13 patients in the erlotinib arm and 5 patients in the chemotherapy arm).[19]

Table 3: Overall survival results of studies included in systemic review

Study label	HR	Lowest	Highest
Tsao 2005 (BR21)	0.73	0.49	1.1
Cappuzzo, 2010	0.77	0.61	0.97
Ciuleanu, 2012 (TITAN)	0.85	0.59	1.22

HR = Hazard ratio

Other randomized studies that compared erlotinib to other agents such as pemetrexed gefitinib or vandetanib did not have biomarkers studies.[20,21] Erlotinib was in both arms of some studies, which defeat the purpose of this study.[22,23]

Since RR was not reported in these studies and PFS was not reported in Tsao study, we only conducted meta-analysis for the outcome of OS [Table 3]. The meta-analysis revealed HR of 0.780 (0.654-0.930) and *P* value of 0.006 in favor of erlotinib used compared with the control areas [Table 4]. There was no statistical heterogeneity in the analysis (I2 < 50%).

The methodological quality of the studies was fair (one was unblinded) and all three had the allocation concealed none was stopped prematurely. None of them had proper stratified randomization procedures according to EGFRWT. Therefore, the results could be biased due to the effect of chance and spurious subgroup effect. The number of patients included in the analysis as well as the number of events were fairly small, leading to possibly lowering the quality of evidence due to imprecision.[24]

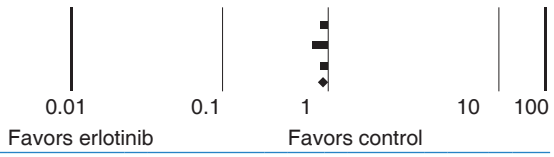
Discussion

Our systematic review of the literature and meta-analysis demonstrated that erlotinib improves OS in patients with EGFRWT. These intriguing results confirm that TKIs are beneficial in this setting compared with other approaches beyond the first line setting. In spite of the limitations of the study that are related mainly to performing EGFR testing on a subset of patients in a retrospective fashion, the results are not surprising and are plausible.

First of all, the current therapy in the salvage setting had very dismal outcome with very limited options, minimal clinical benefits in term of RR or survival. Therefore, it is not a tough competition to compare newer agents with established standards.[4,25,26] The second point is that EGFR research is an evolving field. Techniques performed in clinical practice may not detect the mutation and all possible mutations of EGFR may not have been discovered yet. Therefore, the drug may

Table 4: Meta-analysis results of HR of OS

Study name	Statistics for each study					HR and 95% CI
	Hazard ratio	Lower limit	Upper limit	*Z* value	*P* value	
Tsao, 2005	0.730	0.487	1.094	−1.526	0.127	
Cappuzzo, 2010	0.770	0.611	0.971	−2.209	0.027	
Ciuleanu, 2012	0.850	0.591	1.222	−0.877	0.381	
	0.780	0.654	0.930	−2.765	0.006	



HR = Hazard ratio, OS = Overall survival, CI = Confidence interval

work in these patients with unidentified mutation. One might argue that it is going to be a small fraction of patients with this characteristic. However, the trend in the management of NSCLC patients is to divide them into groups that respond to a personalized therapy irrespective of the group size. The story of crizotinib is a clear demonstration of how targeting a small percentage (4-5%) of patients is justified especially when it comes to a very prevalent disease like lung cancer. Furthermore, TKI may be working on other targets and may have other mechanisms that are not elucidated yet. This was evident by the clinical benefits in studies that exceeded the 10% prevalence EGFR mutation in the study population. Although tumor RR was within that range; stable disease was encountered in a larger proportion of patients including patients who do not match the profile of EGFR mutation such as male patients, smokers and those with squamous cell histology. Furthermore, heterogeneity between primary tumors and distant metastatic lesions may result in not recognizing a response in lesions with EGFR mutations.[27]

Although, we were unable to conduct meta-analysis on tumor response and disease control, these outcomes have been reported in patients with EGFRWT tumors. For example, in the BR21 Study, RR among the 81 patients who had EGFRWT tumor was 7%.[8]

There are other factors that favor the use of TKIs, which are related to the convenience and safety profile. Compared with chemotherapy, erlotinib generally has lesser side-effects apart from diarrhea and skin rash. It usually does not cause cytopenia or neuro toxicity or significant other organ toxicities.[19,20,28] In addition, erlotinib did improve tumor related symptoms and enhance quality-of-life.[29] Furthermore, even in term of cost-effectiveness, erlotinib is likely a reasonable choice in managing NSCLC as it was shown in a study comparing it to docetaxel or even generic docetaxel.[30,31] A very interested study using model simulation revealed that erlotinib maintenance in EGFRWT is cost-effective compared with best supportive care irrespective of the country setting.[32]

There is a major caveat to this approach. If one claimed that erlotinib is as good as chemotherapy in EGFRWT and works better in EGFR Mutation (EGFRMUT), would it be acceptable to give it to all comers with NSCLC? The TORCH study showed improved OS and disease free survival if chemotherapy was given before erlotinib compared with the other way around. Hence, at least for the present time and until further comparative effectiveness research is available; this approach to patients with EGFRWT tumor should be limited to patients who are beyond the first line setting. Patients with EGFRWT and good performance status (PS) should received chemotherapy and not TKI. However, for second and third line, EGFR mutation may not carry the same importance and TKI remains a valid option, which was the setting of the trials included in this systemic review.[33,34]

Conclusion

Our study revealed a clear benefit to erlotinib in EGFRWT NSCLC patients. These findings challenge the established practice of depriving these patients from this well-tolerated option. This therapy is an option maybe even more clearly needed in certain populations with poor PS or those who cannot tolerate standard chemotherapy.

References

1. GLOBACAN Project Estimated cancer Incidence, Mortality, Prevalence and Disability-adjusted life years (DALYs) Worldwide in 2008 [internet]. Lyon (France): IARC WHO 2010. [cited 2013 Mar 19]. Available from: http://globocan.iarc.fr.
2. Kris MG, Natale RB, Herbst RS, Lynch TJ Jr, Prager D, Belani CP, *et al*. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. JAMA 2003;290:2149-58.
3. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, *et al*. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) corrected. J Clin Oncol 2003;21:2237-46.
4. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, *et al*. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.
5. Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, *et al*. TRIBUTE: A phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005;23:5892-9.
6. Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, De Rosa F, *et al*. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: The Tarceva lung cancer investigation trial. J Clin Oncol 2007;25:1545-52.
7. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
8. Tsao MS, Sakurada A, Cutz JC, Zhu CQ, Kamel-Reid S, Squire J, *et al*. Erlotinib in lung cancer-Molecular and clinical predictors of outcome. N Engl J Med 2005;353:133-44.

9. Giaccone G, Rodriguez JA. EGFR inhibitors: What have we learned from the treatment of lung cancer? Nat Clin Pract Oncol 2005;2:554-61.
10. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
11. Rosell R, Gervais R, Vergnenegre A. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European erlotinib versus chemotherapy (EURTAC) phase III randomized trial (abstract #7503). J Clin Oncol 2011;29:476s.
12. Available from: http://www.nccn.org [Last accessed on 2013 May 14].
13. D'Addario G, Früh M, Reck M, Baumann P, Klepetko W, Felip E, *et al*. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:v116-9.
14. Keedy VL, Temin S, Somerfield MR, Beasley MB, Johnson DH, McShane LM, *et al*. American Society of Clinical Oncology provisional clinical opinion: Epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol 2011;29:2121-7.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
17. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczésna A, Juhász E, *et al*. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521-9.
18. Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, *et al*. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): A randomised multicentre, open-label, phase 3 study. Lancet Oncol 2012;13:300-8.
19. Lilenbaum R, Axelrod R, Thomas S, Dowlati A, Seigel L, Albert D, *et al*. Randomized phase II trial of erlotinib or standard chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2. J Clin Oncol 2008;26:863-9.
20. Hong J, Kyung SY, Lee SP, Park JW, Jung SH, Lee JI, *et al*. Pemetrexed versus gefitinib versus erlotinib in previously treated patients with non-small cell lung cancer. Korean J Intern Med 2010;25:294-300.
21. Natale RB, Thongprasert S, Greco FA, Thomas M, Tsai CM, Sunpaweravong P, *et al*. Phase III trial of vandetanib compared with erlotinib in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2011;29:1059-66.
22. Spigel DR, Burris HA 3rd, Greco FA, Shipley DL, Friedman EK, Waterhouse DM, *et al*. Randomized, double-blind, placebo-controlled, phase II trial of sorafenib and erlotinib or erlotinib alone in previously treated advanced non-small-cell lung cancer. J Clin Oncol 2011;29:2582-9.
23. Lynch TJ, Fenton D, Hirsh V, Bodkin D, Middleman EL, Chiappori A, *et al*. A randomized phase 2 study of erlotinib alone and in combination with bortezomib in previously treated advanced non-small cell lung cancer. J Thorac Oncol 2009;4:1002-9.
24. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, *et al*. GRADE guidelines 6. Rating the quality of evidence – Imprecision. J Clin Epidemiol 2011;64:1283-93.
25. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, *et al*. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-62.
26. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, *et al*. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
27. Sun L, Zhang Q, Luan H, Zhan Z, Wang C, Sun B. Comparison of KRAS and EGFR gene status between primary non-small cell lung cancer and local lymph node metastases: Implications for clinical practice. J Exp Clin Cancer Res 2011;30:30.
28. Ciuleanu T, Stelmakh L, Cicenas S. Erlotinib versus docetaxel or premetrexed as second-line therapy in patients with advanced non-small-cell lung cancer and poor prognosis: Efficacy and safety results from the phase III TITAN study. J Thorac Oncol 2010;5:S560.
29. Bezjak A, Tu D, Seymour L, Clark G, Trajkovic A, Zukin M, *et al*. Symptom improvement in lung cancer patients treated with erlotinib: Quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2006;24:3831-7.
30. Lewis G, Peake M, Aultman R, Gyldmark M, Morlotti L, Creeden J, *et al*. Cost-effectiveness of erlotinib versus docetaxel for second-line treatment of advanced non-small-cell lung cancer in the United Kingdom. J Int Med Res 2010;38:9-21.
31. Schwander B, Ravera S, Giuliani G, Nuijten M, Walzer S. Cost comparison of second-line treatment options for late stage non-small-cell lung cancer: Cost analysis for Italy. Clinicoecon Outcomes Res 2012;4:237-43.
32. Walleser S, Ray J, Bischoff H, Vergnenègre A, Rosery H, Chouaid C, *et al*. Maintenance erlotinib in advanced nonsmall cell lung cancer: Cost-effectiveness in EGFR wild-type across Europe. Clinicoecon Outcomes Res 2012;4:269-75.
33. Gridelli C, Ciardiello F, Feld F. International multicenter randomized phase III study of first-line erlotinib (E) followed by second-line cisplatin plus gemcitabine (CG) versus first-line CG followed by second-line E in advanced non-small cell lung cancer (aNSCLC): The TORCH trial [abstract]. J Clin Oncol 2010;28 Suppl 15:Abstract7508.
34. Soulieres D, Wolf J, Shepherd FA. Meta-analysis of the predictive and prognostic value of erlotinib-related biomarkers in phase III, placebo controlled trials in no-small cell lung cancer (NSCLC): Recommendations of the BioLOGUE advisors. J Clin Oncol 2011;2011 Suppl: Abstr7533.

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