Hong Kong J Radiol. 2013;16(Suppl):S23-8

REVIEW ARTICLE

Achieving Response and Improving Outcomes of First-line Therapy for Advanced Non–small-cell Lung Cancer

KK Loh

Suites 504-505, 5/F Admiralty Centre Tower 1, 18 Harcourt Road, Admiralty, Hong Kong

ABSTRACT

The first-line treatment paradigm for advanced non–small-cell lung cancer (NSCLC) has evolved in the past few decades, with marked improvements in therapeutic strategies and choice of active agents. Prior to the 1990s, few cytotoxic agents were available with activity against NSCLC. The era of systemic chemotherapy for NSCLC evolved when doublet chemotherapy, combining a platinum agent and a 'third-generation' agent, became the standard of care for patients with advanced NSCLC. Studies involving pemetrexed, one of the newer cytotoxic agents effective in non-squamous NSCLC, show that treatment selection based on histology provides survival benefit. There has also been major progress in understanding the disease pathogenesis on the molecular level, which led to the discovery of 'actionable' mutations associated with response and a new vista for the development of targeted therapy. For mutation-negative advanced NSCLC, bevacizumab is the first agent to demonstrate significant survival benefit and improved response when used in combination with platinum-based doublet chemotherapy. Maintenance therapy with chemotherapy or a targeted agent following four to six cycles of first-line treatment is a recent approach that has gained extensive interest. Accumulating evidence indicates that bevacizumab is an effective option in both first-line and maintenance settings. This article reviews the recent advances in first-line treatment of advanced NSCLC that lacks actionable mutations, and discusses the emerging role of maintenance therapy to further improve lung cancer outcomes.

Key Words: *Bevacizumab; Carcinoma, non-small-cell lung; Maintenance chemotherapy*

中文摘要

晚期非小細胞肺癌的一線治療達至有效及改善結果

陸凱祖

九十年代前只有數種針對晚期非小細胞肺癌（NSCLC）的細胞毒性藥物。在過去數十年NSCLC的一線治療模式漸漸進化，大大改善了治療策略和有效藥物的選擇。當雙藥化療結合鉑劑和「第三代」藥物成為治療晚期NSCLC的標準後，NSCLC的全身治療進入了新的年代。培美曲塞（pemetrexed）是一種較新的針對非鱗狀NSCLC的細胞毒性藥物，根據組織學以選擇治療的研究顯示，培美曲塞能提供更佳的生存優勢。從分子水平上對於發病機制的理解增加，導致發現「可操作」突變與治療反應相關，並有助針對性的治療發展。對於突變呈陰性的晚期NSCLC患者，與鉑類雙藥化療結合使用時，貝伐單抗（bevacizumab）是首個顯示出更佳生存優勢及治療反應的藥物。四至六個週期的一線治療後再施以化療或靶向藥物作維持治療，近期經已獲得廣泛關注。越來越多的證據顯示，貝伐珠單抗是在第一線和維持治療的一個有效選擇。本文回顧缺乏「可操作」突變的晚期NSCLC在第一線治療的最新研究進展，並討論維持治療在進一步提高肺癌預後的新功能。

Correspondence: *Dr KK Loh, Suites 504-505, 5/F Admiralty Centre Tower 1, 18 Harcourt Road, Admiralty, Hong Kong. Tel: (852) 3588 2400; Fax: (852) 3588 2420; Email: kevin.loh@oncare.com.hk*

INTRODUCTION

In the evolution of first-line therapy for advanced non–small-cell lung cancer (NSCLC), important steps forward have been made in the past few decades. Until the late 1970s, therapy for NSCLC was primarily supportive. The era of chemotherapy for advanced NSCLC began in the late 1970s, when platinum-based agents first demonstrated promise for treatment.[1] By the 1990s and 2000s, other 'third-generation' cytotoxic agents had become available, including taxanes, gemcitabine, and vinorelbine. The combination of one or more of these agents with a platinum-based compound became, and remains, the standard chemotherapy for patients with advanced-stage NSCLC.[2] The addition of a targeted agent to platinum-based chemotherapy became a viable treatment option in the 2000s. Bevacizumab, the anti-angiogenic monoclonal antibody that targets vascular endothelial growth factor, has since played an affirmative role in the treatment landscape when used in combination with chemotherapy.[2] Recently, the addition of pemetrexed to the first-line treatment armamentarium has also demonstrated benefits for patients with advanced NSCLC. The mean survival of patients with stage 4 NSCLC has improved substantially now to more than 1 year from 2 to 4 months in the 1970s.[3,4]

With advances in understanding of the molecular pathogenesis of NSCLC, patients are now sub-divided according to 'actionable' mutations / aberrations associated with the potential use of targeted therapies, or by histologies. The key actionable mutations include mutations in the epidermal growth factor receptor (EGFR) kinase domain, present in about 10 to 15% of Caucasian patients and up to 50% of Asian patients with lung adenocarcinoma,[5-8] and the echinoderm microtubule-associated protein-like 4 (EML4)–anaplastic lymphoma kinase (ALK) fusion oncogene, present in about 2 to 7% of NSCLC patients.[9] Patients with an actionable gene alteration are treated with first-line targeted agents for better outcomes, such as EGFR tyrosine kinase inhibitors or ALK inhibitors. Patients with NSCLC can also be sub-divided by histologies: squamous (about 20% of cases), adenocarcinoma (about 50%), or large cell (about 10%).[10] Recent evidence, arising from studies involving pemetrexed, has shown that histology represents another important variable in clinical decision making for the optimal choice of first-line treatment.[11] Maintenance therapy with chemotherapy or targeted agents is also increasingly recognised as an effective strategy for prolonging disease control after induction therapy.[12] This article summarises the advances in first-line treatment of EGFR mutation-negative, ALK translocation-negative, advanced NSCLC, and discusses the emerging role of maintenance therapy to further improve lung cancer outcomes.

PLATINUM-BASED CHEMOTHERAPY OPTIONS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

The standard chemotherapy for patients with advanced NSCLC and good performance status is a platinum agent in combination with a second agent, generally paclitaxel, gemcitabine, vinorelbine, docetaxel, or, more recently, pemetrexed for patients with non-squamous NSCLC.[13,14] The choice of doublet regimen was evaluated in a randomised study by the Eastern Cooperative Oncology Group (ECOG), which compared four commonly used doublet regimens (cisplatin and paclitaxel, cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel) in 1207 patients with advanced NSCLC.[15] The results showed no significant difference in the response rate and survival between patients assigned to different regimens. Although the doublet regimens differed slightly in toxicity profiles and tolerability, they were equally effective with overall response rates of 17 to 22%, and stable disease achieved in 18 to 25% of patients. The addition of a third chemotherapeutic agent to existing doublet regimens failed to show clear survival benefit over established doublet combinations, indicating that platinum-based doublet chemotherapy had reached a plateau in efficacy.[14] The role of chemotherapy in patients with poor performance status is less certain.

SURVIVAL BENEFIT WITH BEVACIZUMAB COMBINED WITH CHEMOTHERAPY

The addition of targeted agents to standard chemotherapy provides a viable option for increasing efficacy without additional toxicity. Bevacizumab is the first targeted agent to demonstrate a survival benefit with first-line therapy when added to standard chemotherapy in two phase III trials.[16,17] The ECOG E4599 phase III trial showed that addition of bevacizumab (15 mg/kg every 3 weeks) to standard first-line treatment with carboplatin plus paclitaxel was associated with a significantly higher response rate, and longer progression-free survival (PFS) and overall survival (OS) versus standard chemotherapy alone.[16] The primary endpoint, median OS, was 12.3 months in

the bevacizumab arm compared with 10.3 months in the standard chemotherapy arm (hazard ratio [HR] = 0.79; p = 0.003). Survival benefit was even more pronounced in the patient subgroup with advanced adenocarcinoma.

The subsequent Avastin in Lung Cancer (AVAiL) phase III trial investigated the efficacy of adding bevacizumab at 7.5 mg/kg and 15 mg/kg every 3 weeks to cisplatin-plus-gemcitabine combination.[17] Results showed a modest but statistically significant improvement in PFS in patients who received bevacizumab-containing treatment versus standard chemotherapy alone (HR = 0.75; p = 0.0003). The benefit of bevacizumab reported in the E4459 and AVAiL randomised trials was further confirmed in the phase IV Safety of Avastin in Lung Cancer (SAiL) study that recruited a real-world clinical population of patients with advanced NSCLC.[4] Patients received bevacizumab (7.5 or 15 mg/kg every 3 weeks) plus standard chemotherapy for up to six cycles, followed by single-agent bevacizumab until disease progression. The median OS in the overall study population was 14.6 months and similar across the range of treatment regimens commonly used in clinical practice. In a subgroup of patients who received bevacizumab plus standard chemotherapy for up to six cycles, followed by single-agent bevacizumab until disease progression, the median OS was further prolonged to 18.8 months (Figure 1).[4]

The safety profile of bevacizumab with chemotherapy was consistent across different studies.[4,16,17] The incidence of grade ≥3 adverse events of special interest was generally low; thromboembolism occurred in 8% of patients, hypertension in 6%, bleeding in 4%, proteinuria in 3%, and pulmonary haemorrhage in 1%.[4] Very few side-effects required interruption or discontinuation of treatment.

ROLE OF PEMETREXED IN FIRST-LINE TREATMENT

Pemetrexed in combination with cisplatin has recently been shown to be an effective treatment option with favourable toxicity profile for patients with advanced NSCLC. A phase III head-to-head trial compared pemetrexed plus cisplatin with gemcitabine plus cisplatin in 1207 patients with stage IIIB/IV advanced NSCLC.[18] Median OS in the overall population was similar in the two treatment arms but, interestingly, subgroup analysis showed a statistically significant survival benefit in favour of pemetrexed plus cisplatin in patients with adenocarcinoma (12.6 vs. 10.9 months, respectively) and large-cell carcinoma histology (10.4 vs. 6.7 months, respectively). The pemetrexed-plus-cisplatin combination also demonstrated a better safety profile than gemcitabine plus cisplatin, as documented by significantly lower rates of grade 3/4 haematological toxicities, febrile neutropenia and alopecia. For

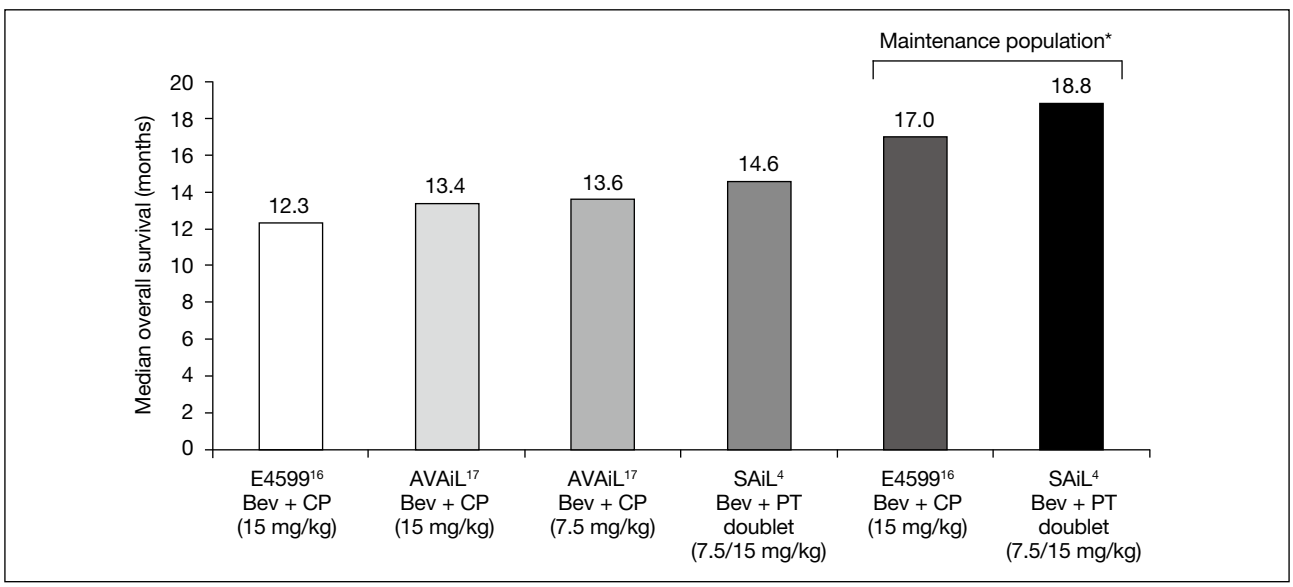

Figure 1. Overall survival with bevacizumab (7.5 or 15 mg/kg) in combination with standard chemotherapy from three phase III/IV clinical studies.

Abbreviations: AVAiL = Avastin in Lung Cancer study; SAiL = Safety of Avastin in Lung Cancer study; Bev = bevacizumab; C = carboplatin; P = paclitaxel; G = gemcitabine; PT = platinum.

* Patients received at least 1 cycle of bevacizumab maintenance treatment, interim analysis.

patients with advanced non-squamous cell NSCLC, the combination of pemetrexed and a platinum agent is an effective first-line treatment option with favourable tolerability and convenient dosing.

Given the efficacy of bevacizumab and pemetrexed, the phase III POINTBREAK study was conducted to compare the efficacy of induction therapy with bevacizumab, carboplatin and pemetrexed followed by maintenance therapy with bevacizumab plus pemetrexed, with bevacizumab/carboplatin/paclitaxel induction therapy followed by bevacizumab maintenance, in patients with advanced NSCLC.[19] The trial was negative and failed to show any statistical difference in median OS between the bevacizumab/carboplatin/pemetrexed arm and bevacizumab/carboplatin/paclitaxel arm. The combination of bevacizumab and pemetrexed is unlikely to add efficacy to the triplet regimen of carboplatin/paclitaxel with bevacizumab.

MAINTENANCE THERAPY: SHIFTING THE PARADIGM IN ADVANCED NON–SMALL-CELL LUNG CANCER

Traditionally, first-line chemotherapy is administered for four to six cycles for advanced NSCLC, followed by a treatment break and watchful follow-up until disease progression for second and further lines of treatment.[20] Maintenance therapy with chemotherapy or a targeted agent is an emerging strategy under extensive research and discussion. It refers to treatment administered after a specified number of treatment cycles once disease stabilisation or tumour response has been achieved; the aim is to prevent or delay disease progression and extend patient survival. Options for maintenance therapy include continuing the initial combination chemotherapy regimen (consolidation), continuing only a single-agent chemotherapy ('continuation' maintenance) or introducing a new agent ('switch' maintenance).[12]

The key to achieving maintenance relies on response to induction therapy. A comparison of response rates with different first-line regimens demonstrated that >60% of patients who received bevacizumab plus chemotherapy entered the fifth cycle of first-line therapy or first cycle of maintenance therapy compared with <60% in patients who received chemotherapy alone.[16,17,19,21-23] This suggests that bevacizumab-based first-line therapy is associated with a higher response rate and greater chance of reaching maintenance than with chemotherapy alone.

Various agents have been investigated for maintenance therapy in patients with advanced NSCLC, among which bevacizumab and pemetrexed have shown benefits in prolonging disease control. The ECOG E4599 study demonstrated a significant survival benefit with the use of bevacizumab in combination with carboplatin/paclitaxel compared with carboplatin/paclitaxel chemotherapy alone for patients with advanced NSCLC.[16] This was achieved using bevacizumab as maintenance therapy until disease progressed. A retrospective analysis of the ECOG E4599 data evaluated patients in both treatment arms who were progression-free after completing six cycles of induction therapy. Significantly longer PFS and OS were observed in patients who received bevacizumab maintenance after carboplatin/paclitaxel/bevacizumab induction therapy compared with those who received induction therapy with carboplatin/paclitaxel alone (Figure 2).[24]

The question of whether patients who received pemetrexed induction chemotherapy would benefit from continuous pemetrexed maintenance therapy was investigated in the PARAMOUNT phase III randomised trial.[21] After induction chemotherapy with pemetrexed and cisplatin for 4 weeks, 539 patients with advanced, non-squamous NSCLC whose tumours had not progressed were randomised to receive either pemetrexed maintenance therapy or placebo until

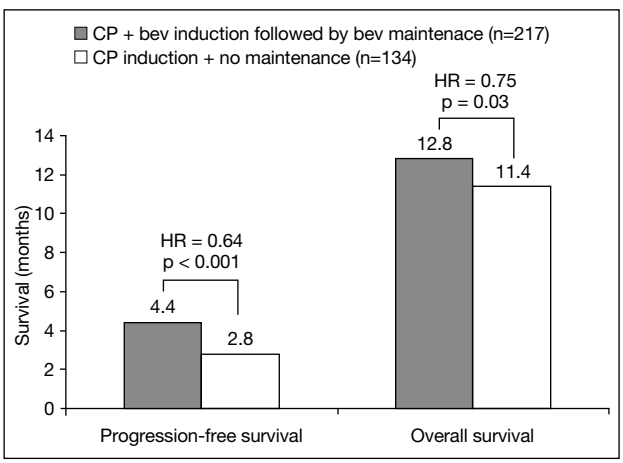

Figure 2. Survival outcomes associated with bevacizumab maintenance therapy in advanced non–small-cell lung cancer from the E4599 retrospective analysis.
Abbreviations: C = carboplatin; P = paclitaxel; bev = bevacizumab; HR = hazard ratio.

disease progression. Patients receiving pemetrexed showed a significant benefit in PFS (median, 4.1 vs. 2.8 months; HR = 0.62; p = 0.00006), OS (median, 13.9 months vs. 11.0 months; p = 0.0195), and reduced risk of disease progression (HR = 0.62; 95% confidence interval [CI], 0.49-0.79; p < 0.0001) versus placebo.[25] The survival benefits were consistent across all subgroups, irrespective of whether patients achieved stable disease, or complete or partial response to induction therapy. Pemetrexed maintenance therapy was well tolerated, without significant deterioration in quality of life. The most common grade 3/4 adverse events in the pemetrexed arm were anaemia (6.4%), neutropenia (5.8%), fatigue (4.7%), and leukopenia (2.2%).

Given the survival benefits of both bevacizumab and pemetrexed as single-agent maintenance therapy, the phase III multicentre AVAPERL study further evaluated the role of bevacizumab/pemetrexed combination as maintenance therapy.[22] A total of 376 patients with advanced, recurrent, or metastatic NSCLC who had achieved disease control after four cycles of induction therapy with bevacizumab/cisplatin/pemetrexed were randomly assigned to maintenance therapy with either bevacizumab alone or bevacizumab/pemetrexed, and treated until disease progression. Results showed that the combination of bevacizumab/pemetrexed as maintenance therapy extended PFS by 4 months compared with bevacizumab alone, and reduced the risk of progression by 50%. At a median follow-up of 8.1 months, PFS was 7.4 months in the bevacizumab/pemetrexed maintenance arm compared with 3.7 months in the bevacizumab-alone arm (HR = 0.48; p < 0.001). The treatment benefits were significant across all subgroups. Although grade ≥3 adverse events were more common in the bevacizumab/pemetrexed arm, treatment was well-tolerated without any new safety signals. The pronounced treatment benefits favour maintenance with a combination of bevacizumab and pemetrexed over bevacizumab alone in patients with advanced non-squamous NSCLC.

The value of switch maintenance therapy is under investigation in the ECOG E5508 phase III study.[26] This study compares maintenance therapy with bevacizumab, pemetrexed, or a combination of both following four cycles of induction therapy with carboplatin, paclitaxel, and bevacizumab in patients with advanced non-squamous NSCLC. This study is expected to provide further information on the optimal approach and choice of agents for maintenance therapy in advanced NSCLC.

CONCLUSION

For patients with advanced NSCLC and preserved performance status, four to six cycles of platinum-based doublet chemotherapy remains an appropriate choice of first-line therapy. The addition of bevacizumab to first-line platinum-based therapy confers significant improvements in survival and response rates over chemotherapy alone, making it a favourable therapeutic option for patients with no contraindications to bevacizumab. Bevacizumab may be continued, as tolerated, until disease progression. Pemetrexed, in combination with a platinum agent, also represents an effective and well-tolerated first-line option for patients with advanced NSCLC of non-squamous histology. For patients who achieve stable disease or response after four cycles of first-line therapy, maintenance therapy can prolong disease control and improve outcomes. The optimal approach (switch versus maintenance) remains to be determined and treatment should be individualised for patients based on their initial response to first-line therapy, histology, toxicities, and preferences.

From an untreatable disease of dismal prognosis in the 1970s, advances in the understanding of tumour biology and expansion of treatment modalities over the last four decades have resulted in significant survival benefits for patients with advanced NSCLC. Ongoing investigations of novel agents and modalities, as well as treatment individualisation based on clinical and molecular characteristics, hold promise for further improvements in patient outcomes.

REFERENCES

1. Cullen M. Lung cancer. 4: chemotherapy for non-small cell lung cancer: the end of the beginning. Thorax. 2003;58:352-6. crossref
2. Stinchcombe TE, Socinski MA. Current treatments for advanced stage non-small cell lung cancer. Proc Am Thorac Soc. 2009;6:233-41. crossref
3. Buccheri G. Chemotherapy and survival in non-small cell lung cancer. The old vexata questio. Chest. 1991;99:1328-9. crossref
4. Crinò L, Dansin E, Garrido P, Griesinger F, Laskin J, Pavlakis N, et al. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study. Lancet Oncol. 2010;11:733-40. crossref
5. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009;361:958-67. crossref
6. D'Angelo SP, Pietanza MC, Johnson ML, Riely GJ, Miller VA, Sima CS, et al. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. J Clin Oncol. 2011;29:2066-70. crossref
7. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong

SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol. 2011;29:2866-74. cross ref

8. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947-57. cross ref
9. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363:1693-703. cross ref
10. Wakelee HA, Bernardo P, Johnson DH, Schiller JH. Changes in the natural history of nonsmall cell lung cancer (NSCLC) — comparison of outcomes and characteristics in patients with advanced NSCLC entered in Eastern Cooperative Oncology Group trials before and after 1990. Cancer. 2006;106:2208-17. cross ref
11. Rossi A, Maione P, Bareschino MA, Schettino C, Sacco PC, Ferrara ML, et al. The emerging role of histology in the choice of first-line treatment of advanced non-small cell lung cancer: implication in the clinical decision-making. Curr Med Chem. 2010;17:1030-8. cross ref
12. Coate LE, Shepherd FA. Maintenance therapy in advanced non-small cell lung cancer: evolution, tolerability and outcomes. Ther Adv Med Oncol. 2011;3:139-57. cross ref
13. Azzoli CG, Baker S, Temin S, Pao W, Aliff T, Brahmer J, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol. 2009;27:6251-66. cross ref
14. Socinski MA, Crowell R, Hensing TE, Langer CJ, Lilenbaum R, Sandler AB, et al. Treatment of non-small cell lung cancer, stage IV: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132:277S-89S.
15. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002;346:92-8. cross ref
16. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355:2542-50. cross ref
17. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol. 2010;21:1804-9. cross ref
18. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26:3543-51. cross ref
19. Patel J, Socinski MA, Garon EB. A randomized, open-label, phase 3, superiority study of pemetrexed (Pem)+carboplatin (Cb)+bevacizumab (B) followed by maintenance Pem+B versus paclitaxel (Pac)+Cb+B followed by maintenance B in patients with stage IIIB or IV non-squamous NSCLC [abstract]. Presented at: 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology. Chicago, IL: 2012. Abstract LBPL1.
20. Azzoli CG, Temin S, Aliff T, Baker S, Brahmer J, Johnson DH, et al. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol. 2011;29:3825-31. cross ref
21. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, 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;13:247-55. cross ref
22. Barlesi F, Scherpereel A, Rittmeyer A, Pazzola A, Ferrer Tur N, Kim JH, 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;31:3004-11. cross ref
23. Kabbinavar F, Miller V, Johnson B, O'Connor PC. Overall survival in ATLAS, a phase IIIb trial comparing bevacizumab with or without erlotinib after completion of chemotherapy with bevacizumab for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer [abstract]. J Clin Oncol. 2010;28(Suppl):7526.
24. Lopez-Chavez A, Young T, Fages S, Leon L, Schiller JH, Dowlati A, et al. Bevacizumab maintenance in patients with advanced non-small-cell lung cancer, clinical patterns, and outcomes in the Eastern Cooperative Oncology Group 4599 Study: results of an exploratory analysis. J Thorac Oncol. 2012;7:1707-12. cross ref
25. Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, 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;31:2895-902. cross ref
26. Eastern Cooperative Oncology Group, National Cancer Institute. Bevacizumab or pemetrexed disodium alone or in combination after induction therapy in treating patients with advanced non-squamous non-small cell lung cancer. [Internet]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2013 Aug 1]. NLM Identifier: NCT01107626: Available from: http://clinicaltrials.gov/show/NCT01107626.