
REVIEW ARTICLE

A Paradigm Shift in Non-small-cell Lung Carcinoma Treatment

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ABSTRACT

The treatment paradigm of advanced non-small-cell lung carcinoma has evolved considerably owing to advances in molecular targeted therapy and the approval of two new classes of therapeutic agents, namely, epidermal growth factor receptor tyrosine-kinase inhibitors and angiogenesis inhibitors. Studies have shown that the presence of epidermal growth factor receptor-activating mutations is a strong predictor for the efficacy of epidermal growth factor receptor tyrosine-kinase inhibitors therapy. Data from recent phase III studies confirm that epidermal growth factor receptor tyrosine-kinase inhibitors therapy with erlotinib or gefitinib is more effective than standard chemotherapy for the first-line management of receptor mutation-positive patients with advanced non-small-cell lung carcinoma. In particular, erlotinib is the only epidermal growth factor receptor tyrosine-kinase inhibitor to prolong progression-free survival by more than 12 months when used for these patients in the setting of first-line therapy. In addition, data from CTONG0803, a phase II study, revealed that erlotinib monotherapy was effective in the treatment of epidermal growth factor receptor mutation-positive non-small-cell lung carcinoma patients with asymptomatic brain metastases. The efficacy and safety of first-line bevacizumab-based chemotherapy in Asian populations with advanced non-squamous non-small-cell lung carcinoma was recently confirmed in subgroup analyses of two studies. Both studies established the benefit of first-line bevacizumab in advanced non-squamous non-small-cell lung carcinoma. Moreover, data from the recent phase III AVAPERL study showed that continued maintenance therapy with bevacizumab and pemetrexed combination was effective in prolonging the survival of patients with advanced non-squamous non-small-cell lung carcinoma who respond to first-line bevacizumab-based induction chemotherapy.

Key Words: Bevacizumab; Carcinoma, non-small-cell lung; Erlotinib; Receptor, epidermal growth factor

中文摘要

非小細胞肺癌療法的方案轉移

吳一龍

隨著分子標靶療法的發展，加上對表皮生長因子受體 - 酪胺酸酶抑制劑（EGFR-TKI）及血管新生抑制劑兩種藥物的認可，治療晚期非小細胞肺癌的方案不斷演進。研究顯示表皮生長因子受體的突變可預測對EGFR-TKI療法的療效。對於受體突變呈陽性的晚期非小細胞肺癌患者，最近的第三期研究結果確定了EGFR-TKI作為第一線治療（結合erlotinib或gefitinib），比傳統化療法更為有效。值得注意的是，當用作第一線藥物時，erlotinib是唯一一個EGFR-TKI可延長患者的無惡化生存期超過12個月。此外，一項第二期研究（CTONG0803）的結果亦顯示erlotinib單一療法可有效醫治帶有無症狀腦

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轉移癌的表皮生長因子受體突變呈陽性的非小細胞肺癌患者。另兩項研究的亞群組分析中，確認了以bevacizumab為基礎的化療對於非鱗狀非小細胞肺癌患者的效用及安全性，確定了bevacizumab醫治非鱗狀非小細胞肺癌患者的好處。另一項第三期研究（AVAPERL）結果顯示對於一線bevacizumab導引治療有反應的晚期非小細胞肺癌患者，結合bevacizumab及pemetrexed的持續性維持治療可以延長其存活期。

INTRODUCTION

Worldwide, lung cancer is the leading cause of death, with non-small-cell lung cancer (NSCLC) accounting for 80% of all the lung cancers. NSCLC is comprised of diverse histological subtypes including adenocarcinoma, squamous carcinoma, and large cell carcinoma. The majority of patients present with advanced disease which, if untreated, is associated with a median survival of 4 to 5 months and a 1-year survival of less than 10%.¹

Combination chemotherapy with cytotoxic agents and platinum compounds is the standard first-line therapy for advanced NSCLC.^{2,3} Randomised studies in patients with advanced NSCLC show that standard chemotherapy is associated with overall response rates (ORRs) of 25 to 30%, median survival of 9 to 12 months, and 1-year survival rates of 30 to 40%. However, it is now believed that the benefits derived from cytotoxic chemotherapy have plateaued, and that replacement of new cytotoxic agents in platinum-based chemotherapy is unlikely to further improve survival.⁴ Advances in molecular targeted therapy are shifting the paradigm of NSCLC treatment. Two new classes of agents are now approved for the management of advanced NSCLC — inhibitors of the tyrosine-kinase domain of the epidermal growth factor receptor (EGFR) and inhibitors of angiogenesis.⁵

EGFR tyrosine-kinase inhibitor (EGFR-TKI) therapy is effective in the treatment of advanced NSCLC,¹ and particularly beneficial in patients whose tumours have activating mutations in EGFR (exon 19 deletions or exon 21 point mutations).⁶⁻¹¹ Notably, EGFR mutations are more frequent in never smokers versus ever smokers, females versus males, adenocarcinomas versus other histological subtypes, and Asians versus other ethnicities.^{6,11,12}

In addition to EGFR, NSCLC tumours also express large quantities of vascular endothelial growth factor (VEGF), an endothelial-cell-specific mitogen that regulates angiogenesis in both normal and malignant

tissues.^{13,14} NSCLC tumours and other malignant solid tumours that express VEGF are associated with increased risks of recurrence, metastasis and death.¹⁵⁻¹⁸ Bevacizumab, a humanised monoclonal antibody that inhibits VEGF, has demonstrated significant clinical efficacy when used for the first-line treatment of advanced NSCLC in combination with carboplatin-based chemotherapy.¹⁹⁻²³

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) TYROSINE-KINASE INHIBITOR THERAPY FOR CHEMOTHERAPY-NAÏVE PATIENTS WITH EGFR MUTATION-POSITIVE ADVANCED NON-SMALL-CELL LUNG CANCER

Numerous studies have demonstrated the efficacy of EGFR-TKI therapy with erlotinib or gefitinib, used as second- or third-line therapy for advanced NSCLC.^{24,25} Furthermore, when used first-line in NSCLC patients harbouring EGFR mutation-positive tumours, there is a high ORR of 54.8 to 81.6% and relatively longer progression-free survival (PFS) of 9.7 to 13.3 months.^{6,26,27}

The efficacy of erlotinib versus doublet chemotherapy was recently demonstrated in two randomised phase III trials — EURTAC (European Erlotinib Versus Chemotherapy) and OPTIMAL (Open label, Phase III study comparing first-line Tarceva versus cisplatin plus gemcitabine In Chinese advanced/Metastatic non-small-cell Lung cancer patients with EGFR activating mutations).^{28,29} While the former included Caucasians, the latter was conducted in Chinese patients only. Both studies showed statistically significant PFS improvements in chemotherapy-naïve, EGFR mutation-positive patients with advanced NSCLC.

In the EURTAC trial, chemotherapy-naïve, EGFR mutation-positive patients with advanced NSCLC were randomised to erlotinib or platinum-based chemotherapy.²⁸ Interim analysis revealed that erlotinib

treatment was associated with significantly better response rates (54.5% vs 10.5%; $p < 0.0001$) and longer PFS (9.7 months vs 5.2 months; hazard ratio [HR]=0.42; $p < 0.0001$) compared with chemotherapy. Median survival was not significantly different in the two treatment arms (18.8 months with chemotherapy vs 22.9 months with erlotinib; HR=0.80; $p = 0.42$).²⁸

In the OPTIMAL trial, erlotinib conferred a significant PFS benefit in EGFR mutation-positive patients with advanced NSCLC (13.1 vs 4.6 months; HR=0.16, 95% confidence interval [CI], 0.10-0.26; $p < 0.0001$) versus chemotherapy.²⁹ Patients whose tumours had exon 19 deletions (52%) had longer PFS than those with L858R point mutations (48%; PFS, 15.3 vs 12.5 months; HR=0.58; 95% CI, 0.33-1.02; $p = 0.0567$). Notably, PFS improved across all clinical subgroups irrespective of age, gender, performance status, disease stage, tumour histology, or smoking status. These data suggest that EGFR mutation status is the most important predictor of PFS, irrespective of clinical characteristics. Compared to chemotherapy, erlotinib treatment was associated with significantly higher ORR (36% vs 83%; $p < 0.0001$). The chemotherapy group was associated with more grade 3-4 adverse events such as neutropenia and thrombocytopenia, more treatment-related serious events, and a much higher rate of dose reduction and discontinuation than erlotinib.²⁹

As such, OPTIMAL was the first phase III study to show that EGFR-mutation positive patients who had advanced NSCLC can survive for more than 1 year without disease progression with first-line erlotinib therapy. Furthermore, the study underscored the clinical benefits of testing for EGFR mutation status to guide treatment decisions and improve the survival of patients with advanced NSCLC.²⁹

Several other phase III randomised studies have also demonstrated the efficacy of first-line EGFR-TKI therapy in Asian patients with EGFR mutation-positive advanced NSCLC.^{7-9,30} The Iressa Pan-Asia Study (IPASS) study evaluated the efficacy of gefitinib versus carboplatin-based chemotherapy as first-line therapy in such East Asian patients with specific clinical characteristics (i.e. they were non- or light-smokers, and tumour histology showed adenocarcinoma).⁷ Among patients with EGFR mutation-positive NSCLC tumours, PFS was significantly longer with gefitinib versus standard chemotherapy (9.5 vs 6.3 months; HR=0.48; 95% CI, 0.36-0.64; $p < 0.0001$). However, gefitinib

treatment was detrimental to those without EGFR mutations; in this subgroup PFS was significantly shorter among patients receiving gefitinib than those receiving chemotherapy (HR=2.85; 95% CI, 2.05-3.98; $p < 0.001$).⁷ Similarly, in the Japanese WJTOG3405 study, gefitinib treatment was superior to cisplatin plus docetaxel therapy in chemotherapy-naïve NSCLC patients with EGFR mutations (median PFS, 9.2 vs 6.3 months; HR=0.48; 95% CI, 0.34-0.71; $p < 0.0001$).⁸ The Japanese NEJGSG002 trial that included chemotherapy-naïve patients with EGFR mutation-positive advanced NSCLC also showed significantly longer median PFS with gefitinib (10.8 vs 5.4 months; HR=0.30; 95% CI, 0.22-0.41) as well as a higher response rate (73.7% vs 30.7%; $p < 0.001$) versus standard chemotherapy.⁹

All these data confirm that EGFR-TKI therapy has more first-line efficacy than standard platinum-based chemotherapy in EGFR mutation-positive NSCLC. They therefore provide the rationale for considering first-line EGFR-TKI as the treatment of choice in patients with EGFR-mutation positive NSCLC.²⁹

ERLOTINIB THERAPY IN EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION-POSITIVE NON-SMALL-CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES

About 20 to 30% of NSCLC patients develop brain metastases.³¹ These patients have a poor prognosis, with a median survival of less than 6 months after whole brain radiotherapy.³² EGFR mutation status has prognostic implications in NSCLC patients who develop brain metastases and erlotinib has demonstrated efficacy in prolonging the survival of such patients.³³⁻³⁶

A retrospective analysis of NSCLC patients with brain metastases who received erlotinib therapy showed a high ORR of 82.4% among those who were EGFR mutation-positive.³³ The median time-to-progression (TTP) within the brain for patients harbouring EGFR mutations was 11.7 months (95% CI, 7.9-15.5) compared with 5.8 months (95% CI, 5.2-6.4) for control patients with unknown EGFR mutational status ($p = 0.05$). Overall survival (OS) was 12.9 months and 3.1 months, respectively in the two groups ($p = 0.001$).³³

Rarely, NSCLC patients also develop leptomeningeal metastases which are less frequent than parenchymal brain metastases, but are associated with worse

clinical outcomes. It is believed that the frequency of leptomeningeal metastases in NSCLC is increasing due to improved survival with novel therapies and advances in neuroimaging. As these patients often have poor performance status, they are not eligible for systemic chemotherapy.³⁴ Data from case reports in Japan show that erlotinib is effective in the treatment of EGFR mutation-positive NSCLC patients who develop central nervous system (CNS) disease including parenchymal and leptomeningeal metastases after an initial good response of extra CNS disease to gefitinib. Erlotinib therapy resulted in improved performance status and prolonged survival (up to 12 months) and was not associated with any intolerable adverse effects.^{34,35}

Data from CTONG0803 Trial

The CTONG0803 (Chinese Thoracic Oncology Group) trial was conducted to examine the efficacy of erlotinib as second-line treatment for patients with confirmed adenocarcinoma or activating EGFR mutation-positive NSCLC who had asymptomatic brain metastases without extracranial progressive disease after two to six cycles of first-line platinum-doublet chemotherapy.³⁶ Patients received erlotinib until intracranial disease progression or development of clinically symptomatic brain metastases. The overall median PFS was 10.1 months (95% CI, 8.97-13.97); median PFS in patients with ≤ 3 and > 3 brain metastases was 10.2 months and 8.3 months, respectively. Median PFS in patients with EGFR wild-type tumours and tumours of unknown EGFR mutation status was 8.2 months and 15.3 months, respectively; median PFS in patients with EGFR mutations was not reached when the findings were reported. Six-month and one-year OS rates were 87% and 74%, respectively. The ORR was 56.3%, with complete remission and partial remission of 4.2% and 52.1%, respectively. The treatment was well-tolerated with no unexpected adverse events or interstitial lung disease-like events. These data suggest that erlotinib monotherapy has promising efficacy for NSCLC patients with asymptomatic brain metastases after first-line systemic chemotherapy. Moreover, the treatment may also be considered in NSCLC patients with unknown EGFR mutation status.³⁶

BEVACIZUMAB-BASED CHEMOTHERAPY IN ASIANS WITH ADVANCED NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER: SUBGROUP ANALYSES OF SAiL AND AVAiL

First-line treatment of advanced non-squamous NSCLC with bevacizumab in combination with standard chemotherapy significantly improves clinical outcomes, as demonstrated in two phase III trials — E4599 (Eastern Co-operative Oncology Group 4599) and AVAiL (Avastin in Lung).^{19,21} In the former, treatment with first-line bevacizumab plus carboplatin/paclitaxel was associated with an OS of 12.3 months versus 10.3 months in patients receiving chemotherapy alone (HR=0.80; 95% CI, 0.69-0.93).¹⁹ This was the first study to demonstrate improved survival beyond the historical one-year benchmark. Of note, NSCLC patients with adenocarcinoma histology (68.8%) reached a median OS of 14.2 months with bevacizumab-based chemotherapy.¹⁹ Furthermore, the median PFS was also significantly longer in the bevacizumab arm versus the chemotherapy arm (6.2 vs 4.5 months; HR=0.66; $p < 0.001$).²⁰ In AVAiL, patients were randomised to up to six cycles of cisplatin and gemcitabine plus bevacizumab (low-dose, 7.5 mg/kg or high-dose, 15 mg/kg) or placebo every 3 weeks until disease progression. Patients in both bevacizumab arms showed significant improvements in PFS and ORR compared to those in the placebo arm. The HR for PFS was 0.75 ($p = 0.003$) in the low-dose bevacizumab group versus placebo (median PFS, 6.7 vs 6.1 months) and 0.82 ($p = 0.03$) in the high-dose bevacizumab group versus placebo (median PFS, 6.5 vs 6.1 months). The ORRs were 20.1%, 34.1%, and 30.4% in the placebo, low-dose bevacizumab ($p < 0.0001$), and high-dose bevacizumab ($p = 0.0023$) arms, respectively.²¹

The efficacy of first-line bevacizumab-based therapy in advanced non-squamous NSCLC was confirmed in two phase IV studies — SAiL (Safety of Avastin in Lung) and ARIES (Avastin Regimens: Investigation of Treatment Effects and Safety).^{22,23} In SAiL, treatment with a maximum of six cycles of bevacizumab (7.5 or 15 mg/kg) in combination with standard chemotherapy was associated with a TTP of 7.8 months and median OS of 14.6 months.²² ARIES is an observational study that confirmed the efficacy of bevacizumab in combination with various first-line chemotherapy regimens in a broad population of advanced NSCLC patients. Median PFS and OS were 6.3 months and 10.6 months, respectively.²³

As response to targeted therapies may vary across ethnic populations,^{25,37-39} subgroup analyses were conducted on data from SAiL and AVAiL to evaluate the efficacy of first-line bevacizumab-based chemotherapy in

Asian patients with advanced non-squamous NSCLC. Subgroup analysis of SAiL showed that the safety and efficacy of first-line bevacizumab-based therapy in Asian patients was comparable to that of the overall SAiL population.⁴⁰ The frequency of grade 3-4 adverse events was relatively low (15.6% overall) with no reports of any new safety signals. The median TTP and OS in Asian patients were 8.3 months and 18.9 months, respectively.⁴⁰ ORR and disease control rate (DCR) were 57.7% and 94.1% in the Asian population versus 52% and 89%, respectively in the overall SAiL population (Table 1).^{22,40} In addition, subgroup analysis of Chinese patients included in SAiL revealed high PR (66.7%) and DCR (96.4%) values.⁴¹ Compared to the intention-to-treat SAiL population, the Chinese population experienced longer median OS (14.6 vs 18.5 months) and median TTP (7.8 vs 8.8 months).^{22,41}

Similar results were obtained in the retrospective subgroup analysis of AVAiL data. OS in the Asian population was 28.2 months in the 7.5 mg/kg bevacizumab-arm (HR=0.46; 95% CI, 0.22-0.97) and 25.8 months in the 15 mg/kg bevacizumab arm (HR=0.79; 95% CI, 0.40-1.57) versus 13.6 months (HR=0.93; 95% CI, 0.78-1.11) and 13.4 months (HR=1.03; 95% CI, 0.86-1.23), in the low-dose and high-dose bevacizumab arms, respectively, of the overall AVAiL population (Table 2).^{21,42} PFS with low-dose and high-dose bevacizumab-based chemotherapy in the Asian population was 8.8 months (HR=0.49; 95% CI, 0.29-0.83) and 8.7 months (HR=0.61; 95% CI, 0.36-1.04), respectively (Table 2).⁴⁰

Table 1. Efficacy of first-line bevacizumab-based chemotherapy in SAiL: overall findings and in the Asian population.^{22,40}

	Overall population	Asian population
TTP (months)	7.8	8.3
OS (months)	14.6	18.9
ORR (%)	52.0	57.7
DCR (%)	89.0	94.1

Abbreviations: SAiL = Safety of Avastin in Lung; TTP = time-to-progression; OS = overall survival; ORR = overall response rate; DCR = disease control rate.

These data confirm the safety and efficacy of first-line bevacizumab-based chemotherapy in Asian patients with advanced non-squamous NSCLC, and are consistent with those of the global SAiL and AVAiL populations. OS data from the subgroup analyses of both trials suggest that the bevacizumab-based regimens may be more beneficial to Asians with advanced non-squamous NSCLC than for other ethnicities. Furthermore, the worldwide incidence of adenocarcinoma histology is the highest in Chinese patients,⁴³ and NSCLC tumours with this histology demonstrate high response rates to bevacizumab-based chemotherapy.⁴⁰

BEVACIZUMAB PLUS PEMETREXED FOR CONTINUATION MAINTENANCE THERAPY IN ADVANCED NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER: DATA FROM AVAPERL

AVAPERL was a randomised phase III study designed to investigate the efficacy of continuation maintenance therapy with a combination of bevacizumab plus pemetrexed in prolonging the survival of patients with advanced non-squamous NSCLC. Previously untreated patients with advanced non-squamous NSCLC were treated with bevacizumab, pemetrexed, and cisplatin. Patients whose disease did not progress were randomised to continuation maintenance therapy with bevacizumab plus pemetrexed or bevacizumab alone. At a median follow-up of 11 months, PFS was significantly longer in patients receiving bevacizumab plus pemetrexed maintenance therapy versus bevacizumab alone (PFS from induction, 10.2 vs 6.6 months; HR=0.50; 95% CI, 0.37-0.69; $p < 0.001$ and PFS from randomisation, 7.4 vs 3.7 months; HR=0.48; 95% CI, 0.35-0.66; $p < 0.001$).⁴⁴ All subgroups of patients benefitted from the combination maintenance therapy. OS evaluated from induction was 15.7 months in the bevacizumab alone arm; median OS was not reached in patients receiving combination therapy when the findings was reported.⁴⁴ Both treatments

Table 2. Efficacy of first-line bevacizumab-based chemotherapy in AVAiL in the overall and Asian populations.^{21,40,42}

	Overall population		Asian population	
	Bevacizumab 7.5 mg/kg + CG	Bevacizumab 15 mg/kg + CG	Bevacizumab 7.5 mg/kg + CG	Bevacizumab 15 mg/kg + CG
PFS (months)	6.7	6.5	8.8	8.7
OS (months)	13.6	13.4	28.2	25.8

Abbreviations: AVAiL = Avastin in Lung; CG = cisplatin-gemcitabine; PFS = progression-free survival; OS = overall survival.

were well-tolerated, although combination therapy was associated with more frequent adverse events due to the chemotherapy component of the regimen.⁴⁴ These data strongly favour the use of bevacizumab plus pemetrexed as continuation maintenance therapy in patients with advanced non-squamous NSCLC.

CONCLUSION

The paradigm of NSCLC treatment has evolved considerably with the approval of novel targeted therapy including the EGFR-TKI agents, erlotinib and gefitinib, and anti-VEGF monoclonal antibody bevacizumab. Data from IPASS, OPTIMAL, and EURTAC confirm that EGFR-TKI therapy is more effective than standard chemotherapy for the first-line treatment of EGFR mutation-positive patients with advanced NSCLC. These agents may well be considered as first-line treatments of choice in this patient subgroup. To date, erlotinib is the only EGFR-TKI to prolong survival by more than 1 year when used as first-line treatment of EGFR mutation-positive patients with advanced NSCLC. Recent data from the phase II CTONG0803 trial suggest that erlotinib is a promising agent for the treatment of EGFR mutation-positive NSCLC patients with asymptomatic brain metastases.

Subgroup analyses from SAiL and AVAiL confirm the efficacy and safety of first-line bevacizumab-based chemotherapy in Asian patients with advanced non-squamous NSCLC. Data from the AVAPERL study strongly favour the use of bevacizumab plus pemetrexed combination as continuation maintenance therapy to prolong survival of patients with advanced non-squamous NSCLC who show disease control with bevacizumab-based induction treatment.

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