Special Report

Chinese expert consensus on molecularly targeted therapy for advanced non-small cell lung cancer (2013 edition)

Guoming Wu[1*], Caicun Zhou[2*], Chunxue Bai[3], Guisheng Qian[1]

[1]Xinqiao Hospital of the Third Military Medical University, Chongqing 400037, China; [2]Pulmonary Hospital of Tongji University, Shanghai 200433, China; [3]Zhongshan Hospital of Fudan University, Shanghai 200032, China

*These authors contributed equally to this work.

Correspondence to: Chunxue Bai. Pulmonary Hospital of Tongji University, Shanghai 200433, China. Email: bai.chunxue@zs-hospital.sh.cn; Guisheng Qian. Xinqiao Hospital of the Third Military Medical University, Chongqing 400037, China. Email: qiangs1220@163.com.

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Lung cancer is one of the most common malignant tumors worldwide, ranking the first of all cancers in terms of mortality. More than 80-85% lung cancers are non-small cell lung cancer (NSCLC), and most of them are in advanced stages at the time of diagnosis (1). Although the role of chemotherapy for NSCLC remains virtually unchanged in recent years, the therapeutic efficacy has reached a plateau. Moreover, toxic and adverse reactions have limited its further clinical applications. Instead, targeted therapy has aroused the widest attention and become one of the most promising therapeutic strategies owing to the reliable therapeutic effect, low toxicity and mild adverse reactions (2). The expert panels from the Respiratory Disease Branch Lung Cancer Study Group of the Chinese Medical Association and the Chinese Alliance Against Lung Cancer have discussed issues related to molecularly targeted treatments for advanced NSCLC and reached consensus on molecularly targeted treatments for advanced NSCLC (2013 edition) in the contest of the national conditions in Mainland China.

Detection of lung cancer driver genes

Epidermal growth factor receptor (EGFR) gene mutations

The results of numerous studies have demonstrated that the *EGFR* mutation status is the most important predictive factor for assessing the therapeutic effect of EGFR-tyrosine kinase inhibitors (EGFR-TKIs) for the treatment of advanced NSCLC. Such mutations usually occur within exon 18-21, in which exon 19 deletion and exon 21 L858R mutation (defined as sensitive mutations) are the most common mutations indicative of the sensitivity to EGFR-TKI treatment. Multiple studies (3,4) have demonstrated that the overall mutation rate in unselected Chinese NSCLC patients is about 30%, about 50% in patients with lung adenocarcinoma, or even as high as 60-70% in non-smoking patients with lung adenocarcinoma. The *EGFR* mutation rate in patients with squamous cell carcinoma is about 10%. It is therefore necessary for clinicians to enhance their awareness about the routine detection of *EGFR* mutations.

The detection of *EGFR* mutations can be performed on surgically resected specimens, histology biopsy specimens and cytology specimens, but whatever specimen is used, it should contain at least 200-400 tumor cells. The use of blood specimens for the detection of *EGFR* mutations has not been well established due to less sensitive as compared with tissue specimens, and therefore is not recommended for routine use for the time being. Quality control (QC) of the specimen to be detected should be under the supervision of experienced pathologists (4).

There are various methods for the detection of *EGFR* mutations at present, including the direct sequencing assay and real-time fluorescence quantitative polymerase chain reaction (FQ-PCR)-based assays such as scorpion amplification refractory mutation system-scorpion assay (ARMS), fragment length analysis and denaturing high performance liquid chromatography. These methods have their respective advantages and disadvantages, and there is no consensus at present about which is more advantageous.

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The DNA direct sequencing assay is widely utilized to detect known and unknown mutations, but it has a high requirement on the content (more than 50% and at least 30%) of tumor cells in the specimen. Real-time FQ-PCR-based methods such as ARMS is more sensitive and can detect 1.0-0.1% mutant cells in the specimen, and therefore is more suitable for detecting small specimens that contain a relatively small number of tumor cells. ARMS is the most common method used in clinical practice due to simplicity. However, it can only detect known mutations, the specimen needs to be pre-treated, and the cost is relatively high (4,5).

Anaplastic lymphoma kinase fusion gene

Anaplastic lymphoma kinase (ALK) fusion gene is a newly discovered NSCLC driver gene, where echinoderm microtubule-associated protein-like4 (EML4) and ALK fusion (EML4-ALK) is the most common type. ALK fusion gene is mainly found in non-smoking or light-smoking patients with lung adenocarcinoma, and usually does not co-exist with *EGFR* mutations in the same patient. The occurrence of ALK fusion gene in NSCLC patients is about 5% *vs*. 25% in NSCLC patients without *EGFR*, *KRAS*, *HER2* or *TP53* mutations. In Mainland China, the positive rate of ALK fusion gene in NSCLC patients with both *EGFR* and *KRAS* wild type lung adenocarcinoma is as high as 30-42% (4). There are mainly three methods to detect ALK fusion gene at present: fluorescence in situ hybridization (FISH), PCR amplification-based techniques and immunohistochemistry (IHC). FISH remains the reference standard for confirming ALK fusion gene at present. But as it is costly and has high technical requirements, it is not applicable to screen ALK positive patients. qRT-PCR is easy to follow with a high sensitivity, but it needs specific reagent kits and instruments and there have been commercially available kits approved by the Chinese Food and Drug Administration (CFDA) for clinical qRT-PCR assays at present. IHC is easy to follow, inexpensive and technically mature. The antibody specificity and sensitivity of high affinity D5F3 (Cell Signaling) and 5A4 (Abcam) have reached 100% and 95-99% respectively. The Ventana ALK fusion protein IHC diagnostic reagent kit has improved the sensitivity without affecting the specificity. Its coincidence rate with FISH is as high as 98.8%, and the reproducibility is as high as 99.7%. It has been approved by the CFDA for the diagnosis of ALK-positive NSCLC patients. The detection method should be selected appropriately according to the histological specimen type and the laboratory conditions. Specimen QC should be supervised by experienced pathologists. When the reliability of a test method is suspected, another method should be employed for verification (6).

ROS-1 fusion gene

ROS1 is another receptor tyrosine kinase (RTK) gene that forms fusions and a newly discovered NSCLC driver gene as well. The most common type is CD74–ROS-1, occurring in about 1% of NSCLC patients (7), especially in non-smoking or light-smoking young patients with lung adenocarcinoma. It usually does not overlap with other driver genes. ROS-1 fusion gene is very much like ALK fusion gene with respect to the clinical characteristics, suggesting that these two mutation subsets may share the same pathogenic mechanism. There are various methods for detection ROS-1 fusion gene, among which the FISH method is the most commonly used (7).

Conclusions: (I) every possible effort should be made to obtain specimens for the detection of *EGFR* mutations before treatment for NSCLC patients; (II) specimen QC for the detection of *EGFR* mutations should be supervised by experienced pathologists, and an appropriate detection method should be selected, preferably by selecting a highly sensitive method such as ARMS; (III) it is advisable to undertake ALK and ROS-1 fusion gene detection in patients without *EGFR* mutations; (IV) it is advisable to undertake detections of *EGFR* mutations, ALK and ROS-1 fusion genes simultaneously if it is possible.

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs)

First-line treatment

The IPASS study reported in 2009 was a large-scale, international, multi-center, randomized controlled phase III clinical trial (8), the primary endpoint of which was progression-free survival (PFS). The results of IPASS showed that PFS in patients with *EGFR* mutations who used gefitinib as the first-line treatment was obviously superior to that in patients who used carboplatin + paclitaxel (9.8 *vs*. 6.4 months; HR =0.48, P<0.001). The objective response rate (ORR) in Gefitinib group was also improved significantly, accompanied with better tolerance and quality of life (QoL), though there was no significant difference in overall survival (OS) between the two groups, probably

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because a relatively large proportion of the patients received crossover or other treatments in subsequent periods. IPASS study is of milestone significance in targeted therapy because it opens the door of true individualized therapy for lung cancer.

The WJTOG 3405 study is an open-label, multi-center, randomized controlled phase III clinical trial. It compared the therapeutic effect between gefitinib and cisplatin + docetaxel as the first-line treatment in 177 advanced NSCLC patients with *EGFR* mutations. The results showed that PFS in the two groups was 9.2 and 6.3 months respectively, indicating that the therapeutic effect of gefitinib was obviously superior to that of cisplatin + docetaxel (HR =0.49, P<0.0001) (9).

The NEJ 002 study compared the therapeutic effect between gefitinib and carboplatin + paclitaxel as the first-line treatment in 230 advanced NSCLC patients with *EGFR* mutations. The results showed that the therapeutic effect of gefitinib was obviously superior to that of carboplatin + paclitaxel in terms of PFS (10.8 *vs.* 5.4 months; HR =0.30, P<0.001) (10).

OPTIMAL is a randomized phase III clinical trial sponsored by the Chinese Thoracic Oncology Group (CTONG). It compared the therapeutic effect between Erlotinib and gemcitabine + carboplatin as the first-line treatment in 165 advanced NSCLC patients with *EGFR* mutations. The results showed that the therapeutic effect of Erlotinib was obviously superior to that of gemcitabine + carboplatin in terms of PFS (13.1 *vs.* 4.6 months; HR =0.16, P<0.0001), accompanied with better QoL, though there was no significant difference in OS between the two groups (11). However, the results of subgroup analysis showed that the survival duration was relatively short in patients who only received chemotherapy, with a median OS of 11.7 (n=21) *vs.* 20.6 months in patients who only received EGFR-TKI (n=33) and 30.4 months in patients who first received EGFR-TKI and then chemotherapy (n=94), suggesting that EGFR-TKI makes great contributions to the improvement of survival in patients with *EGFR* mutations (12).

EURTAC is a study equivalent to OPTIMAL conducted in Caucasian population. It compared the therapeutic effect between Erlotinib and chemotherapy as the first-line treatment in 174 NSCLC patients with *EGFR* mutations, using PFS as the primary endpoint of research. The results showed that PFS of the two groups was 9.7 and 5.2 months respectively, suggesting that the therapeutic effect of erlotinib was obviously superior to that of chemotherapy alone (HR =0.37, P<0.0001) (13).

A more recent randomized phase III clinical trial (FASTACT-II) showed that PFS in patients receiving double agents chemotherapy in combination with intercalated use of erlotinib as the first-line treatment for 6 cycles followed by erlotinib maintenance therapy was 7.6 *vs.* 6.0 months in patients who received double agents chemotherapy + placebo (HR =0.57, P<0.0001), and OS was 18.3 and 15.2 months respectively (HR =0.79, P=0.0420). The result of subgroup analysis on the *EGFR* mutation status showed that only patients with *EGFR* mutations rather than patients with wild-type *EGFR* benefited from this mode of treatment (14).

The LUX-LUNG3 study is an international, multi-center, randomized controlled phase III clinical trial, showing that PFS in advanced lung adenocarcinoma patients with *EGFR* mutations who received irreversible inhibitor of the erbB family Afatinib as the first-line treatment was obviously superior to cisplatin + pemetrexed (11.1 *vs.* 6.9 months; HR =0.58, P=0.001). In addition, ORR in Afatinib group was also significantly improved (56% *vs.* 23%; P=0.001) (15).

LUX-LUNG6 is another randomized controlled phase III clinical trial conducted in Asian population. The results showed that Afatinib as the first-line treatment was also obviously superior to gemcitabine + cisplatin in advanced lung adenocarcinoma patients with *EGFR* mutations in terms of PFS as the primary endpoint of research (11.0 *vs.* 5.6 months; HR =0.28, P<0.0001). In addition, ORR in Afatinib group was also significantly improved (66.9% *vs.* 23.0%; P<0.0001) (16).

The adverse reactions of EGFR-TKIs are relatively mild, mainly including skin reactions (rash, pruritus, skin dryness and acne) and diarrhea. Adverse reactions occur in more than 50% NSCLC patients who received the first-generation EGFR-TKIs but they are usually mild. Adverse reactions more than grade 3 usually occur in about 2-10% patients, of which interstitial pneumonia is a rare but severe adverse reaction, accounting for about 1%, and needs special attention, because it may lead to death if not treated properly or positively. The occurrence of adverse reactions with the second-generation EGFR-TKI Afatinib is even higher and the symptoms are more severe than the first-generation EGFR-TKIs.

Conclusions: (I) EGFR-TKIs are recommended as the first-line treatment for advanced NSCLC patients with *EGFR* mutations (gefitinib and erlotinib have been approved as the first-line treatment agents in many countries, but only gefitinib has been approved in Mainland China.

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Afatinib has been approved as the first-line treatment agent in the United State and Taiwan region of China); (II) the first-line chemotherapy + intercalated use of erlotinib for 6 cycles followed by erlotinib as maintenance therapy can be considered in advanced NSCLC patients with *EGFR* mutations.

Maintenance therapy

The INFORM study conducted in Mainland China compared the therapeutic effect of maintenance therapy between gefitinib and placebo in advanced NSCLC patients, finding that PFS in gefitinib group was significantly longer than that in placebo group (4.8 *vs.* 2.6 months; HR =0.42, P<0.0001). Notably, the PFS was more significantly longer in the subgroup of advanced NSCLC patients with *EGFR* mutations using gefitinib than that in placebo group (16.6 *vs.* 2.8 months; HR =0.17), indicating that advanced NSCLC patients, especially those with *EGFR* mutations can benefit from gefitinib maintenance therapy (17). In another phase III study (WJTOG0203), 604 patients with stage IIIb or IV NSCLC were randomly assigned to two groups: one group receiving 3 cycles of standard first-line platinum-doublet chemotherapy followed by gefitinib maintenance therapy, and the other group receiving 6 cycles of platinum-doublet chemotherapy. PFS of the two groups was 4.6 *vs.* 4.3 months (P<0.001). Although there was no significant difference in OS between the two groups, OS in gefitinib maintenance therapy group was significantly longer than that in chemotherapy group alone in the adenocarcinoma subgroup (15.4 *vs.* 14.3 months; P=0.03) (18).

A meta-analysis on erlotinib maintenance therapy (included SATURN, ATLAS and IFCT-GFPC0502 study) showed that erlotinib was able to prolong PFS and OS of patients with advanced NSCLC who achieved disease control (DC) [partial response (PR)/complete response (CR)/stable disease (SD)] after first-line chemotherapy. All subgroup patients benefited from Erlotinib maintenance therapy, especially female patients, non-smokers and non-squamous cell carcinoma patients, probably because the *EGFR* mutation rate in these patients is relatively high (19). The subgroup analysis of SATURN study showed that PFS in patients with *EGFR* mutations who received Erlotinib maintenance therapy was significantly longer than that in placebo group (HR =0.10, P<0.0001) (20,21).

Conclusions: gefitinib or erlotinib maintenance therapy can be considered in advanced NSCLC patients who achieved DC (PR/CR/SD) after first-line chemotherapy.

Second-line and subsequent therapies

A meta-analysis enrolling four phase II/III clinical trials showed that the risk of disease progression in unselected Asian patients with pretreated advanced NSCLC who received Gefitinib was 19% lower than that in those who received Docetaxel, and ORR increased remarkablely (117%) (22). The Chinese subgroup analysis of INTEREST study showed that ORR of gefitinib and docetaxel was 21.9% and 9.1% respectively (P=0.016), in which the median PFS in adenocarcinoma subgroup was 5.4 months for Gefitinib and 3.9 months for docetaxel (23). A Korean phase III KCSG-LU-0801 study showed that ORR in Asian non-smoking patients with previously treated advanced lung adenocarcinoma who used Gefitinib and Pemetrexed was 58.8% *vs.* 22.4% respectively (P<0.001), median PFS was 9.0 *vs.* 3.0 months respectively (P=0.0006) (24). BR.21 study showed that OS in unselected previously treated advanced NSCLC who used Erlotinib and Placebo was 6.7 and 4.7 months respectively, and the difference was significantly different (HR =0.70, P<0.001) (25). TITAN and HORG study compared the therapeutic effect of erlotinib, pemetrexed and docetaxel, finding that the therapeutic effect of erlotinib was equivalent to that of Pemetrexed or Docetaxel as the standard second-line single chemotherapy agent but had better tolerance (26,27).

ICOGEN, a non-inferiority phase III clinical trial conducted in Mainland China (28), compared the therapeutic effect of icotinib and gefitinib in unselected patients with previously treated advanced NSCLC, and found that PFS of icotinib and Gefitinib was 4.6 and 3.4 months respectively (P=0.13), confirming that icotinib was not inferior to gefitinib in unselected patients with pretreated advanced NSCLC.

Studies comparing the therapeutic effect of gefitinib and erlotinib (29,30) and that comparing the therapeutic effect of gefitinib and icotinib (28) suggested that the therapeutic effect of the three EGFR-TKIs as second-line treatment agents was similar for advanced NSCLC patients.

TAILOR ,an international, multi-center, phase III clinical trial, showed that PFS and OS in advanced NSCLC patients with wild-type EGFR who received erlotinib as the second-line treatment were significantly shorter than those who received docetaxel (PFS 2.4 *vs.* 2.9 months, HR =0.71, P=0.02; 6-month OS 16.5% *vs.* 27.3%) (31). The DELTA study also demonstrated that PFS and ORR in advanced NSCLC patients with wild-type EGFR who received Erlotinib as the second-line treatment were also inferior than those who received docetaxel (PFS 1.3 *vs.* 2.9, P=0.013;

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ORR 5.6% *vs.* 20.0%, P=0.003) (32). The CTONG0806 study showed that PFS in advanced non-squamous NSCLC patients with wild-type EGFR who received Pemetrexed or Gefitinib was 4.8 *vs.* 1.6 months (P<0.001), and the disease control rate (DCR) was 61.3% and 32.0% respectively (P<0.001) (33). The results of the above three studies all showed that second-line chemotherapy should be the first treatment choice in advanced NSCLC patients with wild-type *EGFR*.

Conclusions: (I) EGFR-TKIs (gefitinib, erlotinib or icotinib) can be used as second- or third-line treatment agents in advanced NSCLC patients, while EGFR-TKIs are preferably recommended in advanced NSCLC patients with *EGFR* mutations; (II) EGFR-TKIs are not preferably recommended as second-line treatment in advanced NSCLC patients with wild-type EGFR.

Treatment of elderly patients and patients with poor performance status

Elderly (>70 years) patients with lung cancer are usually intolerable to platinum-doublet chemotherapy due to relatively poor organ functions and the existence of complications, in whom EGFR-TKIs can be considered as the first-line treatment because of relatively good tolerance. A systematic analysis on three NEJ studies (001,002,003) compared ORR and PFS in elderly patients with advanced NSCLC and *EGFR* mutations who used Gefitinib or chemotherapy, and found that ORR was 73.2% *vs.* 26.5%, and PFS was 14.3 *vs.* 5.7 months, both showing significant differences between the two groups (34). Of the three studies, NEJ002 showed that there was no significant difference in toxicity and QoL between elderly and young patients who used Gefitinib, indicating that the therapeutic effect of Gefitinib as the first-line treatment is relatively good and the toxicity is tolerable in elderly patients with lung cancer of *EGFR* mutations. Another randomized phase III clinical trial TOPICAL in advanced NSCLC patients who received erlotinib or placebo because of being intolerable to first-line chemotherapy showed that the risk of disease progression in erlotinib group was 17% lower than that in placebo group (35).

A pooled analysis on the therapeutic effect of gefitinib or erlotinib and single agent chemotherapy in elderly patients or patients with poor performance status included five studies (330 patients) in EGFR-TKI group and ten studies (1,095 patients) in single agent chemotherapy group. The results showed that ORR was 18% and DCR was 50% in EGFR-TKI group *vs.* 12% and 36% in single agent chemotherapy group (36).

The WJTOG 0402 study showed that ORR was 20%, DCR was 47%, median PFS was 2.7 months, and median OS was 11.9 months in elderly patients with adenocarcinoma who received Gefitinib as the first-line treatment. The most common toxic reactions included rash, followed by diarrhea, anorexia, hepatic dysfunction and anemia, but all these toxic reactions were relatively mild and could be managed without difficulty. In non-smokers, ORR was 43%, DCR was 57%, median PFS was 7.1 months, and median OS was 13 months, suggesting that both the therapeutic effect and tolerance of Gefitinib as the first-line treatment are relatively good in elderly patients or patients with poor performance status of selected populations (37).

Conclusions: (I) EGFR-TKI (gefitinib or erlotinib) is recommended in elderly NSCLC patients with *EGFR* mutations; (II) EGFR-TKI (gefitinib or erlotinib) can be tried in elderly NSCLC patients or NSCLC patients who are intolerable to chemotherapy or whose *EGFR* mutation status is uncertain, knowing that the *EGFR* mutation rate in Chinese patients is relatively high and there is no other effective treatment at present. At the same time, the therapeutic effect and toxic/adverse reactions should be observed and followed up closely.

Treatment after EGFR-TKI resistance

Disease progression is often observed 9-10 months after initiation of EGFR-TKIs as the first-line treatment in NSCLC patients with *EGFR* mutations, suggesting the occurrence of acquired EGFR-TKI resistance (8-13). A retrospective study enrolled 227 patients with acquired resistance and explored the therapeutic mode in patients who received EGFR-TKI treatment and developed disease progression. The patients were assigned into three clinical failure modes according to the duration of DC, evolution of tumor burden and 6 clinical symptoms: (I) dramatic progression (DC lasting ≥3 months with EGFR-TKI treatment, where the tumor burden increases quickly as compared with the previous assessment and the symptom score reaches 2); (II) gradual progression (DC lasting ≥6 months with EGFR-TKI treatment, where the tumor burden increases mildly as compared with the previous assessment and the symptom score is ≤1); and (III) local progression (DC lasting ≥3 months with EGFR-TKI treatment, with solitary extra- or intra-cranial progression and the symptom score is ≤1). The results showed that PFS

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of the three modes was 9.3, 12.9 and 9.2 months respectively (P=0.007), and the median survival was 17.1, 39.4 and 23.1 months respectively (P<0.0001). The survival duration of the patients with dramatic progression who continued TKI treatment was shorter than that in those who converted to chemotherapy. It is therefore suggested that EGFR-TKIs should be discontinued and replaced by chemotherapy in patients with dramatic progression. The median OS in gradual progression patients who continued TKI or converted to chemotherapy was 39.4 and 17.8 months respectively (P=0.02). It is therefore suggested that TKI treatment should be continued in patients with gradual progression. OS in local progression patients who continued TKI was similar to that in patients who converted to chemotherapy. However, continuation of TKI treatment in combination with local treatment is suggested in local progression patients, given QoL of the patients and limitation of the local-progression focus (38).

In a retrospective study enrolling 78 patients with acquired resistance to EGFR-TKI (including 70 patients with *EGFR* mutations), the results showed that ORR in 34 patients who received chemotherapy + erlotinib was 41% *vs*. 18% in 44 patients who received chemotherapy alone (P=0.02), and PFS was 4.4 *vs*. 4.2 months (P=0.34) (39).

According to the recommendation of the National Comprehensive Cancer Network (NCCN) guidelines (2013 edition), EGFR-TKIs should be continued in NSCLC patients with *EGFR* mutations who are asymptomatic when disease progression with first-line EGFR-TKI treatment, but chemotherapy in combination with EGFR-TKI should be considered in symptomatic patients.

There are few high-level evidence-based medical references about treatment after EGFR-TKI resistance, but a series of related studies is under way or on the way, such as the IMPRESS study concerning the therapeutic mode by comparing TKI + chemotherapy and chemotherapy alone after EGFR-TKI resistance; the ASPIRATION study on continuous use of TKIs after EGFR-TKI resistance; research on TKIs in combination with other drugs; and research on new drugs specific to EGFR-TKI resistance. It is anticipated that these studies could provide more evidence-based medical references.

Conclusions: (I) continuation of the original EGFR-TKI treatment or EGFR-TKIs in combination with chemotherapy is suggested in patients with gradual progression; (II) discontinuation of EGFR-TKIs and conversion to chemotherapy are suggested in patients with dramatic progression; (III) continuation of EGFR-TKI plus local treatment is suggested in patients with local progression and whose primary lesion is well controlled.

ALK and ROS-1 fusion gene inhibitors

The results of two multi-center clinical trials showed that the ALK inhibitor Crizotinib could offer a remarkable therapeutic effect in advanced NSCLC patients with positive EML4-ALK fusion genes. The A8081001 study showed ORR in Crizotinib group was 60.8%, the median duration of response was 49.1 weeks, and the median PFS was 9.7 months (40). The A8081005 study showed that ORR was 50% in previously treated NSCLC patients with positive *ALK* who received crizotinib, and the median duration of response was 41.9 weeks. Common adverse reactions (occurrence ≥25%) included visual disorders, nausea, diarrhea, edema and constipation (41).

The phase III clinical trial A8081007 compared the therapeutic effect and safety of crizotinib, pemetrexed or docetaxel in advanced NSCLC patients with positive *ALK* who had a previous history of receiving chemotherapy. Using PFS as the primary end-point, 347 patients with positive *ALK* who had received platinum-based chemotherapy before enrollment were randomly assigned to Crizotinib group and chemotherapy group. The results showed that PFS of the two groups was 7.7 and 3.0 months respectively (HR =0.49, P<0.001), and ORR was 65% and 20% respectively (P<0.001) (42). In January 2013, the CFDA approved the use of Crizotinib in the treatment of local advanced or metastatic NSCLC patients with positive *ALK* in Mainland China.

Shaw *et al.* reported the preliminary therapeutic effect of Crizotinib in the treatment of 13 NSCLC patients with positive *ROS-1*, where ORR was 54% and the 8-week DCR was 85%, showing good tolerance in 2012 ASCO (43). Ou *et al*. reported the therapeutic effect of Crizotinib in 25 assessable patients with advanced NSCLC of positive *ROS-1*, showing that ORR was 56%; the 8- and 16-week DCR was 76% and 60% respectively; and the median PFS has not yet reached at the time in 2013 ASCO. This study re-demonstrated the effectiveness of Crizotinib for the treatment of *ROS-1* positive advanced NSCLC patients (44).

Conclusions: crizotinib is recommended for advanced NSCLC patients harboring positive ALK or ROS-1 fusion genes.

Angiogenesis inhibitors

Two phase III randomized studies demonstrated the

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therapeutic effect of the angiogenesis inhibitor Bevacizumab in combination with chemotherapy as the first-line treatment for non-squamous NSCLC patients (45,46). In the study group, Bevacizumab was continued as maintenance therapy after chemotherapy until disease progression or the occurrence of intolerable drug toxicity. The E4599 study showed that the protocol using Carboplatin/Paclitaxel in combination with Bevacizumab (15 mg/kg/3w) improved OS, PFS and ORR of the patients: 12.3 months, 6.2 months and 35% *vs*. 10.3 months (HR =0.79, P=0.003), 4.5 months (HR =0.66, P<0.001) and 15% (P<0.001) respectively as compared with the control group (46). The AVAIL study demonstrated that the protocol of bevacizumab 7.5 or 15 mg/kg/3w in combination with cisplatin/gemcitabine improved PFS and ORR of the patients as compared with the protocol of placebo in combination with cisplatin/gemcitabine, though OS was not prolonged significantly (45). The most common adverse reactions of Bevacizumab include hypertension, proteinuria and hemorrhage, but the occurrence of grade 3 hypertension, grade 4 hypertension, grade 4 proteinuria and hemorrhage was lower than 4%, 0.5%, 0.5% and 2% respectively. Bevacizumab is not recommended in case of the following conditions: (I) squamous cell carcinoma or mixed-type lung cancer dominated by squamous cell carcinoma; (II) tumor invasion into major vessels; (III) history of hemoptysis (>2.5 mL at a time); and (IV) uncontrollable primary hypertension and other cardiovascular diseases.

The result of a randomized phase III clinical trial conducted in Mainland China showed that recombinant human endostatin (rh-Endo) in combination with Vinorelbine/Cisplatin significantly improved ORR and time to progression (TTP) in advance NSCLC patients as compared with placebo + vinorelbine/cisplatin (35.4% *vs*. 19.5%, P=0.0003; 6.3 *vs*. 3.6 months, P<0.0001). In addition, there was no significant difference in the occurrence of adverse reactions between the two groups (47).

Conclusions: (I) the addition of bevacizumab to the basis of first-line chemotherapy (carboplatin/paclitaxel or cisplatin/gemcitabine) is recommended for non-squamous advanced NSCLC patients with PS 0-1 without significant signs of hemoptysis and major vessel invasion. Although there is no lung cancer indication for Bevacizumab in Mainland China for the time being, it is expected to be approved by the CFDA in the future; (II) vinorelbine/cisplatin in combination with rh-Endostatin can be considered in advanced NSCLC patients.

Group members of the Chinese Expert Consensus on Molecularly Targeted Therapy for Advanced NSCLC include: BAI Chunxue, HONG Qunying and HU Jie (Zhongshan Hospital of Fudan University, China); CHEN Lian'an (CPLA General Hospital, China); HAN Baohui (Chest Hospital of Shanghai Jiaotong University, China); HU Chengping (Xiangya Hospital of Central South University, China); HUANG Jian'an (1st affiliated hospital of Suzhou University, China); LI Qiang (Changhai Hospital of the Second Military Medical University, China); ZHONG Nanshan and LI Shiyue (Guangzhou Institute of Respiratory Disease, China); LI Weimin (Huaxi Hospital of Sichuan University, China); JIN Faguang (Tangdu Hospital of the Fourth Military Medical University, China); QIAN Guisheng and WU Guoming (Xinqiao Hospital of the Third Military Medical University, China); SONG Yong (General Hospital of Nanjing Military Command Region, China); WU Yilong (Guangdong Provincial People's Hospital, China); XIE Canmao (1st affiliated Hospital of Zhongshan University, China); YANG Shuanying (2nd affiliated hospital of Xi'an Jiaotong University, China); ZHOU Caicun (Pulmonary Hospital of Tongji University, China); ZHOU Jianying (1st affiliated hospital of Zhejiang University School of Medicine, China); ZHANG Li (Beijing Union Hospital, China).

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