Springer Medizin

www.memoinoncology.com

05/17

memo – inOncology SPECIAL ISSUE

Congress Report CSCO 2017

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the 20th Annual Meeting of Chinese Society of Clinical Oncology, CSCO 2017 Congress, Xiamen. September 26th–30th, 2017

IMPRESSUM/PUBLISHER

Media owner and publisher: Springer-Verlag GmbH, Professional Media, Prinz-Eugen-Straße 8–10, 1040 Vienna, Austria, **Tel.:** +43(0)1/330 24 15-0, **Fax:** +43(0)1/330 24 26-260, **Internet:** www.springernature.com, www.SpringerMedizin.at. **Copyright:** © 2018 Springer-Verlag GmbH Austria. Springer Medizin is a Part of Springer Nature. **Managing Directors:** Joachim Krieger, Dr. Alois Sillaber, Dr. Heinrich Weinheimer. **Medical writing** in cooperation with Springer Healthcare Shanghai, Ying Ding. **Editorial Management:** Judith Moser, MD, Stefanie Wurm, PhD. **Corporate Publishing:** Elise Haidenthaller. **Layout:** brandlgrafik. **Published in:** Vienna. **Produced in:** Fulda. **Printer:** Druckerei Rindt GmbH & Co KG, Fulda, Germany;
The editors of "memo, magazine of european medical oncology" assume no responsibility for this supplement.

Table of Contents

Editorial Board:

Boehringer Ingelheim

Supported by Boehringer Ingelheim in the form of an unrestricted grant

Preface

Dear Colleagues,

In the global fight against cancer, clinical trials across multiple regions of the world have become common practice, with the ultimate goal to bring good medicinal products to patients around the world, as fast as scientifically possible. Safety and efficacy data generated from local patients are a regulatory requirement in many countries including China. As a non-governmental association, the Chinese Society of Clinical Oncology (CSCO) holds its academic meeting annually to provide a platform for scientific exchange to oncology research professionals from China and abroad. The theme of the 20th conference, which took place in Xiamen from September 26th to 30th, was "Together we innovate on our inheritance". Adhering to CSCO's principles, the conference provided great opportunities for communications and cooperations in clinical oncology with a focus on Chinese patients. Clinical trials conducted in Asia have contributed considerably to the development of targeted therapies, such as EGFR or ALK tyrosine kinase inhibitors, and immunotherapies, but also to the implementation of cytotoxic drugs. Particularly in lung cancer, Eastern Asia has evolved into a stronghold of cancer research over the previous years. From the point of view of thoracic oncology, the goal of last year's CSCO meeting was to introduce the Chinese guidelines for the treatment of non-small-cell lung cancer and encourage innovation in clinical research in this area.

The large amount of clinical data coming out from oncology trials internationally presents an information flood and an increasing pressure on oncologists working on personalized medicine and biomarker research. This report of memo inOncology provides a concise summary of topics focused on lung cancer care, which were discussed at the CSCO 2017 Annual Meeting. It covers various subjects ranging from guidelines for the treatment of NSCLC in China, diagnosis and treatment of *EGFR*-mutated NSCLC, different therapies for lung squamous cell carcinoma, the response to immunotherapy as well as the clinical care of lung cancer patients with brain metastasis.

Overall, the data presented at the conference highlighted progress in all of these areas. We hope that the implementations of the CSCO NSCLC guidelines, further drug development and the identification of reliable biomarkers will make cure a feasible goal for many of our patients in the near future.

© authors own

Caicun Zhou, MD, PhD
Director of the Department of Oncology,
Shanghai Pulmonary Hospital,
Affiliated to Tongji University School of Medicine,
Shanghai, China

Guidelines for the treatment of NSCLC in China: progress and controversies

Lung cancer (LC) is the leading cause of tumor deaths worldwide. Per year, 1.8 million people are diagnosed with LC, and the annual death toll amounts to 1.6 million. Non–small-cell lung cancer (NSCLC) is the most common type, which accounts for 85% of LC cases. Squamous cell carcinoma (SqCC), adenocarcinoma (AC), and large-cell carcinoma are subtypes of NSCLC. The 5-year survival rate of NSCLC is only approximately 15%, and nowadays almost 70% of NSCLC patients are in advanced stages at the time of diagnosis [1].

The guidelines of the Chinese Society of Clinical Oncology (CSCO) for LC are based on evidence-based medicine and precision medicine. However, the availability of health resources should be considered simultaneously. China is an unequally developed country, and implementing the guidelines for LC treatment should consider imbalanced development of regions, accessibility to drugs and treatment methods as well as the value of cancer treatment. Thus, for each clinical problem, the Chinese guidelines give a standard recommendation for cancer care as a basic strategy, as well as a cost-effective therapeutic strategy for regions with low accessibility to drugs as an optional strategy. At CSCO 2017, which was held in Xiamen from September 26th to 30th, 2017, the objective was to introduce these guidelines for the treatment of

NSCLC and to discuss the main controversies these recommendations bring.

Guidelines for stage IA-IB NSCLC – controversy: stereotactic ablative radiotherapy or sublobectomy?

For stage IA-IB NSCLC patients who are suitable for surgery, the 2017 CSCO guidelines recommend that pulmonary lobectomy plus systematic mediastinal lymph node dissection by minimally invasive technique should be the basic strategy (IIA). An additional recommendation is the participation in a clinical trial which compares surgery to stereotactic ablative radiotherapy (SABR) (level 3 evidence).

For stage IA-IB NSCLC patients who are not suitable for surgery, stereotactic body radiation therapy (SBRT)/SABR should be the basic strategy (IIA), and SBRT/SABR by other advanced radiotherapy (RT) technology, such as RT with photons, protons and carbon-ions, should be the optional strategy (IIA) [2].

SBRT or SABR has been the standard of care (SOC) for NSCLC patients who are not suitable for surgery. However, as for early-stage NSCLC patients who are suitable for surgery, the controversy whether SABR/SBRT should be an alternative treatment option besides the SOC (i.e., pulmonary lobectomy and lymph node dissection) still exists.

The studies STARS and ROSEL compared SABR to surgery in operable early-stage NSCLC. Histological confirmation of NSCLC by biopsy or cytological evaluation was required in the STARS trial but was not mandatory in ROSEL. In ROSEL, Dutch patients were enrolled. Furthermore, patients for whom no pathological confirmation of diagnosis was available were eligible if they had a new or growing pulmonary lesion with radiological features consistent with malignant disease and avidity on 18F-fluorodeoxyglucose (18F-FDG-PET). Patients in these two studies were randomly assigned in a 1:1 ratio to receive either SABR or surgery. In total, 58 patients were enrolled in the two studies, as 36 patients participated in STARS and 22 in ROSEL. The median follow-up times were 40.2 and 35.4 months for the group that received SABR and the group that underwent surgery, respectively. Estimated overall survival (OS) at 3 years was 95 % in the SABR group compared to 79 % in the surgery group ($p = 0.037$), and recurrence-free survival (RFS) at 3 years was 86 % and 80 % for the SABR and the surgery groups, respectively ($p = 0.54$) [3]. Six patients in the surgery group died, compared to one patient in the SABR group.

In summary, these results showed longer OS, better RFS and fewer deaths in the SABR group compared to the surgery group in early-stage NSCLC. The data suggests that SABR could be a better choice for early-stage NSCLC compared to surgery. Surprisingly, another large study, NCDB, was found to contradict these results. Data from this study showed that SABR was associated with a significantly reduced 5-year survival rate compared to surgery in both the unmatched analysis (30.9 % vs. 55.2 %; $p < 0.001$) and the analysis adjusted for covariates (31.0 % vs. 49.9 %; $p < 0.001$). In this study, SABR was associated with worse OS compared to the surgery group according to 2 subgroup analyses in propensity-matched patients (both $p < 0.05$) [4].

In operable stage IA-IB NSCLC patients, surgery is still the standard treatment, with SABR as an optional treatment. In inoperable stage IA-IB NSCLC patients, stereotactic ablative radiotherapy is the preferred treatment for LC care.

Guidelines for stage IIIA-N2 NSCLC – controversy 1: neoadjuvant therapy plus surgery or concurrent chemoradiotherapy

Stage IIIA NSCLC is a heterogeneous disease. The treatment strategies differ depending on the stage of the tumor (T), the presence of lymph node metastasis (N) and resectability of the tumor **(Table 1)**.

The main controversies regarding stage IIIA NSCLC relate to whether neoadjuvant therapy plus surgery could substitute concurrent chemoradiotherapy and whether post-operative RT is necessary in operable patients with clinical stage IIIA-N2 after surgery. The opinions uttered in various studies on whether neoadjuvant therapy should be added to the basic strategy or substitute the concurrent radiochemotherapy are conflicting.

In the INT0139 trial, which enrolled 429 patients with stage IIIA NSCLC, all patients were randomized into surgery or radical RT groups after treatment with concurrent chemoradiotherapy. The study revealed increased progression-free survival (PFS; 12.8 months vs. 10.5 months; $p = 0.017$) and OS (33.6 months vs. 21.7 months; $p = 0.002$) for neoadjuvant treatment plus surgery compared to neoadjuvant treatment plus concurrent RT in operable stage IIIA-N2 NSCLC patients [5]. In contrast, other studies showed no PFS or OS differences between neoadjuvant therapy plus surgery and concurrent RT. In the EORTC08941 study that enrolled 579

TABLE 1
Different treatment strategies for different subtypes of stage IIIA-N2 NSCLC

stage IIIA-N2 type	neoadjuvant	surgery	adjuvant	post-operative RT	concurrent RT
Operable single station – basic strategy		x	x	x	x
Operable single station – optional strategy	x	x	x	x	
Operable multi station – basic strategy					x
Operable multi station – optional strategy	x	x	x	x	
Operable, cannot be resected					x

patients, all patients were randomized to either the surgery group or the RT group after 3 weeks of neoadjuvant therapy, and received relevant treatment. No statistically significant difference in OS (16.4 months vs. 17.5 months; p = 0.596) and PFS (9 months vs. 11.3 months; p = 0.605) was observed across the surgery and RT groups [6]. Similar results were reported from the SAKK, ESPATUE and GLCCG studies, which showed no significant difference between neoadjuvant therapy plus surgery and concurrent RT.

Thus, based on the current evidence for treatment of operable stage IIIA-N2 NSCLC patients, concurrent RT is still the basic strategy. Additional studies on neoadjuvant therapy for the treatment of NSCLC patients with stage IIIA-N2 are required.

Guidelines for stage IIIA-N2 NSCLC – controversy 2: post-operative radiotherapy

Another controversy in the treatment of stage IIIA-N2 NSCLC patients is whether post-operative radiation therapy (PORT) should be applied or not. Precise RT technologies, such as three-dimensional conformal radiation therapy and intensity-modulated radiation therapy, have been widely used for the treatment of LC. This treatment strategy decreases non-cancer-related deaths caused by cardiotoxicity.

Corso et al. conducted a retrospective case-control study, which included 6,979 stage II-III-N2 NSCLC patients. The results showed that the 5-year OS rate in the PORT group was significantly higher than in the control group (34.1% vs. 27.8 %; p < 0.001), with a 6.3% OS increase in the PORT group [7] **(Figure 1)**. According to Urban et al., who analyzed data of 4,773 N2 patients from the SEER database who underwent surgery, the risk of death was notably decreased in the PORT group (HR,0.9; p = 0.026) [8]. Mikell et al. and Robison et al. reported similar results in pN2 NSCLC patients that favored PORT [9, 10]. However, Wisnivesky et al. reported that PORT did not improve survival in old (≥65 years) pN2 NSCLC patients, (HR, 1.1; p = 0.3) [11].

Thus, the treatment with post-operative radiotherapy revealed a notably increased efficacy in the treatment of stage III-N2 NSCLC patients. However, it is still not clear whether PORT is suitable for older patients. Therefore, additional studies are called for.

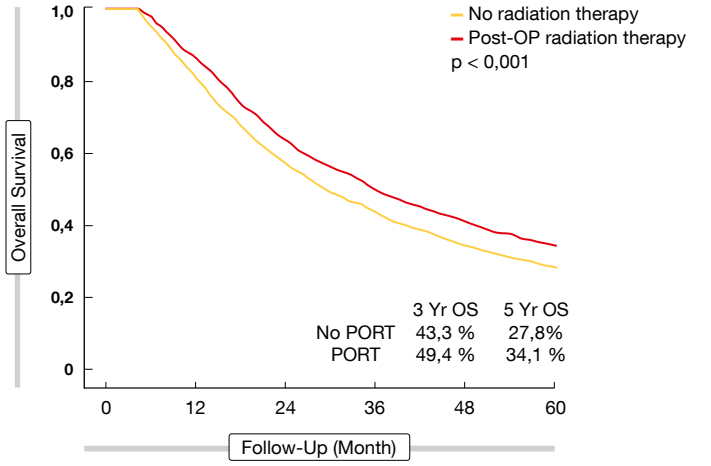


Figure 1: Overall survival of stage IIIA-N2 patients with and without PORT

Guidelines for stage IV *EGFR*-mutant NSCLC: afatinib as first-line recommendation

In the 2017 CSCO guidelines, the standard first-line strategy for patients with stage IV epidermal growth factor receptor (EGFR)-mutant NSCLC includes the tyrosine kinase inhibitors (TKIs) afatinib, gefitinib, icotinib and erlotinib. Optional strategies include erlotinib or gefitinib plus chemotherapy, platinum-based chemotherapy or platinum-based chemotherapy plus the VEGF inhibitor bevacizumab (performance status [PS], 0–1; IIA). For stage IV patients with *EGFR*-mutant NSCLC after resistance to first-line EGFR TKI, treatment decisions should be made based on the status of progression. The guidelines recommend continuing EGFR TKI plus local therapy (IIA) for localized progression, and continuation of initial EGFR TKI therapy (IIA) for slow progression as basic strategies. In patients with rapid progression, *EGFR* mutation testing should be performed. Osimertinib or platinum-based chemotherapy should be considered as a basic strategy for *EGFR* T790M-positive patients (grade I evidence), while platinum-based chemotherapy is indicated in T790M-negative patients (grade I evidence). Participation in clinical trials based on the resistance mutation should be considered as an optional strategy for stage IV patients with *EGFR*-mutant NSCLC after resistance to first-line EGFR TKI [12].

Guidelines for advanced SqCC

According to the 2017 CSCO guidelines, the treatment strategy for SqCC patients should be selected based on the PS score and patient tolerance to platinum. For the first-line treatment of patients with a PS of 0-1 who are suitable for platinum treatment, the basic strategy is platinum-based chemotherapy, including cis-platinum-based chemotherapy (cis-platinum plus gemcitabine/docetaxel/paclitaxel/vinorelbine) (grade I evidence) or carboplatin-based chemotherapy (carboplatin plus gemcitabine/docetaxel/paclitaxel/vinorelbine) (Grade I evidence). The optional strategy is the participation in clinical trials. For patients with a PS of 2 who are not suitable for platinum treatment, single-agent chemotherapy should be the basic strategy, and best support care should be the optional strategy [12].

For the second-line treatment of SqCC patients, single-agent chemotherapy should be the basic strategy (grade I evidence), and afatinib should be the optional strategy (IB).

As previously established, SqCC is a heterogeneous disease, and there has hardly been any progress with respect to the treatment of this entity, especially for advanced SqCC. However, in the 2017 CSCO guidelines for LC, the recommendation for the second-line treatment of advanced SqCC was updated. This update was mainly based on evidence from the LUX Lung 8 (LL8) trial. LL8 compared afatinib with erlo-

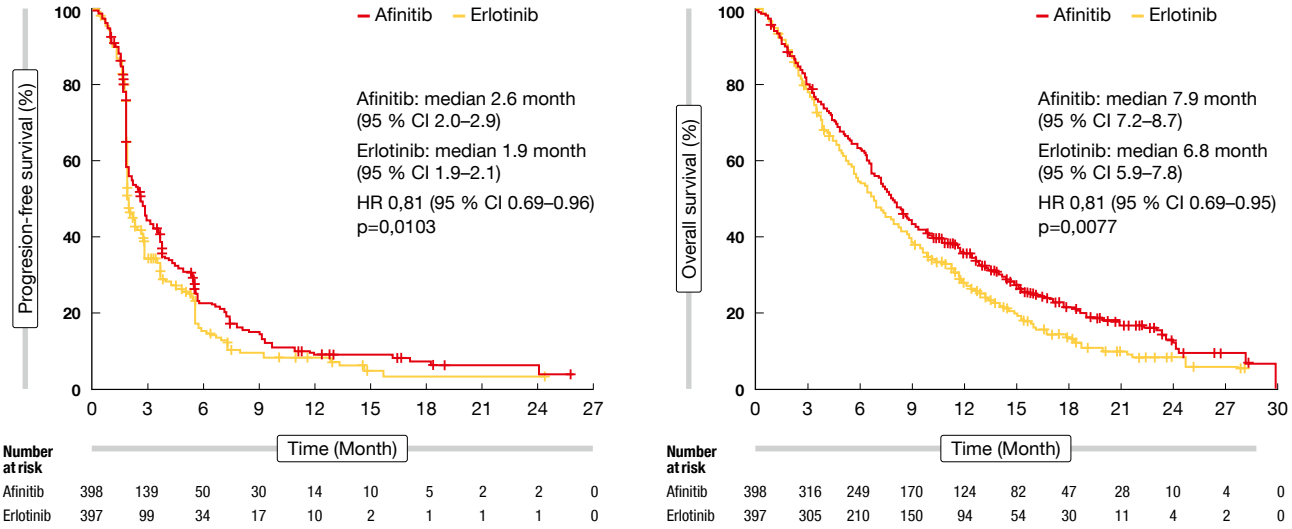


Figure 2: PFS (left) and OS (right) with afatinib compared to erlotinib in advanced SqCC

tinib in advanced SqCC after first-line chemotherapy. Results showed improved PFS (median 2.6 [95 % CI 2.0-2.9] vs. 1.9 months [1.9-2.1]; HR 0.81 [95 % CI 0.69-0.96], p = 0.0103) and OS (median 7.9 months [95 % CI 7.2-8.7] vs. 6.8 months [5.9-7.8]; HR 0.81 [95 % CI 0.69-0.95], p = 0.0077) in the afatinib group compared to the erlotinib group [13] **(Figure 2)**. Thus, CSCO 2017 recommends afatinib as a second-line treatment for advanced SqCC patients. (please see additional information on SqCC on page 9–11)

Guidelines for *HER2*-positive NSCLC: Afatinib as a recommended treatment in China

HER2 is a driver gene identified in NSCLC, with a prevalence of the *HER2* mutation of about 1.92 % in China [14]. However, there is no SOC for *HER2*-mutant NSCLC, which constitutes a problem in clinical practice. The activity of afatinib was demonstrated in preclinical *HER2*-mutant LC models and in clinical studies with *HER2*-mutant NSCLC patients. At CSCO 2017, the study design of afatinib for the treatment of *HER2*-mutant NSCLC patients in China (NCT02597946) was introduced, which was initiated in March 2016 [15]. ■

REFERENCES

1 Goldstraw P et al., Non-small-cell lung cancer. Lancet 378:1727-1740.
2 Fan Y et al., Guidelines for I-IIIa LC CSCO 2017
3 Chang JY et al., Stereotactic ablative radiotherapy *versus* lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015 Jun;16(6):630-7.
4 Yerokun BA et al., A national analysis of wedge resection *versus* stereotactic body radiation therapy for stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg. 2017 Aug; 154 (2): 675-686.e4.
5 Albain KS et al., Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009 Aug 1; 374(9687): 379-86.
6 Jan P et al., Randomized controlled trial of resection *versus* radiotherapy after induction chemotherapy in stage IIIA-N2 non – small-cell lung cancer. J Natl Cancer Inst 2007; 99: 442-50
7 Corso CD et al., Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the National Cancer Database. J Thorac Oncol. 2015 Jan;10 (1):148 - 55.
8 Urban D et al., Lymph node ratio may predict the benefit of postoperative radiotherapy in non-small-cell lung cancer. J Thorac Oncol. 2013 Jul; 8 (7):940 - 6. 7.
9 Mikell JL et al., Postoperative radiotherapy is associated with better survival in non-small cell lung cancer with involved N2 lymph nodes: results of an analysis of the National Cancer Data Base. J Thorac Oncol. 2015 Mar;10(3):462-71.
10 Robinson CG et al., Postoperative radiotherapy for pathologic N2 non–small-cell lung cancer treated with adjuvant chemotherapy: A review of the National Cancer Data Base. J Clin Oncol. 2015 Mar 10; 33(8): 870–876.
11 Wisnivesky JP et al., Postoperative radiotherapy for elderly patients with stage III lung cancer. Cancer. 2012 Sep 15;118 (18):4478 - 85.
12 Zhefeng L et al., Guidelines for advanced LC therapy CSCO 2017
13 Soria JC et al., Afatinib *versus* erlotinib as second -line treatment of patients with advanced squamous cell carcinoma of the lung (LUX lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol, 2015, 16 (8):897 - 907.
14 Zhangzhou H et al., Mutational subtypes and prognosis of non-small-cell lung cancer harboring HER2 mutations. CSCO 2017
15 Caicun Z et al., Afatinib in patients with advanced *HER2* mutation-positive NSCLC previously treated with chemotherapy. CSCO 2017

Diagnosis of *EGFR*-mutated NSCLC: from guidelines to reality

Over the last decade, the increasing understanding of critical molecular and cellular mechanisms which drive tumor initiation, maintenance, and progression in non-small-cell lung cancer (NSCLC) have contributed to the discovery of various novel drug targets and the development of new treatment strategies. The standard of care (SOC) for patients with advanced-stage NSCLC is shifting from selecting therapies empirically based on patient clinicopathologic features to using biomarker-driven treatment algorithms according to the molecular profile of the patient's tumor. The most frequent mutation in Asian patients is *EGFR* mutation, which occurs in 60.5 % of lung adenocarcinomas (ACs). Thus, to the effective and accurate detection of the *EGFR* mutation has become important for the selection of subsequent therapies, especially for Asian NSCLC patients. At CSCO 2017, the discussion on the diagnosis of *EGFR*-mutated NSCLC mainly focused on how to choose the appropriate method for detecting *EGFR* mutation. Another topic of intense discussion was recent progress in the field of mechanisms of resistance to third-generation EGFR TKIs.

Suitable shoes for appropriate feet – ARMS, IHC, NGS, tissue biopsy or liquid biospy?

Molecular subtyping of LC is essential for selecting the appropriate therapeutic strategy. Precision oncology is now the evidence-based SOC for the management of many patients with advanced NSCLC. The application of palliative targeted therapies consisting of oral TKIs such as gefitinib, erlotinib and afatinib in advanced/metastatic lung ACs harboring *EGFR* abnormalities has consistently contributed to more favorable outcomes compared to the use of traditional cytotoxic agents. However, choosing a suitable method for the accurate, rapid and consistent detection of *EGFR* mutations or other mutations, is gaining importance in the treatment of NSCLC. Chinese guidelines for the treatment of NSCLC, developed based on expert consensus, define minimum requirements for routine testing and optional strategies for the identification of *EGFR* mutations in advanced NSCLC [1].

Among methods frequently used to detect *EGFR* mutation, Sanger Sequencing is the most sensitive procedure, followed by Amplification Refractory Mutation System (ARMS) and Next-Generation Sequencing (NGS). According to the 2017 CSCO guidelines for the detection of molecular subtypes of advanced non-squamous NSCLC, ARMS should be used as the standard strategy for the detection of *EGFR* mutation in patients who were diagnosed by immunohistochemistry (IHC). Only when tissue is difficult to obtain, a blood sample is the optional choice for ARMS detection. However, the recommendations differ from the National Comprehensive Cancer Network (NCCN) guideline for ACs, which recommends subtyping by NGS to detect *EGFR* and *ALK* mutations. One explanation for this discrepancy might be the imbalance of health resources across different regions, and the value of diagnosis.

With regard to osimertinib, a third-generation EGFR TKI that was approved by the China Food and Drug Administration as second-line treatment of *EGFR*-mutant advanced NSCLC, the Chinese guidelines recommend that the T790M mutation should be detected by tissue biopsy using PCR-ARMS, Cobas, NGS or ddPCR. Only when tissue samples are difficult to acquire, liquid biopsy by PCR-ARMS, super-ARMS, Cobas, cDNA-NGS or ddPCR should be considered as a standard strategy in advanced non-squamous NSCLC patients who were resistant to first-line EGFR TKI treatment.

Liquid biopsies are based on the detection of DNA fragments in blood, sweat, urine and other liquids obtained from human beings by high-throughput DNA sequencing such as NGS. The main subjects of liquid biopsies are circulating tumor DNA (ctDNA), circulating tumor cells (CTC) and exosomes. As reported by Reckamp KL et al. [2], the sensitivity for the detection of *EGFR* T790M and L858R mutations as well as deletion 19 in plasma was 93 %, 100%, and 87 %, respectively, and the specificity was 94 %, 100%, and 96 %, respectively **(Table 1)**.This indicated a suitable performance of mutation enrichment NGS assays for the detection of *EGFR* mutations in advanced NSCLC. Meanwhile, Thress KS et al. also reported that *EGFR* T790M mutation and *EGFR* C797S mutation can be detected by ctDNA liquid biopsy in patients resistant to EGFR TKI treatment [3]. Sundaresan et al. indicated high consistency of liquid biopsy by CTC, ctDNA, CTC/ctDNA with tissue biopsy (74 %, 62 % and 69 %) in relation to the detection of T790M mutation [4].

Thus, the 2017 CSCO guideline recommends that tissue biopsy by ARMS should be the standard strategy for molecular subtyping of advanced NSCLC patients who were diagnosed by IHC. Even though liquid biopsy displays higher sensitivity and specificity in detecting *EGFR* mutations or *EGFR* T790M after resistance to EGFR TKI, the 2017 CSCO guideline recommended liquid biopsy as an optional choice only when tissue biopsy was not available. In summary, CSCO developed the guidelines for the diagnosis of Chinese NSCLC patients to consider several aspects and not only the sensitivity and specificity of the respective technology.

New insights on resistance mechanisms of osimertinib – focus on the L792 mutation

Osimertinib, a third-generation EGFR TKI that selectively inhibits both EGFR TKI–sensitizing and *EGFR* T790M resistance mutations, has changed the second-line SOC for *EGFR*-mutant advanced NSCLC. The phase III FLAURA study focused on the efficacy of osimertinib in previously untreated, *EGFR*-mutant (exon 19 deletion or L858R mu-

tation) patients with advanced NSCLC. The results of FLAURA showed higher PFS for osimertinib compared to first-generation EGFR TKIs. However, acquired resistance was again inevitable. *EGFR* C797S mutation was suggested to represent the most notable resistance mechanism to this drug, but other *EGFR* mutations may also exist.

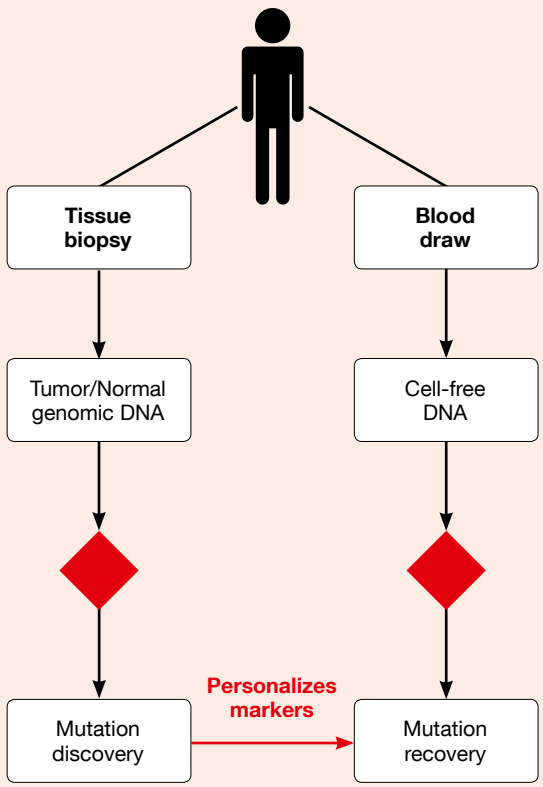
At CSCO 2017, professor Caicun Zhou from the Tongji University Medical School presented a case report, where a novel mutation of *EGFR* at Leu792 was reported which may represent another resistance mechanism to osimertinib [6]. Patients with stage IV lung ACs, who progressed on the third-generation TKI osimertinib when administered as second-line treatment, were investigated. Plasma samples and samples obtained from pleural effusions were collected for cell free DNA (cfDNA) and sequenced by NGS for 416 cancer-related genes. The results showed that besides the most common T790M/C797S mutations, Leu792 was also mutated, including the mutations L792F, L792Y and L792H. In-depth analyses and structural predictions suggest a role of C797S mutation in the interruption of osimertinib binding to EGFR [7].

Rate of T790M mutation – data from studies in China

The first- and second-generation EGFR TKIs can significantly prolong PFS in patients with advanced, *EGFR*-mutant NSCLC. However, resistance has been observed. *EGFR* T790M mutation occurs in 60 % of patients resistant to first- and second-generation EGFR TKIs [8]. While the data on T790M has mainly been obtained from foreign studies, at CSCO 2017, a large sample study was presented that evaluated the T790M mutation rate specifically for Chinese patients [9].

The study was conducted in 79 centers across 32 cities in the northern, eastern, middle and southern areas of China. A total of 2,693 samples, including 1,427 blood samples (53 %) and 1,266 tissue samples (47 %), were obtained from patients who developed progressive disease (PD) after EGFR TKI treatment since March 31st, 2017. Among all tissue samples, 81.7 % were obtained from tissue biopsies. In 91.8 % of the samples, the percentage of cancer cells was more than 10 %. T790M mutations were detected in 62.8 % and 27.5 % by tissue and blood examination, respectively **(Figure 1)**. Results according to tissue examination showed that in T790M-mutant patients, 39.3 %, 22 %, 0.7 % and 0.8 % of patients simultaneously had 19 deletion, L858R mutation, rare mutations (or both exon 19 deletion and L858R mutation) and no other *EGFR* mutations, respectively. Patients without any *EGFR* mutations were only observed in 7.2 % of cases. Results by blood examination showed that in *EGFR* T790M-mutant patients,

TABLE 1
Performance of NGS assays in the detection of *EGFR* mutations in plasma



Reckamp KL et al. J Thorac Oncol. 2016 11(10):1690-700

Characteristics	Specimen Type	Value, n %
T790M		
Sensitivity	All urine volumes, 10–100 ml	72 % (34 of 47)
	Urine volumes, 90–100 ml*	93 % (13 of14)
	Urine volumes, 10–89 ml*	64 % (21 of 33)
	Plasma	93 % (38 of 41)
Specificity	Urine	96 % (54 of 56)
	Plasma	94 % (60 of 64)
L858R		
Sensitivity	All urine volumes, 10–100 ml	75 % (12 of 16)
	All urine volumes, 90–100 ml*	80 % (4 of 5)
	Urine volumes, 10–89 ml*	73 % (8 of 11)
	Plasma	100 % (17 of 17)
Specificity	Urine	100 % (50 of 50)
	Plasma	100 % (48 of 48)
Exon 19 defetions		
Sensitivity	All urine volumes, 10–100 ml	67 % (28 of 42)
	Urine volumes, 90–100 ml*	83 % (10 of 12)
	Urine volumes, 10–89 ml*	60 % (18 of 30)
	Plasma	87 % (34 of 39)
Specificity	Urine	94 % (47 of 50)
	Plasma	96 % (47 of 49)

* Recommended urine volume ≥ 90ml

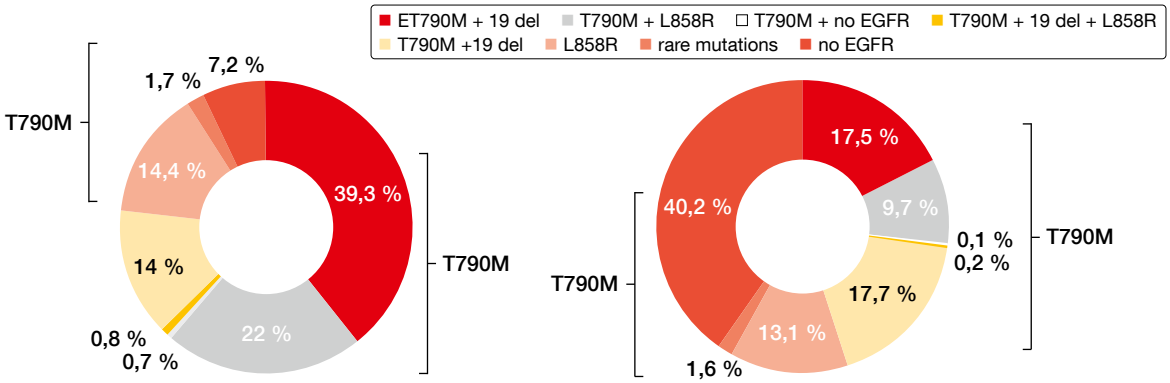


Figure 1: The rate of T790M rate according to tissue (left) or blood (right) examination

17.5 %, 9.7 %, 0.2 % and 0.1 % had 19 deletion, L858R mutation, rare mutations and no other *EGFR* mutations, respectively. Patients without any *EGFR* mutations were observed in 40.2 % of-cases. Subgroup analysis showed no differences with regard to age, sex, amount, method, or site of the tissue obtained. The mutation ratio of T790M was 50 % and 63.9 % in tissues with fractions of tumor cells of < 10 % and ≥10 %, respectively. This means that even in biopsies with a fraction of tumor cells below 10 %, T790M mutation detection could be used as a marker for diagnosis.

Thus, Professor Ying Cheng from the Cancer Hospital of Jilin Province, Changchun (China), indicated that the prevalance of the T790M mutation was 62.8 % by tissue examination, which is similar to results from previous studies. Relatively low sensitivity for the detection of T790M was found in blood examinations, which suggests that more sensitive methods will be needed in the future [8]. ■

REFERENCES

1 Li Y et al., Molecular typing for LC CSCO 2017
2 Reckamp KL et al., A highly sensitive and quantitative test platform for detection of NSCLC EGFR mutations in urine and plasma. J Thorac Oncol. 2016 Oct; 11(10):1690-700.
3 Thress KS et al., Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. Nat Med. 2015 Jun; 21(6):560-2.
4 Sundaresan TK et al., Detection of T790M, the acquired resistance EGFR mutation, by tumor biopsy *versus* noninvasive blood-based analyses. Clin Cancer Res. 2016 Mar 1 ;22(5):1103-10.
5 Soria JC et al., Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113-125. doi: 10.1056/NEJMoa1713137.
6 Caicun Zhou et al., Development of precision medicine in advanced NSCLC CSCO 2017
7 Chen K et al., Novel mutations on EGFR Leu792 potentially correlate to acquired resistance to osimertinib in advanced NSCLC. J Thorac Oncol. 2017 Jun;12(6):e65-e68.
8 Camidge DR et al., Acquired resistance to TKIs in solid tumours: learning from lung cancer. Nat Rev Clin Oncol. 2014 Aug;11(8):473-81.
9 Cheng Y et al., T790M rate in Chinese advanced NSCLC after resistance to EGFR TKI CSCO 2017

Different therapies for treatment of squamous cell carcinoma

Squamous cell carcinoma (SqCC) is one of the histopathological subtypes of non–small-cell lung cancer (NSCLC), and it accounts for 20 % to 30 % of these patients [1]. Unfortunately, few studies have explored the treatment options for patients with SqCC, and progress in SqCC treatment lags behind other histopathological and/or molecular subtypes of NSCLC [2]. At CSCO 2017, the main information relating to SqCC indicated that immunotherapies and targeted therapies do not provide satisfactory results. Additionally, the latest progress on afatinib for SqCC patients was reported.

Immunotherapies – hopeful prospect *versus* cruel reality?

The CheckMate 017 trial compared nivolumab to docetaxel as second-line treatment for SqCC patients, where nivolumab showed improved progression-free survival (PFS; 3.6 *vs.* 2.8 months; hazard ratio [HR] for death or disease progression, 0.62; 95 % confidence interval [CI], 0.47–0.81; p = 0.00004) and overall survival (OS; 9.2 *vs.* 6.0 months; HR, 0.59; 95 % CI, 0.44–0.79; p = 0.00025) compared to docetaxel [3]. The OAK trial compared atezolizumab to docetaxel as second-line or third-line treatment for SqCC patients, where atezolizumab also showed improved OS compared to docetaxel (8.9 *vs.* 7.7 months; p = 0.0383) [4].

Although these CheckMate 017 and OAK trials indicated promising results for immunotherapies as second-line treatments for SqCC patients, poor responses have been shown for SqCC pa-

tients treated with immunotherapies as first-line treatments. Govindan R et al. [5] conducted a phase III study to compare paclitaxel plus carboplatin in combination with ipilimumab (10 mg/kg) or placebo as first-line treatments for SqCC patients. However, no differences were seen between the two treatment groups for PFS (5.6 *vs.* 5.6 months) and OS (13.4 *vs.* 12.4 months; p = 0.25).

Thus, at CSCO 2017, Professor Qing Zhou from the Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou (China) indicated that although immunotherapies have critical roles in the treatment of various cancers, they have shown little efficacy for treatment of SqCC patients [6].

Combining targeted therapy: multiple drugs, but poor benefit

According to the CSCO 2017 guidelines, the basic strategy for treatment of SqCC patients is platinum-based chemotherapy.

An *EGFR*-blocking antibody as first-line treatment of advanced SqCC

The SQUIRE trial compared the recombinant human IgG1 anti-*EGFR* monoclonal antibody necitumumab plus chemotherapy with chemotherapy alone, as first-line treatments for SqCC patients. Here the OS curves for necitumumab plus chemotherapy and chemotherapy alone almost overlapped. Although the absolute difference in OS was small (11.5 *vs.* 9.9 months; HR, 0.84; 95 % CI, 0.74–0.96; p = 0.01), this *EGFR* blocking antibody was approved by the US Food and Drug Administration as first-line treatment in advanced SqCC patients [7].

Afatinib as second-line treatment of advanced SqCC

The LUX-Lung 8 trial compared afatinib to erlotinib as second-line treatment in advanced SqCC patients. For all patients, afatinib showed greater improvements for PFS (2.6 *vs.* 1.9 months; HR, 0.81; 95 % CI, 0.69–0.96; p = 0.0103) and OS (7.9 *vs.* 6.8 months; HR, 0.81; 95 % CI, 0.69–0.95; p = 0.0077), compared to erlotinib [8]. In the updated subgroup analyses that focused on the Chinese patients, afatinib provided numerically greater PFS (2.79 *vs.* 2.76 months; p = 0.2250) and OS (10.84 *vs.* 8.21 months; p = 0.1957), compared to erlotinib **(Figure 1)** [9]. Although there was no significant superiority of afatinib over erlotinib in the Chinese subgroup, the Chinese guidelines for NSCLC treatment indeed recommend afatinib as second-line treatment for advanced SqCC.

In summary, although targeted therapies have not shown preponderant superiority as first-line or second-line treatments compared to the 'traditional' standard of care for SqCC patients, most organizations and countries have still focused on targeted therapies as the recommended treatment options for SqCC patients.

Afatinib long-term responders

Additionally, a *post-hoc* analysis was reported from the LUX-Lung 8 trial, on the afatinib long-term responders (LTRs; with ≥ 12 months afatinib treatment). Here, 5 % of these SqCC patients were LTRs, with median PFS of 16.6 months and median OS of 21.1 months. The patient gene expression profiles obtained from next-generation sequencing were also compared between the LTRs and the rest of the afatinib-treated patients. *ErbB*-aberrations were more common in the LTRs than the overall afatinib-treated patients **(Figure 2)** [10]. Mass spectrometry analyses of the patient serum proteins using Veristrat also showed improvement for the LTRs compared to the overall afatinib-treated patients, in terms of those graded as Veristrat-good (88 % *vs.* 62 %). All of the patients who progressed received subsequent therapy, where 8/14 LTRs discontinued afatinib and received ≥1 subsequent line of systemic therapy, and 6/14 LTRs remained on afatinib at data cut-off; one of these patients received afatinib until death. Thus, the conclusion from this *post-hoc* analysis of afatinib LTRs was that after failing chemotherapy, 5 % of these SqCC patients were able to achieve long-term responses. The presence of *ErbB*-family

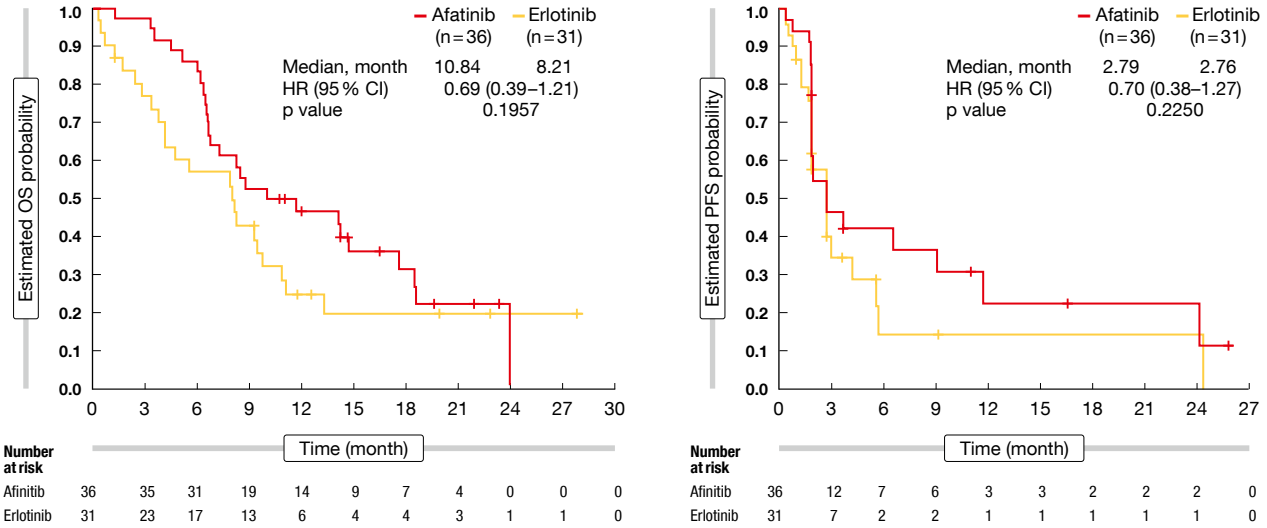


Figure 1: Estimated overall survival probability (left) and progression-free survival (right) with afatinib compared to erlotinib in the Chinese SqCC subgroup

mutations or Veristrat-good status might represent biomarkers of long-term responses to afatinib in advanced SqCC patients.

Afatinib plus cetuximab as second-line treatment of advanced SqCC

The unmet need for additional second-line treatments along with afatinib in advanced SqCC patients is still a clinical problem, and particularly for those with *EGFR*-T790M-mutant-negative tumors.

The EGFR inhibitor cetuximab has shown synergistic activity with afatinib in preclinical studies [11]. Data of a phase IB study of afatinib plus cetuximab were reported at CSCO 2017, as study 1 (S1; NCT01090011) in *EGFR*-mutant-positive NSCLC patients with resistance to gefitinib/ erlotinib (G/E), and Study 2 (S2; NCT02020577) in unselected patients with heavily pretreated advanced solid tumors, which included SqCC patients. In S1, these *EGFR*-mutant-positive NSCLC patients who were resistant to G/E were treated with afatinib (40 mg once daily) plus cetuximab (500 mg/m^2 every 2 weeks). In S2, these patients with advanced solid tumors that included SqCC were treated with afatinib (40 mg once daily) plus cetuximab (250 mg/m^2 weekly). In S1, the disease control rate (DCR) was 71 %, the median PFS was 4.7 months, and the discontinuation rate due to treatment-related adverse events was 13%. In S2, the overall DCR was 55%, but was higher for the SqCC patients, at 75 %. The median PFS was 11.9 weeks for the SqCC patients, and treatment-related adverse events occurred in 12 % of the total patient population, similar to that seen for study S1 [12]. The conclusion from these studies was that afatinib plus cetuximab provides benefits for *EGFR*-mutant-positive NSCLC patients who are resistant to G/E and for heavily pretreated SqCC patients, and that these benefits are accompanied by an acceptable safety profile.

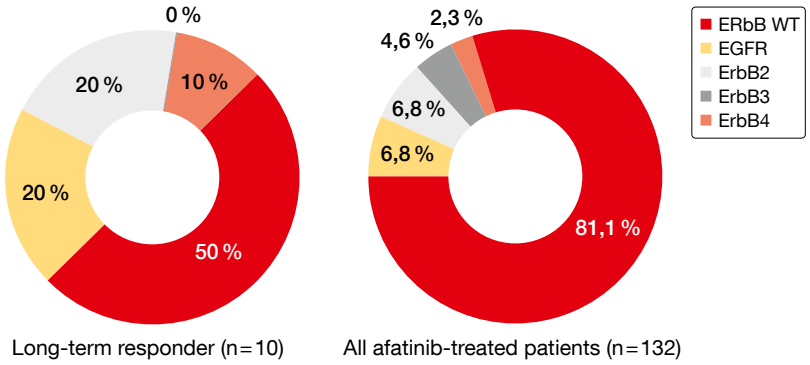


Figure 2: Comparison of ErbB-family variant mutations between long-term responders (left) and all afatinib-treated patients (right).

On-going investigations into new targeted therapies

New targeted therapies for SqCC patients have been explored; however, most studies have not yielded the desired results. Studies on a fibroblast growth factor receptor inhibitor (dovitinib), a phosphoinositide 3-kinase inhibitor (pictilisib), a platelet-derived growth factor receptor inhibitor (motesanib) and a poly(adenosine diphosphate-ribose) polymerase inhibitor (iniparib) were all terminated early because of lack of efficacy or adverse events. The S1400 study was the first to be conducted through a government, academia, and pharma collaboration that focused on SqCC, which included the S1400B/C/D/E and S1400A/1 substudies for driver-oncogene-positive and -negative SqCC, respectively. The data from S1400B/C/D were presented at ASCO 2017, which compared the efficacies of GDC-0032 (phosphoinositide 3-kinase inhibitor), palbociclib (cyclin-dependent kinase 4/6 inhibitor) and AZD4547 (fibroblast growth factor receptor inhibitor) with docetaxel; however, these substudies were terminated early due to lack of efficacy.

Although the present situation is not favorable for new targeted therapies for SqCC patients, investigations into new potential therapies are still on-going, including those with an antisense oligonucleotide (apatorsen) and a cell-cycle blocker (abemaciclib). Professor Zhou thus indicated that although most studies of new therapies for SqCC patients have not been successful, the field is still moving forward [6]. ■

REFERENCES

1 Hirsh V et al., New Developments in the Treatment of Advanced Squamous Cell Lung Cancer: Focus on Afatinib. Onco Targets Ther. 2017;10:2513-2526.
2 Schumacher TN et al., Neoantigens in Cancer Immunotherapy. Science. 2015;348(6230):69-74.
3 Brahmer J et al., Nivolumab *versus* Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. N Engl J Med. 2015;373:123-135.
4 Rittermeyer A et al., Atezolizumab *versus* Docetaxel in Patients with Previously Treated Non–Small-Cell Lung Cancer (OAK): a Phase 3, Open-Label, Multicentre Randomised Controlled Trial. The Lancet. 2017;389(10066):255-265.
5 Govindan R et al., Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non–Small-Cell Lung Cancer. J Clin Oncol. 2017;35(30):3449-3457.
6 Zhou Q et al., Progression and Challenge of SqCC. CSCO 2017.
7 Thatcher N et al., Necitumumab plus Gemcitabine and Cisplatin *versus* Gemcitabine and Cisplatin Alone as First-Line Therapy in Patients with Stage IV Squamous Non–Small-Cell Lung Cancer (SQUIRE): an Open-Label, Randomised, Controlled Phase 3 Trial. Lancet Oncol. 2015;16(7):763-774.
8 Soria JC et al., Afatinib *versus* Erlotinib as Second-Line Treatment of Patients with Advanced Squamous Cell Carcinoma of the Lung (LUX-Lung 8): an Open-Label Randomised Controlled Phase 3 Trial. Lancet Oncol. 2015;16(8):897-907.
9 Lu S et al., Afatinib *versus* Erlotinib for Second-Line Treatment of Chinese Patients with Advanced Squamous Cell Carcinoma of the Lung: a Subgroup Analysis of the Phase III LUX-Lung 8 Trial. CSCO 2017.
10 Lu S et al., *Post-hoc* Analysis of Afatinib Long-Term Responders in the Phase III LUX-Lung 8 Trial in Patients with Advanced Squamous Cell Carcinoma of the Lung. CSCO 2017.
11 Regales L et al., Dual Targeting of EGFR Can Overcome a Major Drug Resistance Mutation in Mouse Models of EGFR Mutant Lung Cancer. J Clin Invest. 2009;119(10):3000-3010.
12 Charles J et al., The Story of Afatinib plus Cetuximab in the Treatment of Patients with NSCLC to Date. CSCO 2017.

Optimal strategy for the treatment of *EGFR*-mutant lung cancer

The emergence of EGFR TKIs has changed the standard of care in *EGFR*-mutant NSCLC patients. IPASS was the first open-label randomized study to compare the first-generation EGFR TKI gefitinib with platinum-based chemotherapy in Chinese patients with *EGFR*-mutant NSCLC. It showed that the disease-free survival (DFS) rate was remarkably higher in the gefitinib group compared to chemotherapy. Therefore, IPASS laid the foundation for the use of first-generation EGFR TKIs in advanced *EGFR*-mutant NSCLC [1].

At CSCO 2017, discussions on *EGFR*-targeted treatment were mainly focused on three topics. First, first-, second- and third-line standard treatment strategies as well as optional treatment strategies for advanced *EGFR*-mutant NSCLC patients; second, combination of targeted therapy and radiotherapy for *EGFR*-mutant NSCLC patients; third, latest data and novel insights from studies focused on *EGFR*-targeted treatment in Chinese NSCLC patients.

Optimal strategy for the treatment of *EGFR*-mutant positive lung cancer: first-line treatment

In the guidelines on lung cancer (LC) treatment recently published by CSCO, first-generation EGFR TKIs (erlotinib or gefitinib) and the second-generation EGFR TKI afatinib were recommended as the standard first-line treatment in patients with advanced *EGFR*-mutant NSCLC [2].

In China, afatinib altered the first-line treatment recommendations for patients with stage IV, *EGFR*-mutant, advanced NSCLC according to the 2017 CSCO guidelines. Data from the LUX-Lung (LL) 3, 6, and 7 trials demonstrated that afatinib can prolong patient PFS and OS and increase objective response rate (ORR) compared to first-generation EGFR TKI treatment or chemotherapy [3, 4]. At CSCO 2017, updated data focusing on Chinese patients were presented. LL6 compared afatinib (n = 217) 40mg/d to 6 cycles of gemcitabine/cisplatin (G/C) (n = 110). PFS was longer for afatinib compared to G/C (median, 11.0 vs. 5.6 months; HR, 0.30; $p < 0.0001$). In addition, afatinib improved OS vs. G/C in patients with deletion 19 (median, 31.6 vs. 16.3 months; HR, 0.61; $p = 0.0146$). No unexpected AEs were observed with afatinib treatment in Chinese patients [5]. LL7, which compared afatinib to gefitinib as first-line treatment for *EGFR*-mutant NSCLC patients, showed that PFS, ORR and time to treatment (TTF) were remarkably higher in the afatinib group than in the gefitinib group. In-depth analyses revealed improved OS (27.9 vs. 24.5 months) and increased TTF (13.7 vs. 11.5 months; $p = 0.007$) for afatinib compared to gefitinib irrespective of the *EGFR* mutation type. Safety results showed that afatinib dose reduction decreased the incidence/severity of treatment-related AEs [6,7]. Thus, the authors concluded that *EGFR*-mutant NSCLC patients can benefit from first-line afatinib treatment with regard to PFS, OS, TTF and safety.

Additionally, long-term survival analyses of LL3, LL6 and LL7 were reported at CSCO 2017. According to these, long-term responders (LTRs; treatment with afatinib for ≥ 3 years) occurred in 10 %, 10 % and 12 % in LL3, LL6 and LL7, respectively. In contrast, the respective number for gefitinib was only 4 % in LL7. Finally, Professor Yi-Long Wu from the Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou (China), indicated that afatinib 30mg or 40mg might be the optimal choice for Chinese patients with *EGFR*-mutant NSCLC [8].

Analyses of different second-line treatments in patients who received first-line afatinib showed promising results for osimertinib: A total of 37 patients who discontinued afatinib received subsequent osimertinib, mostly in the third-line setting and beyond. For these patients, median time on osimertinib in any treatment line was long at 20.2 months, and after a median follow-up of more than 4 years, OS had not yet been reached **(Figure 1)** [9]. Thus, these findings support that treatment with first-line afatinib, followed by subsequent therapy including osimertinib, may be an optional strategy for patients with *EGFR*-mutant advanced NSCLC.

Osimertinib – upgrade from second-line to first-line treatment?

Osimertinib is a third-generation EGFR TKI that was tested in the studies AURA, AURAext, AURA2, AURA3, AURA17 and AURA18, which showed an ORR of approximately 60 %–70 % and PFS of 9.6–10.1 months in patients with advanced NSCLC who were resistant to first- and second-generation EGFR TKIs. The AURAext and AURA2 studies demonstrated that, once patients have become resistant to first-generation EGFR TKIs, osimertinib may be the optional choice instead of platinum-based chemotherapy for *EGFR* T790M-positive NSCLC [10]. However, it should be noted that AURAext and AURA2 were single-arm studies, which provided insufficient evidence that osimertinib could be used instead of chemotherapy as second-line treatment in patients who are resistant to first-generation EGFR TKIs. AURA3 was a head-to-head study that compared osimertinib to platinum-pemetrexed as a second-line treatment for patients with *EGFR* T790M-positive, advanced NSCLC who had previously received EGFR TKI treatment. AURA3 demonstrated improved PFS in the osimertinib treatment group compared to the platinum-pemetrexed group (10.1 vs. 4.4 months; HR, 0.3; $p < 0.001$) [11]. Thus, the 2017 NCCN guideline suggests that osimertinib should be the standard of care (SOC) as second-line treatment for *EGFR* T790M-positive advanced NSCLC.

FLAURA was the first head-to-head study that compared osimertinib with first-generation TKIs as first-line treatment for *EGFR*-mutant (i.e., exon 19 deletion or L858R mutation) advanced

NSCLC. Patients were randomized into two groups and were treated with osimertinib (80 mg once daily) or first-generation EGFR TKIs (gefitinib 250 mg or erlotinib 150 mg once daily), respectively. The primary endpoint was disease progression according to RECIST 1.1. Median PFS was significantly longer in the osimertinib group compared to SOC (18.9 vs. 10.2 months; p < 0.0001) **(Figure 2)**. The ORR was slightly higher in the osimertinib group (80 % vs. 76 %; p = 0.2335), and median duration of response (DoR) was also higher with osimertinib (17.2 vs. 8.5 months). Safety profiling indicated that patients in the osimertinib group experienced fewer AEs than those who received SOC. Moreover, the occurrence of serious AEs (grade > 3) was also reduced with osimertinib (34 % vs. 45 %). The interim analysis of OS (data maturity, 25 %) did not reach formal statistical significance with regard to osimertinib superiority, but encouraging data indicated a trend for a survival benefit (HR for death, 0.63) [12]. If osimertinib is chosen as first-line treatment, other hurdles, such as limitations of detection of the T790M mutation, heterogeneous mechanisms of osimertinib resistance and cross-resistance among the first-, second- and third-generation EGFR TKIs, should also be considered. Thus, Professor James Chih-Hsin Yang from the National Taiwan University Hospital, Taipei (Taiwan), indicated that the designation of the third-generation EGFR TKI osimertinib as a first-line treatment is still uncertain and that its efficacy in *EGFR*-mutant NSCLC is not completely understood yet [13].

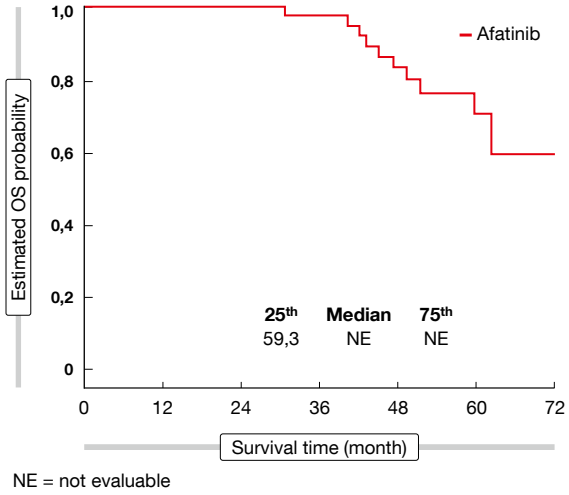


Figure 1: Exploratory OS analysis in patients starting on afatinib who received subsequent osimertinib in any line

3.1.3. Dacomitinib in Chinese patients – ARCHER 1050

At ASCO 2017, data from the ARCHER 1050 trial was reported. This trial tested another *EGFR*-targeted drug, dacomitinib, a second-generation EGFR TKI. In the first-line treatment of *EGFR*-mutant advanced NSCLC, dacomitinib was associated with longer PFS than the first-generation EGFR TKI (gefitinib) (14.7 vs. 9.2 months; HR, 0.59; p < 0.0001). Interestingly, among the 452 patients who were enrolled in this study, 231 patients were Chinese. Thus, at CSCO 2017, the data was presented with a focus on these patients.

The main inclusion criterion for ARCHER 1050 was advanced NSCLC and the presence of one *EGFR* mutation (deletion 19 or Leu858Arg mutation). Patients were randomized into two groups and received either oral dacomitinib (45 mg/day, in 28-day cycles) or oral gefitinib (250 mg/day, in 28-day cycles) until disease progression or until another discontinuation criterion was met. The primary endpoint was PFS assessed by masked independent review. In the subgroup analysis of Chinese patients, PFS was significantly higher in the dacomitinib group compared to gefitinib (16 vs. 9.2 months according to masked independent review and 18.4 vs. 11.1 months according to investigator analysis). The ORR in Chinese patients was similar to that in the total population, and DoR was higher for dacomitinib than for gefitinib (15.6 vs. 8.3 months).

The data of ARCHER 1050 showed favorable results for dacomitinib as first-line treatment for *EGFR*-mutant advanced NSCLC. However, the authors pointed out that even though the data on PFS was promising, it remained unclear whether satisfactory results would be obtained in terms of OS. Furthermore, several other important questions remained unanswered: how effective is dacomitinib for the treatment of CNS metastases in LC patients? As a broad-spectrum TKI, what is the resistance mechanism to dacomitinib? Are there any alternative treatment strategies if patients become resistant to dacomitinib? Thus, further studies investigating the efficacy of dacomitinib as first-line treatment of *EGFR*-mutant advanced NSCLC are still needed [14].

Third-line treatment of *EGFR*-mutant NSCLC – ALTER0303

In the 2017 CSCO guidelines for LC treatment, first- and second-line therapies for advanced NSCLC patients were defined as follows: most patients should receive EGFR TKI therapy, anaplastic lymphoma kinase (ALK) TKI treatment or chemotherapy as first-line treatment depending on their driver oncogene status. In case of resistance to first-line treatment (afatinib), patients should receive osimertinib or chemotherapy as second-line treatment. An increasing number of patients have the chance to receive third-line treatment and further therapy. However, to date, there is no SOC for the third-line treatment setting in NSCLC. The ALTER0303 trial provided useful information on how to treat NSCLC patients after failure of second-line treatment.

ALTER0303, a phase III study investigating anlotinib, was a randomized, double-blind, placebo-controlled study. Anlotinib is a multi-targeted TKI that inhibits VEGFR, PDGFR and FGFR, among others. The main inclusion criterion for ALTER0303 was advanced-stage NSCLC in patients who previously failed first- and second-line therapy. Patients were randomized into an anlotinib arm or a placebo arm. The primary endpoint analysis showed that OS was signifi-

cantly higher in patients treated with anlotinib than in those receiving placebo (9.6 vs. 6.3 months; HR, 0.68 [95 % CI 0.54, 0.87]; p = 0.0018). Also, ORR and DCR analyses showed better outcomes for anlotinib (ORR, 9.18 % vs. 0.7 %; p < 0.0001; DCR, 80.95 % vs. 37.06 %; p < 0.0001). All AEs were predictable, including fatigue, hypertension, dermal toxicity, TSH elevation and hypertriglyceridemia.

Thus, Professor Baohui Han from the Shanghai Chest Hospital, Jiaotong University, Shanghai (China), indicated that additional studies with larger sample sizes will be necessary to evaluate the safety profile of anlotinib in depth. However, considering the current data, anlotinib is expected to become the standard NSCLC treatment in the third-line setting [15].

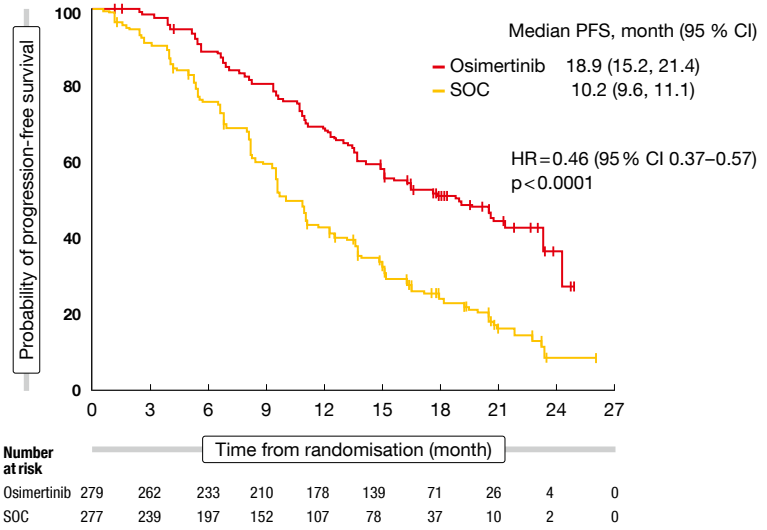


Figure 2: PFS with osimertinib compared to first-generation EGFR TKI (gefitinib or erlotinib) as first-line treatment of *EGFR*-mutant, advanced NSCLC

Treatment strategy after resistance to EGFR TKI

Precision medicine has changed the therapeutic landscape for LC patients. However, as reported based on previous studies including IPASS, First-SIGNAL, WJTOG3405, NEJ002, OPTIMAL, ENSURE, LL3 and LL6, PFS was 8–14 months in *EGFR*-mutant patients that received EGFR TKIs. This means that acquired drug resistance will ultimately occur after treatment with EGFR TKIs. What is the optimal treatment strategy after the development of EGFR TKI resistance?

Mok TS et al. showed that treatment with osimertinib significantly increased PFS, ORR and DCR compared to platinum-based chemotherapy in patients positive for T790M mutation who were resistant to first-line EGFR TKIs. Patients negative for T790M should be treated differently, according to the type of progression.

The ASPIRATION trial included patients with slow progression after resistance to first-line EGFR TKI treatment. Continued treatment with erlotinib prolonged PFS without the occurrence of new AEs [16]. However, IMPRESS enrolled patients with fast progression, and no benefit from prolonged gefitinib treatment was demonstrated [17]. Local therapy combined with EGFR TKIs also played a central role in the treatment of patients with resistance to first-line EGFR TKI treatment. Weickhardt AJ et al. reported that the PFS ranged from 10 to 13.8 months in patients treated with local therapy plus EGFR TKI.

Besides the most common mutation, i.e. T790M mutation which occurs in 61 %, Piotrowska et al. presented additional strategies for other relatively rare resistance mechanisms, such as the etoposide/platinum (EP) scheme for SCLC transformation (3 %) and chemotherapy or immunotherapy for unidentified resistance mechanisms (21 %) [18].

Thus, the author concluded that patients with the T790M mutation should receive osimertinib, and if patients present with SCLC transformation, the EP strategy should be applied. However, there are no specific treatment strategies in patients with unidentified resistance mechanisms, and additional studies are required [19].

Targeted therapy and radiotherapy in *EGFR*-mutant lung cancer

Radiotherapy (RT) and concurrent chemoradiotherapy are frequently used in stage I-III NSCLC. At CSCO 2017, results on the combination of radiotherapy and targeted therapy were reported.

The RTOG0617 study compared concurrent chemoradiotherapy with or without targeted treatment in stage IIIA or IIIB NSCLC patients. This trial showed no OS benefit due to the combination. Ongoing studies compare the efficacy of RT plus EGFR TKI to RT alone in locally advanced (LA), *EGFR*-mutant NSCLC patients. Even though in vitro data revealed promising results favoring the combination of EGFR TKI plus RT [20], the results of the Alliance 31101 and RTOG 1210 clinical trials, which compared RT plus EGFR TKI with RT alone in LA, *EGFR*-mutant NSCLC patients, were inconclusive.

In contrast, promising results were observed for combination therapies of RT plus EGFR TKIs as first-line and second-line treatment of patients with *EGFR*-mutant advanced NSCLC. Helena A et al. reported that for *EGFR*-mutant advanced NSCLC patients with resistance to first-line EGFR TKIs, PFS and OS were 10 and 41 months, respectively, which is an encouraging result in the second-line setting. Another retrospective study, which was reported by Magnuson WJ et al., showed OS outcomes of 46 and 30 months for patients treated with stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT), respectively, followed by EGFR TKI as first-line treatment .

Thus, the authors concluded that in unselected NSCLC patients, the addition of RT to *EGFR*-targeted therapy did not improve clinical outcomes. The efficacy of the addition of RT to *EGFR*-targeted therapy was still unclear in LA, oncogene-positive NSCLC patients, and thus further studies will be needed. The efficacy of RT in advanced *EGFR*-mutant NSCLC patients looks promising but needs confirmation, and a prospective study is required [21].

Different mechanisms, differences in dose determination – lessons learned from developing the third-generation EGFR TKIs in China

The first preclinical experiment with osimertinib, a third generation EGFR TKI, started in 2011. After only 5 years, in August 2016, osimertinib was approved by the China Food and Drug Administration (CFDA) for clinical practice in China. This is in contrast to other new drugs whose approval may take more than 7.5 years. At CSCO 2017, Professor Yi-long Wu talked about lessons learned from the development of avitinib, another third-generation EGFR TKI, in China.

The phase I study evaluating avitinib was an open-label, dose-escalation study. The initial dose was 50mg twice a day, and doses were increased once patients developed partial response (PR). The final results showed no differences in safety across all dose groups, which differs from previous observations showing that the frequency of AEs increases with dose escalation. The highest ORR was observed at a dose of 300mg (52 %), which also indicated favorable pharmacokinetics with regard to avitinib. Thus, these data suggested that an avitinib dose of 300mg should be used for phase 2 studies [22]. ■

REFERENCES

1 Mok TS et al., Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009 Sep 3;361(10):947-57.
2 Yang N et al., Upgrade of osimertinib to first line treatment? CSCO 2017
3 Yang JC et al., Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol. 2015 Jul;16(7):830-8.
4 Park K et al., Afatinib *versus* gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 2016 May;17(5):577-89.
5 Xu CR et al., Afatinib vs cisplatin/gemcitabine for the first-line treatment of Chinese patients with advanced EGFR-mutation positive (EGFRm+) NSCLC: subgroup analysis of the LUX-Lung 6 trial. CSCO 2017
6 Zhang L et al., Afatinib *versus* gefitinib in patients with EGFR mutation positive (EGFRm+) NSCLC: updated OS data from LUX-Lung 7. CSCO 2017
7 Zhang L et al., Afatinib vs gefitinib for the first-line treatment of EGFR-mutation positive (EGFRm+) NSCLC (LUX-Lung 7): time to treatment failure and impact of afatinib dose adjustment. CSCO 2017
8 Wu YL et al., Long-term response to first-line afatinib in patients with advanced EGFR mutation-positive (EGFRm+) NSCLC: analysis of LUX-Lung (LL) 3, 6 and 7. CSCO 2017
9 Sequist L et al., Subsequent therapies post-afatinib among patients with EGFR mutation positive NSCLC in LUX-Lung (LL) 3, 6, 7. CSCO 2017
10 Goss G et al., Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2016 Dec;17(12):1643-1652.
11 Mok TS et al., Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017 Feb 16;376(7):629-640.
12 Soria JC et al., Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. N Engl J Med. 2018 Jan 11;378(2):113-125. doi: 10.1056/NEJMoa1713137.
13 Yang JC et al., Optimal strategy for treatment of EGFR mutation positive lung cancer Choice and Sequence. CSCO 2017
14 Zhou Q et al., Dacomitinib vs gefitinib for first-line (1L) treatment of advanced EGFR+ non-small-cell lung cancer (NSCLC) in Chinese patients (ARCHER 1050). CSCO 2017
15 Han B et al., Third-line treatment: A randomized, double-blind, placebo controlled phase III ALTER-0303 study—Efficacy and safety of anlotinib treatment in patients with refractory advanced NSCLC. CSCO 2017
16 Park K et al., First-line erlotinib therapy until and beyond response evaluation criteria in solid tumors progression in Asian patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer: the ASPIRATION study. JAMA Oncol. 2016 Mar;2(3):305-12.
17 Soria JC et al., Gefitinib plus chemotherapy *versus* placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):990-8.
18 Piotrowska Z et al., Treatment of EGFR-mutant lung cancers after progression in patients receiving first-line EGFR tyrosine kinase inhibitors: a review. JAMA Oncol. 2016 Jul 1;2(7):948-54
19 Zhao J et al., Treatment strategy after resistance in driver oncogene positive NCLCL. CSCO 2017
20 Baumann M et al., Selective inhibition of the epidermal growth factor receptor tyrosine kinase by BIBX1382BS and the improvement of growth delay, but not local control, after fractionated irradiation in human FaDu squamous cell carcinoma in the nude mouse. Int J Radiat Biol. 2003 Jul;79(7):547-59.
21 Fu X et al., Radiotherapy and target medicine for LC. CSCO 2017
22 Wu YL et al., Lessons learned from developing the 3rd Generation EGFR inhibitors in China. CSCO 2017

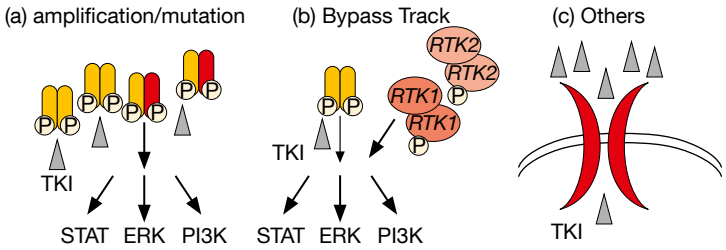
New insights into the treatment of *ALK*-mutant-positive NSCLC patients

Anaplastic lymphoma kinase *(ALK)* is a fusion oncogene, and the prevalence of *ALK* mutations in NSCLC patients is similar across different races. At CSCO 2017, the main progress for the treatment of *ALK*-mutant-positive NSCLC patients related to the new recommendations for first-line and second-line treatments, and the optimal strategies to manage patients before and after resistance to *ALK* tyrosine kinase inhibitors (TKIs). Strategies for the management of patients with concomitant *EGFR-ALK* mutations were also reported.

First-line treatment of *ALK*-mutant-positive NSCLC patients

Crizotinib is recommended by CSCO as first-line treatment of *ALK*-mutant-positive NSCLC patients. However, the recently published J-ALEX and ALEX studies that compared alectinib to crizotinib as first-line treatments for these patients showed improved progression-free survival for alectinib compared to crizotinib [1]. Thus, the NCCN guidelines for NSCLC recommend alectinib as first-line treatment for *ALK*-mutant-positive NSCLC patients [2].

Based on the results of the J-ALEX and ALEX trials, Professor Jie Wang Key from the Department of Thoracic Medical Oncology, Peking University Cancer Hospital and Institute, Beijing (China) indi-



Crizotinib resistance	*ALK* Fusion gene amplification, L1196M, G1269A,	EGFR, cKIT with SCF, IGF1R	P-gp mediated drug export
Alectinib	I1171T/N/S, G1202R, V1180L	*cMET* gene amplification	
Ceritinib resistance	F1174C/V, G1202R, G1202del, D1203N + F1174C	MEK mutation, Src activation, *cMET* amplification	P-gp mediated drug export
Lorlatinib resistance	C1156Y + L1198F		
Brigatinib resistance	(G1202R), E1210K + S1206C, E1210K + D1203N		

Lin JJ et al., Cancer Discov. 2017 Feb;7(2):137-155. doi: 10.1158/2159-8290.CD-16-1123. Epub 2017 Jan 25.

Figure 1: Illustration of the three main mechanisms of resistance to second-generation and third-generation ALK TKIs

cated that although alectinib has already been shown to be more effective than crizotinib, the currently ongoing Phase III studies on other *ALK* inhibitors still use crizotinib as first-line treatment for the control group; i.e., the ALTA-1L trial with brigatinib, the CROWN trial with lorlatinib, and the eXalt3 trial with ensartinib. Thus, whether this set-up with crizotinib as the control first-line treatment is appropriate is now questionable [3].

Second-line treatment of *ALK*-mutant-positive NSCLC: a new breakthrough?

Acquired resistance is the major limitation of ALK TKIs as first-line treatments in clinical practice. Roughly 30% of crizotinib-treated refractory tumors have been shown to have resistance mutations in the *ALK* kinase domain, which include G1269A, L1196M, C1156Y, L1152R, S1206Y, 1151Tins, G1202R, and F1174L [4]. Lorlatinib is a third-generation ALK TKI that has shown efficacy against most resistance mutations in preclinical studies [5]. While these data are promising, they still need to be confirmed in clinical studies in *ALK*-mutant-positive NSCLC patients with resistance to first-line treatments.

Resistance mechanisms to ALK TKIs: investigations and findings

There are several studies that are exploring the mechanisms of resistance to crizotinib, while there remain few such studies for second-generation and third-generation ALK TKIs. However, at CSCO 2017, Professor Wang indicated that there appear to be three main mechanisms of resistance to second-generation and third-generation ALK TKIs: (i) amplification/ mutation, such as G1202R for alectinib resistance, F1174C/V for ceritinib reistance, C1156Y+L1198F for lorlatinib resistance, and G1202R for brigatinib resistance; (ii) bypass track, such as *cMET* gene amplification for alectinib resistance and MEK mutation for ceritinib resistance; and (iii) other mechanisms, such as P-gp–mediated drug export **(Figure 1)**. Thus, Professor Wang said that combination therapy stategies might be beneficial to prevent bypass-activating resistance, such as combinations with EGFR TKIs, to prevent resistance arising through *EGFR* bypass pathways.

Heterogeneous diagnosis and treatment of *ALK*-positive NSCLC

Concomitant mutations have been observed in NSCLC patients, with the prevalence of *EGFR-ALK* concomitant mutations at about 0.1 % [6]. Lou et al. [7] reported that first-line treatment of *EGFR-ALK*-mutant NSCLC patients with EGFR TKIs provided better outcomes compared to chemotherapy, crizotinib or vascular endothelial growth factor receptor TKIs. However, a study by Lo Russo G et al. [8] reported that for NSCLC patients with co-occurrence of *EML4-ALK* rearrangement and *EGFR* mutations, the ALK TKI provided greater complete/ partial responses than the EGFR TKI (51.3 % vs. 43.4 %). The authors indicated that the discrepancy between Lou et al. [7] and Lo Russo G et al. [8] might be due to heterogeneous patterns of concomitant *ALK*/*EGFR* mutations [9]. ■

REFERENCES

1 Peters S et al., Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. N Engl J Med. 2017;377(9):829-838.
2 NCCN Clinical Practice Guidelines in Oncology: Non–Small Cell Lung Cancer; version 7, 2017.
3 Jie W et al., Treatment Strategy for Advanced ALK-Positive NSCLC. CSCO 2017.
4 Gainor JF et al., Emerging Paradigms in the Development of Resistance to Tyrosine Kinase Inhibitors in Lung Cancer. J Clin Oncol. 2013;31:3987-3996.
5 Zou HY et al., PF-06463922, an ALK/ROS1 Inhibitor, Overcomes Resistance to First and Second Generation ALK Inhibitors in Preclinical Models. Cancer Cell. 2015;28(1):70-81.
6 Ulivi P et al., Nonsquamous, Non–Small-Cell Lung Cancer Patients Who Carry a Double Mutation of EGFR, EML4-ALK or KRAS: Frequency, Clinical-Pathological Characteristics, and Response to Therapy. Clin Lung Cancer. 2016;17(5):384-390.
7 Lou NN et al., Clinical Outcomes of Advanced Non–Small-Cell Lung Cancer Patients with EGFR Mutation, ALK Rearrangement and EGFR/ALK Co-Alterations. Oncotarget. 2016;7(40):65185-65195.
8 Lo Russo G et al., Concomitant EML4-ALK Rearrangement and EGFR Mutation in Non–Small Cell Lung Cancer Patients: a Literature Review of 100 Cases. Oncotarget. 2017;8(35):59889-59900.
9 Cai W et al., Intratumoral Heterogeneity of ALK-Rearranged and ALK/EGFR Coaltered Lung Adenocarcinoma. J Clin Oncol. 2015;33(32):3701-3709.

Determination of clinical responses to immunotherapy

In the past 13 years, an earthshaking change has occurred in treatment of non–small-cell lung cancer (NSCLC). The emergence of two new treatment methods – targeted treatment and immunotherapy – has overturned doctors' and patients' perception of standard of care for NSCLC. However, not all of the driver oncogenes in NSCLC have been identified. There is still a large number of patients with unknown driver-oncogene mutations who do not benefit from the currently available targeted therapies. Furthermore, acquired resistance to these targeted therapies invariably develops.

The development of immunotherapies is based on three important features of the immune system: specificity, adaptability, and memory. The concept of immunotherapy is based on elimination of cancer cells through regulation of the immune microenvironment or breaking of immunological tolerance, which is different from other conventional treatment concepts. Immunotherapies have been applied for treatment of various cancers, which has shown that they can significantly prolong patient progression-free survival (PFS) and overall survival (OS) for solid tumors. At CSCO 2017, the topics on immunotherapy for NSCLC mainly focused on: 1. First-line and second-line immunotherapies; 2. Determination of responses to immunotherapies; 3. Choice of suitable biomarker(s); and 4. Duration of immunotherapy use.

Status of immunotherapy in advanced NSCLC: first-line and second-line treatments

The CheckMate 017 and CheckMate 057 trials compared nivolumab immunotherapy and docetaxel as second-line treatments in advanced NSCLC patients who had failed first-line chemotherapy. In these studies, nivolumab versus docetaxel provided improved objective response rate (ORR; 20 % vs. 9 %) and OS (9.2–12.2 vs. 6.0–9.5 months; CheckMate 017: hazard ratio [HR], 0.62; CheckMate 057: HR, 0.75). Furthermore, the safety results were also more favorable for immunotherapy (grade 3–4 adverse events: 8 %-10 % vs. 54 %-56 %). The subsequent Keynote 010 and OAK studies verified these immunotherapy benefits with comparisons of pembrolizumab and atezolizumab, respectively, to docetaxel for treatment of advanced NSCLC patients, with comparable results (i.e., improved ORR, OS with immunotherapies; **Table 1**) [1].

Improved efficacy has also been shown for immunotherapy as first-line treatment in advanced NSCLC patients. KEYNOTE-024 compared the single immune agent pembrolizumab to platinum-based chemotherapy as first-line treatment for PD-L1 ≥ 50%, *EGFR/ALK*-mutant-negative, advanced NSCLC. Here, patients treated with pembrolizumab had improved PFS (10.3 vs. 6 months; HR, 0.50; 95 % confidence interval [CI], 0.37–0.68; p < 0.001), with estimated patient survival at 6 months for pembrolizumab of 80.2 % (95 % CI, 72.9 %–85.7 %), and for chemotherapy of 72.4 % (95 % CI, 64.5 %-78.9 %). Median OS was not reached in either group, although OS was significantly improved with pembrolizumab over chemotherapy (HR for death, 0.60; 95 % CI, 0.41–0.89; p = 0.005) [2].

Immunotherapy combined with chemotherapy has also demonstrated increased patient benefits compared to chemotherapy alone. KEYNOTE-021 cohort G compared pembrolizumab plus chemotherapy with chemotherapy alone as first-line treatment for *EGFR/ALK*-mutant-negative, advanced NSCLC patients. The combination versus chemotherapy alone provided improved PFS (19.0 vs. 8.9 months; HR, 0.54; 95 % CI, 0.33–0.88; p = 0.0067) and OS (not reached vs. 20.9 months; HR, 0.59; 95 % CI, 0.34–1.05; p = 0.0344) [3]. This pembrolizumab plus chemotherapy PFS of 19 months is particularly encouraging as it is higher than that for the vascular endothelial growth factor inhibitor bevacizumab plus chemotherapy in the ECOG 4599 study (PFS, 12.5 months), which became first-line treat-

TABLE 1
Main results of immunotherapy as second-line treatment for patients with advanced NSCLC

study	Nivolumab (PD-1)				Pembrolizumab (PD-1)			Atezilizumab (PD-L1)	
	CheckMate 017		CheckMate 057		Keynote 010			OAK	
	Nivolumab	docetaxel	Nivolumab	docetaxel	Pembro 2	Pembro 10	docetaxel	Atezolizumab	docetaxel
ORR	20%	9%	20%	9%	18%	18%	9%	14%	13%
OS (months)	9.2	6	12.2	9.5	10.5	13.4	8.6	13.8	9.6
HR	0.62		0.75		0.72	0.60		0.73	
1-year OS	42%	24%	51%	39%	43.2%	52.3%	34.6%	55%	41%
PFS (months)	3.5	2.8	2.3	4.2	3.9	4.9	4	2.8	4.0
HR	0.63		0.92		0.88	0.79		0.95	
G3-≥ 4AEs	8%	56%	10%	54%	13%	16%	35%	15%	43%

ment for advanced NSCLC in the USA [4]. Indeed, at CSCO 2017, Professor Lu from the Lung Tumour Clinical Centre, Shanghai Chest Hospital, Shanghai Jiaotong University (China) indicated that with these data from KEYNOTE-021 cohort G, pembrolizumab plus chemotherapy has already demonstrated superiority over bevacizumab plus chemotherapy. However, the current results are based on a phase II study. Pembrolizumab plus chemotherapy might thus be promoted to first-line treatment for advanced NSCLC instead of bevacizumab plus chemotherapy if the KEYNOTE-189 phase III study provides similar results [5].

Promising results were also obtained in studies that combined different immune agents as first-line treatments for advanced NSCLC patients. CheckMate 012 compared the nivolumab plus ipilimumab combination with nivolumab as single agent, as first-line treatment for stage IIIB or IV NSCLC patients. The ORR was higher for the combination compared to nivolumab alone in the total patient population (43 % vs. 23 %). Furthermore, for the combination therapy, a greatly improved ORR of 92 % was seen for the patients with PD-L1 ≥ 50%. Safety results showed a slightly higher rate of any grade adverse events for the combination compared to nivolumab alone, although the current result remains acceptable [6].

Thus, Professor Lu concluded that anti-PD-L1/PD-1 treatments should be considered as second-line treatments for advanced NSCLC patients. Further studies are still needed to determine whether immunotherapies might become first-line treatments for these patients [5].

Determination of responses to immunotherapy: *EGFR*-mutation and tumor mutational burden

While the efficacy of immunotherapy has been demonstrated for treatment of advanced NSCLC patients, only a fraction of these patients benefits from anti-PD-L1/PD-1 therapies. Gainor JF et al. [7] showed that patients with *EGFR* wild-type or who are heavy smokers are likely to benefit from PD-L1/PD-1 inhibitors, but not patients with *EGFR* mutations or who are never/ light smokers. Similar results were obtained in the CheckMate 057 and Keynote 010 trials [8].

To determine why the therapeutic efficacies differ between patients with *EGFR* wild-type and *EGFR* mutations, Gainor JF et al. [7] analyzed for concurrent PD-L1 expression and CD8+ tumor-infiltrating lymphocytes (TILs). Here, only 4.3 % of the patients showed concurrent high PD-L1 expression (PD-L1+; 50 %) and high levels of CD8+ TILs (TIL+). Teng MW et al. [9] reported that tumor microenvironment can affect the efficacies of anti-PD-L1/PD-1 treatments, whereby patients with type I (TIL+/PD-L1+) tumors were most likely to benefit from single-agent anti-PD-L1/PD-1 therapies. They also suggested that the small proportion of *EGFR*-mutant NSCLC patients with concurrent TIL+/PD-L1+ might be the reason why poor prognosis with immunotherapy was seen in their full patient group [10].

As previously suggested, tumor mutational burden (TMB) might also be a factor in the response to therapy [11]. Gibbons DL et al. [12] compared TMB between current smokers and lifelong nonsmokers, with significantly higher TMB seen for current smokers **(Figure 1)**. Rizvi NA et al. [13] then reported that NSCLC patients with high TMB can obtain longer survival rates than patients with low TMB. Thus, they proposed that the small fraction of TIL+/PD-L1+ patients means that *EGFR*-mutant tumors are generally not sensitive to immunotherapy. Furthermore, high TMB in the smoker subgroup suggested that smokers are more sensitive to immunotherapy than nonsmokers.

PD-L1: a good biomarker, or not?

PD-L1 expression has long been used as a prognostic factor or stratification fac-

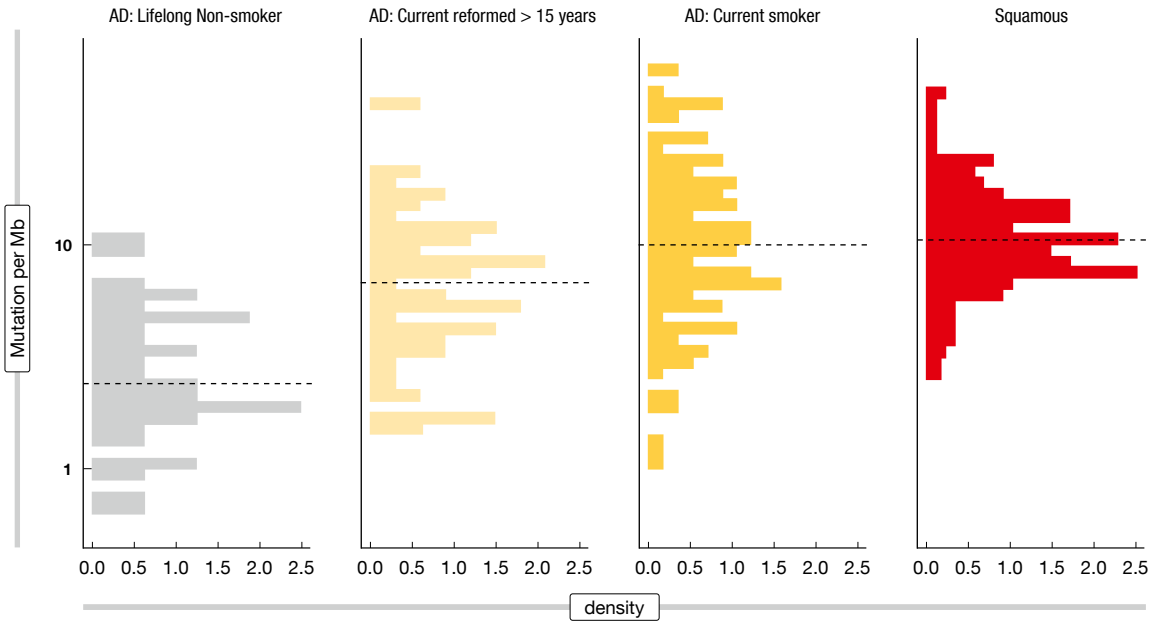


Figure 1: Tumor mutation burden in current smokers compared to life-long non-smokers, for lung adenocarcinomas and squamous cell carcinomas

tor in clinical trials. However, more recent evidence suggests that PD-L1 might not be the best biomarker.

CheckMate 012 showed 2-fold to 3-fold greater ORR in patients with PD-L1 ≥ 1 % versus PD-L1 < 1 %. However, KEYNOTE-010 showed that only patients with PD-L1 ≥ 50% have greater OS for pembrolizumab compared to docetaxel. When PD-L1 of 1 % was chosen as the cut-off, no PFS benefit was seen for the PD-L1 ≥ 1 % subgroup with pembrolizumab. Similar results were seen in CheckMate 026, which again showed that patients might not benefit from immunotherapy when PD-L1 of 1 % was chosen as the cut-off. Thus, at CSCO 2017, Professor Fred Hirsch from the University of Colorado, Denver (USA), said that the guidelines for the care of patients with lung cancer indicate 50 % PD-L1 expression as the cut-off. However, these results are from phase II studies, and therefore phase III studies are still needed to confirm them [14].

The further molecular feature of TMB was suggested as a biomarker from the exploratory analysis of CheckMate 026, which stratified the patients into groups who were likely to benefit from immunotherapy versus patients who were not. In the subgroup analysis of CheckMate 026, median PFS for patients with high TMB was significantly greater for nivolumab compared to chemotherapy (9.7 vs. 5.8 months). When the combination of TMB and PD-L1 expression was used as the stratification factor, for the patients treated with nivolumab, those with high TMB and PD-L1 ≥ 50 % showed improved PFS compared to those with low TMB or PD-L1 < 50 %. Professor Hirsch pointed out that TMB might thus represent an alternative biomarker for the selection of NSCLC patients who are likely to benefit from immunotherapy. However, further studies are still needed to combine PD-L1 expression with TMB and/or other biomarkers as stratification determinants to guide clinicians in their selection of the appropriate therapy for NSCLC patients.

Duration of immunotherapy: continuous treatment versus treatment withdrawal

The CheckMate 153 trial compared continuous nivolumab with 1-year fixed-duration nivolumab in patients with advanced NSCLC. Patients in the continuous treatment group showed both greater PFS (not reached vs. 10.3 months) and greater 6-month PFS rates (80 % vs. 69 %). As well as this improved PFS for patients in the continuous treatment group, they also achieved more improved complete/ partial responses (not reached vs. 10.6 months; HR, 0.45; 95 % CI, 0.24–0.85) and stable disease (not reached vs. 9.6 months; HR, 0.44; 95% CI, 0.17–0.19), compared to 1-year fixed-duration nivolumab. Thus, as Professor Lu indicated, continous treatment provides improved results over only 1 year of treatment. However, whether continous treatment will be superior to 2 years of treatment remains to be seen [5]. ■

REFERENCES

1 Horn L et al., Nivolumab *versus* Docetaxel in Previously Treated Patients with Advanced Non–Small-Cell Lung Cancer: Two-Year Outcomes from Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol. 2017;35(35):3924-3933.
2 Reck M et al., Pembrolizumab *versus* Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med. 2016;375:1823-1833.
3 Borghaei H et al., Updated Results from KEYNOTE-021 Cohort G: a Randomized, Phase 2 Study of Pemetrexed and Carboplatin (PC) with or without Pembrolizumab (pembro) as First-Line Therapy for Advanced Nonsquamous NSCLC. Annals of Oncology (2017) 28 (suppl_5): v605-v649. 10.1093/annonc/mdx440
4 Tyagi P et al., Bevacizumab, When Added to Paclitaxel/Carboplatin, Prolongs Survival in Previously Untreated Patients with Advanced Non–Small-Cell Lung Cancer: Preliminary Results from the ECOG 4599 Trial. Clin Lung Cancer. 2005;6(5):276-278.
5 Lu S et al., Progression of Immunotherapy for LC. CSCO 2017
6 Hellman MD et al., Nivolumab plus Ipilimumab as First-Line Treatment for Advanced Non–Small-Cell Lung Cancer (CheckMate 012): Results of an Open-Label, Phase 1, Multicohort Study. The Lancet Oncol. 2017;18(1):31-41.
7 Gainor JF et al., EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non–Small Cell Lung Cancer: a Retrospective Analysis. Clin Cancer Res. 2016;22(18):4585-4593.
8 Lee CK et al., Checkpoint Inhibitors in Metastatic EGFR-Mutated Non–Small Cell Lung Cancer – a Meta-Analysis. J Thorac Oncol. 2017;12(2):403-407.
9 Teng MW et al., Classifying Cancers Based on T-cell Infiltration and PD-L1. Cancer Res. 2015;75(11):2139-2145.
10 Gainor JF et al., The Role of Immunotherapy in Oncogene Driven Lung Cancer. CSCO 2017.
11 Alexandrov LB et al., Signatures of Mutational Processes in Human Cancer. Nature. 2013;500(7463):415-421.
12 Gibbons DL et al., Smoking, p53 Mutation, and Lung Cancer. Mol Cancer Res. 2014;12(1): 3-13.
13 Rizvi NA et al., Cancer Immunology. Mutational Landscape Determines Sensitivity to PD-1 Blockade in Non–Small-Cell Lung Cancer. Science. 2015;348(6230):124-128.
14 Hirsch FR et al., PD-L1 vs Tumor Mutation Burden and Other Immune Markers. CSCO 2017.

Combination of targeted therapy with radiotherapy for treatment of brain metastasis

Lung adenocarcinomas often metastasize to the brain, and the prognosis of patients with brain metastases is poor. The *EGFR* gene is mutated in a considerable fraction of patients with primary lung adenocarcinomas and brain metastases, and especially in Asian patients. As reported at CSCO 2017, the prevalence of *EGFR* mutation among these patients with brain metastases is about 44 % in Taiwan (China) and 63 % in Japan, which is dramatically higher than in America or Europe (at 0 %–2 %) [1]. At CSCO 2017, the main progress on treatment of these brain metastases focused on the efficacy of driver-oncogene-positive targeted therapy with or without radiotherapy, and the optimal sequence of radiotherapy with EGFR/ALK tyrosine kinase inhibitors (TKIs) in patients with driver-oncogene-positive non–small-cell lung cancer (NSCLC).

Targeted therapy for brain metastases in driver-oncogene-positive NSCLC

The first generation EGFR/ALK TKIs showed improved progression-free survival (PFS) in driver-oncogene-positive NSCLC patients with brain metastases. Kim JE et al. [2] conducted a study that enrolled *EGFR*-mutant-positive NSCLC patients with asymptomatic brain metastases. The patients were treated with gefitinib (250 mg) or erlotinib (150 mg) once daily as first-line treatment. The results showed that out of 23 patients, 16 achieved partial response (PR), three stable disease (SD), and four progressive disease. The median PFS and overall survival (OS) were 7.1 and 18.8 months, respectively [2].

The PROFILE 1005 and 1007 studies retrospectively analyzed the efficacy of the ALK and ROS1 inhibitor crizotinib in advanced *ALK*-rearranged NSCLC patients with previously untreated asymptomatic brain metastases. The results showed that systemic disease control rate (DCR) at 12 weeks was 63 %, intracranial DCR was 56 %, and median intracranial time to progression (TTP) was 7 months. Importantly, 20 % of the patients with newly developed progressive disease after initiation of crizotinib treatment were diagnosed with brain metastases. Thus, the first generation TKIs (including EGFR TKIs and ALK TKIs) are efficacious for treatment of driver-oncogene-positive NSCLC patients with brain metastases. However, only relatively short extensions of PFS, OS, and TTP, and relatively low DCR, were reached [3]. Additionally, the high proportion of patients who still developed brain metastases after ALK TKI treatment was not encouraging.

Central nervous system response to osimertinib

The emergence of osimertinib and alectinib opened new options for treatment of driver-oncogene-positive NSCLC patients with brain metastases. The AURA3 trial was the first comparative evidence for the efficacy of osimertinib *versus* platinum–pemetrexed in patients with metastases in the central nervous system (CNS). Osimertinib improved the objective response rate compared to chemotherapy (70 % vs. 31 %), with significantly improved PFS in the osimertinib group (10.1 vs. 4.4 months; hazard ratio [HR] after adjustment for Asian or non-Asian race, 0.30; 95 % confidence interval [CI], 0.23 to 0.41; $p < 0.001$) The HR for PFS favored osimertinib across all predefined subgroups that were analyzed, including patients with CNS metastases (median PFS, 8.5 vs. 4.2 months; HR, 0.32; 95 % CI, 0.21 to 0.49) [4].

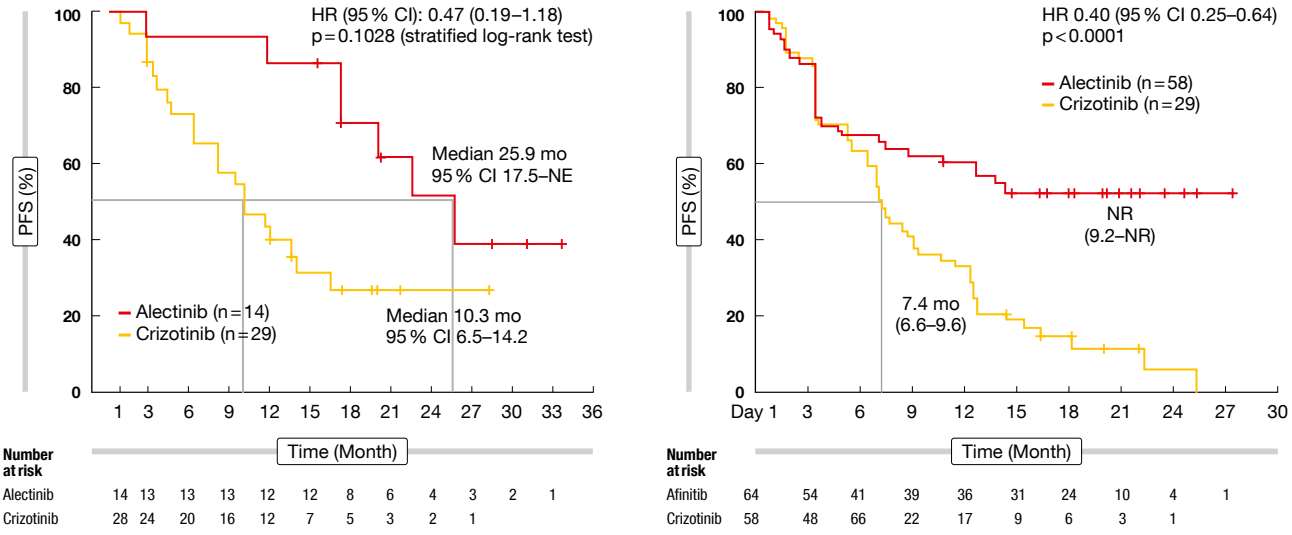


Figure 1: Progression-free survival for alectinib *versus* crizotinib for treatment of *ALK*-mutant-positive NSCLC patients with CNS metastasis at baseline in the J-ALEX (left) and ALEX (right) studies.

Compared to these data for the first-generation EGFR TKI, the FLAURA trial then showed that in first-line treatment of *EGFR*-mutant-positive NSCLC with brain metastases, median PFS was improved for osimertinib *versus* first generation EGFR TKI (15.2 vs. 9.6 months; HR 0.47; 95 % CI 0.30–0.74; p < 0.001) [5].

The recently published J-ALEX and ALEX studies compared the efficacy of alectinib *versus* crizotinib as first-line treatment for *ALK*-mutant-positive NSCLC patients. Alectinib was reported to show improved penetration of the blood brain barrier. Thus, alectinib treatment provided improved PFS for NSCLC patients with co-occurrence of CNS metastases, compared to crizotinib (J-ALEX: 25.9 months vs. 10.3 months, p = 0.1028; ALEX: not reached vs. 7.4 months, p < 0.0001) **(Figure 1)**. Furthermore, the alectinib group showed lower 12-month cumulative CNS metastasis incidence rate, compared to the crizotinib group (16.0 % vs. 58.3 %) [6].

Strategies to fight brain metastasis – upfront radiosurgery *versus* radiation therapy *versus* tyrosine kinase inhibitors

Tyrosine kinase inhibitors have demonstrated efficacy against the incidence of brain metastases and have prolonged PFS in NSCLC patients with brain metastases. Additionally, whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) have been used for treatment of NSCLC patients with brain metastases. WBRT is regarded as the standard treatment for tumors of large size, or for patients with more than three lesions. Common side effects include neurocognitive dysfunction, such as cognitive impairment and altered executive function. SRS is suitable for patients with better prognosis, and according to a report by Shultz DB et al. [7], multiple courses of SRS and deferring WBRT for distant brain metastases after initial SRS appears to be a safe and effective approach. To further prolong patient survival, combined SRS, WBRT and targeted therapy appears to be effective.

Magnuson WJ et al. [8] conducted a retrospective study that compared the efficacies of these treatments for *EGFR*-mutant NSCLC patients with intracranial progression: SRS followed by EGFR TKI; WBRT followed by EGFR TKI; and EGFR TKI followed by either SRS or WBRT. Their results showed that median OS for these SRS (n = 100), WBRT (=120), and EGFR TKI (n = 131) cohorts was 46, 30, and 25 months, respectively (p < 0.001) [8]. The use of up-front SRS provided the best OS and showed lower potential neurocognitive sequelae for the WBRT. Finally, they also indicated that although up-front SRS appeared to be the best choice, in the era of targeted therapies there remain several uncertainties. Hence, a prospective phase III study is needed [1].

Optimal strategy to manage central nervous system metastases in driver-oncogene-positive NSCLC in China.

Yang JJ et al. [9] conducted a phase 3 study in China that compared the efficacies of the EGFR TKI icotinib and whole-brain irradiation (WBI) in patients with driver-oncogene-positive NSCLC and brain metastases. The results showed that median intracranial PFS was improved with icotinib compared to WBI (10 vs. 4.8 months; p = 0.014), and the rate of adverse events higher than grade 3 was lower in the icotinib group compared to the WBI treatment group (8 % vs. 38 %) [9]. Thus, they suggested that in China, EGFR TKIs should be the treatment of choice in *EGFR*-mutant-positive NSCLC patients with brain metastases. ■

REFERENCES

1 Lu Y et al., Management of CNS Metastasis in Patients with Driver Oncogene Positive NSCLC. CSCO 2017

2 Kim JE et al., Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors as a First-Line Therapy for Never-Smokers with Adenocarcinoma of the Lung Having Asymptomatic Synchronous Brain Metastasis. Lung Cancer. 2009 Sep;65(3):351-4.

3 Costa DB et al., Clinical Experience With Crizotinib in Patients with Advanced ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastases. J Clin Oncol. 2015 Jun 10;33(17):1881-8.

4 Mok TS et al., Osimertinib or Platinum–Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017 Feb 16;376(7):629-640.

5 Soria JC et al., Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113-125. doi: 10.1056/NEJMoa1713137.

6 Peters S et al., Alectinib *versus* Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. N Engl J Med. 2017 Aug 31;377(9):829-838.

7 Shultz DB et al., Repeat Courses of Stereotactic Radiosurgery (SRS), Deferring Whole-Brain Irradiation, for New Brain Metastases after Initial SRS. Int J Radiat Oncol Biol Phys. 2015 Aug 1;92(5):993-999

8 Magnuson WJ et al., Management of Brain Metastases in Tyrosine Kinase Inhibitor-Naïve Epidermal Growth Factor Receptor-Mutant Non–Small-Cell Lung Cancer: a Retrospective Multi-Institutional Analysis. J Clin Oncol. 2017 Apr 1;35(10):1070-1077.

9 Yang JJ et al., Icotinib *versus* Whole-Brain Irradiation in Patients with EGFR-Mutant Non–Small-Cell Lung Cancer and Multiple Brain Metastases (BRAIN): a Multicentre, Phase 3, Open-Label, Parallel, Randomised Controlled Trial. Lancet Respir Med. 2017 Sep;5(9):707-716.

memo-inOncology特刊 ASCO2016大会报告

作者： 来源： 发布时间：2016-11-09 09:10:57 今日访问/总访问：2|500

中国临床肿瘤学会（CSCO）荣幸地宣布美国临床肿瘤学会（ASCO）2016年度报告备忘录特刊正式发布。

此最新报告收录了美国临床肿瘤学会在2016年6月3日至7日在伊利诺伊州芝加哥市召开的2016年年度会议上发表的非小细胞肺癌（NSCLC）领域的最新临床管理及癌症研究成果。肿瘤学备忘录特刊系列现提供英文以及中文普通话两个版本，可免费下载。

此备忘录特刊为备忘录（欧洲肿瘤医学杂志）的增刊，由施普林格（Springer）制作完成，并得到德国勃林格殷格翰制药公司赞助。要了解更多有关肿瘤学备忘录特刊系列的信息并免费获得往年的版本，请访问肿瘤学备忘录网站。

下载完整报告（中文）

下载完整报告（英文）

业内新闻

- [PCCA 2017]中国抗癌协会胰腺癌专业委员会年会盛大开幕
- 临床必备|气管支架在恶性肿瘤中应用的常见问题一览
- 【秒懂视频】肿瘤是如何逃避免疫应答的？

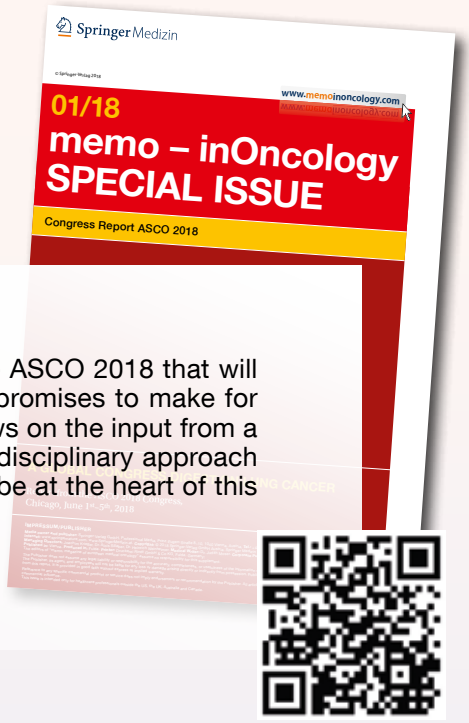
更多>>

团体会员新闻

- 2014 CSCO•罗氏肿瘤论坛
- 赛于未萌 肝脏说“化”——MAGIC-301研究入组900例
- 赛于未萌 肝脏说“化”——MAGIC-301研究入组800例

更多>>

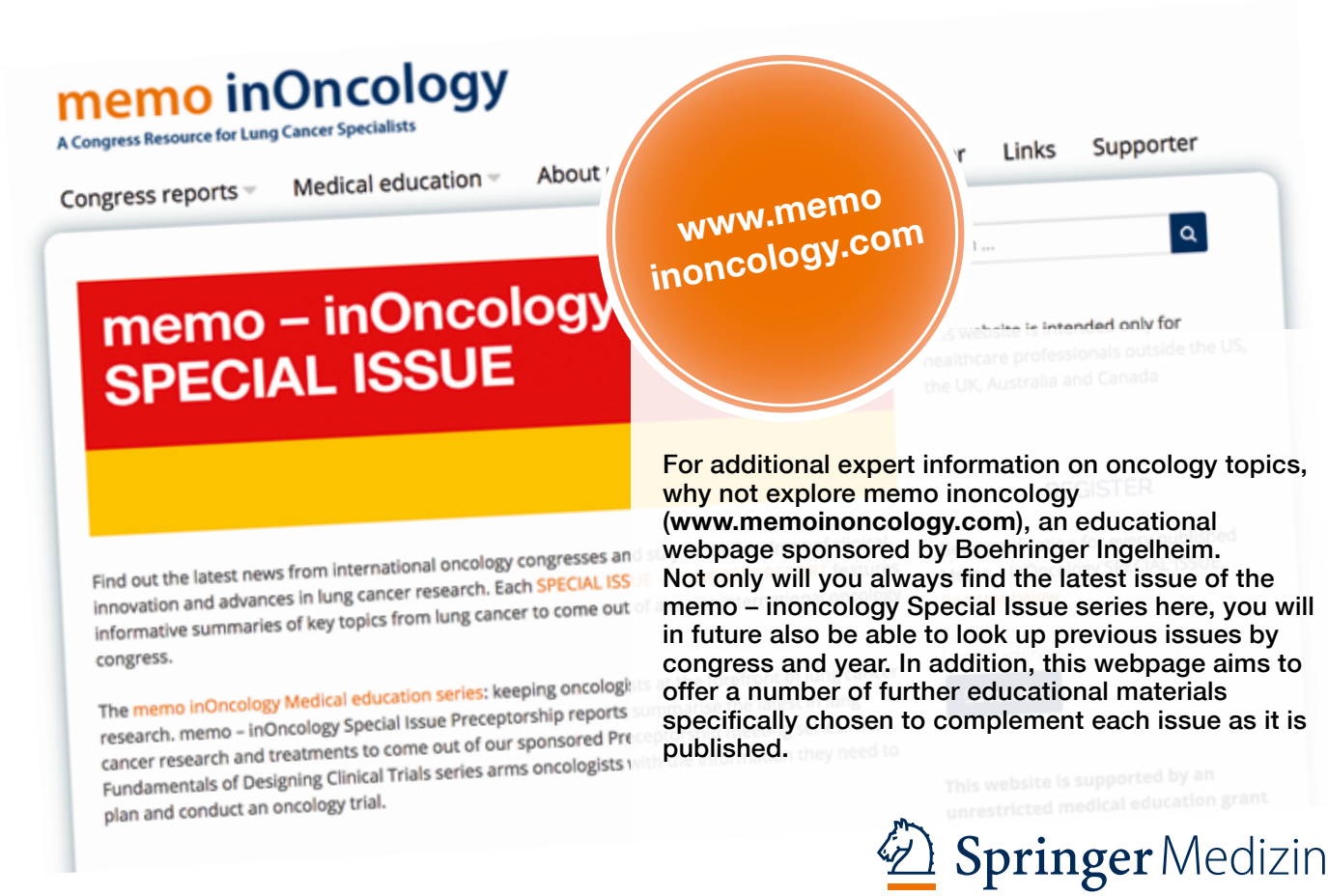
京ICP备05047300号-1
京公网安备 11010502031203号



Forthcoming Special Issue

This special issue will be offering a synopsis from the ASCO 2018 that will be held in Chicago, in June of next year. The report promises to make for stimulating reading, as the ASCO Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

ASCO 2018
Annual Meeting
CHICAGO, 1–5 JUNE 2018



For additional expert information on oncology topics, why not explore memo inoncology (www.memoinoncology.com), an educational webpage sponsored by Boehringer Ingelheim. Not only will you always find the latest issue of the memo – inoncology Special Issue series here, you will in future also be able to look up previous issues by congress and year. In addition, this webpage aims to offer a number of further educational materials specifically chosen to complement each issue as it is published.

Springer Medizin