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MODERN MANAGEMENT OF ADVANCED LUNG CANCER: IMMUNOTHERAPY & TARGETED AGENTS

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Preface

Dear Colleagues,

On 28th and 29th June, 2018, a Lung Cancer International Preceptorship directed towards medical oncologists took place in Shanghai, China. The scientific provider was the Shanghai Pulmonary Hospital affiliated to the local Tongji University. In the course of these two days, lectures and workshops were held with the aim of improving the participants' knowledge about lung cancer management in China and internationally. Most of the 24 delegates attending the Preceptorship are working at Chinese hospitals. The range of topics covered screening, diagnostics and pathology of lung malignancies as well as various types of treatment. A tour of the Shanghai Pulmonary Hospital concluded the meeting.

Lung cancer is a major issue in China, as incidence and mortality of this disease are still increasing due to several risk factors such as serious air pollution caused by industrial and traffic fumes as well as smoking. Two thirds of males and 15 % of females are smokers. Moreover, the Chinese society is ageing, which explains in part the rising incidence of lung cancer. Given these factors and the enormous population of our country, China accounts for one third of the world's new lung cancer cases.

Controlling this disease poses huge challenges that need to be addressed at several levels including screening, diagnosis and treatment. In this special issue of memo inOncology, we have summarized the lectures given on treatment with immunotherapy and EGFR-/ALK-targeted agents. In both areas, huge progress has been made over the last years that has provided unprecedented outcomes in the face of this devastating disease. With immunotherapy in particular, some patients can hope to experience clinical cure, although EGFR- and ALK-targeted therapies also work wonders in responding patients. There is still a long way to go to defeat lung cancer, but research has just begun for all of these agents, and we can expect many more practice-changing data in the years to come.

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Immunotherapy: the emerging paradigm of cure

The introduction of molecularly targeted agents 15 to 20 years ago marked the beginning of a new era. Today, immune-checkpoint–inhibiting drugs have established yet another level of treatment. While both chemotherapy and targeted agents exert their effects directly at the tumor, which implies the eventual emergence of resistance, immunotherapy targets the immune system, enabling a certain percentage of patients to survive over extended periods of time. Patients with advanced non–small-cell lung cancer (NSCLC) who are alive at 2 years after treatment initiation have a realistic chance to live on for more than 5 years. Thus, cure in advanced cancer has emerged as a new paradigm.

Three types of immune checkpoint inhibitors are currently in use: anti-CTLA-4 antibodies (e.g., ipilimumab, tremelimumab), anti-PD-1 antibodies (e.g., nivolumab, pembrolizumab), and anti-PD-L1 antibodies (e.g., atezolizumab, durvalumab, avelumab).

Advantages of first-line treatment

The anti-PD-1 antibody pembrolizumab outperformed chemotherapy with docetaxel in the KEYNOTE-010 study even though patients were pretreated [1]. The group with at least 50 % of tumor cells expressing PD-L1 (tumor proportion score [TPS] ≥ 50 %) derived the greatest benefit. Here, pembrolizumab treatment led to significant improvements in both overall survival (OS) and progression-free survival (PFS).

In the first-line setting, the KEYNOTE-024 trial evaluated pembrolizumab 200 mg every 3 weeks over 2 years compared to platinum-doublet chemotherapy for 4-6 cycles in 305 patients with a PD-L1 TPS of ≥ 50 % [2]. Crossover from the control arm to the experimental arm was permitted in case of disease progression; at that time, patients went on to receive the pembrolizumab regimen administered in the experimental arm.

The analysis revealed a significant PFS difference in favor of pembrolizumab (10.3 vs. 6.0 months; HR, 0.50; $p < 0.001$; **Figure 1**). In spite of the crossover, patients in the experimental arm fared significantly better with respect to OS than those in the control arm (not reached in either group; HR, 0.60; $p = 0.005$). According to the updated results of KEYNOTE-024, a high degree of separation of the OS curves was maintained despite an effective crossover rate of 60 % [3]. All of this suggests that immunotherapy should be administered from the beginning rather than after chemotherapy.

Biomarkers other than PD-L1 expression

Gettinger et al. described the characteristics of 16 patients surviving for 5 years in the phase I CA209-003 study investigating nivolumab in the pretreated setting [4]. Nivolumab had been discontinued after 2 years of treatment. Apparently, initial responses predicted long-term survival, as most of the patients (75 %) had achieved partial remission (PR) soon after the start of the study.

However, absence of response constitutes a major issue in the context of immunotherapy. Approximately one third of patients do not respond to treatment, even in the presence of high PD-L1 expression. Tumors grow rapidly in the majority of cases, and prognosis is poor. PD-L1 expression does not suffice as a biomarker here, as it results from the interaction between tumor cells and the immune system and therefore lacks stability.

A Japanese study identified the expression of the homing molecule CD62L on T cells as a potential biomarker [5]. The researchers evaluated this option based on the hypothesis that distinct pre-existing anti-tumor immunity in certain patients might lead to different responses to anti-PD-1 therapy. In a group of 50 consecutive NSCLC patients who were treated with nivolumab, those achieving PR or stable disease (SD) were shown to have significantly more CD4-positive T cells down-regulating CD62L (i.e., CD62L-^{low}) than those experiencing progressive disease ($p = 4.1 \times 10^{-7}$). The percentages of CD62L^{low} in CD4-positive T

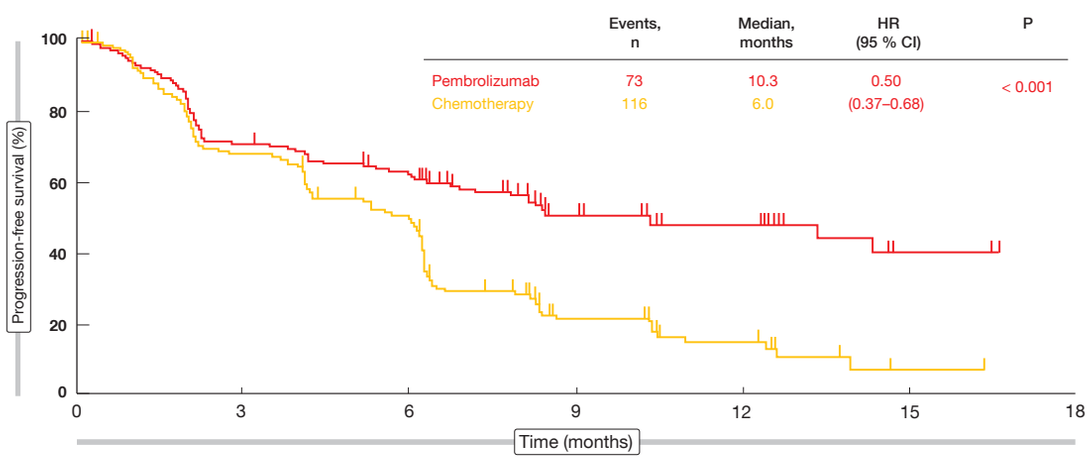

Figure 1: Progression-free survival obtained with pembrolizumab vs. chemotherapy in KEYNOTE-024

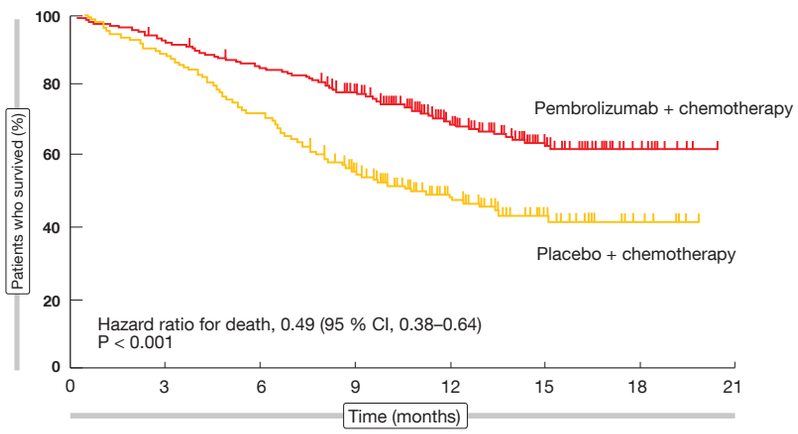

Figure 2: KEYNOTE-189: overall survival benefit in patients treated with pembrolizumab plus standard chemotherapy

cells provided sensitivity of 92.9 % and specificity of 96.7 % with regard to the prediction of progression. Moreover, SD patients had a significantly smaller regulatory T cell subpopulation than the PR population ($p = 0.0067$), which means that it was possible to predict PR from SD. A prospective study investigating these findings is already ongoing in Japan.

Combination therapy

The KEYNOTE-189 trial assessed first-line pembrolizumab in combination with pemetrexed and cisplatin or carboplatin for 4 cycles in non-squamous NSCLC [6]. Patients in the control arm received placebo instead of pembrolizumab together with the other components as described for the experimental arm. The protocol stipulated no enrichment by PD-L1 expression status, although this was a stratification factor.

The addition of pembrolizumab to standard chemotherapy resulted in significant improvements in PFS (HR, 0.52; $p < 0.001$) and OS (HR, 0.49; $p < 0.001$; **Figure 2**) compared to chemotherapy alone. At 12 months, 69.2 % vs. 49.4 % of patients were alive. The separation of both PFS and OS curves commenced directly after treatment initiation. Both PFS and OS benefits were most pronounced in the group with PD-L1 expression ≥ 50 %, even though patients showing lower expression levels also fared better with the pembrolizumab-based regimen.

The ongoing KEYNOTE-407 study follows in the steps of KEYNOTE-189, investigating first-line chemotherapy with or without pembrolizumab in patients with tumors of squamous histology. At the ASCO 2018 Congress, the second interim analysis was presented [7]. As for KEYNOTE-189, the pembrolizumab combination was superior to chemotherapy alone regarding both PFS (6.4 vs. 4.8 months; HR, 0.56; $p < 0.0001$) and OS (15.9 vs. 11.3 months; HR, 0.64; $p = 0.0008$). Here, too, the results obtained in the experimental arm exceeded those in the control arm regardless of PD-L1 expression.

Overall, combinations of immunotherapy and chemotherapy appear to give rise to improved clinical outcomes irrespective of histology and PD-L1 expression status. These findings compare favorably to those obtained with immune checkpoint inhibitor monotherapy, which implies that most of the patients with advanced NSCLC will be treated with combination regimens once these have received approval. However, it must be kept in mind that this entails enormous healthcare costs. Monotherapy might be sufficient for some patients with high PD-L1 expression, although of course physicians would generally prefer to be on the safe side for the sake of the patient.

Locally advanced NSCLC & neoadjuvant setting

Immunotherapy has not only excelled in metastatic disease, but also in the locally advanced setting. Patients with stage III, locally advanced, unresectable NSCLC that had not progressed following platinum-based chemoradiotherapy were treated with either durvalumab or placebo in the PACIFIC study [8]. Indeed, compared to placebo, durvalumab treatment gave rise to significant improvements in PFS (16.8 vs. 5.6 months; HR, 0.52; $p < 0.001$) and time to distant metastasis or death (23.2 vs. 14.6 months; HR, 0.52; $p < 0.001$).

Neoadjuvant treatment represents one step further to the very front lines. Here, a pilot study evaluated two preoperative doses of nivolumab in adults with untreated, surgically resectable early (stage I, II, or IIIA) NSCLC [9]. Surgery was performed approximately 4 weeks after the first dose. Neoadjuvant administration of nivolumab appeared feasible, with an acceptable side-effect profile. It did not delay surgery and induced major pathological responses in 9 of 20 resected tumors (45 %). Responses occurred in both PD-L1–positive and PD-L1–negative tumors.

Adverse effects with predicting capacity

Immune-related adverse events (irAEs) are not necessarily bad news. Beyond embodying a simple side effect, they can be a sign of reactivation of the patient immune response. Haratani et al. demonstrated that patients with irAEs, as compared to those without, had improved outcomes with regard to PFS (9.2 vs. 4.8 months; $p = 0.04$) and OS (not reached vs. 11.1 months; $p = 0.01$) [10]. Of course, irAEs can be life threatening and require appropriate management. Detailed guidelines have been established for this purpose [11].

Take home message

Immune checkpoint inhibition represents an enormous progress in lung cancer treatment and has brought about the prospect of cure, even in the advanced setting. Monotherapy is more efficient than chemotherapy in the first line, but approximately one third of patients do not respond. Responses can be improved by the combined use of immunotherapy and chemotherapy. High PD-L1 expression beyond 50 % predicts treatment success. Moreover, early responses appear to suggest long-term survival. The emergence of immune-related adverse events hints at reactivation of immune responses. Use of immune checkpoint inhibitors in earlier stages of disease has shown promising results.

Keunchil Park

EGFR- and ALK-targeted treatment: present and future

Chemotherapy for advanced or metastatic lung carcinoma has evolved slowly with limited progress between 1948 and the beginning of the 21st century. Until then, only minimal gains in long-term OS had been achieved, and the benefit of chemotherapy was discussed in a controversial manner. Fortunately, this was the very time when the rise of molecularly targeted agents started. Amazing progress has occurred during the past two decades. Today, a multitude of agents is available for the treatment of patients with oncogene-driven lung cancer.

EGFR TKI treatment

The beginning: gefitinib & erlotinib

Drugs targeting activating *EGFR* mutations include erlotinib, gefitinib, afatinib, dacomitinib, icotinib, osimertinib, and nazartinib. Phase II data published in 2002 were the first to demonstrate that gefitinib, administered as a once-daily oral pill, elicits substantial responses after failure of chemotherapy [12, 13]. In 2003, gefitinib received accelerated approval by the U.S. Food and Drug Administration (FDA) as monotherapy after failure of both platinum-based and docetaxel chemotherapies. In 2004, Lynch et al. found that activating mutations in the epidermal growth factor receptor underlie the responsiveness of NSCLC to gefitinib [14]. This marks the beginning of precision oncology in solid tumors.

However, it took several years for TKI treatment to enter the NCCN Practice Guidelines for the first-line management of NSCLC, until after the IPASS trial was reported in 2009. In this Asian study, 1,217 untreated patients were randomized to either gefinitib or carboplatin plus paclitaxel [15]. The trial population contained two groups, one with *EGFR* mutations and one without. In the *EGFR*-mutant group, gefitinib was significantly superior to chemotherapy with regard to PFS (HR, 0.48; $p < 0.001$). On the other hand, those without *EGFR* mutation fared significantly better when treated with chemotherapy (HR, 2.85; $p < 0.001$).

From 2010, four randomized first-line trials assessed gefitinib and erlotinib in the first-line setting in *EGFR*-mutation–selected patients. The OPTIMAL study yielded an unprecedented risk reduction for PFS with erlotinib compared to chemotherapy (HR, 0.16; $p < 0.0001$) [16]. In 2013, the NCCN guidelines (version 2.2013) provided gefitinib and erlotinib with a category-1 recommendation for the first-line treatment of *EGFR*-positive NSCLC.

Second-generation agents afatinib and dacomitinib

Afatinib was the first second-generation EGFR TKI to enter the stage. In the LUX-Lung 3 and 6 trials, first-line afatinib was compared to cytotoxic chemotherapy [17, 18]. Both trials revealed PFS improvement, establishing afatinib as a first-line option equal to erlotinib and gefitinib with a category-1 recommendation according to the NCCN guidelines (version 3.2014). Notably, patients with brain metastases also derived significant PFS benefit from afatinib, according to combined analyses from LUX-Lung 3 and 6 (HR, 0.50; $p = 0.03$) [19]. Median time to CNS progression was longer with afatinib than with chemotherapy for both patients with or without baseline brain metastases.

The LUX-Lung 7 trial demonstrated that first- and second-generation EGFR TKIs are not equal [20]. In this head-to-head study, afatinib gave rise to significant improvements in PFS and response rate compared to gefitinib **(Table)**. Likewise, the second-generation agent dacomitinib improved PFS over gefitinib in the ARCHER 1050 trial (14.7 vs. 9.2 months; HR, 0.59; $p < 0.0001$ according to blinded independent review; **Table**), although patients with brain metastases were excluded from this study [21].

TABLE
Cross-trial comparison of LUX-Lung 7, ARCHER 1050, and FLAURA

	LUX-Lung 7	ARCHER 1050	FLAURA
Median overall survival	27.9 vs. 24.5 months	34.1 vs. 26.8 months	Immature
Phase	IIb (n = 319)	III (n = 452)	III (n = 556)
Arms	Afatinib vs. gefitinib	Dacomitinib vs. gefitinib	Osimertinib vs. gefitinib/ erlotinib
Response rate	70 % vs. 56 %	75 % vs. 71.2 %	80 % vs. 76 %
Progression-free survival (all comers)	11 vs. 10.9 months (BIRC) HR, 0.73 p = 0.017	14.7 vs. 9.2 months (BIRC), no brain metastases HR, 0.59 p < 0.0001	17.7 vs. 9.7 months (BIRC) HR, 0.45 p < 0.001
Progression-free survival (no brain metastases)		16.6 vs. 11.0 months (INV) HR, 0.62 p < 0.0001	19.1 vs. 10.9 months (INV) HR, 0.46 p < 0.001

BIRC, blinded independent review committee
INV, investigator

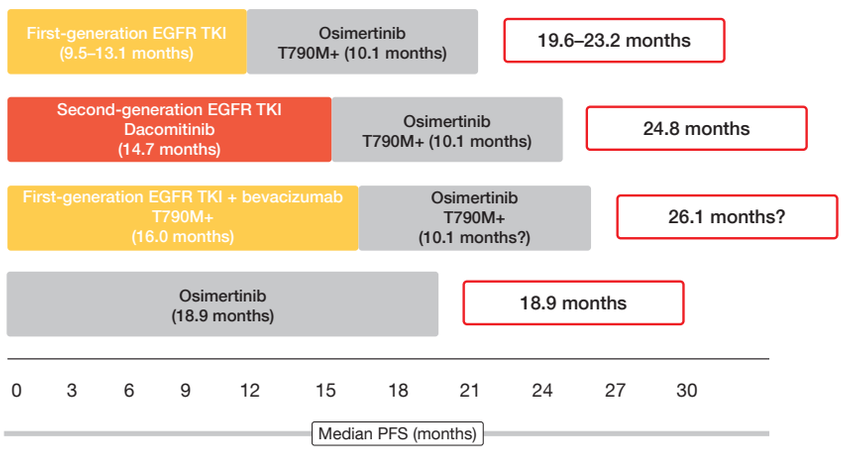

Figure 3: Sequential treatment strategies and cumulative progression-free survival with first- and next-generation EGFR TKIs

Osimertinib: AURA3 & FLAURA

Initial responses to EGFR TKI treatment are often dramatic, but resistance emerges over time, leading to recurrence. In half of the cases, the secondary *EGFR* T790M mutation underlies acquired resistance. The third-generation EGFR TKI osimertinib has been designed to target this mutation. Patients progressing after first-line EGFR TKI therapy who had documented T790M mutation participated in the phase III AURA3 trial that compared osimertinib with platinum-based chemotherapy [22]. Stable asymptomatic CNS metastases were allowed.

PFS by investigator assessment was defined as the primary endpoint. Osimertinib proved superior to chemotherapy here, with a risk reduction of 70 % (PFS 10.1 vs. 4.4 months; HR 0.30, $p < 0.001$). Overcoming T790M mutation is another meaningful step in lung cancer treatment. Also, according to a subset analysis, patients with brain metastases experienced encouraging activity of osimertinib [23]. The CNS overall response rates were 70 % and 31 % for osimertinib and chemotherapy, respectively ($p = 0.015$). Seven patients with CNS lesions had leptomeningeal metastases at baseline; four of these experienced CR or PR with osimertinib treatment, and three had stable disease. Consistent with these encouraging data, the NCCN guidelines (version 4.2017) recommended the use of osimertinib for patients with T790M mutation and both asymptomatic and symptomatic progression.

The FLAURA trial tested osimertinib as a first-line treatment option in patients with common *EGFR* mutations [24]. Patients in the control arm received gefitinib or erlotinib. The protocol permitted stable CNS metastases. PFS by investigator assessment constituted the primary endpoint and was significantly in favor of the osimertinib treatment (18.9 vs. 10.2 months; HR, 0.46; $p < 0.001$). Blinded independent central review yielded comparable PFS results (17.7 vs. 9.7 months; **Table**). Accordingly, the NCCN guidelines (version 9.2017) included osimertinib as a first-line option along with gefitinib, erlotinib and afatinib.

The issue of first-line treatment selection

Given this wealth of choice, the individual treatment decision can be difficult. An indirect comparison of the LUX-Lung 7, ARCHER 1050 and FLAURA trials reveals some differences between the studies **(Table)**. It is arguable that the comparator was suboptimal in FLAURA, which employed gefitinib and erlotinib in the control arm. The data obtained in two other studies, the JO25567 and NEJ026 trials, show that the addition of bevacizumab to erlotinib markedly improves PFS over erlotinib monotherapy (JO25567: 16.4 vs. 9.8 months; HR, 0.52; $p = 0.0005$; NEJ026: 16.9 vs. 13.3 months; HR, 0.605; $p = 0.0157$), raising the median outcomes to the levels observed in ARCHER 1050 and FLAURA [25, 26].

Also, the question of sequencing remains, as salvage options should be available after the failure of first-line treatment. In their review, Ferrara et al. noted that the longest PFS could be achieved by sequencing first- or second-generation EGFR TKIs with osimertinib, rather than by using osimertinib upfront **(Figure 3)** [27]. There are currently no established options after osimertinib failure, apart from cytotoxic chemotherapy. It remains to be seen how sequencing of TKIs compares to osimertinib with or without subsequent chemotherapy.

Survival may be the best surrogate marker to answer the question of treatment selection. However, OS data from AURA3 and FLAURA are not mature yet, and data from other trials tend to be confusing. So far, the only head-to-head trial to yield a survival benefit was ARCHER 1050 (34.1 vs. 26.8 months with dacomitinib and gefitinib, respectively; HR, 0.76; $p = 0.0438$) [28]. The JO 25567 study showed no difference with respect to OS between erlotinib plus bevacizumab and erlotinib alone. In NEJ009, a trial comparing gefitinib plus chemotherapy with gefitinib monotherapy, patients in the combination arm experienced improved OS (52.2 vs. 38.8 months; HR, 0.695; $p = 0.013$) [29]. According to a post-hoc analysis of LUX-Lung 7, approximately one fifth of patients who discontinued afatinib or gefitinib subsequently received third-generation EGFR TKIs including osimertinib, olmutinib, and rociletinib [30]. Here, OS rates at 3 years exceeded 80 % in both arms, and median OS had not been reached with afatinib (vs. 48.3 months with gefitinib; HR, 0.49).

For the time being, first-line treatment selection is still under debate, and positioning of osimertinib has to be agreed upon. The phase II EORTC 1613 trial is trying to find an answer by comparing osimertinib until progression with the sequence of gefinitib followed by osimertinib.

Lung cancer with *EML4-ALK* rearrangement

Crizotinib: long-term standard

The first-generation ALK TKI crizotinib received approval in 2011 and was the only targeted first-line option in patients with advanced *EML4-ALK*–rearranged NSCLC for several years. The initial trial showed an overall response rate of 57 %, and at 6 months, 72 % of pa-

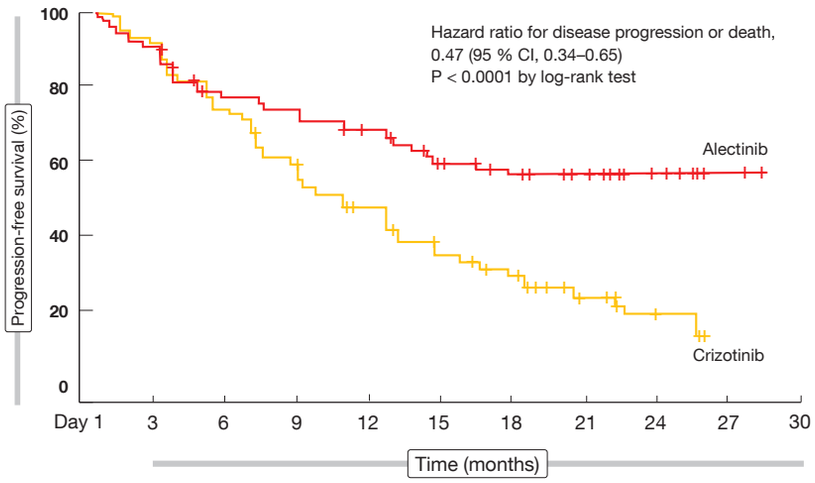

Figure 4: Investigator-assessed progression-free survival in the ALEX trial (crizotinib *versus* alectinib)

tients were progression-free [31]. Further evidence was provided by the phase III PROFILE 1007 and PROFILE 1014 studies that successfully compared crizotinib to chemotherapy in the second- and first-line settings, respectively [32, 33].

Ceritinib and alectinib

However, as for anti-EGFR therapy, resistance invariably develops, which calls for effective later-line treatment options. CNS failure constitutes a notorious pattern of relapse in lung cancer patients with *EML4-ALK* rearrangement.

The second-generation ALK TKI ceritinib demonstrated pronounced antitumor activity in the phase I ASCEND-1 trial that recruited both ALK-inhibitor-naïve and -pretreated patients [34]. In 2014, ceritinib was recommended by the NCCN guidelines (version 4.2014) after crizotinib failure. Three years later, ceritinib received a category-1 recommendation for the first-line treatment of *ALK*-positive NSCLC (version 6.2017) based on the ASCEND-4 study, which compared ceritinib with chemotherapy in untreated patients [35]. PFS in the experimental arm by blinded independent review was more than twice as long as PFS obtained with chemotherapy (16.6 vs. 8.1 months; HR, 0.55; $p < 0.00001$).

Likewise, impressive results have been observed with the second-generation ALK TKI alectinib. This treatment elicited an objective response rate of 55 % in the phase I/II setting and showed CNS activity even in heavily pretreated patients [36]. Based on these data as well as on the phase II NP28673 and NP28761 trials that confirmed the robust efficacy of alectinib [37], FDA approval after crizotinib failure was granted in 2015. Finally, the global phase III ALEX study established alectinib as a first-line agent [38]. Compared to crizotinib, it gave rise to an impressive PFS improvement (not reached vs. 11.1 months; HR, 0.47, $p < 0.001$; **Figure 4**) and again showed excellent activity in patients with brain lesions. Eighty-one percent of those with measurable CNS metastases at baseline responded on the CNS level (vs. 50 % with crizotinib). The NCCN guidelines (version 7.2017) recommended alectinib as the preferred first-line option.

Treatment sequence: times of change

After failure of first-line alectinib, crizotinib or ceritinib, subsequent use of ceritinib, alectinib or brigatinib can be considered. Brigatinib has shown substantial responses in the phase II ALTA study in heavily pretreated patients progressing on crizotinib [39]. Later-line options still need to be established.

To date, no ideal sequence of ALK TKI therapy has been identified in prospective clinical trials. First-line alectinib appears to be the best treatment, as it outperforms other TKIs including sequential regimens with regard to PFS [27]. However, results from three first-line studies testing next-generation ALK TKIs (brigatinib, lorlatinib, ensartinib) need to be awaited. Pre-clinical and clinical trials are required to determine the best combination regimens to delay or prevent resistance to ALK TKI therapy.

Take home message

Since 2002, first- to third-generation EGFR TKIs have been established in clinical practice. Today, they are recommended as first-line agents.
A debate is ongoing regarding the ideal sequencing of treatment. The longest PFS might be achieved by the use of first- or second-generation EGFR TKIs followed by osimertinib. Survival outcomes from the AURA3 and FLAURA trials will contribute to clarifying the situation. Further, combinations of EGFR TKIs with anti-angiogenic agents also showed promising PFS.
In patients with *EML4-ALK*-rearranged lung cancer, first-line options include alectinib, crizotinib and ceritinib. There are limited data regarding the efficacy of next-generation ALK TKIs after progression. No optimal treatment sequence has been defined yet, but ongoing trials might change the picture in the near future.

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