ESMO Open
Cancer Horizons

From crizotinib to lorlatinib: continuous improvement in precision treatment of ALK-positive non-small cell lung cancer

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To cite: Pirker R, Filipits M. From crizotinib to lorlatinib: continuous improvement in precision treatment of ALK-positive non-small cell lung cancer. *ESMO Open* 2019;**4**:e000548. doi:10.1136/esmoopen-2019-000548

Received 23 May 2019
Accepted 24 May 2019

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Patients with advanced non-small cell lung cancer (NSCLC) have received first-line chemotherapy with a platin-based doublet in case of good performance status and with a single agent or well tolerated doublet in case of older age for many years.[1–3] Chemotherapy has been combined with bevacizumab or necitumumab in selected patients. Two major advances have changed this therapeutic landscape. The first change refers to the identification of driver mutations and the establishment of corresponding tyrosine kinase inhibitors (TKIs) as preferred first-line therapy for patients harbouring these mutations in their tumours. The second change refers to the establishment of immune checkpoint inhibitors in routine clinical practice. Patients with driver-negative NSCLC and good performance status nowadays receive first-line therapies with either chemotherapy plus pembrolizumab or atezolizumab, pembrolizumab as single agent in case of PD-L1 expression in ≥50% of tumour cells, or nivolumab plus ipilimumab in case of high tumour mutational load. Second-line therapies are docetaxel (plus/minus nintedanib or ramucirumab), pemetrexed, erlotinib, afatinib or immune checkpoint inhibitors.

The identification of driver mutations has affected both diagnosis and therapy of NSCLC.[4 5] Advanced NSCLC is currently classified based on histology, immunohistochemistry and driver mutation status. Adenocarcinomas are routinely assessed for the presence of EGFR mutations, anaplastic lymphoma kinase (ALK) or ROS1 re-arrangements, and BRAF mutations. Additional tests are performed based on both their availability and access to corresponding targeted drugs. Patients with driver mutation-positive NSCLC receive corresponding TKIs as preferred first-line therapy. ALK-positive NSCLC is a representative example on how continuous improvements in precision treatment have been achieved. Here, we summarise the clinical establishment of ALK inhibitors for the treatment of patients with advanced NSCLC with focus on phase III trials.

ALK INHIBITORS

In 2007, a transforming ALK fusion gene was described in NSCLC.[6] ALK fusion genes can be detected in approximately 4% of patients with advanced NSCLC, particularly among patients with adenocarcinomas, never-smokers or light smokers, and younger patients. ALK re-arrangements are detected by means of fluorescence in situ hybridisation (FISH) analysis, immunohistochemistry, next generation sequencing and/or PCR-based methods. Immunohistochemistry is often used for screening and, if necessary, followed by confirmatory FISH analysis. Several ALK inhibitors have clinically been developed.[7] They include first-generation, second-generation and third-generation inhibitors.

CRIZOTINIB

Crizotinib, a first-generation ALK TKI, has improved outcome compared with chemotherapy in patients with advanced NSCLC and an ALK re-arrangement in their tumours.[8–10] The PROFILE 1007 phase III trial randomised ALK-positive patients (n=347) who had received one prior platinum-based chemotherapy regimen to either crizotinib (250 mg two times per day) or chemotherapy with pemetrexed or docetaxel.[8] Patients of the chemotherapy arm were allowed to crossover to crizotinib at the time of disease progression. Randomised patients had the following baseline characteristics: median age 50 years, 66% females, 63% never-smokers, 91% Eastern Cooperative Oncology Group (ECOG) performance status 0–1 and 95% adenocarcinomas. Crizotinib increased progression-free survival with a HR of 0.49 (95% CI 0.37 to 0.64; p<0.001) and median progression-free survival times of

7.7 and 3 months, respectively. Crizotinib also improved response rates (65% vs 20%), tumour-related symptoms and global quality of life. An interim analysis revealed no significant differences in overall survival between the two treatment arms. The main crizotinib-related adverse events were visual disorders, gastrointestinal side effects and elevated liver aminotransferase levels. These findings led to the approval of crizotinib for ALK-positive patients who had been pretreated with chemotherapy.

The PROFILE 1014 trial then demonstrated superior outcome of crizotinib over platinum-based chemotherapy in treatment-naive patients with advanced ALK-positive NSCLC.[9 10] The HR for progression-free survival was 0.45 (95% CI 0.35 to 0.60; p<0.001) and median progression-free survival times were 10.9 versus 7.0 months.[9] Crizotinib also resulted in higher response rates (74% vs 45%), better symptom relief, and greater improvement in quality of life.[8] Overall survival was also improved with a HR of 0.76 (95% CI 0.548 to 1.053; p=0.0978), median survival times of not reached versus 47.5 months, and 4-year survival probabilities of 57% versus 49%.[10] When adjusted for crossover at the time of disease progression, the HR was 0.35 in favour of crizotinib. The most common adverse events with crizotinib were vision disorders, diarrhoea, nausea and oedema. These favourable results led to the establishment of crizotinib as first-line therapy for patients with advanced ALK-positive NSCLC.

Despite excellent responses to crizotinib, patients will eventually acquire resistance and develop disease progression. Mechanisms of acquired resistance are on-target alterations, such as ALK resistance mutations and ALK amplifications, and off-target changes such as upregulation of bypass signalling pathways.[11]

SECOND-GENERATION ALK INHIBITORS

Second-generation ALK TKIs are ceritinib, alectinib and brigatinib.[7] In comparison to crizotinib, these TKIs have broader efficacy and better efficacy against brain metastases due to better penetration of the blood-brain barrier. Second-generation TKIs were compared with crizotinib or chemotherapy within clinical trials in treatment-naive and pretreated patients.

Ceritinib was compared with chemotherapy in patients with ALK-positive stage IIIB or IV NSCLC who had been pretreated with one or two lines of chemotherapy (including a platinum doublet) and crizotinib.[12] Patients (n=331) were randomised to oral ceritinib (750 mg per day fasted) or chemotherapy with pemetrexed or docetaxel. Ceritinib improved progression-free survival with a HR of 0.49 (95% CI 0.36 to 0.67, p<0.0001) and median progression-free survival times of 5.4 versus 1.6 months. Serious adverse events were seen in 43% and 32% of ceritinib and chemotherapy patients, respectively. Treatment-related serious adverse events were 11% in both groups. The most frequent grade 3–4 adverse events among the ceritinib group compared with the chemotherapy group were increased alanine aminotransferase levels (21% vs 2%), increased γ-glutamyltransferase levels (21% vs 1%), and increased aspartate aminotransferase levels (14% vs 1%). These findings established ceritinib as a treatment option for patients in whom treatment with crizotinib had failed.

Next, ceritinib (750 mg orally per day) was shown to increase progression-free survival compared with first-line chemotherapy with a platin plus pemetrexed in patients (n=376) with ALK-positive non-squamous NSCLC.[13] The HR was 0.55 (95% CI 0.42 to 0.73; p<0·00001) and median progression-free survival times were 16.6 and 8.1 months, respectively. Adverse events of ceritinib were diarrhoea (85%), nausea (69%), vomiting (66%) and increased alanine aminotransferase (60%). These findings led to the approval of ceritinib also for first-line therapy of ALK-positive patients.

Alectinib is another potent ALK TKI with activity against mutations that confer resistance to crizotinib and good penetration into the central nervous system (CNS). A phase I–II trial established grade 3 headache and grade 3 neutropenia as dose-limiting toxicities, fatigue as the most common adverse event (30% of patients), and 600 mg two times per day as recommended dose for phase II trials.[14] In the phase II setting, alectinib showed promising efficacy.[15]

Two phase III trials then demonstrated the superiority of alectinib over crizotinib in treatment-naïve patients with advanced ALK-positive NSCLC.[16 17] The J-ALEX trial randomised patients (n=207) to alectinib (300 mg two times per day) or crizotinib.[16] Alectinib improved progression-free survival with a HR of 0.34 (95% CI 0.17 to 0.71; p<0.0001) and median progression-free survival times of not reached versus 10.2 months. The ALEX trial randomised patients (n=303) including patients with asymptomatic brain metastases to alectinib (600 mg two times per day) or crizotinib.[17] Alectinib improved progression-free survival with a HR of 0.47 (95% CI 0.34 to 0.65; p<0.001). The HR for overall survival was 0.76 (95% CI 0.48 to 1.20; p=0.24). Alectinib resulted in liver toxicity, anaemia, oedema and myalgia, while crizotinib led to liver toxicity, nausea, vomiting, diarrhoea and oedema. These results led to the approval of alectinib for ALK-positive patients.

Brigatinib has also shown superior efficacy over crizotinib in the ALTA-1L phase III trial in patients with advanced ALK-positive NSCLC who had not previously received ALK inhibitors.[18] Patients (n=275) received brigatinib (180 mg one time per day; with a 7-day lead-in period at 90 mg) or crizotinib. An interim analysis demonstrated an improved outcome for brigatinib with a HR for progression-free survival of 0.49 (95% CI 0.33 to 0.74; p<0.001), progression-free survival rates at 1 year of 67% and 43%, response rates of 71% and 60%, and intracranial response rates of 78% and 29%, respectively. Based on the results of an earlier trial, brigatinib is currently approved for patients with advanced ALK-positive NSCLC previously treated with crizotinib.

LORLATINIB

Lorlatinib, a third-generation inhibitor of ALK and ROS1 tyrosine kinases, was designed to overcome major limitations of earlier ALK inhibitors.[19] It is active against acquired resistance mutations such as ALK G1202R and ROS1 G2032R, and shows better penetration of the blood brain barrier than earlier TKIs.[20–22]

A phase I study of lorlatinib enrolled patients (n=54) with advanced NSCLC including ALK-positive (n=41) and ROS1-positive patients (n=12).[23] Twenty-eight patients had been pretreated with two or more ALK TKIs and 39 patients had brain metastases. Patients were treated with oral lorlatinib at doses ranging from 10 to 200 mg one time per day or 35–100 mg two times per day. Treatment-related adverse events were hypercholesterolaemia (72%), hypertriglyceridaemia (39%), peripheral neuropathy (39%) and peripheral oedema (39%). The study defined a recommended dose of 100 mg daily for phase II trials but no maximum tolerated dose. The overall response rate was 46% for ALK-positive patients, 42% for ALK-positive patients who had been pretreated with two or more TKIs, and 50% for ROS1-positive patients. Responses were also seen in patients with resistance mutations and in those with brain metastases. These findings suggested lorlatinib as an effective treatment for patients with acquired resistance to ALK TKIs including second-generation TKIs.

The efficacy of lorlatinib was then confirmed in a global phase II trial in patients with ALK- or ROS1-positive advanced NSCLC.[24] The trial enrolled patients with ECOG performance status of 0–2, adequate organ function and with or without CNS metastases. Based on ALK and ROS1 status as well as on pretreatment, patients were enrolled into six different expansion cohorts. Patients received lorlatinib 100 mg orally one time per day. Primary endpoints were overall response and intracranial tumour response. As recently reported,[24] patients (n=276) had been enrolled in one of the following groups: ALK positive and treatment naive (n=30; EXP1); ALK positive and pretreated with crizotinib without chemotherapy (n=27; EXP2); ALK positive and pretreated with crizotinib and chemotherapy (n=32; EXP3A); ALK positive and one previous non-crizotinib ALK TKI with or without chemotherapy (n=28; EXP3B); ALK positive and pretreated with two ALK TKIs with or without chemotherapy (n=66; EXP4); ALK positive and pretreated with three ALK TKIs with or without chemotherapy (n=46; EXP5); ROS1 positive with any pretreatment (n=47; EXP6). Among ALK-positive patients, the objective response was 90% for treatment-naive patients (EXP1) and 47% for those with at least one previous ALK TKI (n=198; EXP2-5). Intracranial responses were seen in 2/3 (67%) treatment-naïve patients and 51/81 (63%) patients pretreated with at least one ALK TKI. Responses were also seen in 41/51 (69.5%) patients with only crizotinib pretreatment (EXP2-3A), 9/28 (32.1%) patients with one previous non-crizotinib ALK TKI (EXP3B), and 43/111 (38.7%) patients with two or more previous ALK TKIs (EXP4-5). Intracranial responses were achieved in 20/23 (87%) patients in EXP2-3A, 5/9 (55.6%) patients in EXP3B, and 26/49 (53.1%) patients in EXP4-5. Treatment-related adverse events were hypercholesterolaemia (81% of patients; 15% grade 3–4), hypertriglyceridaemia (60%; 16% grade 3–4), oedema (43%; 2% grade 3–4) and peripheral neuropathy (30%; 2% grade 3–4). Weight gain was common with 10%–20% increase in 31% of patients. Cognitive side effects were usually mild. Serious treatment-related adverse events were seen in 7% of patients but no treatment-related deaths did occur. Side effects were manageable through dose modifications and supportive therapies. Dose interruptions and dose reductions occurred in 30% and 22% of patients, respectively. The most common cause for these dose modifications were oedema. Permanent discontinuation occurred in only 3% of patients, mainly due to cognitive side effects. Taken together, lorlatinib demonstrated efficacy including intracranial efficacy in both treatment-naive patients and patients pretreated with ALK TKIs including second-generation ALK TKIs.

A recent report suggested that tumour genotyping may identify patients who are more likely to benefit from lorlatinib.[25] ALK mutations were analysed in both plasma samples and tumour tissues. Among patients who failed one or two ALK TKIs, response to lorlatinib was greater for patients with ALK mutations. Progression-free survival was also longer among patients with ALK mutations based on tissue analyses but no such difference was seen based on plasma analyses.

Based on its efficacy and good tolerability, lorlatinib was approved in the European Union (EU) and other countries for the treatment of patients with advanced ALK-positive NSCLC. Lorlatinib is currently also compared with crizotinib in previously untreated patients within a randomised trial (NCT03052608).

CLINICAL IMPACT

Treatment options for patients with ALK-positive NSCLC are ALK TKIs and chemotherapy. In the EU, five ALK TKIs have been approved. These options raise the question whether a preferred sequence of treatments does exist. Treatment decisions should be based on several factors. First, clinical trial results have to be considered. ALK TKIs are superior to chemotherapy, second-generation ALK TKIs are superior to crizotinib and active in patients with crizotinib resistance, and second-generation to third-generation inhibitors are superior to crizotinib among patients with brain metastasis. Second, availability and re-imbursement of drugs will certainly impact on the selection of drugs. Finally, experience and judgement of treating physicians as well as patient preference will play a role, too.

A strategy adopted by many doctors is initial treatment with a second-generation ALK TKI followed by treatment with lorlatinib or chemotherapy at the time of disease progression. Particularly in the absence of

brain metastases, however, some doctors may still prefer crizotinib as initial treatment followed by a next-generation ALK inhibitor at the time of disease progression. Whether the type of documented resistance mutations should guide the selection of TKIs remains unclear and requires prospective studies before such a strategy can be recommended for routine clinical practice. Chemotherapy also remains a valid treatment option any time during the course of the disease. Further studies should also determine whether TKIs combined with stereotactic radiotherapy will improve control of brain metastases compared with TKIs alone.

Contributors Both authors have prepared and approved the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests RP has received speaker's fees from AstraZeneca and Boehringer Ingelheim, honoraria for Advisory Boards from Boehringer Ingelheim, Jansen Oncology as well as Takeda, and honoraria for Data Monitoring Committee participation from Genmab, Gedeon Richter, Merck Sharp Dohme and Regeneron. MF has received speaker's fees and honoraria for Advisory Boards from AstraZeneca, Bayer, Biomedica, Boehringer Ingelheim, Eli Lilly, Merck, Myriad Genetics, Pfizer, and Roche.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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