Alectinib in the treatment of ALK-positive metastatic non-small cell lung cancer: clinical trial evidence and experience with a focus on brain metastases

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Abstract: Molecular profiling of metastatic nonsquamous non-small cell lung cancer (NSCLC) is required to guide the treatment strategy. Anaplastic lymphoma kinase (ALK) gene rearrangements are found in approximately 5% of lung adenocarcinomas and are associated with specific clinical features including a high risk of brain metastases. Crizotinib was the first ALK inhibitor developed and it demonstrated improved outcomes in patients with ALK-positive advanced NSCLC in comparison with chemotherapy. However, despite an initial response, all ALK-positive NSCLC patients develop acquired resistance to crizotinib. Because the most frequent mechanism of resistance is the development of a secondary ALK mutation, second (ceritinib, alectinib, brigatinib) and third-generation (lorlatinib) ALK inhibitors were developed. Alectinib is a second-generation ALK inhibitor and was shown to be effective for a broad spectrum of ALK rearrangements and ALK mutations. It was also shown to have high intracranial efficacy. In this article, we review clinical trial evidence of alectinib efficacy as well as publications reporting the experience of alectinib in daily practice, with a focus on brain metastases.

Keywords: alectinib, ALK, brain metastases, non-small cell lung cancer

Introduction

Lung cancer is the most frequently diagnosed cancer worldwide and is the leading cause of cancer deaths in the world.1 Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancers. Over the last two decades, the emergence of predictive biomarkers leading to the development of targeted therapies improved the prognosis of NSCLC patients. Molecular profiling is needed to select the most reliable therapeutic strategy for advanced lung adenocarcinoma.2 An inversion in chromosome 2 is found in approximately 5% of NSCLC. The latter juxtaposes the 5'-end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3'-end of the anaplastic lymphoma kinase (ALK) gene, resulting in the novel fusion oncogene EML4-ALK.3 ALK gene arrangements are mutually exclusive from epidermal growth factor receptor and KRAS mutations.4

Tumors harboring the EML4-ALK fusion oncogene or its variants are associated with specific clinical features, including no or a light history of smoking, a younger age, and adenocarcinoma with signet ring or acinar pathology.4 Incidence of brain metastases (BMs) is higher in patients with ALK-positive NSCLC: among those patients, up to 50–60% will develop BMs during the course of their disease.3

Advanced NSCLC associated with ALK fusion oncogene is highly sensitive to ALK tyrosine kinase inhibitors (TKIs). Crizotinib was the first
ALK inhibitor developed and has demonstrated a systemic efficacy and strongly improved outcomes in patients with ALK-positive advanced NSCLC in comparison with chemotherapy. First-line median progression-free survival (PFS) was longer with crizotinib in comparison with chemotherapy [10.9 versus 7 months; hazard ratio (HR) 0.45, 95% confidence interval (CI) 0.35–0.60] and the objective response rate (ORR) was increased in the crizotinib arm (74 versus 45%).* However, the intracranial efficacy of crizotinib is poor, due to poor blood–brain barrier (BBB) penetration. Moreover, despite an initial response, all ALK-rearranged NSCLC patients develop resistance to crizotinib, mainly due to ALK mutations. There was thus a need for the development of other ALK inhibitors to improve intracranial disease control and enlarge the spectrum of ALK mutations targeted. For these reasons, the second-generation ALK inhibitors ceritinib, alectinib and brigatinib and the third-generation ALK inhibitor lorlatinib were developed.

Ceritinib also showed improved outcomes in ALK-positive advanced NSCLC patients in the first or second-line setting. In the ASCEND-4 trial, ceritinib demonstrated an improved efficacy over chemotherapy in the front-line setting in terms of median versus PFS (16.6 versus 8.1 months; HR 0.55, 95% CI 0.42–0.73), ORR [72.5 (95% CI 65.5–78.7) versus 26.7% (20.5–33.7)], and duration of response [DOR; 23.9 (95% CI 16.6 to not estimable) versus 11.1 months (7.8–16.4)].

Brigatinib was approved by the United States Food and Drug Administration (US FDA) for clinical use in patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib on the basis of phase I and II clinical trials showing a 54% ORR (97.5% CI, 34% to 56%), a 12.9 months median PFS (95% CI, 11.1 to not reached). Moreover, they showed alectinib to have a higher antitumor activity than crizotinib in intracranial tumor implantation mouse models of EML4-ALK-positive NSCLC due a higher BBB penetration. Unlike ceritinib and crizotinib, alectinib is not a P-glycoprotein (gp) substrate and this may play a role in the higher efficacy of alectinib in the brain and higher BBB penetration. P-gp overexpression has indeed been shown to be a mechanism of resistance to ceritinib, especially in the brain.

Alectinib is a potent second-generation ALK inhibitor and was shown to be effective for a broad spectrum of ALK rearrangements and ALK mutations. The aim of this review is to summarize the clinical trial data on alectinib efficacy and safety for the treatment of advanced ALK-positive NSCLC, with a focus on alectinib intracranial efficacy.

Clinical trial evidence: main studies

Preclinical efficacy

Several preclinical in vitro and in vivo studies were conducted to assess alectinib (previously CH5424802) antitumor activity, pharmacodynamics and pharmacokinetics.

Sakamoto and colleagues first performed monolayer cultures of different NSCLC and anaplastic large-cell lymphoma cell lines. In vitro assays showed a selective activity of alectinib in ALK-rearranged cell lines via the attenuation of ALK, STAT3 and AKT (proteins of downstream signal pathway) auto-phosphorylation. In vivo mouse xenograft models confirmed these results and provided pharmacokinetics data, showing tumor regression was dose-dependent. Both in vitro and in vivo assays showed a potent inhibition activity of alectinib against EML4-ALK L1196M, C1156Y and F1174L mutations known to be responsible for crizotinib resistance.

More recently, Kodama and colleagues also observed a higher apoptosis rate with alectinib compared with crizotinib. They showed that alectinib had potent inhibitory activity against ALK L1196M, G1269A, C1156Y, F1174L, 1151Tins and L1152R point mutations whereas no activity was observed against the ALK G1202R mutation. Moreover, they showed alectinib to have a higher antitumor activity than crizotinib in intracranial tumor implantation mouse models of EML4-ALK-positive NSCLC due a higher BBB penetration. Unlike ceritinib and crizotinib, alectinib is not a P-glycoprotein (gp) substrate and this may play a role in the higher efficacy of alectinib in the brain and higher BBB penetration. P-gp overexpression has indeed been shown to be a mechanism of resistance to ceritinib, especially in the brain.

Phase I studies

Gadgeel and colleagues published a phase I/II study conducted in the USA in ALK-positive crizotinib-resistant NSCLC patients. A total of 47 patients were enrolled, 21 of whom had BMs. Alectinib was
well tolerated, the most common adverse events being fatigue, myalgia and peripheral edema (respectively 30%, 17% and 17%). The most common grade 3–4 adverse events were biological with increased of gamma-glutamyl transpeptidase, decrease of neutrophils or hypophosphatemia (4% each). The ORR was 55% (24 patients) in the whole cohort. Activity, tolerability, and pharmacokinetic data led to recommend the dose of 600 mg twice a day (BID) for phase II.

Seto and colleagues published the AF-001JP phase I/II study of alectinib in ALK-inhibitor-naive ALK-positive NSCLC patients carried out in Japan.22 The phase I part of the trial enrolled 24 patients identified the dose of 300 mg BID as the recommended dose for phase II. Among the 46 patients enrolled in the phase II part of the trial, ORR was 93.5% (95% CI 82.1–98.6). No predictive clinical factor of efficacy has been identified. The tolerance profile was acceptable with no grade 4 and 37% grade 3 adverse events. Alectinib also showed a clinical benefit in patients with BMs, even in the absence of prior cerebral irradiation.

Later on, a 3-year follow up of this phase II study was published.23 The 3-year PFS was 62% (95% CI 45–75) at 3 years but median PFS was not reached. The 3-year overall survival (OS) rate was 78% (13 events).

The most common adverse events were increased blood bilirubin, aspartate aminotransferase and creatinine respectively in 36.2%, 32.8% and 32.8% cases. Most cancer symptoms were relieved and symptom medications decreased.

Phase II studies
The two pilot phase II studies assessed alectinib 600 mg BID efficacy in ALK-positive, crizotinib-resistant NSCLC patients.

The first one enrolled 138 patients, 84 of whom had BMs.24 The ORR was 50% (95% CI, 41% to 59%), median PFS was 8.9 months (95% CI, 5.6 to 11.3 months) and the median DOR was 11.2 months (95% CI, 9.6 months to not reached). Most commons adverse events were constipation (33%), fatigue (26%) and peripheral edema (25%). A total of 21% treatment-related dose reductions and 8% permanent discontinuation were reported.

As a result of both studies, alectinib was approved by the US FDA in the USA for patients with ALK-positive, crizotinib-resistant NSCLC in 2015, via an accelerated procedure.

Phase III studies
The ALUR phase III randomized trial was conducted to assess the efficacy of alectinib in patients with ALK-positive NSCLC previously treated with chemotherapy and crizotinib.26 A total of 107 patients were enrolled to receive either alectinib or chemotherapy. The median PFS was longer in the alectinib arm [9.6 months (95% CI 6.9–12.2)] than in the chemotherapy arm [1.4 months (95% CI: 1.3–1.6); HR 0.15 (95% CI: 0.08–0.29); p < 0.001]. ORR was 36.1% with alectinib and 11.4% with chemotherapy. Grade ≥3 adverse events were more common with chemotherapy (41.2%) than alectinib (27.1%).

J-ALEX was a randomized phase III trial of alectinib versus crizotinib in Japanese patients with ALK-positive, ALK inhibitor-naive advanced NSCLC. It was the first head-to-head comparison of alectinib and crizotinib in the first- or second-line (after chemotherapy) setting.27 A total of 207 patients were enrolled and 103 patients received alectinib 300 mg BID, 64% as a first-line treatment and 36% as a second-line treatment. This study was initially designed with prior hypothesis of non-inferiority, but the protocol was amended after results of the AF-001JP study for a new interim analysis after 33% events. The median PFS was not reached in the alectinib arm (95% CI 20.3–not estimated) versus 10.2 months (8.2–12.0) in the crizotinib arm. The ORR was also higher with alectinib (92% versus 79%). Alectinib had a better safety profile than crizotinib: grade ≥3 adverse events occurred at a greater frequency with crizotinib (54 [52%]) than alectinib [27 [26%]]. The higher rate of adverse events in this Japanese population may be...
Almost concomitantly to this Japanese study, the international ALEX phase III trial randomized 303 patients with ALK-positive, ALK inhibitor-naïve advanced NSCLC to receive first-line alectinib 600 mg BID or crizotinib. PFS was longer with alectinib than crizotinib: 12-month event-free survival rate, 68.4% (95% CI, 61.0 to 75.9) with alectinib versus 48.7% (95% CI, 40.4 to 56.9) with crizotinib; HR 0.47 (95% CI, 0.34 to 0.65); p < 0.001. The median PFS with alectinib was not reached. The ORR was 82.9% (95% CI, 76.0 to 88.5) in the alectinib arm and 75.5% (95% CI, 67.8 to 82.1) in the crizotinib arm. The safety profile was different than in previous Japanese study, with more anemia, myalgia, increased blood bilirubin or increased weight with alectinib, due to the higher dose of alectinib (600 mg BID versus 300 mg BID in the J-ALEX study). However, grade ≥ 3 adverse events were less frequent with alectinib (41% versus 50% with crizotinib). Updated results of the ALEX study were presented at the ASCO (American Society of Clinical Oncology) congress in 2018. The median PFS was 34.8 months with alectinib versus 10.9 months with crizotinib (HR 0.43, 95% CI 0.32–0.58). The ORR was 82.9% (95% CI 75.95–88.51; n = 152) with alectinib versus 75.5% (95% CI 67.84–82.12; n = 151) with crizotinib. The median DOR was 33.3 months (95% CI 31.1–NE; n = 126) with alectinib versus 11.1 months (95% CI 7.5–13.0; n = 114) with crizotinib. The OS data were still immature. Despite a longer treatment duration (27.0 versus 10.8 months), the rate of grade 3–5 adverse events was lower with alectinib (44.7% versus 51.0%).

In 2018, the National Comprehensive Cancer Network guidelines recommended alectinib as the preferred first-line treatment of ALK-positive, advanced NSCLC patients.

Table 1 summarizes the main phase I to III clinical trials of alectinib in ALK-positive NSCLC patients.

**Experience: focus on BMs**

Central nervous system (CNS) metastases, including leptomeningeal (LM) and BMs, are increasingly frequent in ALK-positive NSCLC patients. In 2016, Johun and colleagues published outcome data from a database of 90 patients with BMs from ALK-rearranged NSCLC. The median OS was 49.5 months (95% CI 29.0–not reached) and the median intracranial PFS was 11.9 months (95% CI 10.1–18.2). In this population, 45% patients had progressive BMs at death and repeated intervention for BMs was common. It is thus particularly important to prevent and control CNS metastases in this population of patients. However, the BBB penetration of the different ALK inhibitors is heterogeneous and alectinib showed a specific intracranial activity in preclinical and clinical trials.

In the phase I/II AF-002JG study published by Gadgeel and colleagues, among the 21 patients with BMs enrolled, 11 (52%) had an objective response, including 6 (29%) with complete response, 8 (38%) had stable disease and 2 (10%) had progressive disease. In the 3-year follow up of the Japanese AF-001JP phase I/II study, among the 14 patients with BMs, six remained without CNS and systemic progression. These results were confirmed in a pooled analysis of two phase II clinical trials assessing the efficacy and safety of alectinib 600 mg BID for the treatment of ALK-positive, advanced NSCLC patients previously treated with crizotinib. A total of 136 patients with baseline CNS metastases were identified. Among these patients, 95 (70%) had prior brain radiation therapy, including 55 who completed radiation therapy more than 6 months before alectinib. For 50 (37%) patients with measurable CNS disease, intracranial ORR (icORR) was 64.0% (95% CI, 49.2–77.1%), intracranial disease control rate (icDCR) was 90.0% (95% CI, 78.2–96.7%), and median intracranial DOR (icDOR) was 10.8 months (95% CI, 7.6–14.1 months). The icORR was 35.8% (95% CI, 26.2–46.3%) for patients with prior radiation therapy and 58.5% (95% CI, 42.1–73.7%) for patients without prior radiation therapy. Gadgeel and colleagues also assessed the cumulative incidence rates of CNS and non-CNS progression in these two phase II studies of alectinib 600 mg BID for the treatment of ALK-positive advanced NSCLC patients previously treated with crizotinib. The 2-year cumulative incidence rate for CNS progression was lower in patients without baseline CNS metastases (8%) in comparison with patients with baseline CNS metastases (43.9%). In patients with baseline CNS metastases, the cumulative incidence rate of...
CNS progression was high if they had prior radiotherapy (50.5% versus 27.4% for radiotherapy-naive patients).

Alectinib efficacy in patients with BMs was also assessed in phase III clinical trials. In the ALUR study,26 24 patients in the alectinib arm and 16 patients in the chemotherapy arm had baseline measurable CNS metastases. The icORR was significantly higher with alectinib (54.2%) versus chemotherapy (0%; p < 0.001). In the J-ALEX Japanese study, CNS metastases were not selected as a stratification factor. However, a specific analysis of alectinib CNS efficacy in the J-ALEX study was published in order to determine the time to CNS progression and cumulative incidence rates of CNS progression and non-CNS progression.36 Alectinib tend to reduce the risk of CNS progression in comparison with crizotinib in patients with baseline CNS metastases (HR 0.51, 95% CI: 0.16–1.64; p = 0.2502) and in patients without baseline CNS metastases (HR 0.19, 95% CI: 0.07–0.53; p = 0.0004). The 1-year cumulative incidence rates of CNS progression were 16.8% with crizotinib versus 5.9% with alectinib while the 1-year cumulative incidence rates of non-CNS progression were 38.4% with crizotinib versus 17.5% with alectinib. Similar results were found in the ALEX trial,29 the 12-months cumulative incidence rate of CNS progression was 9.4% with alectinib versus 41.4% with crizotinib. A total of 18 patients (12%) in the alectinib arm had CNS progression versus 68 patients (45%) in the crizotinib arm (HR 0.16; 95% CI, 0.10 to 0.28; p < 0.001).

Moreover, alectinib demonstrated promising efficacy in the CNS for ALK-positive NSCLC patients pretreated with crizotinib, regardless of

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**Table 1. Main phase I to III clinical trials assessing alectinib efficacy in ALK-positive non-small cell lung cancer patients.**

| Study | Line | Treatment | Number of patients | ORR | DCR | DOR* | icORR | icDCR | PFS* |
|-------|------|-----------|--------------------|-----|-----|------|-------|-------|------|
| Phase I/II Gadgeel and colleagues18 | ≥2 Crizotinib-resistant | Alectinib 600 mg BID | 47 [21 with CNS disease] | 22% | 58% | - | 52% | 90% | - |
| Phase I/II AF-001JP19 | ≥1 ALK-TKI-naive | Alectinib 300 mg BID | 46 [15 with CNS disease] | 93% | 95% | - | - | 47% | - |
| Phase II Ou and colleagues21 | ≥2 crizotinib-resistant | Alectinib 600 mg BID | 138 [84 with CNS disease] | 50% | 79% | 11.2 | 57% | 83% | 8.9 |
| Phase II Shaw and colleagues22 | ≥2 crizotinib-resistant | Alectinib 600 mg BID | 87 [16 with CNS disease] | 48% | 80% | 13.5 | 52% | 90% | 8.1 |
| Phase III ALUR23 | ≥3 after chemo and crizotinib | Alectinib 600 mg BID | 72 [50 with CNS disease] | 37.5% | 3% | 81% | - | 54.2% | 80% | 9.6 |
| Phase III J-ALEX24 | 1 or 2 ALK-TKI-naive | Alectinib 300 mg BID | 103 [14 with CNS disease] | 92% | 97% | NR | - | 36% | NR |
| Phase III ALEX25 | 1 ALK-TKI naïve | Alectinib 600 mg BID | 152 [64 with CNS disease] | 83% | 81% | NR | 59% | - | NR |

*months.

ALK, anaplastic lymphoma kinase; BID, twice daily; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; icDCR, intracranial disease control rate; icORR, intracranial objective response rate; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
the assessment criteria used. Gandhi and colleagues compared response evaluation criteria in solid tumors (RECIST, version 1.1) and response assessment in neuro-oncology high-grade glioma (RANO-HGG) criteria in two phase II trials of alectinib in crizotinib-resistant ALK-positive NSCLC patients. The icORR was 64.0% by RECIST (95% CI: 49.2–77.1) and 53.5% by RANO-HGG (95% CI: 37.7–68.8).33

Several real-life retrospective case series confirmed the high efficacy of alectinib on BMs and LM.37,38 Moreover, Ou and colleagues reported the cases of two patients with ALK-positive NSCLC with BMs who received stereotactic radiosurgery (SRS) to the brain prior to alectinib treatment. Both patients had radiation necrosis presenting as pseudo-progression confirmed by neurosurgery and pathologic examination.39 This specific brain evolution after SRS and alectinib has to be known to avoid incorrect classification into progressive disease and alectinib discontinuation.

Experience: alectinib in daily practice

Since alectinib first US FDA approval was in December 2015, data are available on the routine use of alectinib for ALK-positive advanced NSCLC treated without clinical trials. DiBonaventura and colleagues indeed described the real-world usage of alectinib in a case series of 207 crizotinib-resistant ALK-positive NSCLC patients treated in the USA.40 The ORR was 51.3%, lower than the ORR described in clinical trials (67.1%). In the same way, the disease control rate (DCR) was 78.8%, lower than the DCR described in clinical trials (89.9%). Discontinuation (0%) and dose reductions (3.4%) due to treatment-related adverse events were uncommon.

Data on the clinical outcomes after alectinib treatment in specific populations are also available. In a series of 18 patients with Eastern Cooperative Oncology Group performance status (PS) ≥2 receiving alectinib 300 mg BID, the ORR was 72.2% (90% CI 52.9–85.8%).41 The PS improvement rate was 83.3% (90% CI 64.8–93.1%, p < 0.0001). Median PFS was 10.1 months. Alectinib was well tolerated in this population, with no dose reduction or discontinuation due to treatment-related adverse events. Moreover, although clinical trials enrolled patients with ALK-positive nonsquamous NSCLC (nsq-NSCLC), few cases of squamous NSCLC (sq-NSCLC) have been reported. In a case series of five patients with ALK-positive sq-NSCLC, PFS with ALK inhibitors was shorter than previously described in nsq-NSCLC.42 Overall, four case reports of patients with ALK-positive sq-NSCLC treated with alectinib have been published so far, three describing a good response to alectinib,43–45 while the fourth one reported no efficacy of alectinib.46 Alectinib efficacy has also been reported in a patient with ALK-positive large-cell neuroendocrine carcinoma of the lung who exhibited a partial response.47 Finally, as EML4-ALK rearrangement is the most common ALK rearrangement, data are missing regarding alectinib efficacy in less frequent ALK rearrangements. Recent data suggest that different ALK fusion variant induce different sensitivity to the first-generation ALK inhibitor crizotinib48 but the knowledge regarding the predictive role of each ALK fusion variant on alectinib efficacy is poor. Nakanishi et al. reported the case of a patient with STRN-ALK translocation who did not respond to alectinib.49

Furthermore, cost-effectiveness analyses were carried out to assess the place of alectinib in the therapeutic strategy of ALK-positive NSCLC. Treatment with alectinib in comparison with crizotinib results in an incremental cost-effectiveness ratio of US$39,312/quality-adjusted life-year.50 This cost increase was due to longer treatment durations. Moreover, CNS-related costs were significantly lower with alectinib in comparison with crizotinib. These results were confirmed in a study assessing the economic impact of preventing BMs with alectinib.51 In this study of 207 patients with ALK-positive NSCLC with no BMs and 198 patients with BMs, alectinib was estimated to reduce BM-related costs by US$41,434 per patient in comparison with crizotinib.

Future directions

Place in therapy

Since the results of the PROFILE 10-14 trial,6 crizotinib was considered as the standard of care for treatment-naïve patients with metastatic ALK-positive NSCLC. Based on the data of the ASCEND-4 study,12 comparing the second-generation ALK inhibitor ceritinib with platinum-based chemotherapy, ceritinib became another potential option in the first-line setting. However, direct comparison of ceritinib with the standard
of care, that is, crizotinib, is still lacking today. As previously mentioned, two randomized phase III trials (J-ALEX\textsuperscript{27} and ALEX\textsuperscript{29}) in patients with previously untreated, advanced ALK-positive NSCLC recently demonstrated the superiority of alectinib over crizotinib in terms of PFS, CNS progression and safety. Based on these results, alectinib could be considered as the new standard of care for first-line therapy. However, we still do not know whether OS will be longer with alectinib compared with crizotinib as a front-line treatment, as mature OS data have not yet been reported from phase III trials. Alternatively, to first-line alectinib, another strategy could be the sequential prescription of ALK inhibitors, starting with the first-generation crizotinib, then a second-generation, such as alectinib, at disease progression. Results from some retrospective studies support such a sequential approach.\textsuperscript{52,53} In addition, the serial prescription of ALK inhibitors could be tailored according to the biological mechanisms of acquired resistance, that include, on the one hand, ALK-independent mechanisms, such as activation of bypass signaling pathways, lineage changes, and drug efflux pump; and, on the other hand, ALK-dependent mechanisms, such as ALK secondary resistance mutations or amplification.\textsuperscript{54} Performing systematic repeated biopsies in patients with disease progression while on ALK inhibitor therapy could be a way to determine the best-next agent, according to the mechanism of acquired resistance, notably in case of secondary ALK mutations identified.\textsuperscript{55} Furthermore, the detection of ALK mutations in circulating cell-free DNA could avoid invasive rebiopsies in some patients.\textsuperscript{56} However, given its favorable safety profile and efficacy, notably in BMs, alectinib will probably rapidly become the oncologists’ preferred first-line treatment for advanced ALK-rearranged NSCLC, as soon as access to and funding of the drug is set up.

### Perspectives

Several other ALK inhibitors are currently being developed, such as brigatinib,\textsuperscript{14,15} a second-generation ALK inhibitor, but also lorlatinib,\textsuperscript{16} entrectinib\textsuperscript{57} and ensartinib,\textsuperscript{58} which are third-generation ALK inhibitors. Given the promising efficacy and safety results in nonrandomized studies, these new agents are compared with crizotinib in ongoing randomized phase III studies, in patients with advanced ALK-positive NSCLC that have not previously received any ALK inhibitor (ClinicalTrials.gov identifiers: NCT02737501, NCT03052608, NCT02767804). If some of these trials turn out to be positive, the next question will be which ALK inhibitor should be preferred in the first-line setting and additional head-to-head trials will be needed to answer this question. Again, OS will be a key endpoint to determine the optimal strategy for patient management. Furthermore, it will be particularly important to understand how the selection of a first-line agent influences subsequent treatment options and outcomes. In addition, it is likely that a single strategy will not be optimal for all patients, and that it will be necessary to adapt the therapeutic approaches according to some patient profiles. In this context, the type of ALK fusion variant might be taken into consideration in the drug selection process.\textsuperscript{59,48}

Given the impressive results in the last years with immunotherapy in NSCLC, another promising strategy could be the combination of ALK inhibitors with immune checkpoint inhibitors (ICIs). Early phase clinical studies are ongoing, such as a phase Ib study assessing atezolizumab (a monoclonal antibody directed against programmed cell death ligand 1) in combination with either erlotinib or alectinib in patients with NSCLC (ClinicalTrials.gov identifier: NCT02013219). In addition, combinations of crizotinib or ceritinib with pembrolizumab [programmed cell death 1 (PD-1) inhibitor; NCT02511184] or nivolumab (PD-1 inhibitor; ClinicalTrials.gov identifiers: NCT01998126 and NCT02393625) are under investigation in phase I studies. Whereas preliminary data on the efficacy of ALK inhibitors and ICIs showed promising results, this combination is associated with a high rate of toxicity. Spigel and colleagues reported the results of the CheckMate 370 phase I/II study of crizotinib and nivolumab in ALK-positive NSCLC. A total of 13 patients were enrolled before early discontinuation of the trial due to a high rate of severe hepatic toxicity (38%), leading to the death of two patients.\textsuperscript{60} More recently, the combination of alectinib and atezolizumab in treatment-naïve ALK-positive NSCLC was studied in a phase Ib study reported at the ASCO congress in 2018.\textsuperscript{61} Among 21 patients enrolled, the incidence of grade 3 adverse events was 62% and no grade 4–5 adverse event was reported. The ORR was 81% (95% CI 58.1–94.6) and the median PFS was 21.7 months (95% CI 10.3–21.7).
Conclusion
In less than 10 years from the discovery of an ALK-positive NSCLC subgroup of patients, their management moved from standard chemotherapy to several sequential lines of ALK TKIs. While crizotinib has represented the standard of care until recently, alectinib demonstrated an indisputable superiority over crizotinib, both systemically and in the control of intracerebral disease. Alectinib is therefore the new standard of care. In addition to these results, we still need to understand the heterogeneity of ALK disease, the development of the mechanism of resistance to the different ALK TKIs and therefore the best strategy to be offered to these patients.

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Conflict of interest statement
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