Canadian perspectives: update on inhibition of ALK-positive tumours in advanced non-small-cell lung cancer

B. Melosky MD,*a  P. Cheema MD MBiotech,† J. Agulnik MD,‡ R. Albadine MD,§ D.G. Bebb BM BCPhD,|| N. Blais MD MSc,§ R. Burkes MD,‡ C. Butts MD,** P.B. Card PhD,**‡‡ A.M.Y. Chan MSc,|| V. Hirsh MD,‡‡ D.N. Ionescu MD,§ R. Juergens MD PhD,§§ W. Morzycki MDMd,||| Z. Poonja MD,‡‡ R. Sangha MD,** M. Tehfe MD MSc,§ M.S. Tsao MD,*** M. Vincent MD,**‡‡ Z. Xu MDMd,||| and G. Liu MD MSc***

ABSTRACT

Background  Inhibition of the anaplastic lymphoma kinase (ALK) oncogenic driver in advanced non-small-cell lung carcinoma (NSCLC) improves survival. In 2015, Canadian thoracic oncology specialists published a consensus guideline about the identification and treatment of ALK-positive patients, recommending use of the ALK inhibitor crizotinib in the first line. New scientific literature warrants a consensus update.

Methods  Clinical trials of ALK inhibitor were reviewed to assess benefits, risks, and implications relative to current Canadian guidance in patients with ALK-positive NSCLC.

Results  Randomized phase III trials have demonstrated clinical benefit for single-agent alectinib and ceritinib used in treatment-naïve patients and as second-line therapy after crizotinib. Phase II trials have demonstrated activity for single-agent brigatinib and lorlatinib in further lines of therapy. Improved responses in brain metastases were observed for all second- and next/third-generation ALK tyrosine kinase inhibitors in patients progressing on crizotinib. Canadian recommendations are therefore revised as follows:

- Patients with advanced nonsquamous NSCLC have to be tested for the presence of an ALK rearrangement.
- Treatment-naïve patients with ALK-positive disease should initially be offered single-agent alectinib or ceritinib, or both sequentially.
- Crizotinib-refractory patients should be treated with single-agent alectinib or ceritinib, or both sequentially.
- Further treatments could include single-agent brigatinib or lorlatinib, or both sequentially.
- Patients progressing on ALK tyrosine kinase inhibitors should be considered for pemetrexed-based chemotherapy.
- Other systemic therapies should be exhausted before immunotherapy is considered.

Summary  Multiple lines of ALK inhibition are now recommended for patients with advanced NSCLC with an ALK rearrangement.

Key Words  Non-small-cell lung cancer, NSCLC, anaplastic lymphoma kinase, ALK, tyrosine kinase inhibitors, TKIs, CNS, metastases


INTRODUCTION

Lung cancer is the most common cause of cancer-related death in Canada (26%), with an estimated 28,600 new cases diagnosed in 2017. Approximately 85% of those cases are non-small-cell cancer (NSCLC), with 70% of those being of nonsquamous histology; most cases are found to be locally advanced or metastatic at diagnosis. Distinctive chromosomal rearrangements in the ALK gene (ALK-positive)
CRIZOTINIB IN THE FIRST-LINE SETTING

PROFILE 1014
Based on promising results from a phase 1 study, the phase III PROFILE 1007 trial compared second-line crizotinib (n = 173) with standard-of-care chemotherapy (n = 174, pemetrexed or docetaxel) in advanced ALK-positive NSCLC after progression on 1 prior platinum-based chemotherapy regimen. The primary endpoint of median progression-free survival (PFS) was met, favouring crizotinib over chemotherapy (7.7 months vs. 3.0 months; hazard ratio (HR): 0.49; 95% confidence interval (CI): 0.37 to 0.64; p < 0.0001). Results led, in May 2013, to Health Canada approval of second-line crizotinib for patients with ALK-positive disease after progression on platinum doublet therapy.

To assess crizotinib in the first line, the pivotal phase III PROFILE 1014 trial randomized 343 treatment-naïve patients with advanced ALK-positive nonsquamous NSCLC to receive either crizotinib or platinum–pemetrexed chemotherapy without pemetrexed maintenance. The primary endpoint, PFS by independent radiologic review, was significantly longer with crizotinib than with chemotherapy (median: 10.9 months vs. 7.0 months; HR: 0.45; 95% CI: 0.35 to 0.60; p < 0.001). The overall response rate (ORR) was higher for crizotinib than for chemotherapy (74% vs. 45%, p < 0.001). Crizotinib was also associated with reduced lung cancer symptoms and improved quality of life. Based on those results, Health Canada in July 2015 approved crizotinib for treatment-naïve patients with ALK-positive NSCLC. At a median follow-up of approximately 46 months in both arms, median overall survival (OS) was numerically improved for crizotinib compared with chemotherapy (not yet reached vs. 47.5 months; HR: 0.76; 95% CI: 0.55 to 1.05; p = 0.098), although the difference did not reach significance.

After adjustment for crossover in the crizotinib (19.2%) and chemotherapy (84.2%) groups, a more pronounced OS benefit was observed (HR: 0.35; 95% CI: 0.081 to 0.72). The longest OS was associated with crizotinib followed by a second-line ALK TKI; the shortest was associated with chemotherapy followed by treatments not involving an ALK TKI. Discontinuation attributable to treatment-related adverse events (AEs) occurred in 5% of patients receiving crizotinib and in 8% of patients receiving chemotherapy.

Treatment Beyond Progression
Oligometastatic progression on crizotinib can be treated with local therapy, surgery, or radiation. If clinical benefit is apparent, ALK TKIs can also be continued beyond progression in advanced ALK-positive NSCLC. That option is based on retrospective data showing significantly longer median OS from the start of crizotinib in 120 such patients who continued crizotinib compared with those who discontinued it (n = 74; 16.4 months vs. 3.9 months; HR: 0.27; 95% CI: 0.17 to 0.42; p < 0.0001)—an observation that remained significant after adjustment for confounding factors. Although that retrospective analysis might be subject to selection bias and differences in disease biology, it remains a clinically important concept. For patients with minimal disease burden and no cranial involvement, an individualized treatment strategy developed by a multidisciplinary group might include treatment beyond progression.

SECOND-GENERATION ALK TKIS AFTER PROGRESSION ON CRIZOTINIB

Ceritinib: ASCEND-5 and -8
The pivotal phase III ASCEND-5 trial confirmed the efficacy of ceritinib shown in earlier phase I/II trials in patients progressing on crizotinib (Table 1). Patients who had received 1 (88%) or 2 (12%) lines of chemotherapy and who had progressed on crizotinib (n = 231) were randomized to ceritinib (n = 115) or single-agent chemotherapy (n = 116). Compared with chemotherapy, ceritinib was associated with significantly improved median PFS (5.4 months vs. 1.6 months; HR: 0.49; 95% CI: 0.36 to 0.67; p < 0.0001) and with improved ORR (39.1% vs. 6.9%). The most commonly reported AEs in the ceritinib group were gastrointestinal (diarrhea, nausea, vomiting). Discontinuation because of AEs occurred in 5% of patients receiving ceritinib and in 7% of patients receiving chemotherapy. Thus, ASCEND-5 was the first randomized phase III study to establish the option of further targeted therapy after crizotinib for advanced ALK-positive disease.

In earlier studies and in the ASCEND-5 trial, ceritinib was administered at 750 mg daily without food (750 mg fasting). The goal of the phase I ASCEND-8 trial was to determine whether ceritinib at 450 mg or 600 mg taken with a low-fat meal (450 mg or 600 mg fed) could improve the gastrointestinal AEs without compromising efficacy. Compared with the 600 mg fed or 750 mg fasting doses, ceritinib 450 mg fed resulted in similar pharmacokinetic...
<table>
<thead>
<tr>
<th>Variable</th>
<th>Shaw et al., 2017(^{22}) (ASCEND-5)</th>
<th>Novello et al., 2018(^{23}) (ALUR)</th>
<th>Ahn et al., 2017(^{24}) (ALTA)</th>
<th>Shaw et al., 2018(^{25}) (B7461001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational agent</td>
<td>Ceritinib (second generation)</td>
<td>Alectinib (second generation)</td>
<td>Brigatinib (next/third-generation)</td>
<td>Lorlatinib (next/third-generation)</td>
</tr>
<tr>
<td>Study type</td>
<td>Phase III</td>
<td>Phase III</td>
<td>Randomized phase II</td>
<td>Phase II (cohorts 2–5)(^{a})</td>
</tr>
<tr>
<td>Review type</td>
<td>IRC</td>
<td>Investigator</td>
<td>Investigator</td>
<td>IRC</td>
</tr>
<tr>
<td>Line of treatment</td>
<td>Third (88%) Fourth (12%)</td>
<td>Third</td>
<td>≥Second</td>
<td>≥Second</td>
</tr>
<tr>
<td>Prior therapies</td>
<td>≥1 Lines of Platinum CTx and crizotinib</td>
<td>Crizotinib-refractory with (74%) or without (26%) prior CTx</td>
<td>Crizotinib ±CTx</td>
<td>Non-crizotinib ±CTx 2–3 prior TKIs±CTx</td>
</tr>
<tr>
<td>Dosage</td>
<td>Ceritinib 750 mg daily or docetaxel 75 mg/m(^2) every 3 weeks</td>
<td>Pemetrexed 500 mg/m(^2) twice daily</td>
<td>Alectinib 600 mg or docetaxel 75 mg/m(^2) every 3 weeks</td>
<td>Brigatinib 180 mg daily(^{b})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Brigatinib 90 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lorlatinib 100 mg daily</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>115</td>
<td>116</td>
<td>72</td>
<td>35</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>16.6</td>
<td>16.4</td>
<td>Not reported(^{c})</td>
<td>18.6</td>
</tr>
<tr>
<td>Intention-to-treat ORR (%)</td>
<td>39.1</td>
<td>6.9</td>
<td>37.5</td>
<td>2.9</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>30.2 to 48.7</td>
<td>3.0 to 13.1</td>
<td>26 to 50</td>
<td>0 to 15</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.4</td>
<td>1.6</td>
<td>9.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.49</td>
<td>0.15</td>
<td>0.64(^{e})</td>
<td>Not reported</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.36 to 0.67</td>
<td>0.08 to 0.29</td>
<td>0.45 to 0.91</td>
<td>Not reported</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>18.1(^{f})</td>
<td>20.1(^{f})</td>
<td>12.6(^{f})</td>
<td>Not yet reached(^{g})</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.0</td>
<td>0.89</td>
<td>0.67</td>
<td>Not reported</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.67 to 1.49</td>
<td>0.35 to 2.24</td>
<td>0.42 to 1.06</td>
<td>Not reported</td>
</tr>
<tr>
<td>p Value</td>
<td>0.50</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Treatment cohorts included cohorts 2 and 3A (prior crizotinib only or prior crizotinib plus 1–2 lines of prior CTx (n = 59)); cohort 3B (prior non-crizotinib ALK TKI with or without CTx (n = 27)); and cohorts 4 and 5 (2–3 prior ALK TKIs with or without CTx (n = 111)).

\(^{b}\) After a 7-day lead-in with brigatinib 90 mg daily.

\(^{c}\) Median safety follow-up was 6.5 months for the alectinib arm and 5.8 months for the CTx arm.

\(^{d}\) 97.5% Confidence interval for the primary endpoint.

\(^{e}\) At a median follow-up of 8.0 months, median PFS was 12.9 months for Brig-90/180 and 9.2 months for Brig-90 (hazard ratio: 0.55; 95% confidence interval: 0.35 to 0.86)\(^{26}\).

\(^{f}\) OS data were immature at the time of analysis.

\(^{g}\) Investigator-assessed.

IRC = independent review committee; CTx = chemotherapy; TKI = tyrosine kinase inhibitor; PFS = progression-free survival; OS = overall survival; ORR = overall response rate.
levels and treatment exposure at steady state, with fewer dose reductions or interruptions. Although both doses were tolerable (discontinuation because of AEs was 7.9% and 5.6% for the 450 mg fed and 750 mg fasting doses respectively), patients taking the 450 mg fed dose, compared with those taking the 750 mg fasting dose, also experienced fewer grade 3 or 4 gastrointestinal AEs, including diarrhea (1.1% vs. 7.8%), nausea (0% vs. 5.6%), and vomiting (0% vs. 4.4%). In treatment-naive patients, the 450 mg fed compared with the 750 mg fasting dose resulted in median PFS durations of 17.6 months and 10.9 months as assessed by a blinded independent review committee (BIRC). The ORR and time to response were similar in the two arms. The 450 mg fed dose was approved by many regulatory bodies, including the U.S. Food and Drug Administration.

The ASCEND-5 trial demonstrated that ceritinib is an effective ALK inhibitor after crizotinib. Similar efficacy and better tolerability of the lower dose of ceritinib was also confirmed in ASCEND-8. The lower dose improved the cost–benefit ratio of ceritinib therapy, and in 2017, it was approved by Health Canada and the pan-Canadian Oncology Drug Review as a second-line option for patients progressing on crizotinib.

**Alectinib: ALUR**

The pivotal phase III ALUR trial (n = 107) confirmed the efficacy of alectinib shown by earlier trials in patients with ALK-positive NSCLC who had progressed on both platinum-based chemotherapy and crizotinib (Table 1). Patients were randomized 2:1 to either alectinib or standard-second-line chemotherapy (pemetrexed or docetaxel). Investigator-assessed median PFS was significantly better in the alectinib group than in the chemotherapy group (9.6 months vs. 1.4 months; HR: 0.15; 95% CI: 0.08 to 0.29; p < 0.001), with a substantially improved ORR (37.5% vs. 2.9%). Discontinuation because of AEs occurred in 5.7% of patients at receiving alectinib and in 8.8% of patients receiving chemotherapy. Alectinib showed a significant PFS benefit in patients with crizotinib-refractory disease and received Health Canada approval for that indication on 31 October 2016.

**NEXT/THIRD-GENERATION ALK TKIS AFTER PROGRESSION ON CRIZOTINIB**

**Brigatinib: ALTA**

Brigatinib is a next/third-generation ALK TKI designed for potent activity against a broad range of ALK–inhibitor resistant mutations. In preclinical models, brigatinib was associated with inhibition of all ALK resistance mutations tested, including the solvent-front mutation G1202R, which confers resistance to crizotinib, ceritinib, and alectinib.

Following on from an earlier phase I/II trial, the randomized phase II ALTA trial prospectively assessed the efficacy and safety of brigatinib in 222 crizotinib-refractory patients (74% had received prior chemotherapy) with advanced ALK-positive NSCLC, comparing a dose of 180 mg daily preceded by a 7-day 90 mg lead-in regimen (Brig-90/180, n = 110) with a dose of 90 mg once daily (Brig-90, n = 112). The primary endpoint was investigator-assessed ORR, with PFS being a key secondary endpoint. The ORR was 54% for the Brig-90/180 group and 45% for the Brig-90 group, with median PFS durations of 12.9 months and 9.2 months respectively (HR: 0.55; 95% CI: 0.35 to 0.86). Early-onset pulmonary AEs (median: within 2 days) occurred in 14 of 219 patients (6.4%). No events occurred after escalation to 180 mg in the Brig-90/180 arm, and in 7 of 14 patients, brigatinib re-treatment or continued treatment at a lower dose was instituted without pulmonary issues.

**Lorlatinib**

Lorlatinib is a next/third-generation ALK TKI that is highly active in preclinical models of lung cancer harbouring chromosomal rearrangements of ALK, including cell lines with mutations that result in resistance to other ALK inhibitors, and it was specifically designed to penetrate the blood–brain barrier. After determining a 100 mg optimal daily dose for lorlatinib, the ongoing phase I/II trial included multiple patient cohorts with advanced NSCLC and ALK rearrangements, many of whom were heavily pretreated (including 1–3 prior ALK TKIs with or without prior chemotherapy). An expanded analysis of the BIRC-assessed ORR in 197 patients receiving 1 or more prior TKIs was recently presented (cohorts 2–5, Table 1). In 59 patients previously treated with crizotinib with or without chemotherapy (cohorts 2–3A), the systemic ORR was 69% (95% CI: 56% to 81%), and the median PFS was not yet reached (95% CI: 12.5 months to not yet reached). In 27 patients previously treated with one second-generation TKI plus chemotherapy (cohort 3B), the systemic ORR was 33% (95% CI: 16% to 54%), and the median PFS was 5.5 months (95% CI: 2.9 months to 9.0 months). In 111 patients previously treated with 2 or more ALK TKIs with or without chemotherapy (cohorts 4 and 5), the systemic ORR was 39% (95% CI: 30% to 49%), and the median PFS was 6.9 months (95% CI: 5.4 months to 9.5 months). Among all patients in the phase II study (n = 275), treatment-related AEs leading to discontinuation occurred in 3% of patients. Lorlatinib showed substantial activity in patients with heavily pre-treated ALK-positive NSCLC.

**FIRST-LINE TREATMENT WITH SECOND- AND NEXT/THIRD-GENERATION ALK TKIS**

**Ceritinib (Second Generation): ASCEND-4**

The phase III ASCEND-4 trial randomized 376 treatment-naïve patients with ALK-positive advanced NSCLC to receive ceritinib 750 mg daily (n = 189) or platinum–pemetrexed with or without pemetrexed maintenance (n = 187). The primary endpoint assessed by the blinded IRC was met, showing that, compared with chemotherapy, ceritinib...
was associated with a significant improvement in median pfs (16.6 months vs. 8.1 months; HR: 0.55; 95% CI: 0.42 to 0.73; \( p < 0.00001 \)), with orr of 72.5% (ceritinib) and 26.7% (chemotherapy) and similar improvements in duration of response and time to response. Patients treated with ceritinib experienced improved overall quality of life, with significantly prolonged time to definitive deterioration for lung cancer–specific symptoms, and fewer patients discontinued therapy because of treatment-related aes in the ceritinib group (5%) than in the chemotherapy group (11%). A significant and clinically meaningful improvement in pfs was shown for first-line ceritinib compared with chemotherapy in patients with advanced ALK-rearranged nsclc.

**Alectinib (Second Generation): ALEX**

The phase iii alex trial randomized 303 treatment-naïve patients with ALK-positive advanced nsclc to receive either alectinib 600 mg twice daily or crizotinib 250 mg twice daily. At a median follow-up of 18.6 months for alectinib and 17.6 months for crizotinib, the nc showed a significantly longer median pfs for alectinib compared with crizotinib (25.7 months vs. 10.4 months; HR: 0.50; 95% CI: 0.36 to 0.70; \( p < 0.001 \)). The investigator-assessedorr in the alectinib group was 82.9%; it was 75.5% in patients treated with crizotinib (\( p = 0.09 \)). An updated analysis with nearly 8 months’ additional follow-up confirmed those findings, showing improvements in the primary endpoint of investigator-assessed pfs (median: 34.8 months vs. 10.9 months; HR: 0.43; 95% CI: 0.32 to 0.58; \( p \) value not reported) and orr (82.9% vs. 75.5%, \( p \) value not reported) for alectinib compared with crizotinib (Table ii). Moreover, the Japanese phase iii j-alex trial showed an impressive pfs improvement for patients receiving alectinib at a dose of 300 mg twice daily (HR: 0.34; 99.7% CI: 0.17 to 0.71; \( p < 0.0001 \)). Discontinuation for any-cause aes occurred in 11% of patients receiving alectinib and in 13% of patients receiving full-dose crizotinib. First-line alectinib was associated with both a significantly longer pfs and a favourable safety profile.

**Brigatinib and Lorlatinib (Next/Third Generation):**

Ongoing trials evaluating the efficacy of next/third-generation ALK tKIs in the first line are underway. Brigatinib is being compared with crizotinib in the international randomized multicentre phase iii ALTA-1L trial with ALK tKI-naïve patients with ALK-positive advanced nsclc (see NCT02737501 at http://ClinicalTrials.gov/), in which 270 patients have been randomized to the Brig-90/180 regimen or to crizotinib 250 mg twice daily. The primary endpoint, pfs as assessed by a blinded irc, was met on 28 July 2018.

Lorlatinib is also being compared with crizotinib with respect to efficacy and safety in the phase iii CROWN trial in ALK-positive metastatic nsclc (see NCT03052608 at http://ClinicalTrials.gov/). The 280 enrolled patients are being randomized to lorlatinib 100 mg daily or to crizotinib 250 mg twice daily.

**BRAIN METASTASES AND ALK tKIs**

ALK-positive central nervous system (cns) metastases are initially present in approximately 25% of patients with ALK-positive nsclc, and the cns is the most common site of progression for patients taking crizotinib, with approximately 60%–70% of patients eventually developing this complication. Because the presence and treatment of cns metastases can have debilitating consequences for patients, treatment of this patient subset deserves special attention.

**Crizotinib**

In the profile 1014 trial (first-line crizotinib vs. platinum–pemetrexed), brain metastases were present at baseline in 26% of the group receiving crizotinib and in 27% of the group receiving chemotherapy. Brain responses were not reported, but intracranial lesions progressed or new ones developed in 15% of the patients in each arm. Analysis of the 79 patients (23%) with stable treated brain metastases showed that time to progression in the brain nonsignificantly favoured crizotinib (HR: 0.45; 95% CI: 0.19 to 1.07; \( p = 0.063 \)), that the intracranial disease control rate was significantly higher with crizotinib than with chemotherapy at both 12 weeks (85% vs. 45%, \( p < 0.001 \)) and 24 weeks (56% vs. 25%, \( p = 0.006 \)), and that median pfs was significantly improved in patients with treated brain metastases (9.0 months vs. 4.0 months; HR: 0.40; 95% CI: 0.23 to 0.69; \( p < 0.001 \)).

The aLEX trial mandated imaging of the brain at baseline and every 8 weeks throughout the trial; in the 22 patients who had measurable cns metastases at baseline and who were treated with crizotinib, a 50% cns response was seen (Table iii), although the duration of response was only 5.5 months.

**Ceritinib**

Of patients in the phase iii ASCEND-5 post-crizotinib trial who had active-target brain lesions and at least 1 post-baseline tumour assessment, 17 (15%) received ceritinib and 20 (17%) received single-agent chemotherapy. Of those patients, 6 (35%) in the ceritinib arm and just 1 (5%) in the chemotherapy arm experienced an overall intracranial response.

The phase iii ASCEND-4 trial (first-line ceritinib vs. platinum–pemetrexed) included 22 patients in each arm with baseline measurable brain metastases and at least 1 post-baseline confirmed assessment. Of those patients, 16 (72.7%) receiving ceritinib and 6 (27.3%) receiving chemotherapy experienced an overall intracranial response. In ASCEND-4, only patients with confirmed cns metastases were mandated to receive cns imaging with computed tomography (ct) or magnetic resonance imaging (mri) at baseline. Thus, a comparison of the incidence of new brain metastases between the treatment arms was not feasible.

**Alectinib**

Unlike crizotinib and ceritinib, alectinib is not a substrate of P-glycoprotein, a key efflux transporter located at the blood–brain barrier. Alectinib is therefore hypothesized to better penetrate cns sites. In both preclinical and early clinical investigations, alectinib showed promising cns activity.
In the phase III ALUR trial comparing alectinib with single-agent chemotherapy after chemotherapy—crizotinib, CNS response was the key secondary endpoint. All patients were required to undergo imaging by CT or MRI every 6 weeks for the duration of the trial (to coincide with scheduled chemotherapy visits). Measurable lesions in the CNS were seen in 24 patients (33%) in the alectinib group and in 16 patients (46%) in the chemotherapy group, with a CNS ORR of 54.2% being observed in those treated with alectinib (95% CI: 33% to 74%) compared with 0% in the group receiving chemotherapy (95% CI: 0% to 21%; p < 0.001).

The phase III ALEX trial was appropriately designed to observe both the incidence of CNS metastases and the CNS response for first-line alectinib compared with crizotinib; brain imaging every 8 weeks was mandatory throughout the study. Brain metastases were seen at baseline in 64 patients (42%) randomized to alectinib and in 58 patients (38%) randomized to crizotinib. Measurable baseline CNS lesions were observed in 21 patients (13.8%) receiving alectinib and in 22 (14.6%) receiving crizotinib, with a CNS response being observed in 17 patients receiving alectinib (81%; 95% CI: 58% to 95%) and in 11 receiving crizotinib (50%; 95% CI: 28% to 72%). The median duration of CNS response was considerably longer in the patients receiving alectinib (17.3 months; 95% CI: 14.8 months to not yet reached) than in those receiving crizotinib (5.5 months; 95% CI: 2.1 months to 17.3 months), as was the time to CNS progression in the intention-to-treat population (n = 303; HR: 0.16; 95% CI: 0.10 to 0.28; p < 0.001). Progression events in the CNS were seen in 18 patients receiving alectinib (12%) and in 68 patients receiving crizotinib (45%). The more recently reported 12-month cumulative incidence rates of CNS progression in patients without baseline CNS metastases were 4.6% for the alectinib group (95% CI: 1.5% to 10.6%) compared with 31.5% for the crizotinib group (95% CI: 22.1% to 41.3%).

Brigatinib
Brigatinib has impressive CNS activity despite being a substrate for P-glycoprotein. In the phase II ALTA trial evaluating two doses of brigatinib in patients previously treated with crizotinib, 69% (n = 154) had brain metastases at baseline; measurable brain lesions were observed in 18

---

### Table II: Efficacy of first-line first- or second-generation ALK inhibitors in treatment-naïve patients with ALK-positive disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference (study name)</th>
<th>Solomon et al., 2014&lt;sup&gt;47&lt;/sup&gt; (PROFILE 1014)</th>
<th>Soria et al., 2017&lt;sup&gt;40&lt;/sup&gt; (ASCEND-4)</th>
<th>Camidge et al., 2018&lt;sup&gt;42&lt;/sup&gt; (ALEX, poster)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational agent</td>
<td></td>
<td>Crizotinib (1st generation)</td>
<td>Ceritinib (2nd generation)</td>
<td>Alectinib (2nd generation)</td>
</tr>
<tr>
<td>Phase</td>
<td></td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Review</td>
<td></td>
<td>IRC</td>
<td>IRC</td>
<td>Investigator</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td>Crizotinib 250 mg twice daily</td>
<td>Pemetrexed 500 mg/m² plus platinum CTx every 3 weeks</td>
<td>Ceritinib 750 mg daily</td>
</tr>
<tr>
<td>Patients (n)</td>
<td></td>
<td>172</td>
<td>171</td>
<td>189</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td></td>
<td>~46</td>
<td>Not reported</td>
<td>27.8</td>
</tr>
<tr>
<td>Intention-to-treat ORR (%)</td>
<td></td>
<td>74</td>
<td>45</td>
<td>72.5</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td></td>
<td>67 to 81</td>
<td>37 to 53</td>
<td>65.3 to 78.7</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>&lt;0.001</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td></td>
<td>10.9</td>
<td>7.0</td>
<td>16.6</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td>0.45</td>
<td>0.55</td>
<td>0.42 to 0.73</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td></td>
<td>0.35 to 0.60</td>
<td>&lt;0.00001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.00001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>&lt;0.001</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td></td>
<td>Not reached&lt;sup&gt;c&lt;/sup&gt;</td>
<td>47.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Not estimable&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td>0.76</td>
<td>0.73</td>
<td>0.50 to 1.08</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td></td>
<td>0.55 to 1.05</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>0.0978</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

<sup>a</sup> The event-free survival rate at 12 months was 68.4% with alectinib (95% confidence interval: 61.0% to 75.9%) compared with 48.7% with crizotinib (95% confidence interval: 40.4% to 56.9%); the IRC-assessed median PFS was 25.7 months compared with 10.4 months (hazard ratio: 0.30; 95% confidence interval: 0.36 to 0.70; p < 0.001).

<sup>b</sup> The investigator-assessed median PFS was 16.8 months compared with 7.2 months (hazard ratio: 0.49; 95% confidence interval: 0.37 to 0.64; p < 0.00001).

<sup>c</sup> The OS data were immature at the time of analysis.

IRC = independent review committee; CTx = chemotherapy; PFS = progression-free survival; OS = overall survival; ORR = overall response rate.
patients receiving Brig-90/180 (16.4%) and in 26 patients receiving Brig-90 (23.2%)\textsuperscript{26}. A recent update showed that intracranial ORRs were seen in 12 patients receiving Brig-90/180 (67%) and in 13 patients receiving Brig-90 (50%)\textsuperscript{24}. At a median follow-up of 18.6 months in the Brig-90/180 arm, the median duration of CNS response was 16.6 months; in the 73 patients in that arm with any brain metastases at baseline (n = 12, cohort 3B), the intracranial ORR was 42% (95% CI: 37% to 59%). Among those previously treated with 1 second-generation TKI plus chemotherapy (n = 12, cohort 3B), the intracranial ORR was 42% (95% CI: 15% to 72%), and in the patients previously treated with 2 or more ALK TKIs with or without chemotherapy (n = 83, cohorts 4 and 5), the intracranial ORR was 48% (95% CI: 37% to 59%).

The ongoing randomized open-label two-arm phase III crown study (NCT03052608 at http://ClinicalTrials.gov/) is comparing lorlatinib with crizotinib in the first-line treatment of patients with metastatic ALK-positive NSCLC. The primary objective is blinded IRC-assessed PFS; important blinded IRC-assessed secondary objectives include CNS

### Table III: Central nervous system (CNS) response with first- and second-line ALK inhibitors

<table>
<thead>
<tr>
<th>Setting and agent</th>
<th>Reference (study name, phase)</th>
<th>Pts with measurable brain metastases at baseline (n)</th>
<th>CNS ORR [n/N (%)] with ALK inhibitor</th>
<th>Pts with measureable brain metastases at baseline (n)</th>
<th>CNS ORR [n/N (%)] with Chemotherapy</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Solomon et al., 2016\textsuperscript{11} (PROFILE 1014, III)</td>
<td>79\textsuperscript{a}</td>
<td>Not reported\textsuperscript{b}</td>
<td>Not reported\textsuperscript{b}</td>
<td>Not reported\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>Peters et al., 2017\textsuperscript{41} (ALEX, III)</td>
<td>22\textsuperscript{c}</td>
<td>11/22 (50)</td>
<td>Not applicable\textsuperscript{d}</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alectinib</td>
<td>Peters et al., 2017\textsuperscript{41} (ALEX, III)</td>
<td>21\textsuperscript{c}</td>
<td>17/21 (81)</td>
<td>Not applicable\textsuperscript{d}</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Soria et al., 2017\textsuperscript{40} (ASCEND-4, III)</td>
<td>44\textsuperscript{e}</td>
<td>16/22 (72.7)</td>
<td>6/22 (27.3)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brigatinib</td>
<td>Ahn et al., 2017\textsuperscript{24} (ALTA, II, randomized)</td>
<td>Brig-90/180: 18</td>
<td>12/18 (67)</td>
<td>Not applicable</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Shaw et al., 2017\textsuperscript{22} (ASCEND-5, III)</td>
<td>37\textsuperscript{e}</td>
<td>6/17 (35)</td>
<td>1/20 (5)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Alectinib</td>
<td>Novello et al., 2018\textsuperscript{23} (ALUR, III)</td>
<td>40\textsuperscript{e}</td>
<td>13/24 (54.2)</td>
<td>0/16 (0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>Shaw et al., 2018\textsuperscript{25} (II, expansion, pooled cohorts 2–5)</td>
<td>132\textsuperscript{h}</td>
<td>70/132 (53)</td>
<td>Not available</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Patients with stable treated brain metastases.

\textsuperscript{b} Compared with chemotherapy, crizotinib was associated with significantly improved intracranial disease control, including stable disease, at 12 weeks (85% vs. 45%, p \textless 0.001) and at 24 weeks (56% vs. 25%, p = 0.006).

\textsuperscript{c} Patients with measurable CNS disease at baseline.

\textsuperscript{d} Trial compared crizotinib with alectinib (CNS ORR: 50% vs. 81% respectively).

\textsuperscript{e} Eligible patients with active brain metastases and at least 1 post-baseline assessment.

\textsuperscript{f} Brigatinib 90 mg daily after a 7-day lead-in with brigatinib 90 mg daily.

\textsuperscript{g} Eligible patients with active brain metastases and at least 1 post-baseline assessment.

\textsuperscript{h} Eligible patients except those with brain metastases at baseline.

\textsuperscript{i} Intracranial ORR.

\textsuperscript{j} Patients with measureable brain metastases at baseline.

\textsuperscript{k} Intracranial ORR.

\textsuperscript{l} Pts = patients; ORR = objective response rate.

**Lorlatinib**

Lorlatinib was specifically designed to penetrate the blood brain–barrier\textsuperscript{38,39}, and in the ongoing phase I/II trial of lorlatinib in patients previously treated with at least 1 prior ALK TKI (n = 197, cohorts 2–5), 67% of patients (n = 132) had brain metastases at baseline, with an overall intracranial ORR of 53% (Table III)\textsuperscript{25}. Among the patients previously treated with crizotinib with or without chemotherapy (n = 37, cohorts 2–3A), the intracranial ORR was 68% (95% CI: 50% to 82%). Among those previously treated with a second-generation TKI plus chemotherapy (n = 12, cohort 3B), the intracranial ORR was 42% (95% CI: 15% to 72%), and in the patients previously treated with 2 or more ALK TKIs with or without chemotherapy (n = 83, cohorts 4 and 5), the intracranial ORR was 48% (95% CI: 37% to 59%).

The ongoing randomized open-label two-arm phase III crown study (NCT03052608 at http://ClinicalTrials.gov/) is comparing lorlatinib with crizotinib in the first-line treatment of patients with metastatic ALK-positive NSCLC. The primary objective is blinded IRC-assessed PFS; important blinded IRC-assessed secondary objectives include CNS.
ORR from the time of study initiation up to 33 months and intracranial time to progression. Baseline MRI screening and follow-up brain imaging every 8 weeks by either MRI or CT is required.

Improved CNS responses have been observed for all second- and next/third-generation ALK TKIs in patients progressing on crizotinib. Cross-trial comparisons and the direct comparison of crizotinib with alectinib in the aLEX trial suggest that crizotinib has the least CNS activity among all the ALK TKIs.

ALK TESTING

Detection of ALK rearrangements is necessary to select patients for optimal treatment of NSCLC with ALK inhibitors; testing should be performed in all patients eligible for targeted therapy at the time of diagnosis of advanced NSCLC when a component of adenocarcinoma is noted or suspected. Eligible pathologic diagnoses include adenocarcinoma, large-cell carcinoma, sarcomatoid carcinoma, adenosquamous carcinoma, and NSCLC not otherwise specified. Patients not eligible for ALK testing are those with “pure” squamous-cell, small-cell, and large-cell neuroendocrine carcinoma. ALK testing can be considered for atypical patients, such as a lifetime never-smoking individual with squamous-cell carcinoma. Testing has to be performed before systemic therapy is initiated. Tissue samples from the primary tumour or metastases are equally suitable for analysis. Biopsies, resection specimens, and cytology specimens with an available cellblock are all suitable for ALK testing using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH).

Initially, the standard method for detection of ALK gene rearrangements in the United States was FISH using the U.S. Food and Drug Administration–approved ALK Break Apart FISH Probe Kit (Abbott Molecular, Abbott Park, IL, U.S.A.). In Canada, FISH, IHC, and other assays are available for detecting ALK rearrangements. However, FISH is both expensive and labour-intensive, making it challenging to implement as the primary diagnostic test for the identification of ALK rearrangements in all molecular pathology laboratories nationwide. A network of pulmonary and molecular pathologists and cytogenticists working in academic centres across Canada conducted the Canadian ALK study to address the challenge of standardization and optimization of detection tests for ALK-positive NSCLC. Cases deemed weakly positive or equivocal for ALK by IHC were then tested by ALK FISH for confirmation. The results supported the use of appropriately validated IHC laboratory-developed IHC assays using the 5A4 ALK antibody clone to screen for ALK-positive NSCLC. A second Canadian Immunohistochemistry Quality Control study showed good results and high concordance for ALK IHC testing at 21 participating Canadian laboratories. Moreover, recent data from the aLEX trial indicate that, compared with ALK FISH, ALK IHC might identify more patients who benefit from ALK TKIs and that ALK IHC–positive patients might benefit even if ALK FISH results are negative.

In June 2017, the U.S. Food and Drug Administration approved the Ventana ALK (D5F3) CDx IHC Assay (Roche Diagnostics, Risch-Rotkreuz, Switzerland) for the qualitative detection of ALK protein in formalin-fixed paraffin-embedded NSCLC tissue stained with a Ventana BenchMark XT or BenchMark Ultra automated staining instrument. Currently, in Canada, positive ALK IHC is sufficient for obtaining access to ALK TKIs. Nevertheless, the use of ALK IHC alone requires high levels of reliability, and ongoing quality assurance and adoption should be linked to strict validation standards and ongoing quality assurance.

OPTIMAL SEQUENCING OF THERAPY

The optimal sequencing of ALK TKIs in patients with ALK-positive advanced NSCLC continues to evolve, with a suggested sequencing outlined in Figures 1 and 2 for treatment-naïve and crizotinib-refractory patients respectively.

Initial Therapy

In Canada, recommendations for new therapies must meet regulatory requirements and must, in phase III trials, demonstrate improved clinical outcomes compared with the current standard of care. Crizotinib was approved by Health Canada in April 2012 and has since been the standard of care for treatment-naïve patients with ALK-positive NSCLC. However, initial treatment is currently changing given that alectinib and ceritinib both have phase III data to support first-line use (Figure 1).

The aLEX trial is the only study to have compared a second-generation agent, alectinib, with the current first-line standard, crizotinib. The well-designed protocol—which showed an improvement by a factor of almost 2.5 in investigator-assessed median PFS (34.8 months vs. 10.9 months), a significantly reduced incidence of CNS
progression, and a favourable safety profile for alelectinib compared with crizotinib—provides compelling evidence for the use of alelectinib as first-line therapy.

Outcomes from the ascend-4 trial also show good support for the use of ceritinib in this setting, although no randomized comparison with crizotinib was performed. The trial demonstrated strong activity for ceritinib compared with platinum–pemetrexed chemotherapy, with a more-than-doubled median pfs (16.6 months vs. 8.1 months). Gastrointestinal-related aEs were considerably higher in the ceritinib 750 mg arm, although most were grade 1 or 2 and manageable; treatment discontinuation was required in only 3 patients (2%). Results from ascend-8 in previously treated patients also show that lower-dose ceritinib (450 mg) is equally effective, with an improved toxicity profile and cost–benefit ratio. Again, cross-trial comparisons should be interpreted with caution, although it is notable that in these relatively comparable populations, the median pfs for ceritinib in ascend-4 was higher by a factor of 1.5 than the median for high-dose crizotinib in the profile 1014 study.

Level 1 evidence supports the use of alelectinib as a new standard of care for treatment-naive patients with ALK-positive NSCLC, and indirect data support ceritinib as an active and cost-effective option (Figure 1). Because case reports suggest that sequential use of these agents in either order might also impart clinical benefit, both are reasonable choices for initial therapy.

Further Treatments
Recently, data from the ascend-5 and alur trials have respectively demonstrated activity for ceritinib and alelectinib in patients progressing on crizotinib-based therapy, establishing both as viable later-line treatment options (Figure 2). Although cross-trial comparisons should be interpreted with caution, and although those studies included slightly different patient populations (the alur trial was conducted strictly in third-line patients (100% having received both a platinum doublet and crizotinib), and ascend-5 included a mix of third-line (88% same population as alur) and fourth-line patients (12% having received 2 lines of chemotherapy and crizotinib)), the median pfs for alelectinib appears to be slightly higher than the median for ceritinib, and a network meta-analysis suggested less toxicity with alelectinib. It must be noted that alur was conducted in a slightly more favourable population, and outcomes from ascend-8 have shown that lower-dose ceritinib (450 mg) administered with food is as efficacious as the 750 mg dose used in the ascend-5 trial, with an improved safety profile. Ceritinib and alelectinib were both recently approved by the pan-Canadian Oncology Drug Review and are currently in price negotiations at the pan-Canadian Pharmaceutical Alliance. Both should be considered after progression on crizotinib.

Brigatinib has demonstrated activity in second-line or later disease after progression on crizotinib, and lorlatinib has shown benefit after multiple lines of prior ALK TKI therapy. Results from phase I/II studies suggest that either can be used in patients progressing on prior ALK inhibitors. Data for the use of brigatinib after progression on alelectinib are currently lacking, and therefore the optimal sequencing is currently unknown (Figures 1 and 2). Lorlatinib has demonstrated activity after multiple lines of ALK TKIs, which could potentially indicate a preference for the use of brigatinib. However, preclinical and clinical evidence shows activity for lorlatinib against G1202R, and preclinical data to date show activity for brigatinib against this most frequent and challenging ALK resistance mutation. Further treatments could therefore include single-agent brigatinib or lorlatinib, or both sequentially. Rebiopsy to identify resistance mutations to guide therapy is not currently recommended, although that practice might play a role in the future.

Given that patients with advanced NSCLC and an ALK rearrangement might have tumours that are quite sensitive to pemetrexed platinum-doublet chemotherapy, that approach should be considered as an option to be used sequentially after brigatinib and lorlatinib. Although the exact sequence of these regimens in a new era of first-line alelectinib or ceritinib has yet to be determined, the new options provide many treatment sequence alternatives. If single-agent pembrolizumab is being considered in patients with high PD-L1 expression, it should be noted that ALK-positive patients were excluded from the pembrolizumab trial, and other data suggest a low likelihood of response in such patients because their mutational burden is low. Although clinical trials are ongoing, findings to date underscore the importance of exhausting other systemic therapies before considering immunotherapy.
SUMMARY

Emerging data have expanded the role for ALK inhibition in patients with ALK-positive NSCLC, and Canadian recommendations have been updated accordingly:

- Patients with advanced nonsquamous NSCLC have to be tested for the presence of an ALK rearrangement.
- Treatment-naïve patients with ALK-positive disease should initially be offered single-agent alectinib or ceritinib, or both sequentially.
- Crizotinib-refractory patients should be treated with single-agent alectinib or ceritinib, or both sequentially.
- Further treatments could include single-agent brigatinib or lorlatinib, or both sequentially.
- Patients progressing on ALK TKIs should be considered for pemetrexed-based chemotherapy.
- Other systemic therapies should be exhausted before immunotherapy is considered.

ACKNOWLEDGMENTS

We thank Kaleidoscope Strategic, Inc., for their editorial and administrative assistance in the preparation of this article. Pfizer, Roche, Novartis, and Takeda are also thanked for the unrestricted educational grants that made this initiative possible.

CONFLICT OF INTEREST DISCLOSURES

BM serves on advisory boards for Novartis, Pfizer, and Roche; JA serves on advisory boards for Novartis, Pfizer, Takeda, and Roche, and has given talks for, or served on advisory boards for, AstraZeneca, Boehringer Ingelheim, Bristol–Meyers Squibb, Merck, Novartis, and Pfizer; RA serves on advisory boards for Novartis, Pfizer, and Roche; DGB serves on advisory boards for Novartis, Pfizer, and Roche; NB serves on advisory boards for Takeda, Novartis, Pfizer, and Roche; RB serves on advisory boards for Roche, Takeda, Merck, and AstraZeneca; CB serves on advisory boards for AstraZeneca, Boehringer Ingelheim, Bristol–Meyers Squibb, Eli Lilly, Merck, Novartis, Roche, and Pfizer; RJ serves on advisory boards for Novartis, Pfizer, and Roche; DNI has received honoraria from, or has been part of an advisory board for, AstraZeneca, Boehringer Ingelheim, Bristol–Meyers Squibb, Eli Lilly, Merck, Novartis, and Pfizer; WM serves on advisory boards for Novartis, Pfizer, and Roche; ZP has served on advisory boards for AstraZeneca, Merck, and Roche; RS serves on advisory boards for AstraZeneca, Boehringer Ingelheim, Bristol–Meyers Squibb, Merck, Novartis, AbbVie, Roche, and Takeda; MT has served on advisory boards for Takeda; MST has received research funding from Roche; MV serves on advisory boards for AstraZeneca, Boehringer Ingelheim, Celgene, Novartis, Eli Lilly, Takeda, Taiho, Hoffman–La Roche, Pfizer, and Merck, and is a member of the speaker’s bureau for AstraZeneca, Boehringer Ingelheim, AMgen, Merck and Eli Lilly; ZH serves on the advisory board for and has received grants from Pfizer; GL serves on advisory boards for and has received honoraria from AstraZeneca, Novartis, Pfizer, Roche, Merck, AbbVie, Bristol–Meyers Squibb, and Takeda, and has received grants from AstraZeneca and Roche; the remaining authors have no conflicts of interest to disclose.

AUTHOR AFFILIATIONS

*BC Cancer—Vancouver Centre, Vancouver, BC; †William Osler Health System, University of Toronto, Brampton, ON; ‡Sir Mortimer B. Davis Jewish General Hospital, McGill University, and §§Centre hospitalier de l’Université de Montréal, Montreal, QC,

REFERENCES

18. Mok TSK, Kim DW, Wu YL, et al. Overall survival (os) for first-line crizotinib versus chemotherapy in ALK+ lung cancer:


25. Shaw AT, Martini F, Besse B, et al. Efficacy of lorlatinib in patients (pts) with advanced ALK-positive non–small–cell lung cancer (NSCLC) and ALK kinase domain mutations [abstract CT044]. *Cancer Res* 2018;78(suppl): [Available online at: http://cancerres.aacrjournals.org/content/78/13_Supplement/CT044; cited 1 September 2018]


42. Camidge DR, Peters S, Mok T, et al. Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALK) vs. ceritinib (C2) in untreated advanced ALK+ NSCLC [abstract 9043]. *J Clin Oncol* 2018;36: [Available online at: https://meetinglibrary.asco.org/record/160811/abstract; cited 28 August 2018]


47. Gadgeel S, Peters S, Mok TS, et al. Alectinib versus crizotinib in treatment-naive ALK+ NSCLC: CNS efficacy results from the ALEX study [abstract 12980_PR]. *Ann Oncol* 2017;28(suppl 5):.


Steenrod A, Orme M, MacGilchrist K, et al. Alectinib in treatment-naive anaplastic lymphoma kinase–positive (ALK+) metastatic non–small-cell lung cancer (mNSCLC): systematic literature review (SLR) and network meta-analysis (NMA) [abstract 1642]. *Cancer Res* 2018;78(suppl). [Available online at: http://cancerres.aacrjournals.org/content/78/13_Supplement/1642; cited 4 September 2018]


