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PRACTICE GUIDELINE

Canadian consensus: inhibition of *ALK*-positive tumours in advanced non-small-cell lung cancer

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ABSTRACT

Anaplastic lymphoma kinase (ALK) is an oncogenic driver in non-small-cell lung cancer (NSCLC). Chromosomal rearrangements involving the *ALK* gene occur in up to 4% of nonsquamous NSCLC patients and lead to constitutive activation of the ALK signalling pathway. *ALK*-positive NSCLC is found in relatively young patients, with a median age of 50 years. Patients frequently have brain metastasis.

Targeted inhibition of the ALK pathway prolongs progression-free survival in patients with *ALK*-positive advanced NSCLC. The results of several recent clinical trials confirm the efficacy and safety benefit of crizotinib and ceritinib in this population.

Canadian oncologists support the following consensus statement: All patients with advanced nonsquamous NSCLC (excluding pure neuroendocrine carcinoma) should be tested for the presence of an *ALK* rearrangement. If an *ALK* rearrangement is present, treatment with a targeted ALK inhibitor in the first-line setting is recommended. As patients become resistant to first-generation ALK inhibitors, other treatments, including second-generation ALK inhibitors can be considered.

Key Words *ALK*, anaplastic lymphoma kinase, non-small-cell lung cancer, molecular testing, targeted inhibition

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INTRODUCTION

Standard first-line systemic treatment for advanced non-small-cell lung cancer (NSCLC) is chemotherapy with a 2-drug combination including a platinum compound and a non-platinum drug. Response rates range from 20% to 40%, and median time to progression is 4–5 months[1].

Decades of research have revealed a pivotal role for tyrosine kinases as key regulators of the signalling pathways that control cell growth and differentiation. Deregulation of tyrosine kinase–mediated signalling occurs frequently in cancer and is believed to drive disease initiation and progression.

Chromosomal rearrangements involving the tyrosine kinase anaplastic lymphoma kinase (*ALK*) gene in NSCLC were first described in 2007[2]. The most common is a rearrangement resulting in a small inversion within chromosome 2p, leading to the expression of a chimeric tyrosine kinase in which the N-terminal half of the echinoderm microtubule-associated protein-like 4 (*EML4*) is fused to the intracellular kinase domain of *ALK*. *EML4-ALK* has active oncogenic properties.

ALK is a hotspot for other translocation events, and many variations of the *ALK* rearrangements exist. *ALK* can also be altered through point mutations in the kinase domain and by overexpression of the full-length protein[3,4]. *ALK* rearrangements occur in up to 4% of NSCLC patients[4,5]. *ALK* rearrangements and point mutations are present in many other cancer types as well[3,4,6,7]. The physiologic role played by ALK has not yet been well defined.

Patients with NSCLC whose tumours harbour *ALK* rearrangements (*ALK*-positive) are typically younger than

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those without this rearrangement and tend to be light or never-smokers[4]. Central nervous system metastases are the most common site of progression in *ALK*-positive NSCLC patients; such metastases occur in approximately 50% of patients[8].

Several oral small-molecule tyrosine kinase inhibitors of ALK have been developed. Crizotinib is a first-generation inhibitor of surface membrane receptor tyrosine kinases including ALK, hepatocyte growth factor receptor, and ROS (encoded by the *ROS1* gene)[9]. *ALK*-positive patients eventually acquire resistance to crizotinib through a variety of molecular mechanisms, including secondary mutations in the *ALK* tyrosine kinase domain, *ALK* gene amplification, and activation of other signalling pathways[10,11]. Ceritinib is a second-generation ATP-competitive tyrosine kinase inhibitor of ALK[9].

ALK TESTING

Detection of tumours harbouring *ALK* rearrangements is necessary to select patients for treatment with ALK inhibitors. Testing for *ALK* gene rearrangements should be performed in all patients eligible for targeted therapy at time of diagnosis of advanced incurable nonsquamous NSCLC in which a component of adenocarcinoma is noted or suspected[12]. Eligible pathologic diagnoses include adenocarcinoma, large-cell carcinoma, sarcomatoid carcinoma, adenosquamous carcinoma, and NSCLC not otherwise specified. Not recommended for routine testing are "pure" squamous cell, small-cell, and other neuroendocrine carcinomas[b] (for example, large-cell neuroendocrine carcinoma). *ALK* testing can be considered for atypical cases such as non-smoking patients with squamous cell carcinoma. If possible, testing should be conducted before chemotherapy is initiated. Switching therapies can be considered if an *ALK* rearrangement is identified after chemotherapy is initiated. A tissue sample from the primary tumour or a metastasis is equally suitable for the analysis.

Until recently, the standard methodology for detection of *ALK* gene rearrangements in the United States was fluorescence *in situ* hybridization (FISH) using the U.S. Food and Drug Administration–approved Vysis *ALK* Break Apart FISH Probe Kit (Abbott Molecular, Abbott Park, IL, U.S.A.). That test is both costly and challenging to implement across molecular pathology laboratories. The Food and Drug Administration subsequently approved an *ALK* immunohistochemistry (IHC) assay [Ventana *ALK* (D5F3) CDx Assay: Ventana Medical Systems (Roche Group), Tucson, AZ, U.S.A.]. A network of pulmonary and molecular pathologists working in cancer centres across Canada addressed the challenge of standardization and optimization of detection tests for *ALK*-positive NSCLC and supports the use of an appropriately validated IHC assay to screen for *ALK*-positive NSCLC[17]. In many Canadian centres, *ALK*-positive and -equivocal cases by IHC are subsequently tested by *ALK* FISH. Positive *ALK* IHC is sufficient for obtaining access to ALK inhibitors in some Canadian provinces; however, confirmation of weak IHC staining by FISH should remain the standard practice. *ALK* IHC therefore requires high levels of reliability and ongoing external quality assurance; its implementation in pathology laboratories should follow strict validation standards.

[b] Several publications[13–16] have either recommended not testing neuroendocrine tumours or have indicated that ALK rearrangements are not present in these types of tumours.

EVIDENCE DEMONSTRATING THE BENEFITS OF TARGETED INHIBITION OF *ALK*-POSITIVE TUMOURS

PROFILE 1001

The phase I PROFILE 1001 trial evaluated single-agent crizotinib in the treatment of locally advanced or metastatic *ALK*-positive NSCLC[18], showing that crizotinib is well-tolerated, with rapid, durable responses in patients with *ALK*-positive NSCLC.

Of 143 *ALK*-positive patients, 87 experienced an objective response [60.8%; 95% confidence interval (CI): 52.3% to 68.9%]. Median time to objective response was 7.9 weeks (range: 2.1–39.6 weeks), and median duration of response was 49.1 weeks (95% CI: 39.3 to 75.4 weeks). Overall, median progression-free survival (PFS) was 9.7 months (95% CI: 7.7 to 12.8 months). It was 18.3 months (95% CI: 8.3 months to not reached) in the 24 patients receiving first-line crizotinib, and 9.2 months (95% CI: 7.3 to 12.7 months) in the 125 patients receiving crizotinib as second-line or later treatment[18].

Treatment-related adverse events, mostly grade 1 or 2, occurred in 97% of patients overall. The most common treatment-related grades 1 and 2 adverse events were visual effects, nausea, diarrhea, constipation, vomiting, and peripheral edema. The most common treatment-related grades 3 and 4 adverse events were neutropenia (n = 9, 6%), elevated alanine aminotransferase (n = 6, 4%), hypophosphatemia (n = 6, 4%), and lymphopenia (n = 6, 4%)[18].

PROFILE 1007

The multicentre, randomized phase III efficacy and safety study PROFILE 1007 compared crizotinib with standard-of-care chemotherapy in patients with platinum pre-treated *ALK*-positive advanced NSCLC[19]. This second-line trial confirmed the efficacy and safety benefits of crizotinib for the treatment of patients with *ALK*-positive disease in that setting.

The 347 participating patients were randomized 1:1 to crizotinib (n = 173) or to pemetrexed or docetaxel (n = 174). Patients continued on treatment until progressive disease (independent radiology review), unacceptable toxicity, or withdrawal of consent. The primary endpoint was PFS. The independent radiology review used the Response Evaluation Criteria in Solid Tumors to determine PFS. At the discretion of the investigator, patients could continue treatment beyond progression if they were experiencing clinical benefit.

Median PFS was 7.7 months for patients randomized to crizotinib and 3.0 months for patients randomized to chemotherapy [hazard ratio (HR): 0.49; $p < 0.0001$]. The overall response rate for patients on crizotinib was 65% (95% CI: 58% to 72%) compared with 20% (95% CI: 14% to 26%) for

chemotherapy (odds ratio: 3.39; $p < 0.0001$). The median overall survival (OS) was 20.3 months for crizotinib and 22.8 months for chemotherapy (HR: 1.02; $p = 0.5394$), but was confounded by crossover, because 108 patients on the chemotherapy arm (62%) crossed over to receive crizotinib in a separate trial (A8081005)[19].

No new or unexpected adverse events were recorded. Patient-reported outcomes and quality of life favoured crizotinib[19].

PROFILE 1014

The phase III PROFILE 1014 trial compared first-line crizotinib with chemotherapy in 343 patients with advanced *ALK*-positive nonsquamous NSCLC who had received no prior systemic treatment for advanced disease[20], confirming that crizotinib is superior to chemotherapy in patients with previously untreated *ALK*-positive advanced NSCLC.

Patients were randomly assigned to receive crizotinib or intravenous chemotherapy with cisplatin or carboplatin and pemetrexed. The primary endpoint was PFS as assessed by independent radiologic review. Median PFS with crizotinib, at 10.9 months, was significantly longer than it was with chemotherapy (7.0 months; HR: 0.45; 95% CI: 0.35 to 0.60; $p < 0.001$). Objective response rates were 74% for crizotinib and 45% for chemotherapy ($p < 0.001$). Median OS was not reached in either group because of crossover (HR: 0.82; 95% CI: 0.54 to 1.26; $p = 0.36$)[20].

No new or unexpected adverse events were recorded. Crizotinib was associated with a greater reduction in lung cancer symptoms and a greater improvement in quality of life.

TREATMENT BEYOND PROGRESSION

When patients develop progressive disease on crizotinib, either systematically or to brain, consideration should be given to treating oligometastases with local surgery or radiation, and continuing patients on an ALK inhibitor if they are experiencing continued clinical benefit—particularly if most of the disease remains under good control.

A retrospective analysis of the effect of continued ALK inhibition with crizotinib beyond progression in patients with advanced *ALK*-positive NSCLC observed a survival benefit[21]. Of the 194 crizotinib-treated patients, 120 continued crizotinib beyond progression. Those patients experienced a significantly longer median OS (29.6 months from starting crizotinib) than the 10.8 months experienced by those who did not continue treatment after progression (HR: 0.30; 95% CI: 0.19 to 0.46; $p < 0.0001$). Patients who were treated beyond progression had a significantly longer median OS from the time of disease progression: 16.4 months versus 3.9 months for those who stopped crizotinib at progression (HR: 0.27; 95% CI: 0.17 to 0.42; $p < 0.0001$)[21]. This finding might reflect disease biology, but is still an important concept applicable in this patient setting.

ASCEND-1, -2, AND -3

The pivotal phase I ASCEND-1 trial, evaluating the efficacy and safety of ceritinib, was conducted in 20 centres in 11 countries[22]. Of the 246 participating patients with advanced *ALK*-positive NSCLC, 163 had already received an ALK inhibitor, and 83 were ALK-inhibitor naïve. The response rate for all patients was 61.8%; it was 56.4% for pre-treated patients, and 72.3% for inhibitor-naïve patients. The median PFS for all patients in the trial was 6.9 months; for the ALK-inhibitor-naïve patients, median PFS was not reached at 18 months[23].

Ceritinib also demonstrated central nervous system activity. Of the 28 ASCEND-1 patients with measurable brain metastases at baseline, 10 (36%) experienced a partial response[24]. As a result of the trial, the Food and Drug Administration approved ceritinib in April 2014 for patients with advanced *ALK*-positive NSCLC after treatment with crizotinib.

The single-arm phase II ASCEND-2 trial evaluated the efficacy of ceritinib in patients with advanced *ALK*-positive NSCLC who had progressed on both standard chemotherapy and crizotinib. It confirmed the efficacy of ceritinib, showing an overall response rate of 38.6% and a PFS of 5.7 months[25]. The intracranial response rate was 35%, similar to that in ASCEND-1.

The single-arm phase II ASCEND-3 trial evaluated the efficacy of ceritinib in treatment-naïve patients with advanced *ALK*-positive NSCLC[26]. The published PFS was an impressive 11.1 months, and the response rate was 36.3%. Of the 124 patients participating in ASCEND-3, 50 (40.3%) had brain metastases, and of those 50, 27 (54%) had received radiation[26]. The intracranial response was 58.8% as determined by blinded independent central review.

The ASCEND-1, -2, and -3 trials confirmed that ceritinib is an effective ALK inhibitor and has activity against brain metastases. Ceritinib was approved by Health Canada as a second-line option for patients who have progressed after crizotinib.

OPTIMAL SEQUENCING OF THERAPY

A retrospective study evaluated a cohort of patients with advanced *ALK*-positive NSCLC treated sequentially with both crizotinib and ceritinib. Ceritinib was associated with significant antitumour activity in a crizotinib-resistant population[27]. For the 73 *ALK*-positive patients, median PFS on crizotinib was 8.2 months (95% CI: 7.4 to 10.6 months), and median combined PFS for sequential treatment was 17.4 months (95% CI: 15.5 to 19.4 months). Although the study was retrospective and did not include a comparator arm, it sets a benchmark for future clinical trials of sequenced tyrosine kinase inhibitors.

A PROMISING FUTURE WITH AN EVOLVING TREATMENT PARADIGM

New second- and third-generation ALK inhibitors will be entering the *ALK*-positive advanced nonsquamous NSCLC treatment paradigm. As a result, patients who become resistant to first-generation ALK inhibitors will have other treatment options available.

Alectinib, a second-generation ALK inhibitor, has significant efficacy for treating brain metastasis. A small study demonstrated the efficacy of alectinib in 4 patients with *ALK*-positive NSCLC and leptomeningeal metastases

who had already received both crizotinib and ceritinib; median PFS was not reached at 18 months[28].

Sequential treatment with multiple ALK inhibitors is a possibility. We look forward to the results of randomized controlled trials that will evaluate and compare the various ALK inhibitors with each other and with chemotherapy agents to help determine the most effective treatment sequences for *ALK*-positive patients.

RECOMMENDATION

As Canadian physicians involved in the treatment of patients with lung cancer in Canada, we recommend that all patients with advanced NSCLC having the appropriate non-squamous histologic features who are eligible for targeted therapy be tested for the presence of an *ALK* rearrangement. Positive ALK IHC is sufficient for obtaining access to ALK inhibitors in some Canadian provinces. Confirmation by FISH of weak or equivocal IHC staining remains the standard practice. Treatment with crizotinib, a targeted ALK inhibitor, in the first-line setting is recommended for *ALK*-positive NSCLC. Data support the use of ceritinib for second-line treatment after progression on crizotinib.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: BM, RA, SB, NB, DNI, RJ, and WM serve on advisory boards for Novartis, Pfizer, and Roche; JA has given talks for, or served on advisory boards for, AstraZeneca, Boehringer Ingelheim, Bristol–Meyers Squibb, Merck, Novartis, and Pfizer; DB serves on an advisory board for Pfizer; CB serves on advisory boards for AstraZeneca, Boehringer Ingelheim, Bristol–Meyers Squibb, Merck, and Pfizer; JD has served or serves on advisory boards for AstraZeneca, Merck, Pfizer, and Roche; SAL has received honoraria from both Novartis and Pfizer; GL serves on the advisory boards of AstraZeneca, Novartis, Pfizer, Roche, and Takeda; MST received honoraria and research grants from Pfizer Canada; VH serves on advisory boards for Amgen, AstraZeneca, Boehringer Ingelheim, Bristol–Meyers Squibb, Eli Lilly, Merck, Novartis, Roche, and Pfizer. DGB, PCheema, PCheung, VC, and SKR declare that they have no conflicts of interest.

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