Crizotinib inhibition of ROS1-positive tumours in advanced non-small-cell lung cancer: a Canadian perspective

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ABSTRACT

The ROS1 kinase is an oncogenic driver in non-small-cell lung cancer (NSCLC). Fusion events involving the ROS1 gene are found in 1%–2% of NSCLC patients and lead to deregulation of a tyrosine kinase–mediated multi-use intracellular signalling pathway, which then promotes the growth, proliferation, and progression of tumour cells. ROS1 fusion is a distinct molecular subtype of NSCLC, found independently of other recognized driver mutations, and it is predominantly identified in younger patients (<50 years of age), women, never-smokers, and patients with adenocarcinoma histology.

Targeted inhibition of the aberrant ROS1 kinase with crizotinib is associated with increased progression-free survival (PFS) and improved quality-of-life measures. As the sole approved treatment for ROS1-rearranged NSCLC, crizotinib has been demonstrated, through a variety of clinical trials and retrospective analyses, to be a safe, effective, well-tolerated, and appropriate treatment for patients having the ROS1 rearrangement.

Canadian physicians endorse current guidelines which recommend that all patients with nonsquamous advanced NSCLC, regardless of clinical characteristics, be tested for ROS1 rearrangement. Future integration of multigene testing panels into the standard of care could allow for efficient and cost-effective comprehensive testing of all patients with advanced NSCLC. If a ROS1 rearrangement is found, treatment with crizotinib, preferably in the first-line setting, constitutes the standard of care, with other treatment options being investigated, as appropriate, should resistance to crizotinib develop.

Key Words  ROS1; oncogenic drivers; non-small-cell lung cancer, advanced; NSCLC, advanced; targeted therapy; crizotinib; molecular testing; NSCLC, nonsquamous

INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the most common malignant tumour and a leading cause of death worldwide1, with an estimated 1.6 million new global diagnoses annually2. Most patients are diagnosed with advanced-stage disease, which is characterized by a poor survival rate3. Until recently, NSCLC was approached therapeutically as a single-entity disease. The standard first-line treatment for advanced (unresectable or metastatic) NSCLC that had the most efficacy was platinum-based doublet chemotherapy, which resulted in median survival durations of 10–12 months4–6. Subsequent recognition of the genetic diversity and heterogeneity of NSCLC changed the focus to identifying new molecular subsets of NSCLC, with emphasis placed on identifying driver oncogenes and novel biomarkers7,8. Identification of those driver mutations and the capability to analyze the molecular profiles of NSCLC tumours dramatically altered the treatment...
paradigm by identifying actionable target mutations, because a potentially targetable genetic driver alteration is present in nearly half of all cases of metastatic adenocarcinoma. Those targeted treatments have proved to be more effective than standard doublet chemotherapy (either platinum- or non-platinum-based) in increasing PFS, and the resultant increases in quality of life (QoL) and survival have led to the adoption of screening for predictive biomarkers as a standard of care. To date, the most prevalent targetable mutations identified in NSCLC predominantly involve the deregulation of tyrosine kinase receptor–mediated signalling (as seen in EGFR and ALK mutations), which drives both the initiation and progression of cancer cells.

The ROS1 oncogene, which is mutated in a variety of solid tumours and which also results in the deregulation of a tyrosine kinase–mediated signalling pathway, was identified specifically in NSCLC in 2007. Interchromosomal—and occasionally intrachromosomal—rearrangements of ROS1 result in gene fusions involving the 3′ region of ROS1, including the kinase domain, and several different 5′ fusion partners, of which 26 have been identified to date. All ROS1 fusions show conservation of the ROS1 kinase domain and lead to tyrosine kinase activation, a multi-use intracellular pathway involved in the upregulation of SHP-1 and SHP-2 and resultant activation of the PI3K/AKT/MTOR, JAK/STAT, and MAPK/ERK pathways, which act in concert to promote cell survival and proliferation.

ROS1 fusions exist as a distinct molecular subtype of NSCLC and rarely overlap with other oncogenic drivers such as EGFR, KRAS, HER2, RET, MET, and ALK. Specifically, ROS1 and ALK are mutually exclusive, with no evidence of co-expression, but are phylogenetically related, sharing 70% homology and 77% similar amino acid identity within ATP binding sites. ROS1- and ALK-positive patients also share many clinicopathologic features: female sex, younger age at diagnosis (<50 years), propensity toward Asian ethnicity, never-smoking history, adenocarcinoma histology, and advanced nonresectable (compared with advanced resectable) disease at diagnosis are frequent characteristics of patients positive for either ALK or ROS1. Unique to patients with ROS1 rearrangement is the observation that ROSI expression is higher in recurrent tumours than the primary tumour (28% vs. 19%) and that patients who are ROSI-positive, compared with those who are ALK-positive, have lower rates of extrathoracic metastases, including lower rates of brain metastases at initial metastatic diagnosis, and a cumulative lower incidence of brain metastases.

After the discovery of the ROSI fusion gene as an oncogenic driver in NSCLC, and in light of the close homology between the ALK and ROSI tyrosine kinase domains, the utility of crizotinib as a ROSI inhibitor was explored. Oral crizotinib, an ATP-competitive small-molecule tyrosine kinase inhibitor, was developed as a c-MET inhibitor; it was later found to have activity against ALK-rearranged tumours when a phase I single-arm analysis of crizotinib (PROFILE 1001) yielded a response rate of 60% and PFS of 9.7 months.

Based on those results and preliminary data from a single-arm phase I study (PROFILE 1005), accelerated regulatory approval for the use of crizotinib in ALK-positive locally advanced or metastatic NSCLC, was awarded by the U.S. Food and Drug Administration and Health Canada in 2011 and 2012 respectively,6,8,14,22,23. Subsequently, both in vivo and in vitro, crizotinib was found to be a highly robust inhibitor of the ROSI fusion protein, showing up to 5 times greater potency in the suppression of ROSI activity and downstream signalling—and resultant superior inhibition of ROSI-driven tumour growth—than what had been observed in ALK-rearranged tumours. Subsequent clinical trials of crizotinib in ROSI-rearranged NSCLC yielded response rates of 70%–80%, and approval for crizotinib in the management of ROSI-positive locally advanced or metastatic NSCLC was granted in 2016 by the U.S. Food and Drug Administration and in 2017 by Health Canada for use in the first- and subsequent-line settings. To date, crizotinib remains the only approved targeted agent for ROSI-rearranged advanced NSCLC, and ROSI-rearranged NSCLC is now the 3rd genetically distinct population of NSCLC that can be managed through approved, effective targeted therapy.

**ROS1 TESTING**

**Testing Method**

Reliable and efficient detection of tumours harbouring ROSI fusions is required to identify patients whose treatment protocols should include ROSI inhibition. Currently, no companion diagnostic that reliably selects patients with ROSI alterations has been approved.

At present, ROSI fusion in tumour cells can be detected using a variety of techniques: fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), reverse transcriptase polymerase chain reaction (RT-PCR), and next-generation sequencing of RNA and DNA. ROSI break-apart FISH is currently considered the “gold standard” and is used globally for many ROSI–crizotinib studies because of its low tissue requirement and high sensitivity and specificity. However, FISH has some limitations: it is labour-intensive and more costly than IHC, and interpretation of the results requires expertise because false-negative results can occur when the ROSI fusion partner gene is located within several megabases of the ROSI gene on chromosome 6. Next-generation sequencing and RT-PCR both show utility. The former allows for multiplex testing, has the potential to identify the ROSI fusion partner, and can detect novel fusions, but has a higher tissue requirement, is relatively more expensive than IHC or FISH, and yields more information than is often clinically relevant. The latter is limited given the requirement for multiple primer sets and an incapacity to identify novel or rare ROSI fusions. In comparison, IHC is widely used in routine pathology practice, is less expensive and usually automated, and generally shows good sensitivity (compared with FISH results) for ROSI screening when IHC uses the commercially available D4D6 antibody clone 25. However, IHC positive staining has greater discordance with FISH, because some tumours can yield samples that are IHC-positive, but that test negative for rearrangement by FISH. The Canadian ROS Initiative, which involves 14 pathology laboratories in Canada and 1 in Japan, is working to validate IHC and FISH testing for ROSI translocations in...
NSCLC tumour samples\textsuperscript{35} and is using a strategy of \textsc{fISH} as a screening test, followed by confirmation of \textsc{hC} cases by \textsc{fish}\textsuperscript{26,34}. The high level of optimization and validation for a specific purpose, as it applies to all predictive assays, also applies to \textsc{rosi} \textsc{hC} testing\textsuperscript{28}–\textsuperscript{30}. Looking to the future, effective screening methods for \textsc{rosi} rearrangements that hinge on inexpensive, rapid, sensitive, reliable methods and development of a minimally invasive method that can also identify the fusion partner, secondary mutations, or tumour heterogeneity would be of considerable clinical utility\textsuperscript{40,41}.

\textbf{Testing Recommendations}

Screening for actionable mutations in \textsc{nsclc} are recommended by the U.S. National Comprehensive Cancer Network's clinical practice guidelines in oncology, the European Society for Medical Oncology's guidelines, the American College of American Pathologists, the International Association for the Study of Lung Cancer, the Association for Molecular Pathology, the Expert Committee of Lung Cancer Canada, and the American Society of Clinical Oncology. Unanimously, those groups recommend that \textsc{rosi} testing be performed for all patients with advanced lung adenocarcinoma\textsuperscript{3,26,35,42,43}. The 2018 updated joint guideline from the American College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology\textsuperscript{26} (endorsed by the American Society of Clinical Oncology\textsuperscript{43}) now advises that all patients with advanced-stage adenocarcinoma, regardless of other clinical characteristics, be offered either a comprehensive lung panel [\textsc{egfr}, \textsc{alk}, \textsc{rosi}, \textsc{braf}, \textsc{met}, \textsc{erb2} (\textsc{her2}), \textsc{kras}, and \textsc{met}] or target testing for genes in the "must test" category (\textsc{egfr}, \textsc{alk}, \textsc{rosi}), with the option of offering expanded panels that include additional genes [\textsc{braf}, \textsc{met}, \textsc{erb2} (\textsc{her2}), and \textsc{ret}] to patients who are clinical trial candidates, the latter possibly after testing negative in single-panel \textsc{kras} testing\textsuperscript{46}.

Because targeted massively parallel or \textsc{dna}- or \textsc{rna}-based next-generation sequencing panels that enable the simultaneous analysis of a large number of genes and of multiple actionable fusion transscripts, including \textsc{rosi}, are integrated into the health care setting, comprehensive testing of patients presenting with advanced lung adenocarcinoma might prove to be efficient and cost-effective. It would allow for extensive molecular characterization of limited amounts of tumour tissue and achieve the mandate for \textsc{rosi} testing to be integrated for all patients with advanced lung adenocarcinoma as the standard of care\textsuperscript{44,45}.

\textbf{EVIDENCE OF BENEFIT WITH CRIZOTINIB FOR TARGETED INHIBITION OF ROSI-REARRANGED TUMOURS}

\textbf{Clinical Trials}

\textsc{Profile 1001: ROSI-Positive Expansion Cohort}

Originally designed as a single-arm, multi-cohort, multi-centre phase i study to determine the efficacy and safety of crizotinib to treat \textsc{alk}-rearranged locally advanced or metastatic \textsc{nsclc}\textsuperscript{2}, the \textsc{profile} 1001 trial was amended to add an expansion cohort of \textsc{rosi}-positive \textsc{nsclc} patients after \textit{in vitro} evidence showed that crizotinib was an effective suppressor of rosi activity, leading to decreased downstream signalling and inhibition of tumour growth\textsuperscript{6,7}. The expansion cohort contained 53 \textsc{rosi}-positive patients, determined by \textsc{fish}, with no previous use of \textsc{alk} or \textsc{c-met} inhibitors. The objective response rate by independent radiology review was 70% [95% confidence interval (ci): 56% to 82%], with a median duration of response of 17.6 months\textsuperscript{17}, median \textsc{pfs} of 19.3 months (95% ci: 14.8 months to not reached), and a demonstrated 91% (95% ci: 79% to 96%) survival probability at 6 months\textsuperscript{46}. The safety profile of crizotinib in patients with \textsc{rosi}-positive disease was similar to that seen in the \textsc{alk}-positive treatment environment: grades 1 and 2 adverse events including nausea, vomiting, edema, diarrhea, and vision disturbances were experienced by 38%–85% of patients. Grade 3 adverse events such as hypophosphatemia (13%), neutropenia (9%), and elevated transaminases (4%) were present, but no grade 4 adverse events or deaths attributable to treatment were reported\textsuperscript{46}. Additionally, response to crizotinib in \textsc{rosi}-positive disease was achieved regardless of previous lines of therapy\textsuperscript{6} and independent of the percentage of \textsc{rosi}-rearranged cells detected\textsuperscript{46}.

In parallel to the results from the crizotinib-treated \textsc{alk}-positive disease in the same trial, crizotinib treatment in \textsc{rosi}-positive disease similarly demonstrated that crizotinib is associated with a well-tolerated, rapid, and durable response\textsuperscript{46}. The outcome measures from the study were the first to confirm the clinically meaningful benefit and safety of crizotinib in patients with \textsc{rosi}-altered advanced \textsc{nsclc}\textsuperscript{46} and led to the approval of crizotinib use in that population\textsuperscript{47}.

\textsc{eucross}

A collaboration between the Lung Cancer Group in Cologne and the Spanish Lung Cancer Group resulted in the development of a prospective phase ii trial to evaluate the use of crizotinib in \textsc{rosi}-positive lung adenocarcinoma, regardless of previous lines of treatment. The study enrolled 34 patients identified as \textsc{rosi}-positive by \textsc{fish}, who were treated with crizotinib. Of the 34 patients, 20 had sufficient tumour tissue to perform \textsc{cage} (cap analysis of gene expression) to verify \textsc{rosi} status, identifying the exact break-apart point and fusion genes\textsuperscript{46}. \textsc{rosi} fusion was confirmed in 18 patients; the 2 remaining patients were ultimately determined to be negative for \textsc{rosi} rearrangement and quickly experienced primary progression. Analysis of the 18 patients with dually confirmed \textsc{rosi} rearrangement showed an objective response rate of 83% (95% ci: 67.7% to 94.2%). The assessment of safety considered all 34 patients, and adverse events (any grade) were reported in just under 50% of the group\textsuperscript{48}.

The study confirmed that crizotinib is a safe treatment and, in the subset of validated \textsc{rosi}-positive patients, highly effective. The lack of concordance observed between \textsc{fish} and \textsc{cage} sequencing of \textsc{rosi} in 2 of 20 patients who underwent validation of their \textsc{rosi} status, and the failure of crizotinib to show clinical benefit in those deemed \textsc{rosi} wild-type through \textsc{cage} sequencing, highlights the efficacy of \textsc{cage} sequencing in the identification of clinically sensitive \textsc{rosi} gene rearrangements, and the need for orthogonal validation of \textsc{rosi} status\textsuperscript{48}. 

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ACSe Study
A multicentric trans-tumour study, the phase II ACSe trial (NCT01639580 at http://ClinicalTrials.gov/), designed by the French National Cancer Institute, is considering the efficacy and safety of crizotinib as monotherapy in patients with ALK-, ROS1- (by FISH), or MET-positive tumours experiencing progression after at least 1 standard treatment (unless performance status has precluded first-line chemotherapy). The trial was designed to include 23 unique "cohorts," including a ROS1-rearranged NSCLC cohort, with the goal of avoiding uncontrolled off-label use and allowing for nationwide safe access to crizotinib for patient populations demonstrating clinical benefit from this agent.

Preliminary results from the 29 patients in the ROSI-rearranged NSCLC cohort (secondarily confirmed by IHC) demonstrated an objective response rate of 63% (95% CI: 41% to 81%) and a 53% disease control rate at 6 months. Grade 1 adverse events were recorded in approximately 50% of patients, and grade 3 or greater adverse events were recorded in 31% of patients. Study completion and updated trial results were anticipated in spring 2019.

The preliminary results of ACSe reinforce the importance of integrating ROS1 biomarker screening as part of routine care, because crizotinib has been demonstrated to be a safe, effective treatment with clinical benefit for patients harbouring ROS1 rearrangements.

OxOnc Development Study
OxOnc (NCT01945021 at http://ClinicalTrials.gov/) was a phase II trial conducted as an open-label, multinational, and multicentre single-arm study of crizotinib in East Asian patients with advanced (locally advanced or metastatic) ROS1-positive NSCLC, not previously receiving targeted therapy for ALK or ROSI.

Of 127 patients with ROSI-positive disease (detected by RT-PCR) enrolled, 72% (95% CI: 63% to 79%) achieved an objective response. Median time to objective response was 1.9 months (range: 1.5–15.8 months), and the median duration of response was 19.7 months (95% CI: 14.1 months to not reached). Median PFS was 15.9 months (95% CI: 12.9 months to 24 months), with a disease control rate of 80% (95% CI: 72% to 87%) after 16 weeks on treatment, and a survival probability of 83% (95% CI: 75% to 89%) after 12 months of treatment. Treatment-related adverse events were noted in 96.1% of patients, mostly grade 1 or 2 in severity, and included elevated transaminases, vision disorders, nausea, diarrhea, and vomiting. Grades 3 and 4 events were reported in 25.2% of patients and included neutropenia and elevated transaminases. Dose reductions or interruptions attributable to grade 1 or 2 and grade 3 or 4 adverse events occurred in 15.7% and 22.8% of patients respectively, with 1 patient discontinuing crizotinib because of a grade 1 adverse event (diarrhea). Assessments of QoL using the European Organisation for Research and Treatment of Cancer 30-question core Quality of Life Questionnaire and the 13-question lung cancer module revealed either stable (37%) or improved (46.8%) global QoL scores, compared with baseline scores, after 20 cycles of treatment, with statistically significant and clinically meaningful improvements in many lung cancer-related symptoms reported during those first 20 cycles, although significant deterioration from baseline was observed for gastrointestinal symptoms.

This study provided clinical confirmation of the benefit of crizotinib through a high overall response rate, a rapid and durable response, and overall QoL improvement, confirming the known safety profile of crizotinib. On the basis of the study results, crizotinib was approved for the treatment of ROSI-positive NSCLC in Japan, Taiwan, Korea, and China in 2017.

Retrospective Reviews
EUROS1
The EUROS1 European retrospective review (France, Switzerland, Italy, Germany, Poland, Netherlands) was designed to characterize the outcomes of patients with ROSI-positive (identified by FISH) stage IV NSCLC with an adenocarcinoma histology, who had undergone documented (off-label) crizotinib therapy and 0 to 3 or more prior lines of therapy. In the 32 patients identified as meeting the study criteria, median PFS was 9.1 months, with an objective response rate of 80%, a disease control rate of 86.6%, and no reports of unexpected or serious adverse events.

The review confirmed that ROSI-rearranged NSCLC is very sensitive to crizotinib. In the retrospective EUROS1 trial, unlike the prospective clinical trials, comorbidities or health status did not unselect patients for inclusion, and yet the response rate was similar to that in the PROFILE 1001 ROSI-positive expansion cohort. Results from EUROS1 demonstrated that the findings from the highly selected patient populations in the phase I clinical trials of crizotinib could be replicated in the real-world general population of patients with ROSI-rearranged NSCLC.

China: Efficacy of Crizotinib and Pemetrexed-Based Therapy in Chinese Patients with ROSI-Rearranged NSCLC
This retrospective review of 51 Chinese patients with ROSI-rearranged disease (determined by RT-PCR) who received either crizotinib, pemetrexed, or non-pemetrexed therapy demonstrated statistically significant differences in PFS, with crizotinib demonstrating the highest PFS (294 days), followed by pemetrexed-based chemotherapy (179 days) and non-pemetrexed chemotherapy (110 days).

Those findings corroborate previous results showing that, compared with patients having other identified driver mutations and receiving pemetrexed, patients with ROSI rearrangement experience increased clinical benefit from pemetrexed chemotherapy, suggesting that ROSI rearrangement might be a marker of increased pemetrexed sensitivity. Further, despite the efficacy of pemetrexed in this population of patients with ROSI rearrangement, those results reinforce the superior efficacy of crizotinib in the treatment of Chinese patients with ROSI-rearranged NSCLC.

MEETING THE CHALLENGE OF PROGRESSIVE DISEASE
Acquired Resistance
Development of acquired resistance to crizotinib in ROSI-rearranged tumours poses a serious clinical challenge,
given that most patients treated using this agent will acquire resistance\textsuperscript{19} and that the duration of response to crizotinib cannot yet be predetermined and seems to have no relation to the ROS1 fusion partner\textsuperscript{22}. Resistance to crizotinib, and resulting disease progression, comes about by a variety of mechanisms: development of secondary mutations within the kinase domain, which impedes drug binding\textsuperscript{14}, epithelial-to-mesenchymal transition\textsuperscript{47,53}, or upregulation and activation of compensatory pathways\textsuperscript{54} such as EGFR, RAS, and KIT\textsuperscript{19}.

Development of secondary crizotinib-resistant mutations appears to account for most acquired resistance, and the molecular changes involved in crizotinib resistance show a high level of heterogeneity\textsuperscript{53}. The most common secondary mutation, G2032R [c.6094G>A (p.Gly2032Arg)], accounts for 41\% of identified secondary mutations\textsuperscript{19}, and it is unclear whether crizotinib use selects for pre-existing resistant clones or whether the evolution of crizotinib-resistant cells occurs during a period of exposure\textsuperscript{19}. Given the diverse mechanisms that lead to crizotinib resistance, sequential treatment targeting crizotinib-resistant cells, or dual inhibition of ROS1 and potentially upregulated pathways, might show efficacy in minimizing and managing resistance to crizotinib\textsuperscript{14}.

Although secondary mutations in ROS1 and ALK show overlapping sensitivity profiles\textsuperscript{49}, sequential therapy using second-generation ALK inhibitors to combat crizotinib resistance in ROSI-rearranged tumours seems limited in ROSI-positive nsclc. Secondary mutations in ROS1 tend to harbour off-target mechanisms of resistance, such as bypass tracks\textsuperscript{50}, and most show decreased sensitivity to second-generation ALK inhibitors\textsuperscript{19}. Indeed, the second-generation ALK inhibitors—ceritinib, brigatinib, and entrectinib (startrk-1, startrk-2, and ALKA-372-001 trials\textsuperscript{54})—have been associated with clinically meaningful responses in crizotinib-treated patients with ROSI-rearranged tumours and with increased disease control rates for intracranial disease\textsuperscript{20}; however, none has shown effective inhibition against ROSI-rearranged tumours harbouring the common secondary G2032R mutation\textsuperscript{19}, limiting use of those agents as second-line therapy\textsuperscript{39}.

**Therapeutic Options Beyond Progression**

Targeted agents such as DS-605-1, repotrectinib [TPX-005 (see NCT03093116 at http://ClinicalTrials.gov/)], lorlatinib (NCT01970865), cabozantinib, and foretinib have demonstrated anti-ROSI activity in the second-line setting, including activity against G2032R, with all but the latter two agents demonstrating good tolerability, with safety and efficacy data that are being confirmed in ongoing clinical trials\textsuperscript{19,47,55,56}. Cabozantinib has been shown to be effective, but to be associated with higher toxicity, and it is therefore limited as a therapeutic agent for some patients\textsuperscript{3,14,16,47}. Foretinib has been withdrawn from the market (NCT02034097).

With a current paucity of suitable second-line treatments for use in crizotinib-resistant ROSI-rearranged tumours, two methods of management have shown promise as second-line treatments. The conventional cytotoxic chemotherapy agent pemetrexed has been associated with an objective response rate of 40\%–58\% and a PFS of 6.8–7.5 months in various lines of treatment and is therefore a viable treatment option for patients with ROSI-rearranged crizotinib-resistant disease\textsuperscript{1,25}. Alternatively, crizotinib resistance resulting from crizotinib-mediated upregulation of bypass signalling pathways (EGFR, RAS, and KIT)\textsuperscript{19} could be managed through targeted agents designed to modulate those upregulated systems, such as afatinib or PF29984 (EGFR)\textsuperscript{53} and ponatinib (KIT)\textsuperscript{14}.

As the options for treatment beyond crizotinib are explored, it remains true that desirable treatments post-crizotinib have to be highly potent agents with central nervous system penetrability and activity against ROS1 G2032R\textsuperscript{20}. Appropriate treatments and management strategies for patients with ROSI-rearranged disease could then rely on a personalized approach in which repeat molecular characterization, both temporally and spatially, which captures the heterogeneity of ROSI-rearranged tumours and tailors therapies appropriately, should be engaged\textsuperscript{14}.

**RECOMMENDATIONS**

As Canadian physicians involved in the management of patients with advanced lung cancer, we recommend molecular testing (inclusive of IHC), comprising detection of ROSI rearrangements, directly or indirectly by detecting ROSI chimeric mRNA or fusion protein expression in tumours, because such testing is critical to the appropriate and timely therapeutic management of nsclc. The testing should be offered as part of the standard of care to patients presenting with advanced disease, regardless of clinical characteristics\textsuperscript{35}. Given that ROSI-rearranged nsclc represents a molecularly distinct subset of nsclc, the ideal standard of care for these patients is targeted therapy with a rosi-inhibiting agent.

Crizotinib has demonstrated clinical benefit and a favourable benefit–risk profile for patients with advanced nsclc and ROSI rearrangement, and it is the first targeted agent approved for ROSI-positive tumours. Response rates achieved with crizotinib, regardless of treatment line (63\%–83\%), in this susceptible population are greatly superior to the 10\%–35\% and 5\%–22\% response rates obtained with use of the traditional cytotoxic therapies in the first-line and second-line settings respectively\textsuperscript{6}. Low rates of ROSI rearrangement in the population make the initiation of phase iii randomized clinical trials untenable at present, but the observed objective response rate, prolonged PFS, and similar efficacy across all lines of therapy as evidenced by a variety of phase i and ii studies, retrospective analyses, and single-institution experiences in diverse patient populations with advanced nsclc lend credence to the efficacy of crizotinib as an effective pharmaceutical to manage ROSI-altered lung cancer in larger patient populations. In light of current results and experiences, we support and recommend the use of crizotinib in this patient group.

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