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REVIEW PAPER

# National Working Group Meeting on ALK diagnostics in lung cancer

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## Abstract

The global landscape of molecular testing is rapidly changing, with the recent publication of the International Association for the Study of Lung Cancer (IASLC)/College of American Pathologists (CAP) guidelines and the ALK Atlas. The IASLC/CAP guidelines recommend that tumors from patients with non-small cell lung cancer (NSCLC) be tested for *ALK* rearrangements in addition to *epidermal growth factor receptor* (EGFR) mutations. The spur for this recommendation is the availability of novel therapies that target these rearrangements. This article is based on coverage of a Pfizer-sponsored National Working Group Meeting on ALK Diagnostics in Lung Cancer, held around the 15th World Lung Cancer Conference, in Sydney on October 31, 2013. It is based on the presentations given by the authors at the meeting and the discussion that ensued. The content for this article was discussed and agreed on by the authors.

**Key words:** ALK testing, fluorescence *in situ* hybridization, immunohistochemistry, molecular diagnostics, nonsmall cell lung cancer.

## BACKGROUND

Approximately 50% of lung adenocarcinomas are associated with an identifiable genetic mutation resulting in functional or structural alteration of an oncogene.[1] Specific molecular alterations that drive tumor growth and provide targets for therapy include *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*), *epidermal growth factor receptor* (*EGFR*), *ROS1* gene and the *anaplastic lymphoma kinase* (*ALK*) gene, accounting for 25% to 40%, 10% to 30%, 1% to 3%, and 4% to 7% of cases, respectively.[2–4] *ALK* was first identified as a fusion oncogene in 2007 by Japanese researchers. It is

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the result of an inversion or translocation of the functional portion of the *ALK* gene resulting in constitutive activation of the ALK kinase domain.[5]

At the 15th World Conference on Lung Cancer held in Sydney, Australia in October 2013, the development of crizotinib, a targeted therapy that inhibits ALK, was heralded as one of the landmarks in lung cancer research in the last four decades. Crizotinib has been extensively studied in ALK-positive lung cancer through phase I to III studies, and the results from phase III (PROFILE-1007) have been recently published in the *New England Journal of Medicine*.[6] Another phase III randomized study, PROFILE-1014, in the first-line setting is fully enrolled and results are expected in 2014. In the phase 1, first-in-human, dose-finding trial of crizotinib, part of the study investigated the efficacy of this agent in a cohort of patients whose lung cancer was defined as ALK-positive by a split signal in a fluorescence *in situ* hybridization (FISH) assay.[7] Clinical trials reveal consist clinical and imaging response to crizotinib in patients with ALK-positive tumors (Table 1).[8,9] In 2012, the National Comprehensive Cancer Network Guidelines were modified to recommend crizotinib as first-line therapy in patients with ALK-positive nonsmall cell lung cancer (NSCLC).[10]

With the approval of an agent specifically targeting *ALK*, it is important to develop a focused approach toward ALK testing in patients with NSCLC in Australia. To this end, in October 2013, a meeting of leading Australian pathologists and clinicians took place in Sydney to discuss issues around molecular testing including optimal timing of testing, the most appropriate testing method, and the definition of ALK positivity, and to develop a framework for the development of a future molecular diagnostic approach in lung cancer.

## *ALK* IN LUNG CANCER

The finding that ALK inhibitors result in tumor shrinkage *in vivo*, suggesting oncogene addiction, led to the recognition that *ALK* is a target for therapeutic intervention. Up to 20 variants of *EML4-ALK* rearrangement demonstrating gain-of-function properties have been identified in NSCLC. Three of these variants (E13, E20 and E19) account for 90% of *ALK* rearrangements.[11]

The estimated prevalence of *ALK* in lung cancers is highest in adenocarcinomas and adenosquamous carcinomas followed by NSCLC not otherwise specified (Fig. 1).[7] Patients with NSCLC who exhibit *EGFR* or *ALK* mutations tend to have similar clinicopathological features, although patients with ALK-positive tumors tend to be younger than those who have EGFR-positive tumors. These genetic changes are mutually exclusive.

## ALK TESTING – INTERNATIONAL EXPERIENCE

### The Canadian experience

A recently completed multicenter study has investigated the feasibility of ALK immunohistochemistry (IHC) for initial screening followed by FISH for *ALK* gene rearrangements and the implementation of an optimized and standardized testing protocol across Canadian pathology laboratories.[12] Screening of tissue microarrays constructed from approximately 2000 resected lung adenocarcinomas from eight centres with IHC using 5A4/ALK1 or Nichirai ALK kit and with FISH using the Abbott's ALK break-apart FISH probe, identified 22 ALK-positive and 6 ALK-negative tumors as study cases. A central laboratory cut 60 sections per study block. These were distributed to Canadian ALK centers

**Table 1** Efficacy results from phase I to phase III trials of crizotinib in patients ALK-positive tumors[8,9]

| | A8081001 (phase 1-II)[9] | Profile 1005 (phase II)[8] | Profile 1007 (phase III)[8] |
|---|---|---|---|
| | *n* = 143 | *n* = 261 | *n* = 173 |
| Line of therapy | Any line | Second and beyond | Second line only |
| Overall response rate | 64%<br>(95% CI: 53%–70%) | 53%<br>(95% CI: 47%–60%) | 65%<br>(5% CI: 58%–72%) |
| Median duration of response (weeks) | 49.1<br>(95% CI: 39.3–75.4) | 42.9<br>(95% CI: 36.1–49.7) | 32.1<br>(95% CI: 26.4–42.3) |
| Median progression-free survival, months | 9.9<br>(95% CI: 7.7–13.4) | 8.5<br>(95% CI: 6.5–9.9) | 7.7<br>(95% CI: 6.0–8.8) |
| Overall survival probability at 12 months | 75%<br>(95% CI: 66%–82% | 61%<br>(95% CI: 49%–71%) | Not reached |

CI, confidence interval.

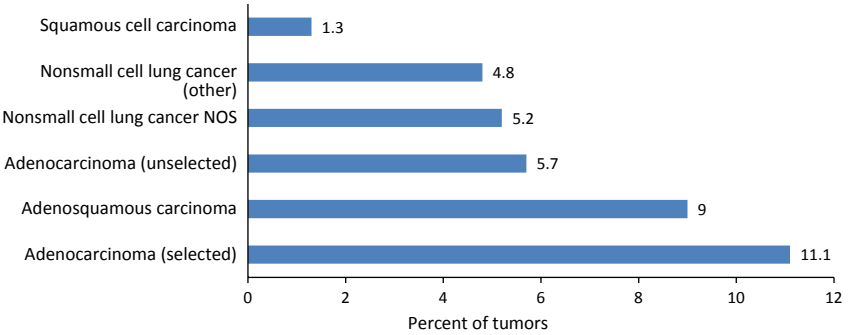


**Figure 1** Estimated prevalence of *ALK* in lung cancers.[7]

for independent IHC and FISH assessment using pre-agreed staining and scoring protocol and score sheets. IHC H-score, which takes into account the percentage of cells as well as each staining intensity category, was used for initial evaluation, followed by FISH. IHC reagents used included ALK1 (Dako), 5A4 (Novocastra/Leica/Nicherei), and DF53 (Cell Signaling). A total of three sites used Dako immune-autostainers, while three and seven sites, respectively, used Leica and Ventana instruments. After a face-to-face group review of IHC-stained slides by representatives of participating centers, the mean H-score was provided to each laboratory to make minor staining protocol adjustments. Tissue microarrays with representative negative, weak and positive staining from a subset of samples was provided for laboratories to adjust staining protocols if necessary. Staining was then repeated using the optimized protocol on a new set of study samples. After the second round of staining, the H-scores were much more concordant than in the first round. The ultimate interclass correlation (estimate of variability of scores across samples and centers) was 0.95 (where >0.85 is considered good in reliability studies).[12]

As data for the false-negative IHC rate in Canada are unknown and the therapeutic implication of FISH-positive/IHC-negative cases is unknown, as a precaution, many centers include in their IHC reports a qualifier to the effect that "ALK immunohistochemistry has been performed using protocol optimized to detect *ALK* gene re-arrangement in lung cancer. However, there remains a possibility that it may not detect all rearrangements."

Key findings from the Canadian ALK study were[12]

- High concordance among centers was reached in initial pre-optimized ALK IHC staining/scoring of study cases.
- Concordance rate was significantly increased after cross-center IHC protocol optimization and standardization.
- There was significant variation in scoring of break-apart signals in FISH analysis of *ALK*-rearranged samples; all outliers were resolved by rescoring after pathologist review of corresponding hematoxylin and eosin section with technician.
- One FISH-positive/IHC-negative discordant case was identified among 28 cases studied. The reason for this remains unclear.
- Screening with IHC but confirmation by FISH is generally acceptable at this time as the strategy to implement ALK testing.

## The French experience

In France, the government sponsors a program to provide nationwide molecular diagnostic tests. A total of 28 centers have been approved to perform molecular testing on tumor specimens from patients with leukemia and a variety of solid tumors, including melanoma, lung, colorectal and breast cancers. The results of a panel of six genes associated with lung cancer from a total of 20 761 patients are summarized in Fig. 2. Note that not all tumors have been tested for alterations in the six genes included in the panel. In 2011, testing of approximately 22% of the lung cancers for *ALK* gene rearrangements detected 200/4543 positive cases, a 4.4% incidence rate (Source: Institut National du Cancer).

## Current status of ALK testing in Australia

In 2011, awareness of ALK testing (compared with *EGFR* mutational analysis) was relatively low in Australia (Fig. 3). However, within a span of 2 years, a significant increase in ALK testing has been noted. In a recent survey, 70% of previously surveyed clinicians have requested ALK testing for at least some of their patients with advanced lung cancer. This increase is in part due to the robust clinical trial program of crizotinib run in

 

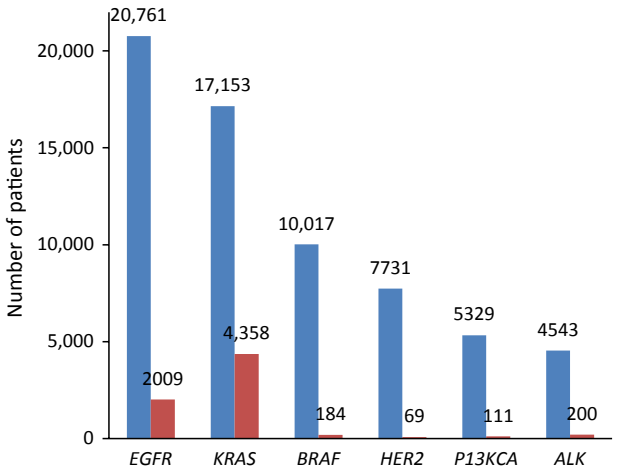


**Figure 2** Molecular alterations found in tumors screened in 2011 from French lung cancer patients. ■: Patients screened; ■: Patients with molecular alteration.

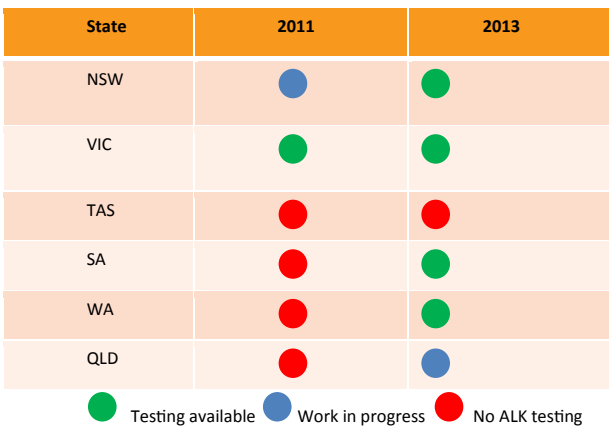


**Figure 3** *ALK* awareness in Australia in 2011 and 2013.

Australia, as well as compassionate access to crizotinib through the manufacturer and recent approval of crizotinib for treatment of ALK-positive advanced NSCLC. The Australian approval label does not specify a specific test for *ALK* rearrangements.

The pathway to Pharmaceutical Benefits Scheme reimbursement for new targeted therapies is complex. There are a series of steps involved and the process can take 2 years or more. Targeted therapies are assessed in tandem with appropriate diagnostic tests. The end result of the assessment process is a Decision Analytic Protocol in which the Medical Services Advisory Committee (MSAC) outlines the approach the sponsoring company should take with regard to diagnostic testing for the target molecular mutation or rearrangement. The results of assessment of crizotinib and accompanying diagnostic testing became available in 2012. MSAC suggested two potential molecular diagnostic testing sequences:

1. *EGFR* testing, followed by IHC screening for ALK over-expression (only if *EFGR* is negative); if IHC is positive or equivocal, *ALK* FISH testing performed
2. IHC screening for ALK over-expression, followed by *EGFR* testing, followed by *ALK* FISH testing (only if IHC positive or equivocal and *EGFR* negative).

MSAC posed the following two questions regarding the patient population eligible for ALK testing:

1. In particular, although the majority of NSCLC patients present with stage IIIB or stage IV disease, should testing be restricted to only those patients with these stages of disease or are there any other subgroups of NSCLC patients who present with an earlier stage of disease that are at high risk of progressing to stage IIIB or stage IV disease?
2. Alternatively, should all patients be considered for testing at initial diagnosis of NSCLC?

The results from a co-dependent assessment of crizotinib for advanced NSCLC and ALK testing through MSAC and PBAC will become known in the first half of 2014.

## ALK testing status on a state-by-state basis

In 2011, ALK testing was confined to sites involved in the crizotinib trials, particularly New South Wales and Victoria. To gain a better understanding of the situation on a state-by-state basis, state-based meetings were held from October 2012 to April 2013. Key pathologists from each state shared their current practices in terms of molecular testing and identified gaps and opportunities in this arena.

In Victoria, Melbourne's Peter MacCallum Cancer Centre is a referral center for FISH and IHC testing. Some centers, such as the Austin Hospital, perform IHC but refer cases for FISH confirmation to Peter MacCallum. Funding for testing for Victorian patients is provided by a Victorian government grant. Following *EGFR* testing, all tissue is tested for *ALK* and *ROS1*. Recent discovery of *ROS1* gene fusion in a subset of lung cancers has raised clinical interest, because *ROS1* fusion-positive cancers are reportedly sensitive to kinase inhibitors.[13]

In South Australia, South Australia Pathology, affiliated with the Royal Adelaide Hospital, is the referral center performing IHC and FISH. Funding is supplied

through an internal budget. The rate of testing for *ALK* rearrangement remains low. The majority of patients tested for *ALK* are younger patients who are found to have *EGFR*-negative tumors.

Currently, Pathwest is the referral center for FISH testing in Western Australia. An internal concordance study using FISH and IHC has recently been completed. The Molecular Oncology Division at St John of God Pathology in Subiaco performs immunohistochemical screening for ALK, concurrently with *EGFR* and *KRAS* mutational analysis. This allows for timely referral for confirmatory *ALK* FISH testing if no *EGFR* or *KRAS* mutations are detected and IHC is positive or equivocal, or there is a high clinical index of suspicion.

ALK testing of lung tumors is not currently performed in laboratories in Tasmania. There is some experience with ALK IHC testing for lymphoma; however, this needs to be modified for testing in NSCLC because of much higher levels of ALK expression seen in lymphoma relative to NSCLC. At this stage, the testing rate is low, with samples being sent to the Peter MacCallum Cancer Centre.

In New South Wales, most samples are referred to one of the two laboratories in Sydney, Royal Prince Alfred Hospital (RPAH) and St. Vincent's Hospital, which both offer IHC and FISH for *ALK* and *ROS1* testing. Some centers, such as the Royal North Shore Hospital, perform IHC but may send samples to Royal Prince Alfred or St. Vincent's Hospital for confirmation. Testing is privately charged at both centers. At RPAH, tissues are prescreened for ALK in parallel with *EGFR* and *KRAS* mutation testing, using IHC, and confirmed by FISH for cases with positive IHC or if there are particularly suggestive clinicopathological features.

In Queensland, the state-wide public pathology provider Pathology Queensland is performing IHC screening at The Prince Charles Hospital, Brisbane, with positive cases being referred to either Peter MacCallum in Melbourne or Royal Prince Alfred in Sydney for FISH. In the private sector, testing is available at Sullivan Nicolaides; however, FISH is still being validated. Testing rates have increased due to growing awareness.

### Challenges and proposed solutions

A number of challenges face Australian clinicians in their efforts to incorporate ALK testing for lung cancer into routine practice. These include determining patient eligibility, timing of testing, reliability of testing methods and tissue availability, sequencing of testing, and reimbursement issues.

## PATIENT ELIGIBILITY AND TIMING OF TESTING

### Challenge

It is generally accepted that only patients with non-squamous lung cancer should be tested for *ALK*. However, in small biopsy samples that may be squamous tumors, it is not possible to be sure there is no adenocarcinoma component because of frequent heterogeneity.

### Proposed solution

In a small biopsy or cytology sample that looks like a pure squamous cell cancer, if the clinicopathologic features are otherwise suggestive, molecular testing may still be considered. This is recommended by the IASLC/CAP guidelines.[14]

## ACCESS TO AND RELIABILITY OF TESTING AND TISSUE AVAILABILITY

### Challenges

- Many laboratories in Australia will not set up FISH testing facilities specifically for *ALK* as the volumes would not justify the cost.
- The expertise is not present in many laboratories.
- *ALK* FISH testing can be very difficult to interpret in some cases.
- The reliability of IHC depends on the robustness of the assay and the training of scorers. Data from the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program has shown a significant number of laboratories over many years do not adequately perform IHC for ER, PR and HER2 in breast cancer.
- Guidelines state that there is a need to have tumor-specific positive controls when performing ALK IHC in lung cancer. However, many laboratories do not have access to these given the low incidence of *ALK* gene rearrangement and the limited nature of most lung cancer biopsies.
- If IHC for triage and confirmation with FISH becomes standard practice, problems may arise when centers need to refer samples to other laboratories for FISH confirmation because of tissue availability.

### Proposed solutions

- Where feasible, *ALK* FISH testing should be performed at centralized laboratories with a high level of experience.
- The RCPA is currently in the process of working with the federal government to review the funding of

 

genetic testing in Australia, and somatic mutation testing is part of this broader initiative.
- Questions of proficiency could be answered by a national quality assurance (QA) program such as exists for other IHC assays, which have a direct clinical consequence although there will be challenges securing positive samples of sufficient size.
- The National Association of Testing Authorities (NATA) currently provides accreditation for paraffin ISH testing (which includes *ALK* testing, but not as a separately listed test).
- Laboratories could be required, where possible, to provide tissue as part of their enrolment in the QA program.
- Further education regarding the importance of acquiring adequate tissue for testing is necessary in community centers.
- Centers of excellence should perform this type of testing.
- It is anticipated that within a couple of years, new technologies such as massively parallel sequencing (or next generation) assays will probably be widely used, although gene fusions provide challenges for testing especially on the generally poor quality RNA obtained from formalin-fixed, paraffin-embedded (FFPE) samples. With multiplex assays, several mutations can be tested simultaneously, which is useful when sample sizes are small.

## REIMBURSEMENT

### Challenges

- There is a need for the Australian government to put in place a comprehensive system to fund molecular testing as an increasing number of tests that impact clinical practice become available and to recognize the patient and cost-benefits of multiplexed testing.
- Reimbursement for ALK testing is dependent on the recommendation made by MSAC.
- Reimbursement currently varies from state to state.

### Proposed solutions

- Pathologists, clinicians and other interested stakeholders should lobby the government to set up a population-based molecular testing program. There are at least two large international models (i.e. in France and Germany) demonstrating how governments have successfully introduced programs to support molecular testing.
- Cost-effectiveness data are essential when lobbying the government. It should be emphasized that molecular testing can reduce the cost of cancer therapies as it ensures that therapies are targeted to those patients who will benefit most. The industry should be involved to help demonstrate the economic benefits of targeted molecular testing.

### Issues for further consideration

- Opinion remains divided as to whether all patients with nonsquamous, NSCLC should be tested for ALK by IHC as a triage tool in the first instance.
- While IHC screening is currently a suitable starting point for ALK testing, there is a need to continue to accumulate information regarding its reliability.
- IHC (performed in centers with appropriate experience in controls and validation) is a reasonable way to select cases that require FISH *ALK* testing.
- Simultaneous IHC and FISH testing can reduce turnaround time; however, sequential testing is more cost-effective.
- Reflex testing has logistical advantages, particularly in optimal use of small samples, but will only occur if the funding model allows for this.
- It would be useful to collect local data on concordance between IHC and FISH *ALK* testing as most currently available data are from overseas.
- Additional study and experience is needed to understand the clinical significance of variant patterns of results with *ALK* FISH testing.
- There is a need to educate pathologists regarding the important responsibility that they have when reporting tests such as *ALK* that directly impact clinical decision making, and to preserve tissue, especially in small biopsy specimens, for subsequent molecular testing.
- Clinicians should be aware of the need to obtain satisfactory amounts of well-preserved tumor tissue, when obtaining diagnostic biopsies.
- It is necessary to set up a national QA program to ensure that IHC and FISH *ALK* testing is reliable and well-validated.
- It should be mandated that a pathologist, and not just a scientist, is involved in reading *ALK* FISH results as recognizing and selecting malignant cells only for scoring is essential.
- Clinician confidence will be enhanced with high-quality testing promoted by a QA program.
- Access to ALK-positive tissue is a key issue for the QA program. Laboratories should be strongly encouraged to provide tissue as part of their enrolment in the QA program.

- Laboratories need to test a sufficient number of cases to develop appropriate expertise and experience in this challenging area of ISH testing.
- There should be at least one central laboratory in each state equipped to perform *ALK* FISH testing.
- Laboratories that perform FISH need to consider having a second methodology to resolve difficult cases.
- It would be useful to have more data on how clinical response correlates with concordant and discordant ALK testing results and the government should be encouraged to fund the collection of this data.
- ALK testing should be added to the Australian Cancer Council's Clinical Practice Guidelines for the Treatment of Lung Cancer.
- An addendum regarding ALK testing should be added to the RCPA Cancer Reporting Protocol.
- Molecular testing is the future of oncology so there is a pressing need for all stakeholders, including clinicians, pathologists and advocacy groups to come together to lobby the government to set up a comprehensive program that supports and funds molecular testing in oncology.
- There must be a strong cost-effectiveness argument when discussing the issue of funding for molecular testing with the government.

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## REFERENCES

1 Pao W, Hutchinson KE. Chipping away at the lung cancer genome. *Nat Med* 2012; **18**: 349–51.
2 Cooper WA, Lam DC, O'Toole SA, Minna JD. Molecular biology of lung cancer. *J Thorac Dis* 2013; **5**: S479–90.
3 Johnson BE, Kris MG, Kwiatkowski D *et al*. Clinical characteristics of planned 1000 patients with adenocarcinoma of lung (ACL) undergoing genomic characterization in the US Lung Cancer Mutation Consortium (LCMC). Presented at: *14th World Conference on Lung Cancer*. Amsterdam, The Netherlands 2011.
4 Kris MG, Johnson BE, Kwiatkowski DJ *et al*. Identification of driver mutations in tumor specimens from 1000 patients with lung adenocarcinoma: the NCI's Lung Cancer Mutation Consortium (LCMC). *J Clin Oncol* 2011; **29** (suppl; abstr CRA7506).
5 Soda M, Choi YL, Enomoto M *et al*. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007; **448**: 561–6.
6 Shaw AT, Kim DW, Nakagawa K *et al*. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013; **368**: 2385–94.
7 Tsao MS, Hirsch FR, Yatabe Y (eds). *IASLC Atlas of ALK Testing in Lung Cancer*. International Association for the Study of Lunger Cancer, Aurora, CO 2013.
8 *Xalkori (Crizotinib) Product Information*. Pfizer Australia Pty Ltd, West Ryde, NSW 2013.
9 Camidge DR, Bang YJ, Kwak EL *et al*. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 2012; **13**: 1011–9.
10 Non–small cell lung cancer update. *J Natl Compr Cancer Netw* [Cited 31 January 2014.] Available from URL: http://www.jnccn.org/site/highlights2012/nsclc.xhtml.
11 Ou SH, Bartlett CH, Mino-Kenudson M, Cui J, Iafrate AJ. Crizotinib for the treatment of ALK-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology. *Oncologist* 2012; **17**: 1351–75.
12 Tsao MS, Craddock K, Brandao G *et al*. Canadian ALK (CALK): a pan-Canadian multicenter study to optimize and standardize ALK immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) for ALK gene rearrangements. *J Clin Oncol* 2013; **31**: Abstr 8096.
13 Yoshida A, Kohno T, Tsuta K *et al*. ROS1-rearranged lung cancer: a clinicopathologic and molecular study of 15 surgical cases. *Am J Surg Pathol* 2013; **37**: 554–62.
14 Lindeman NI, Cagle PT, Beasley MB *et al*. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013; **8**: 823–59.

 