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Personalised first-line treatment of advanced NSCLC – the role of EGFR mutation testing

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This review has been created to provide a summary of information about personalised first-line treatment options for advanced non-small cell lung cancer (NSCLC) in New Zealand and the role of epidermal growth factor receptor (EGFR) mutation testing for predicting the benefit of treating advanced NSCLC with an EGFR tyrosine kinase inhibitor (TKI).

This article is intended to offer guidance to oncologists, respiratory and general physicians, surgeons and pathologists who treat people with lung cancer by reviewing and highlighting information and publications that could change investigation and treatment decisions.

In July 2012, PHARMAC changed the treatment options for lung cancer in New Zealand by agreeing to fund the EGFR-TKI gefitinib (Iressa®; AstraZeneca) as a first-line treatment for advanced non-squamous NSCLC, if mutations in *EGFR* are demonstrated to be present.[1] Previously, the EGFR-TKI erlotinib (Tarceva®; Roche) had been available for unselected NSCLC patients following standard first-line chemotherapy. Erlotinib is currently funded as a second-line treatment option.[1]

Epidemiology of lung cancer

Lung cancer is the leading cause of cancer-related mortality among both men and women in New Zealand, with the rate being one of the highest in the developed world. In 2009, it accounted for 18.9% of all deaths from cancer in New Zealand,[2] and was associated with a five-year relative survival rate of 10.2% – considerably worse than in Australia (14%), the USA (15.5%) and Canada (16%).[3-5]

Whilst the poor survival overall reflects the advanced stage at which patients with lung cancer characteristically present, geographical differences in outcomes are thought to be partially due to variations in clinical management.[6] Ethnic disparities also exist, with an increased incidence among Māori and Pacific people.[7,8] An audit of lung cancer care conducted in 2004 reported that Māori were more likely to have locally advanced disease, less likely to receive curative treatment and more likely to receive palliative treatment compared with Europeans.[9] A second audit in 2008 in the Northern Region of New Zealand revealed little change over the intervening four years, with both audits revealing presentation with advanced disease to healthcare, with the majority of patients having incurable disease at diagnosis.[9,10]

Treatment of advanced (stage IIIB-IV) NSCLC

Standard chemotherapy in advanced NSCLC in New Zealand is doublet treatment: platinum (cisplatin or carboplatin) plus usually either a taxane (paclitaxel or docetaxel) or gemcitabine. The inclusion of third-generation chemotherapy drugs, such as paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, and pemextred, in platinum-based doublets has improved response rates and survival. Disappointingly, even with the addition of third-generation agents, the maximum median overall survival with chemotherapy has plateaued at 8-10 months.[11] However, the discovery of specific tumour mutations in NSCLC has led to the development of targeted therapies that can increase chemotherapeutic efficacy in selected patients with advanced NSCLC.

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Disclaimer: *This publication is an independent review of personalised first-line treatment options for advanced NSCLC in New Zealand and the role of EGFR testing for predicting the benefit of treating advanced NSCLC with an EGFR-TKI. It provides summaries and opinions of published data that are the opinion of the writer and commentators rather than that of the scientific journal or research group. It is suggested the reader reviews the full trial data before forming a final conclusion on any recommendations.*

EGFR-targeted chemotherapy

The EGFR was the first receptor to be proposed for lung cancer therapy. Two EGFR-targeted pharmacological approaches have been successfully developed: monoclonal antibodies (mAbs) and small-molecule inhibitors of the EGFR tyrosine kinase enzymatic activity. The orally administered agents gefitinib and erlotinib were the first small-molecule TKIs introduced clinically to selectively block EGFR signaling; their anti-tumour activity was subsequently found to be related to the presence of *EGFR* activating mutations (EGFR M+ status). The observation that treatment with EGFR-TKIs produces response rates of 68% versus 11% and median times to progression/progression-free survival of 12.0 versus 3.4 months in patients selected for EGFR M+ status versus unselected patients is evidence of the beneficial effects on clinical outcome of EGFR-targeted therapy for advanced NSCLC.[12]

For advanced NSCLC patients who are EGFR M+, the advantages provided by TKIs over standard chemotherapy, include:

- Longer progression-free survival
- Higher response rates
- More favorable toxicity profile
- Rapid and significant improvement in quality of life and disease-related symptoms
- Convenience of oral dosing.[13-17]

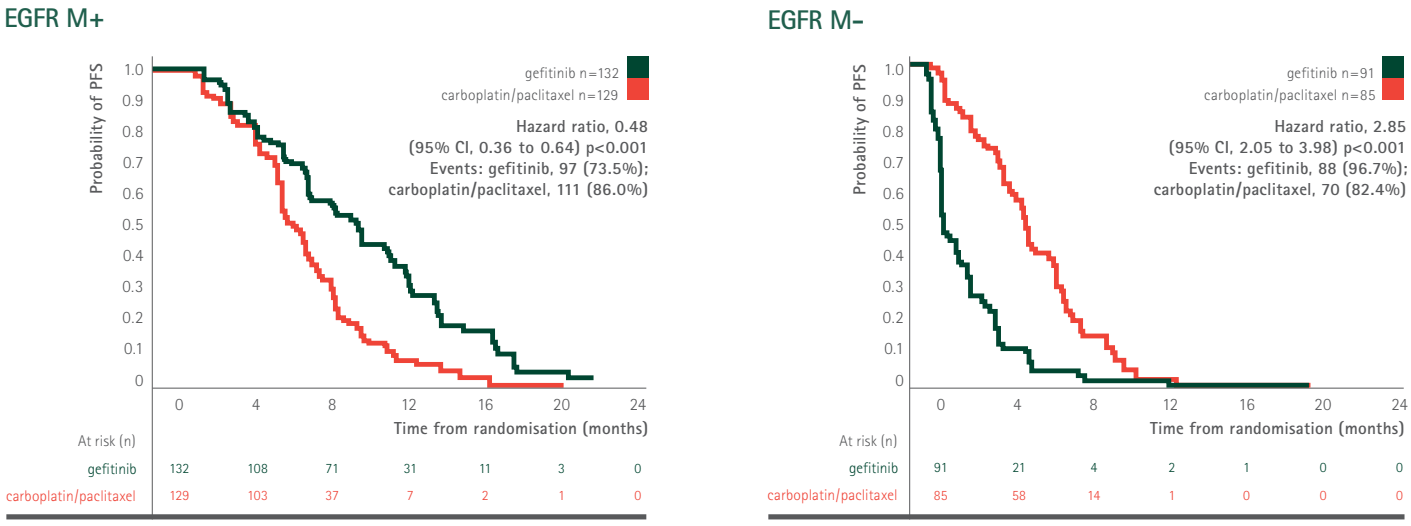
On the basis of evidence from the large IPASS trial,[18] and four other smaller phase III randomised controlled trials,[19-22] which used progression-free survival and/or overall survival as primary end-points, the American Society of Clinical Oncology (ASCO) developed a provisional clinical opinion stating that treatment-naïve patients with NSCLC being considered for first-line therapy with an EGFR-TKI should be tested for *EGFR* mutations to determine whether EGFR-TKI or chemotherapy is the appropriate first-line treatment.[23] Some of the same first-line data set was used in the Central European Cooperative Oncology Group's (CECOG) consensus on the systemic treatment of NSCLC, which states that *EGFR* mutations predict a better response to EGFR-TKIs compared with chemotherapy in advanced NSCLC; hence, *EGFR* mutation testing is encouraged before treatment decision.[24]

Details of this first-line data set are provided in the following individual study summaries.

IPASS confirmed that *EGFR* mutations are not simply a biomarker of prognosis but also a predictor of therapeutic benefit.[18] IPASS was an open-label study that randomly assigned previously untreated patients in East Asia who had advanced pulmonary adenocarcinoma and who were non-smokers or former light smokers to receive gefitinib (250 mg/day; n=609) or carboplatin (at a dose calculated to produce an area under the curve [AUC] of 5 to 6 mg/mL/min) plus paclitaxel (200 mg/m^2 of body-surface area; n=608). The presence of an *EGFR* mutation was a robust predictor of PFS with gefitinib, as compared with carboplatin-paclitaxel, and of the benefit of gefitinib with respect to the objective response rate; indicating that patients in whom an *EGFR* mutation has been identified will benefit most from first-line therapy with gefitinib (**Figure 1**). Gefitinib significantly prolonged median PFS by 3.2 months in EGFR M+ patients compared with carboplatin/paclitaxel (9.5 vs 6.3 months; p<0.0001).[18,25]

First-SIGNAL found that *EGFR* mutations are predictive of improved PFS and response rate with gefitinib compared with chemotherapy.[19] In this phase III Korean study, 313 never-smokers with stage IIIB or IV lung adenocarcinoma were randomised to receive gefitinib (250 mg/day) or chemotherapy (gemcitabine 1,250 mg/m^2 on days 1 and 8 plus cisplatin 80 mg/m^2 on day 1 every 3 weeks for up to 9 courses). In a subgroup analysis of 96 patients who were assessable for *EGFR* mutations, EGFR M+ status was significantly (p<0.001 vs EGFR M- status) predictive of both a higher ORR and longer PFS among patients who received gefitinib but not among those who received chemotherapy.

First-line gefitinib for patients with advanced NSCLC selected on the basis of *EGFR* mutations improved PFS, with acceptable toxicity, as compared with standard chemotherapy.[20] This Japanese study randomly assigned 230 patients with metastatic NSCLC and *EGFR* mutations who had not previously received chemotherapy to receive gefitinib (250 mg/day; n=115) or standard chemotherapy comprising carboplatin (at a dose equivalent to an AUC of 6, given intravenously over a 1-hour period) and paclitaxel (at a dose of 200 mg/m^2 of body-surface area, given intravenously over a 3-hour period), both administered on the first day of every 3-week cycle. Gefitinib-treated patients demonstrated significantly longer median progression-free survival (10.8 vs 5.4 months; p<0.001) and a higher response rate (73.7 vs 30.7%; p<0.001) compared with standard chemotherapy-treated patients.



Adapted from Mok TS, et al.[18,25]

Figure 1. IPASS trial: Progression-free survival (PFS) for gefitinib vs chemotherapy in EGFR M+ advanced NSCLC.[18,25]

In another Japanese investigation, gefitinib significantly prolonged PFS in chemotherapy-naïve patients aged ≤75 years diagnosed with stage IIIB/IV NSCLC or postoperative recurrence harbouring *EGFR* mutations (either the exon 19 deletion or L858R point mutation).[21] Patients were randomised to receive gefitinib (250 mg/day; n=88) or cisplatin (80 mg/m^2) plus docetaxel (60 mg/m^2; n=89), administered every 21 days for 3 to 6 cycles. PFS was significantly prolonged in the gefitinib arm compared with the cisplatin plus docetaxel arm (median 9.2 vs 6.3 months; p<0.0001).

OPTIMAL compared erlotinib (150 mg/day; n=82) to gemcitabine (1000 mg/m^2, D1, 8, every 3 weeks) plus carboplatin (AUC = 5, n=72) in advanced NSCLC patients with positive *EGFR* mutations.[22] Erlotinib was significantly superior to chemotherapy in terms of PFS (median PFS of 13.1 months vs 4.6 months; HR 0.16; p<0.0001) and response rates (83% vs 36%, respectively). Erlotinib was better tolerated than chemotherapy. In the subgroup analysis, almost all subgroups (gender, histology, smoking status) obtained better clinical benefit from erlotinib than from chemotherapy.

Second-line data from two studies published after the ASCO and CECOG consensus statements provide additional support for the importance of *EGFR* mutation testing and strengthen the rationale for using EGFR TKIs in mutation-positive NSCLC.

Erlotinib was compared with chemotherapy (cisplatin or carboplatin plus gemcitabine or docetaxel) in the first-line setting for advanced *EGFR* mutation-positive NSCLC in the EURTAC trial.[26] Compared with platinum-based chemotherapy (n=87), erlotinib (n=86) significantly (p<0.0001) extended PFS (9.7 vs 5.2 months) and resulted in a higher response rate (58% vs 15%). There was also a better safety profile, consistent with previous erlotinib studies.

A large prospective biomarker study found that EGFR M+ patients derived the greatest PFS benefit from erlotinib maintenance therapy.[27] Mandatory diagnostic tumour specimens were collected (prior to first-line chemotherapy) from 889 patients with advanced NSCLC who participated in a phase III, randomised, placebo-controlled trial of erlotinib maintenance therapy. A significant (p<0.001 vs placebo) predictive effect on PFS of erlotinib was observed in a subgroup of patients with EGFR M+ status.

When considering possible *EGFR* mutation differences among various ethnic groups in New Zealand, it is relevant to note that no significant differences in the types and locations of *EGFR* mutations were found between the NSCLCs of Asians and non-Asians in the five phase III trials that formed basis of the ASCO's provisional clinical opinion, which states that all *EGFR* mutations are in the same loci of the DNA of NSCLC tumours (exons 18 to 21). In addition, this seems to be true for the secondary mutation T790M, which confers resistance to EGFR-TKIs, and for the *MET* gene amplification resistance mechanism between people of different ethnicities.[23]

Other molecular targets for chemotherapy

Mutations in the *K-RAS* genes have been found in 20–30% of NSCLC tumour samples.[28] Their role in selecting specific treatment for NSCLC remains undefined; however, *K-RAS* mutation has been shown to predict poor response to EGFR-TKIs and conventional chemotherapy.[28,29] No specific treatment is currently available for *K-RAS* mutant patients.[28]

About 5% of NSCLC patients harbour an anaplastic lymphoma kinase (ALK) gene rearrangement that both initiates and maintains tumour growth.[30] Compared to patients with EGFR-positive or wild-type NSCLC, ALK-positive patients have a lower response rate to platinum-based chemotherapy and worse survival with standard chemotherapy.[31] The first clinically available ALK inhibitor, crizotinib, produces objective responses and prolonged overall survival in patients with ALK-positive NSCLC and is generally well tolerated.[32,33] The emergence of crizotinib resistance has resulted in the development of a number of second-generation, oral ALK inhibitors, currently undergoing investigation.[34]

Specialists' Commentary: Molecular targets and future directions

In New Zealand, it is most likely that testing will be restricted to targets for which a therapeutic intervention is available. It is critical to develop national expertise to enable molecular testing on appropriate patients, and to ensure appropriate quality test results on all patients. Testing is likely to involve a panel of molecular targets in the future, and therefore close collaboration across the country will be important to ensure that an optimal service is provided. EGFR could be considered as the "prototype" first test to be evaluated and set up in this way, given the evidence of benefit of the TKI therapies previously outlined in EGFR M+ patients.

Given the absence of a therapeutic target, *K-RAS* testing is unlikely to be universally adopted, although this may change as the relevance and utility of this mutation evolves in the future. *ALK* fusion mutation has also been shown to be an important target in treating patients with lung cancer. Currently, crizotinib (an ALK inhibitor) is not funded in New Zealand by PHARMAC, although it is available in very selected cases as part of clinical trials, access programmes, or where individual funding can be found. However, this situation may also change in the future. *ALK* mutations are more commonly found in substantially younger than average patients with NSCLC, with a lighter smoking history. Testing for *ALK* involves either a fluorescence in-situ hybridisation (FISH) test – felt to be more accurate but also more expensive and time consuming – or immunohistochemistry (IHC) – felt to be less accurate but cheaper. The latter has reduced sensitivity – which is problematic in a rare mutation affecting younger, lighter smokers with advanced NSCLC who may have much to gain from targeted treatment. FISH testing is available from two New Zealand laboratories (in Christchurch and Auckland) and some laboratories are currently looking into the possibility of using IHC as an initial test and, if positive, confirming with FISH testing. This approach has been adopted in many centres but is not recommended in the recent US and European guidelines.

Monoclonal antibodies such as bevacizumab – a vascular endothelial growth factor (VEGF) inhibitor – and cetuximab have demonstrated activity in patients who overexpress EGFR on IHC and also have a role to play in the treatment of lung cancer, having shown in some studies progression-free survival (PFS) benefits, and in one an overall survival benefit.

There are currently many new reversible and irreversible EGFR inhibitors in advanced phase clinical trials that are also likely to play an important role in the treatment of patients with EGFR-mutated lung cancer, and potentially a role in some of the known resistant mutations, such as T790M.

New Zealand will need to be prepared for the discovery of further relevant mutations and evolution of targeted therapeutic options. It is likely that in the future, lung cancer specimens will be subjected to a "panel" of genetic tests providing detailed molecular profiling of lung and other cancers. This will potentially enable cost-effective treatment, and improve both the quality of life and survival of patients with lung cancer.

Role of *EGFR* mutation status in determining first-line NSCLC treatment

PHARMAC's decision to fund gefitinib as first-line treatment for NSCLC came with the proviso that *EGFR* mutation testing be done to determine which patients will benefit most from TKI therapy.[1] However, gefitinib was approved before a formalised nationwide testing protocol was put in place. Development of a protocol is underway; in the meantime, *EGFR* mutation testing is available to all DHBs, either internally or externally, with funding of the testing through the DHB.

The need for nationwide *EGFR* mutation testing to determine eligibility for TKI therapy necessitates that *EGFR* mutation testing methods have appropriate analytical sensitivity and performance characteristics. Hence, the Health Research Council, in partnership with the National Health Committee (NHC), has sought, via a Request for Proposals, to purchase research to determine the characteristics of *EGFR* mutation assays in the context of management of NSCLC in the New Zealand healthcare system. The decision to fund gefitinib as first-line therapy and to test for *EGFR* mutation is consistent with many other countries that are already testing for *EGFR* mutations to determine appropriate treatment with TKIs, driven by guidelines and consensus statements from ASCO, CEGOG, NCCN, and ESMO that recommend testing for *EGFR* mutation status in the diagnostic pathway of patients with advanced adenocarcinoma NSCLC, who are being considered for first-line therapy with an EGFR-TKI.[23,24,35-37]

The testing and treatment algorithm for stage IIIB and IV NSCLC patients proposed by PHARMAC's primary clinical advisory committee, the Pharmacology and Therapeutics Advisory Committee (PTAC) is depicted in **Figure 2**. In short, it proposes to test all patients with non-squamous unresectable stage IIIB or IV NSCLC for *EGFR* mutation. Patients who are EGFR M+ should receive first-line treatment with gefitinib, patients who are EGFR M- receive first-line treatment with platinum-based chemotherapy, and patients of undetermined *EGFR* mutation status receive first-line treatment with platinum-based chemotherapy and second-line treatment with erlotinib.[38]

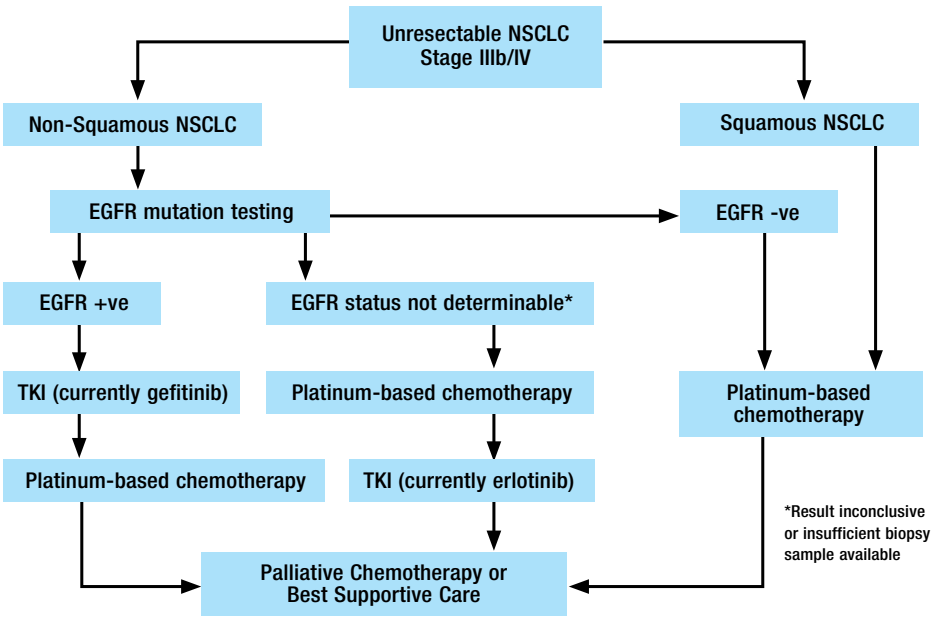


Figure 2. PHARMAC's proposed testing and treatment algorithm for stage IIIB or IV NSCLC.[38]

PHARMAC funds gefitinib in the first-line setting (treatment-naïve) for *EGFR*-positive patients. Currently, patients do not have to be *EGFR*-positive to access funded erlotinib in the second-line setting (failed platinum-based chemotherapy), but such funding will cease from 1 January 2014. PHARMAC considered that the current funding criteria for erlotinib were no longer appropriate, because it allowed erlotinib to be funded for EGFR M- patients in whom TKI therapy was unlikely to be effective. In order to access funding for TKI therapy, patients with advanced NSCLC are required to undergo *EGFR* mutation testing.[1,38] If such testing is not possible due to inadequate tissue availability, provision remains for a second-line TKI to be used (erlotinib).

New Zealand follows the clinical practice guidelines for the treatment of lung cancer developed by Cancer Council Australia (http://wiki.cancer.org.au/australia/Guidelines:Lung_cancer).

Specialists' Commentary: How *EGFR* mutation prevalence affects the testing strategy

The prevalence of *EGFR* mutations in New Zealand has not yet been determined. Characteristics associated with increased *EGFR* mutation rates overseas are female gender, never smokers, east-Asian ethnicity and adenocarcinoma subtype of NSCLC. However, mutation rates in Māori and Pacific Island populations are unknown, having not yet been systematically studied. This is a very important question, given the possible utilisation of oral, targeted, more effective, less toxic treatment in these groups. Audit data from 2004 suggest that in Auckland, patients of these ethnicities were less likely to receive specific anti-cancer treatment including chemotherapy. It would be inappropriate to use any specific characteristics to select patients for *EGFR* testing in New Zealand. If universal testing were adopted initially, incorporation of findings into a national database would aid subsequent characterisation of *EGFR* mutation rates and future decision-making. The future of lung cancer treatment is likely to rely heavily on molecular testing of the tumour, and therefore developing this capability in order to deliver the right care to the right patient is critical. Furthermore, at relapse on treatment, re-biopsy and directing subsequent therapy towards molecular alterations might also be considered.

European and US lung cancer guidelines on testing for *EGFR* mutation status

The importance of establishing *EGFR* mutation status in determining the most appropriate first-line treatment for patients with NSCLC has been shown in a number of randomised trials in recent years.[18-22,26]

In 2010, a European workshop consisting of 122 molecular biologists, pathologists, surgeons, chest physicians and medical oncologists was tasked with finding a consensus for *EGFR* mutation testing in NSCLC.[39] The workshop concluded that while clinical characteristics and histology had previously been documented as predictive factors for response to EGFR-TKIs in NSCLC, e.g., female gender, never-smokers, and adenocarcinoma histology, tumour molecular profiling was emerging as a key predictive

biomarker for EGFR-TKI treatment and should supersede those selection factors in this dawning era of personalised care in advanced NSCLC.

The workshop agreed that:

1. Close collaboration, communication flow, and coordination between the departments involved in the management of lung cancer is essential to implement *EGFR* mutation testing in routine practice. This process involves clinicians, pathologists, molecular biologists and radiologists.
2. *EGFR* mutation testing should only be done in a quality-assured setting.
3. Awareness of the need for sufficient tumour material for routine mutation testing has to be raised.
4. Timelines are a key consideration in the management of patients with advanced NSCLC.

More recently, the College of American Pathologists, in conjunction with the International Association for the Study of Lung Cancer and Association for Molecular Pathology, have published a comprehensive evidence-based molecular testing guideline for selection of lung cancer patients for targeted therapies.[12] One of its major recommendations is that *EGFR* molecular testing should be used to select patients for EGFR-targeted TKI therapy in all patients with advanced NSCLC, and that testing for EGFR should be prioritised ahead of other molecular markers in lung adenocarcinoma.

Other recommendations of the guideline include which NSCLC to test (large samples with adenocarcinoma elements or small samples where this cannot be confidently excluded), which site to test (either primary or metastases and not both), timing of testing (at diagnosis), stage to be tested (recommendation for stage IV to be tested, suggestion that stages I to III are tested with local discretion), timelines for testing (result within a maximum of 2 weeks), specimen requirements and test to be used, and recommended standard method for reporting of results.[12]

Specialists' Commentary: Determining a testing strategy

The identification of new, driver and actionable, mutations in lung cancer is progressing apace and it is certain that the testing strategy will evolve rapidly over the next few years. Although many of the drugs may not be automatically funded in New Zealand, it seems likely that there will be clinical and public pressure to identify a wider range of mutations in most common solid cancers. In the case of NSCLC, this is likely to see a shift in the mutation detection techniques, from commercial panels that detect a subset of common mutations in EGFR to approaches that detect a wider range of mutations in EGFR and in other genes. Currently this would include FISH testing for ALK fusions but there is also a demand for FISH testing to include RET and ROS fusions. At the moment these fusions cannot be detected in the same assay as the point mutations and deletions in EGFR but the introduction of targeted Next Generation Sequencing is likely to see the development of methods that can detect all of the relevant mutations in a single assay. At this point it is likely that we will also see the incorporation of additional DNA sequence information, which will reflect prognosis and resistance to therapy, into the routine assays. There will be increasing issues that relate to the interpretation of this information and to the development of appropriate external quality control programmes.

Sampling requirements for successful *EGFR* mutation testing

The increased diagnostic demands of the modern diagnostic paradigm for NSCLC require that the amount of tumor material obtained for histological and molecular analysis is maximised and its use optimised so that the need for invasive resampling procedures for the patient is minimised.[40] Capturing as much material as possible without harming the patients also helps to avoid delays in diagnosis and hence the treatment timeline.

In order to perform a successful *EGFR* mutation test, a sufficient quantity of tumour cells is required to ensure that an adequate amount of tumour DNA is extracted for analysis.[39,41,42] Tumour biopsy samples are the most suitable and most commonly available samples for *EGFR* mutation testing and are therefore the preferred sample type.[39,41,42] Cytology samples are frequently used to diagnose advanced NSCLC and, in the absence of a biopsy, should be analysed, taking into consideration that the sample quantity and tumour cell content may be low.[43-48]

Other sample types, such as circulating free DNA (cfDNA) extracted from blood (serum or plasma), is an emerging area of diagnostic testing but carries a higher false negative rate, so is not part of the standard testing algorithm as yet.[42,49-51]

A number of unstained sections are required for *EGFR* mutation testing. These can be cut at the same time as the histology samples to reduce the turnaround time for the *EGFR* mutation testing process.

The pathologist should record information on tissue adequacy. There should ideally be >200 tumour cells present, but successful *EGFR* mutation testing can be performed on fewer tumour cells, provided that a sensitive method is used.[49,52] Information on the percentage of tumour in the sample and the amount of necrosis and/or sample quality is also useful for the *EGFR* mutation testing laboratory for troubleshooting difficult samples. This information should be recorded and passed on with the samples to the testing laboratory.[49,52]

For samples with a low percentage of tumour cells, the pathologist should either mark on the slide the area containing the tumour or provide a hematoxylin and eosin stained section marked with the area of tumour to be used as a template to identify the tumour-containing regions. This will assist the testing laboratory to select the tumour area and maximise the chance of a successful test. Histological sections may be returned to the pathologist on completion of *EGFR* mutation testing.[41,53]

Activating *EGFR* mutations are found in four exons of the *EGFR* gene, exons 18 to 21, with around 90% of all mutations being the result of a deletion in exon 19 or an L858R point mutation in exon 21.[54,55] Different *EGFR* mutation testing methods have been designed to detect these mutations. The choice of testing method should be based primarily on the available sample type. The tests must be optimal for these samples. Consideration should also be given to the relevant laboratory expertise and available equipment.

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Specialists' Commentary: "TISSUE IS THE ISSUE"

The need for adequate tissue sampling in lung cancer in the era of more targeted therapy has meant another "paradigm shift" in the diagnostic and testing algorithms used by respiratory physicians and other members of the lung cancer multidisciplinary team (MDT). In previous years, identification of simply "non-small cell lung cancer" would have been considered adequate; a diagnosis which may be made from small cytological samples such as bronchoscopic washings, brushings, or slightly larger blind transbronchial needle aspirations (TBNA). In addition, endobronchial ultrasound-guided TBNA has emerged as an invaluable tool for accurate and non-invasive sampling of mediastinal and hilar lymph node stations – previously, many respiratory physicians were reluctant in practice to perform "blind" TBNAs without such guidance, and thus surgical sampling via mediastinoscopy was then required to properly stage the mediastinum.

The greater availability of endobronchial ultrasound (EBUS)-TBNA has encouraged physicians to attempt diagnosis and staging in the same procedure, considerably shortening work-up times. Thus, a patient with a peripheral lesion and enlarged mediastinal nodes may now forego a percutaneous biopsy of the peripheral lesion followed by mediastinoscopy, and proceed straight to EBUS-TBNA of the mediastinal nodes as a diagnostic and staging procedure. However, the samples obtained at EBUS-TBNA, with a 21 or 22 gauge needle, are likely to contain less material than those obtained at percutaneous biopsy or mediastinoscopy.

In our opinion, the time has come for specialists investigating lung cancer to weigh into their diagnostic approach the need to obtain sufficient tissue for accurate cytological classification of NSCLC and subsequent molecular/mutational analysis. This will require a knowledge of the likely treatment approach to that patient – palliative or curative, and whether the patient is likely to harbour mutations and be suitable for targeted chemotherapy. The presence of ROSC (rapid on-site cytological evaluation) at EBUS or computed tomography (CT)-guided fine-needle aspirations is also very important for addressing the likely adequacy of sampling for such testing. Core biopsy, rather than just fine needle aspiration (FNA), may also need to be considered at radiologically-guided percutaneous sampling. In other words, a diagnostic approach will be required that tries to achieve as rapid a diagnosis and staging as possible, whilst also obtaining as much tissue as possible at an acceptable risk to the patient. It is likely that in the future, increasing numbers of patients may require "re-biopsy" following diagnosis, in order to obtain sufficient tissue for more detailed testing.

Multidisciplinary care now remains the cornerstone of care in treating patients with lung cancer and all patients should have their case discussed within a MDT, to ensure that they are receiving the optimal treatment and care.

EGFR mutation test sensitivity

Different *EGFR* mutation tests have different sensitivities or limits of detection. The sensitivity (limit of detection) is the smallest amount of mutant DNA that can be routinely detected in a background of normal DNA. The use of sensitive *EGFR* mutation testing can increase the number of *EGFR* mutation-positive patients identified. Sensitive *EGFR* mutation testing methods are critical when the percentage of tumour cells in the sample is low.

Substantial data support sensitivity to EGFR-TKI therapy in patients whose tumours harbour the common exon 19 deletions and L858R point mutations, which make up about 90% of all *EGFR* mutations.[18-22,55] However, for the less common *EGFR* mutations, the evidence for sensitivity to EGFR-TKI therapy based on clinical trials or individual case reports may be limited or absent. Effective interpretation of *EGFR* mutation test results will lead to the most appropriate prescribing of treatment for individual patients.

Pathology review

Pathology review is required to confirm the diagnosis of NSCLC and to check that amount of tumour tissue present in the sample is sufficient for an accurate *EGFR* mutation testing. The pathologist's report confirms the underlying histology:

- Small cell lung cancer, NSCLC or other
- Squamous, adenocarcinoma, other subtype for "not otherwise specified".

The latest guidance on NSCLC for pathologists discusses the importance of accurate subtyping and the impact of *EGFR* mutations and *ALK* rearrangements on pathology and clinical practice.[52,56]

Multidisciplinary approach to diagnosis and treatment of lung cancer

The diagnosis of lung cancer involves the following:

1) Identification and classification of the tumour
2) Immunohistochemistry to predict the likely NSCLC subtype, i.e. squamous cell versus adenocarcinoma
3) Molecular testing.

The addition of molecular testing to histological differentiation of squamous from non-squamous disease has shifted the diagnosis and treatment of NSCLC from a relatively simple approach catering to most patients to a more complicated approach in which individual patient histology and molecular phenotype are important factors. The increased complexity drives the need for a multidisciplinary approach in the management of NSCLC.[57]

The current multidisciplinary approach for successful *EGFR* mutation analysis is depicted in **Figure 3**.[39] The respiratory physician requests the *EGFR* mutation testing and works with the thoracic surgeon in the initial assessment of patients and in obtaining tissue samples. Indeed, the respiratory physician, thoracic surgeon, radiologist and pathologist working together is critical in ensuring that an adequate tissue sample is obtained. Pathologists and molecular biologists play a crucial role in determining the diagnosis of lung cancer, with the pathologist being responsible for providing the correct part of the sample for DNA analysis, interpretation of the outcome and preparation of the pathology report. The role of the molecular biologist is DNA extraction, molecular testing and reporting.[39,40,57]

In the current multidisciplinary approach, the respiratory physician is primarily responsible for driving *EGFR* mutation testing. However, the National Health Committee's working group recommendations on *EGFR* mutation testing place the pathologist at the centre of testing and the rationale for pathologist-driven *EGFR* mutation testing is described in the accompanying *Specialists' Commentary: NHC role in a national approach for EGFR mutation testing*.

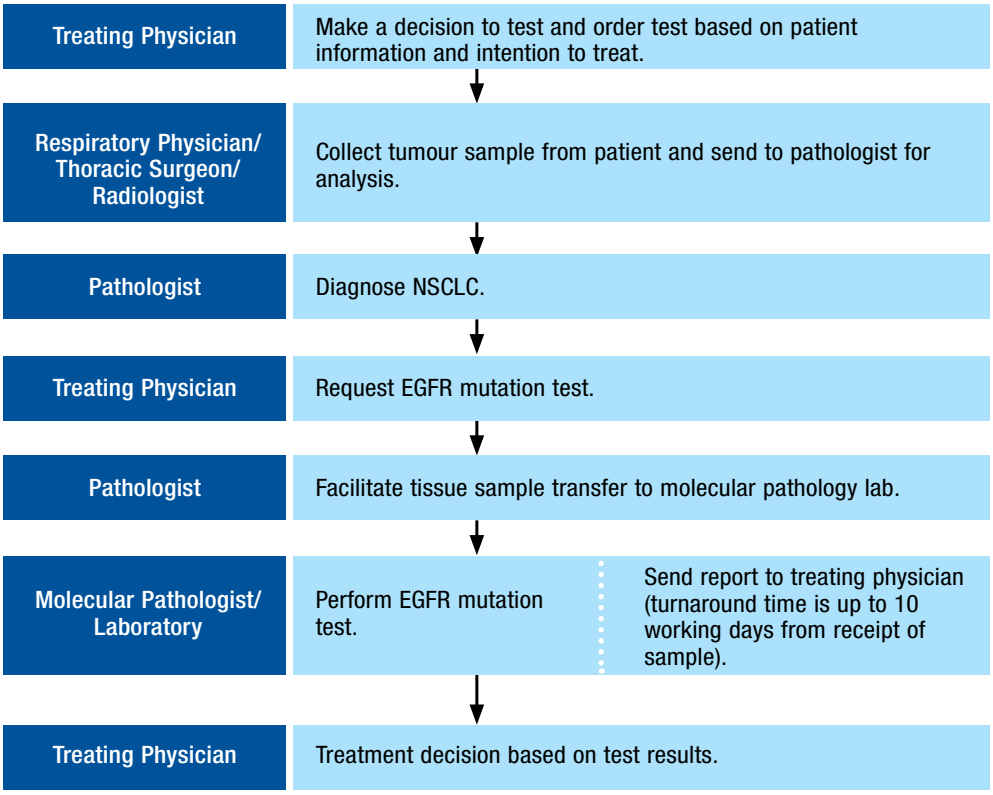

Figure 3. The current multidisciplinary approach to *EGFR* mutation testing.[39]

The need for histological and molecular testing in the current day management of NSCLC has raised concerns about the potential for delays in diagnosis and hence an increased frequency of advanced disease at the time of treatment. The timeline for an *EGFR* mutation test should not be more than ten working days.[39] Close collaboration, effective communication, forward planning and efficient co-ordination among the physicians involved in the management of lung cancer is essential for successful and timely *EGFR* mutation testing. Poor collaboration within a multidisciplinary approach to management can result in a delay in starting treatment. The time taken to complete diagnostic investigations is a significant contributor to treatment delays, with delays in completing diagnostic tests often exacerbated by tests being ordered sequentially by multiple physicians. Poor collaboration resulting in an inadequate tissue sample being collected can also contribute to delays because of the need for re-biopsy.[57,58]

Specialists' Commentary: NHC role in a national approach for *EGFR* mutation testing

In our opinion, all patients with non-squamous NSCLC should have timely *EGFR* mutation testing in order that they may receive TKI therapy if they are found to harbour an *EGFR* mutation.

In 2012, the New Zealand National Health Committee (NHC) published a "Rapid Review" outlining issues around *EGFR* testing and TKI provision in New Zealand. In particular, they outlined the importance of what has been termed "co-dependent" technologies: in other words, the fact that first-line EGFR inhibitor prescribing is dependent on the ability to perform *EGFR* testing. Decisions around funding of TKIs in New Zealand fall under the jurisdiction of PHARMAC, whereas access to testing does not. Therefore, last year, a difficult situation evolved when PHARMAC approved funding for and access to gefitinib in the first-line setting for EGFR M+ NSCLC, but there was no unified approach to or funding identified for *EGFR* testing. This initially lead to a somewhat haphazard approach to testing, dependent on testing availability and the willingness of individual services and District Health Boards to fund it.

In 2013, an NHC working party developed draft guidance for the approach to *EGFR* testing in New Zealand, which will then be considered by the National Health Board (NHB). A number of considerations frame this discussion.

Firstly, the issue of the actual test recommended needs evaluation, weighing cost, diagnostic accuracy, quality assurance and availability.

Secondly, the recommended timeframe in which results should be made available and the impact this has on cost needs to be considered: batching of tests or restriction of testing to fewer centres drives down cost but may increase test turn-around time. This is framed by a wider debate regarding turn-around times for pathology reporting itself in lung cancer, including results of immunohistochemistry – in the context that as accurate a subtyping of NSCLC as possible is now required to aid treatment selection such as chemotherapy and also potentially mutation testing. This leads to the issue discussed earlier of who should be tested in New Zealand: all NSCLC, non-squamous NSCLC or those in whom a mutation is deemed more likely to be present?

Finally, the point at which testing should be requested needs to be defined. Pathologist-initiated testing of suitable specimens offers a universal approach without delay, but risks testing patients who may never in practice receive TKIs – either those "cured" or unsuitable for any specific anti-cancer treatment. Whilst clinician-initiated testing might reduce such cases, this also attracts delay – which may itself then lead to unnecessary cost, such as delayed treatment awaiting results. Other "hidden" delays and costs may include retrieving samples already analysed and transportation to a suitable testing centre. Much education of respiratory physicians (who are responsible for arranging diagnostic tissue sampling in most cases) would be required in order to expedite *EGFR* testing and not leave this until MDTs or review by medical oncologists. Recommendations for *EGFR* testing in NZ are likely to be finalised this year.

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