A Canadian Collaboration

Highlights from CLCCO and Beyond

INSIDE THIS ISSUE

LUNG CANCER
Delineating the Treatment Landscape of Lung Cancer in Canada

Insights from Dr. Blais, Dr. Butts, Dr. de Marinis, Dr. Drucker, Dr. Ellis, Dr. Raphael, and Dr. Soulières
New Evidence in Oncology is a publication that provides oncology specialists with scientific data from research presented at international and Canadian oncology conferences. A special feature of the journal, the Canadian Perspective, gives key opinion leaders a forum to discuss recent developments in oncology and to comment on how these advances may shape Canadian clinical practice. In addition, the Investigator Commentary sections provide information on key clinical studies from interviews with principal investigators. New Evidence also publishes discussion and expert opinion papers on timely topics of interest to oncologists in Canada.

Our June 2016 issue presents highlights from the 2016 Canadian Lung Cancer Conference (CLCCO) in Vancouver. This issue reports on presentations and perspectives about the latest diagnostic and therapeutic developments in lung cancer.

We would like to thank Dr. Normand Blais, Dr. Charles Butts, Dr. Filippo de Marinis, Dr. Arik Drucker, Dr. Peter Ellis, Dr. Simon Raphael, and Dr. Denis Soulières for their contributions.

We invite you to visit our website at www.newevidence.com for the online version of New Evidence and more reports on current research.
To be added
Contributors

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After completing his medical degree at the Université de Sherbrooke in 1990, Dr. Blais trained in Internal Medicine, Hematology and Medical Oncology at the Université de Montréal. Thereafter, he took a year’s sabbatical to receive specialized training at McMaster University where he completed a master’s degree in Physiology. He currently practises at the Centre hospitalier de l’Université de Montréal (CHUM) Cancer Centre, where he is Chair of the Thoracic Oncology program and Director of both the fellowship program and clinical research unit in Thoracic Oncology. He also serves on the Genitourinary Oncology team.

Dr. Blais has been the vice-president and webmaster of GEOQ, the Oncology Task Force of Quebec (Groupe d’étude en oncologie du Québec, www.geoq.info), since its creation in 1998. He participated as an organizer and speaker in several of the workshops sponsored by GEOQ, as well as in many other continuing medical education events. He is principal investigator of many studies related to lung cancer, cancer of the pleura, and bladder cancer. Dr. Blais holds a position as Associate Professor in the Faculty of Medicine at the Université de Montréal.

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Contributors (Cont.)

Filippo de Marinis, MD
Dr. Filippo de Marinis has been the Director of the Division of Thoracic Oncology at the European Institute of Oncology (IEO) in Milan, Italy, since November 2013. He earned his medical degree in 1978 from La Sapienza University in Rome, followed by a dual specialization in Lung Diseases (La Sapienza University) and Medical Oncology (La Cattolica University in Rome).

From 1987 to 1991, Dr. de Marinis has been a Member of the Board of Directors of the Medical Hospital School in Rome and from 2007 to 2013 he became an Adjunct Professor in Thoracic Oncology at the Biomedical Campus University of Rome and La Sapienza University. Between 2000 and 2013, Dr. de Marinis was the Director of the First Oncological Pulmonary Division at San Camillo Hospital in Rome. He was a founding Member of the Italian Association of Thoracic Oncology (AIOT) and became its first President in 2007, a post he held for five years.

Dr. de Marinis has been Associate Editor for the Lung Cancer journal from 2011 to 2013. He has published over 170 original papers in international indexed reviews and 14 books/monographers on Thoracic Oncology. Dr. de Marinis is an Expert in Good Clinical Practice Trials on New Antineoplastic Drugs in Lung Cancer (phase II/III).

Arik Drucker, MD, FRCPC
Dr. Drucker is a Medical Oncologist and Associate Professor at the Queen Elizabeth II Health Sciences Centre and Dalhousie University Faculty of Medicine in Halifax. His clinical practice focuses on the treatment of thoracic and breast cancer patients. Dr. Drucker’s interests include research in selective biomarkers; he has previously received grants from the Canadian Breast Cancer Foundation and his current project includes a concordance study of cfDNA in non-small cell lung cancer tumour and plasma specimens.

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Dr. Peter Ellis is a Professor in the Departments of Oncology and Clinical Epidemiology & Biostatistics at McMaster University. He is also Division Head of Medical Oncology at the Juravinski Cancer Centre (JCC). He obtained his medical degree at the University of Sydney. He completed a Masters of Medicine (Clinical Epidemiology) and a PhD, also at the University of Sydney. Dr. Ellis moved to Canada in October, 2000. He is currently Chair of the JCC Lung Disease Site Team, an Executive Member of the National Cancer Institute of Canada (NCIC) Clinical Trials Group Lung Disease Site Committee, and Co-Chair of Cancer Care Ontario’s Practice Guideline Initiative, Provincial Lung Disease Site Group. He is also an investigator on several NCIC and pharmaceutical industry-sponsored multicentre phase III clinical trials in breast and lung cancer.
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Dr. Simon Raphael obtained his medical degree at the University of Western Ontario, where he also completed his specialty training in Anatomical Pathology. He practised medicine and was a faculty member at the University of Western Ontario for 10 years.

Dr. Raphael obtained a position at Sunnybrook Health Sciences Centre and the University of Toronto in 2000. In 2004, he completed his masters of education at the University of Toronto. Dr. Raphael was in charge of Pulmonary Pathology at Sunnybrook Health Sciences Centre and the Odette Cancer Centre for 13 years. During this time, he developed an interest in the pathologists’ role in personalized medicine for Pulmonary Oncology. He worked closely with his clinical colleagues to develop unique and innovative ways to make molecular pathology information readily available.

Since 2013, he has been the Chief of Pathology at North York General Hospital, and has held a faculty appointment as an Associate Professor at the University of Toronto. During this time, he has brought his interest and expertise in delivering personalized medicine in oncology to the wider community.

Denis Soulières, MD, MSc, FRCPC

Dr. Denis Soulières is a Hemato-oncologist and Director of the Special Hematology and Molecular Biology Laboratory at the Centre hospitalier de l’Université de Montréal (CHUM). He is also an Associate Professor at the Université de Montréal. He obtained his medical degree at Université Laval and then trained in Pediatrics, Pediatric and Adult Hematology, and Pediatric and Adult Medical Oncology at the Université de Montréal. He also completed postdoctoral training in clinical development in Switzerland and the United States. His research interests include predictive and prognostic factors in head and neck cancers, Pulmonary Oncology, and Urologic Oncology. In addition, he is interested in the standardization of diagnostic tests in oncology. Dr. Soulières has been involved in clinical trials in non-small cell lung cancer, head and neck cancer, and renal cancer.
A Canadian Update on Recent Advances in Lung Cancer

Lung cancer is the most commonly diagnosed cancer in Canada. It represents approximately 1 in 8 of all new cancer cases in both women and men and accounts for more than 25% of all cancer related deaths.1 Significant therapeutic advances in lung cancer have been made in the past few years. These advances have highlighted the need for a national conference dedicated to lung cancer in Canada, where new medical data, clinical practices, and experiences can be shared and discussed among Canadian physicians.

The Canadian Lung Cancer Conference (CLCCO) is held annually in Vancouver, British Columbia, during the first week of February. The first symposium took place 16 years ago; since then, CLCCO has evolved from a regional meeting to a national symposium and has become a premier event for healthcare practitioners who are interested in improving the treatment and management of lung cancer patients. This event is an Accredited Group Learning Activity, approved by the University of British Columbia (UBC) Division of Continuing Professional Development. The program consists of general sessions for all attendees as well as parallel sessions designed to meet the needs of various specialists, such as medical oncologists, respirologists, radiation oncologists, thoracic surgeons, and oncology nurses.

This year’s conference, held from February 11–12th, highlighted recent advances in the treatment, diagnosis, and staging of lung cancer. This issue of New Evidence includes summaries of key presentations, perspectives from Canadian physicians, and a debate from CLCCO 2016, as well as an interview on lung biopsy and mutation testing, all of which provide insight into current and future clinical practices for lung cancer across Canada.

The Importance of Attending CLCCO

Perspectives from Canadian Lung Experts

Dr. Normand Blais
“[CLCCO] is truly a Canadian ‘go-to’ conference that has to be attended by anyone that is interested in lung cancer in the country.”

Dr. Denis Soulières
“The way we are able to interact [with colleagues at CLCCO] brings us more possibilities of collaborating with friends, so we might down the road change our attitudes of how we practice.”

Recent Developments in EGFR TKI Therapies for NSCLC

A Summary of the Presentation by Dr. Filippo de Marinis at CLCCO 2016

At the Canadian Lung Cancer Conference (CLCCO) 2016 Annual Meeting, Dr. Filippo de Marinis, Director of the Thoracic Oncology Division at the European Institute of Oncology, Milan, Italy, presented an update on new therapeutic developments for lung cancer. His presentation, summarized in this article, highlighted previous findings and recent breakthroughs in targeted therapies for patients with non-small cell lung cancer (NSCLC).

Presently, various treatment options are available for patients with advanced NSCLC, most of which have been developed in the last few years. In 2000, the differentiation between the squamous and nonsquamous forms of NSCLC led to treatment selection being based on the histology of the cancer. A few years later, the discovery of specific mutations in NSCLC led to the use of targeted treatments. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase mutations were the first to be treated with targeted therapies. This ability to identify a molecular target in a tumour through a biopsy, also known as precision medicine, allowed doctors to treat each patient with a drug specific to that particular target.

Since 2004, the landscape of molecular testing in lung adenocarcinoma has evolved drastically, from the identification of a single driver mutation to multiple driver mutations, and most recently multiplex sequencing (the ability to identify multiple mutations in different genomic locations at the same time). Multiplex sequencing plays two important roles: first, it can collect large amounts of data on patient mutations; and second, it can be beneficial in assessing how well a specific therapy works in the presence of certain mutations.

Targeted therapies have been shown to significantly improve survival in patients with driver mutations when compared with nontargeted therapies. A number of clinical trials have compared the efficacy and safety of EGFR tyrosine kinase inhibitors (TKIs), such as afatinib, gefitinib, and erlotinib, to standard chemotherapy. In all of these trials, EGFR TKIs demonstrated a significant improvement in progression-free survival (PFS) when compared with chemotherapy.1-9 (Table 1)

Table 1. Benefit of first-line EGFR TKIs: nine randomized phase III studies

<table>
<thead>
<tr>
<th>Study</th>
<th>TKI</th>
<th>CTx</th>
<th>N</th>
<th>PFS (months)</th>
<th>HR (95% CI)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS1</td>
<td>Gefitinib</td>
<td>Cb/Pac</td>
<td>261</td>
<td>9.5 vs. 6.3</td>
<td>0.48 (0.36–0.64)</td>
<td>21.6 vs. 21.9</td>
</tr>
<tr>
<td>First-signal2</td>
<td>Gefitinib</td>
<td>Cis/Gem</td>
<td>42</td>
<td>8.0 vs. 6.3</td>
<td>0.54 (0.26–1.10)</td>
<td>27.2 vs. 25.6</td>
</tr>
<tr>
<td>NEJ0023</td>
<td>Gefitinib</td>
<td>Cb/Pac</td>
<td>194</td>
<td>10.8 vs. 5.4</td>
<td>0.35 (0.22–0.41)</td>
<td>30.5 vs. 23.6</td>
</tr>
<tr>
<td>WJTOG 34054</td>
<td>Gefitinib</td>
<td>Cis/Doc</td>
<td>172</td>
<td>9.2 vs. 6.3</td>
<td>0.49 (0.33–0.71)</td>
<td>30.9 vs. NR</td>
</tr>
<tr>
<td>OPTIMAL3</td>
<td>Erlotinib</td>
<td>Cis/Gem</td>
<td>164</td>
<td>13.1 vs. 4.6</td>
<td>0.16 (0.10–0.26)</td>
<td>Not mature</td>
</tr>
<tr>
<td>EURTAC4</td>
<td>Erlotinib</td>
<td>Cis/Doc or Gem</td>
<td>174</td>
<td>10.4 vs. 5.1</td>
<td>0.34 (0.23–0.29)</td>
<td>19.3 vs. 19.5</td>
</tr>
<tr>
<td>ENSURE7</td>
<td>Erlotinib</td>
<td>Cis/Gem</td>
<td>217</td>
<td>11.0 vs. 5.6</td>
<td>0.42 (0.27–0.66)</td>
<td>26.3 vs. 25.5</td>
</tr>
<tr>
<td>LUX-Lung 34</td>
<td>Afatinib</td>
<td>Cis/Pem</td>
<td>308</td>
<td>11.1 vs. 6.9</td>
<td>0.47 (0.34–0.65)</td>
<td>31.5 vs. 28.3</td>
</tr>
<tr>
<td>LUX-Lung 65</td>
<td>Afatinib</td>
<td>Cis/Gem</td>
<td>364</td>
<td>11.0 vs. 5.6</td>
<td>0.28 (0.20–0.39)</td>
<td>23.6 vs. 23.5</td>
</tr>
</tbody>
</table>

Cb = carboplatin; CI = confidence interval; Cis = cisplatin; CTx = comparing treatment; Doc = docetaxel; EGFR = epidermal growth factor receptor; Gem = gemcitabine; HR = hazard ratio; NR = not reached; OS = overall survival; Pac = paclitaxel; Pem = pemetrexed; PFS = progression-free survival; TKI = tyrosine kinase inhibitor
Afatinib in LUX-Lung 3 and 6

LUX-Lung 3 and 6 were two pivotal trials that evaluated the efficacy and safety of afatinib versus chemotherapy in the first line in patients with EGFR mutation-positive (M+) NSCLC. Afatinib showed an advantage in PFS when compared with chemotherapy in both trials (LUX-Lung 3: 11.1 months vs. 6.9 months, HR = 0.588; LUX-Lung 6: 11.0 months vs. 5.6 months, HR = 0.288). (Figure 1) These findings, coupled with an improved 12-month PFS with afatinib when compared with chemotherapy in both trials, outlined the advantage of targeted biological agents over chemotherapy.

In addition to positive PFS results, afatinib demonstrated an advantage in overall survival (OS) when compared with chemotherapy in patients with NSCLC carrying an exon 19 deletion (Del19). In this patient population, the combined OS from LUX-Lung 3 and 6 was 31.7 months for afatinib, compared to 20.7 months for chemotherapy (p = 0.0001). (Figure 2) Interestingly, an ancillary study to LUX-Lung 3 demonstrated that reducing the dose of afatinib to below 40 mg could maintain the efficacy achieved with higher doses while minimizing the side effects of the drug. Patients treated with <40 mg of afatinib had a median PFS of 11.3 months when compared with patients treated with ≥40 mg of afatinib who had a median PFS of 11.0 months (p = 0.175).11

Afatinib in LUX-Lung 7

LUX-Lung 7 was the first head-to-head randomized trial to compare a first-generation (gefitinib) to a second-generation (afatinib) EGFR TKI in patients with NSCLC harbouring Del19 or the exon 21 L858R point mutation (L858R). Afatinib had a significantly improved median PFS when compared with gefitinib (11.0 months vs. 10.9 months, HR = 0.73, p = 0.0165). (Figure 3) Additionally, at 18 and 24 months, significantly more patients were progression-free with afatinib when compared with gefitinib (27% vs. 15%; p = 0.0176 and 18% vs. 8%; p = 0.0184, respectively). Interestingly, LUX-Lung 7 showed that the PFS advantage with afatinib versus gefitinib was maintained across the two main EGFR mutation subgroups, Del19 (HR = 0.76 [95% CI: 0.55–1.06]) and L858R (HR = 0.71 [95% CI: 0.47–1.06]).

Figure 1. Progression-free survival with afatinib in LUX-Lung 3 and 6

<table>
<thead>
<tr>
<th></th>
<th>LUX-Lung 3, N = 345</th>
<th>LUX-Lung 6, N = 364</th>
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<tbody>
<tr>
<td></td>
<td>(Afatinib vs. Cis/Pem)</td>
<td>(Afatinib vs. Cis/Gem)</td>
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<tr>
<td>Median PFS</td>
<td>11.1 vs. 6.9</td>
<td>11.0 vs. 5.6</td>
</tr>
<tr>
<td>HR for PFS</td>
<td>0.58</td>
<td>0.28</td>
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<tr>
<td>12-month PFS</td>
<td>47% vs. 22%</td>
<td>47% vs. 2%</td>
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Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Cis/Pem</th>
<th>Cis/Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>230</td>
<td>115</td>
<td>122</td>
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<td>72</td>
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<td>151</td>
<td>41</td>
<td>25</td>
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<td></td>
<td>120</td>
<td>21</td>
<td>8</td>
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<tr>
<td></td>
<td>77</td>
<td>11</td>
<td>1</td>
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<tr>
<td></td>
<td>50</td>
<td>7</td>
<td>0</td>
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<td></td>
<td>31</td>
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<td></td>
<td>10</td>
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Cis = cisplatin; Gem = gemcitabine; HR = hazard ratio; Pem = pemetrexed; PFS = progression-free survival

**Other EGFR TKIs: erlotinib, gefitinib, and dacomitinib**

Other EGFR TKIs, both first- and second-generation, have recently been evaluated in the first-line setting in patients with advanced nonsquamous NSCLC. A randomized, phase II study in Japan (JO25567) evaluated erlotinib alone or with the addition of bevacizumab, an angiogenesis inhibitor. The addition of bevacizumab to erlotinib led to significantly improved PFS when compared with erlotinib alone (16.0 months vs. 9.7 months; HR = 0.54 [95% CI: 0.36–0.79]).13 (Figure 4) While a phase III trial is required to confirm these results, JO25567 demonstrates the potential for the use of EGFR TKIs combination therapies. BEVERLY is a planned phase III study in Italy and other parts of Europe aiming to evaluate the same treatments as JO25567.

Another head-to-head trial comparing two EGFR TKIs was ARCHER 1050. In this randomized, phase III trial, dacomitinib, a second-generation irreversible EGFR TKI, was compared to gefitinib in patients with NSCLC harbouring activating EGFR mutations.14 The trial was completed in Asia in 2015 and the final results are expected soon.

Despite the promising recent advancement in therapies for NSCLC, patients often develop resistance to EGFR TKIs. The most common mechanism of acquired resistance is the exon 20 T790M point mutation (T790M). Other mechanisms include rare EGFR second-site mutations, human epidermal growth factor receptor 2 amplification, small-cell transformation, and MET proto-oncogene amplification.

The accurate identification of these resistant mechanisms is vital to selecting the best second-line treatment for each patient. This process requires re-evaluating the patient, which can be done through a rebiopsy, of the tumour sample. A number of methods are available for rebiopsy including fibre bronchoscopy, transbronchial needle aspiration, thoracoscopic biopsy, mediastinoscopy, and computed tomography-guided fine needle biopsy.

A more recent advancement in obtaining a biopsy sample from a lung tumour is liquid biopsy. In this method, blood is extracted, the plasma and serum are separated, and real-time PCR is performed on the DNA found circulating in the blood.

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**Figure 2. Overall survival in patients harbouring Del19 from LUX-Lung 3 and 6**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n = 236)</th>
<th>Chemotherapy (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months (95% CI)</td>
<td>31.7 (28.1–35.1)</td>
<td>20.7 (16.3–25.6)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.59 (0.45–0.77)</td>
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<tr>
<td>p-value</td>
<td>0.0001</td>
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**Table: Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
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<td>236</td>
<td>119</td>
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<tr>
<td>0</td>
<td>230</td>
<td>113</td>
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<tr>
<td>3</td>
<td>223</td>
<td>103</td>
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<tr>
<td>6</td>
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<td>9</td>
<td>202</td>
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<tr>
<td>48</td>
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<td></td>
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<tr>
<td>51</td>
<td>0</td>
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</tbody>
</table>

CI = confidence interval; Del19 = exon 19 deletion; HR = hazard ratio

Adapted from Yang JC, et al. Lancet Oncol 2015.10
Liquid biopsy allows clinicians to collect important information about the level of expression of a predictive biomarker, such as T790M. The two-day turnaround time of liquid biopsy is also of great benefit to the patient.

**Treatment beyond progression**

Two types of progression can be observed in patients with NSCLC: oligo-progression and systemic progression. When a patient experiences oligo-progression, EGFR TKI treatment can be continued with the addition of a local therapy until systemic progression. At this point, the patient can be treated with second-line therapy that may consist of a third-generation EGFR TKI (targeting the T790M resistance mutation), an agent targeting another resistant gene, or chemotherapy. (Figure 5)

ASPIRATION was a phase II trial assessing the efficacy of first-line erlotinib until Response Evaluation Criteria in Solid Tumors (RECIST) progression, or beyond progression if continued by the investigator, and safety in Asian patients with EGFR M+ NSCLC. Treatment beyond progression led to improved PFS when compared with patients who stopped treatment at progression as determined by RECIST. (Figure 6)

ASPIRATION was an important trial because it showed that it is possible to treat patients with EGFR TKIs beyond the RECIST criteria for progression.

**The emergence of third-generation EGFR TKIs**

A number of third-generation irreversible EGFR TKIs that target the T790M mutation are currently being tested. These include osimertinib, rociletinib, ASP8273, and BI 1482694. (Table 2)

Osimertinib has been evaluated in a number of clinical trials. AURA2 was an open label, single-arm study assessing its efficacy and safety in patients with locally advanced/metastatic NSCLC, whose disease had progressed with previous EGFR TKI therapy and whose tumours were T790M+. The overall response rate in AURA2 was 71%. Furthermore, the duration of response was 7.8 months and the median PFS was 8.6 months. Patients also had a relatively low frequency of treatment-related high-grade adverse events. Importantly, the findings from AURA2 and its predecessor, AURA, were the basis for the FDA granting osimertinib accelerated approval in November 2015.
Another trial evaluating osimertinib is ASTRIS. ASTRIS is a real-world treatment study of single agent osimertinib in patients with T790M+, advanced or metastatic NSCLC, who have received prior therapy with an EGFR TKI. The trial is ongoing in Europe.

Additionally, FLAURA is a planned phase III study evaluating the efficacy and safety of osimertinib versus a standard of care EGFR TKI (gefitinib or erlotinib) in the first line, in patients with locally advanced or metastatic NSCLC. The primary objective of the study is efficacy, as assessed by PFS. A subgroup analysis of patients carrying the T790M mutation is also planned.

Rociletinib is a novel irreversible EGFR TKI that targets activating EGFR mutations and the T790M resistance mutation. It is currently being tested in the TIGER program of clinical trials:

- TIGER-1 is a phase II/III trial comparing rociletinib to erlotinib in the first line in treatment-naïve patients;
- TIGER-2, a phase II trial using rociletinib as second-line treatment for patients with T790M+ NSCLC, has been completed; and
- TIGER-3 is a phase III trial comparing rociletinib versus chemotherapy in patients with NSCLC who have acquired EGFR TKI resistance.

Finally, BI 1482694 is a promising third-generation EGFR TKI. A phase I study was completed in healthy volunteers in Korea. Preliminary results demonstrated that >60% of patients with T790M+ NSCLC responded to BI 1482694. Patients are currently being recruited for one phase I/II and two phase II studies. Two phase III trials are also planned, where BI 1482694 will be evaluated against chemotherapy in the second line in patients with T790M+ NSCLC and in the first line in patients with EGFR M+ NSCLC.
**Figure 5. Algorithm for treatment of EGFR M+ TKI resistance**

- **NSCLC EGFR M+ responder to EGFR TKI**
  - Oligo-progression
  - Systemic first progression
  - Local therapy + EGFR TKI continuation
  - Systemic progression

- **Systemic second-line therapy**
  - Third-generation EGFR TKI*
  - Targeting the resistant gene
  - Chemotherapy

*For T790M.

**Figure 6. ASPIRATION Trial: study design and progression-free survival**

- **Patients ≥ 18 years with stage IV, EGFR M+ NSCLC**
  - Erlotinib
  - PD by RECIST
  - PD by physician assessment

- **PFS (probability)**
  - PFS 1: 11.0 months
  - PFS 2: 14.1 months

EGFR = epidermal growth factor receptor; M+ = mutation-positive; NSCLC = non-small cell lung cancer; T790M = exon 20 T790M resistance mutation; TKI = tyrosine kinase inhibitor

*For T790M.

Adapted from Park K, et al. JAMA Oncol 2016.
Resistance to third-generation EGFR TKIs

A new resistance mutation (C797S) has recently been identified in patients who become resistant to the third-generation EGFR TKI, osimertinib. Early clinical data have suggested that it might be possible to use first-generation EGFR TKIs to treat patients expressing this resistance mutation.

Summary and conclusions

The road in the fight against lung cancer is long and winding. It is, however, a very important road that all patients with lung cancer need to take. Fortunately, recent advances in therapies against lung cancer offer more possibilities and hope than ever before.

References:

As part of our commitment to improving each patient’s treatment journey, Boehringer Ingelheim Canada is dedicated to providing healthcare professionals and patients with resources and tools to support their fight against EGFR mutation-positive metastatic lung cancer. That’s why we developed the GIOTRIF® Patient Kit.

In the GIOTRIF® Patient Kit, you will find:

- GIOTRIF® Patient Booklet and Diary
- Information for caregivers
- Instructions to download the My GIOTRIF App
- Side effect management “tip sheets”
- Doctor-recommended product samples
- GIOTRIF® reminder fridge magnet
- And much more!

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GIOTRIF® (afatinib) is indicated as monotherapy for the treatment of Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor naïve patients with metastatic (including cytologically proven pleural effusion) adenocarcinoma of the lung with activating EGFR mutation(s).1

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Lung Cancer in 2016: The Canadian Context

A Summary of the Presentation by Dr. Peter Ellis at CLCCO 2016

At the 2016 Canadian Lung Cancer Conference (CLCCO), Dr. Peter Ellis, Head of Medical Oncology at Juravinski Hospital and Cancer Centre, Hamilton, Ontario, gave a Canadian perspective on therapeutic developments in lung cancer. His presentation, summarized in this article, highlighted significant changes in systemic therapies for lung cancer as well as the challenges faced when implementing those changes.

The first Western Canada Lung Cancer meeting took place 16 years prior to the 2016 CLCCO. At that time, few options were available for patients with lung cancer and the biggest challenge among oncologists was to ensure that the appropriate patients were considered for chemotherapy. The field of lung cancer has made great advances since then. Presently, there are a plethora of new treatment options available and the main challenge now is how to best integrate them into clinical practice. There are three factors in the treatment of lung cancer that are currently important to Canadian healthcare: the effectiveness of the treatment, the challenges to implementing the treatment, and finally, the costs associated with each treatment.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)

EGFR TKIs are a group of relatively new treatment options for lung cancer and are currently a hot topic of discussion. At the European Society of Medical Oncology Asia 2015 congress, data from the LUX-Lung 7 trial, comparing afatinib with gefitinib as first-line treatments for patients with EGFR mutation-positive non-small cell lung cancer (NSCLC), were presented.\(^1\) Progression-free survival (PFS) significantly favoured afatinib over gefitinib (11.0 months vs. 10.9 months; hazard ratio [HR] = 0.73; \(p = 0.0165\) ). The benefit was consistent across the majority of the prospectively defined patient subgroups. Notably, afatinib appeared to have the most benefit in patients with an Eastern Cooperative Oncology Group performance status of 1. The data also suggested that females may benefit more from afatinib than males. On the other hand, toxicities such as diarrhea, rash, stomatitis, and paronychia were more pronounced with afatinib when compared with gefitinib.

Although the difference in PFS between afatinib and gefitinib was statistically significant and afatinib resulted in a higher response rate when compared with gefitinib, many physicians have questioned whether this small difference is really important. Additionally, the difference in PFS between afatinib and gefitinib was not apparent in the first 12 months of treatment, raising further questions about the clinical relevance of these findings.\(^1\) While the results have so far been promising and afatinib has received reimbursement in all provinces except for Quebec and Prince Edward Island (as of February 2016), it is unclear whether it is the preferred treatment strategy for all patients with mutated EGFR protein.

Immune checkpoint inhibitors

There is great excitement in oncology about implementing immune checkpoint inhibitors into the routine management of patients with lung cancer. Nivolumab, a programmed death-1 (PD-1) inhibitor, has demonstrated superiority over docetaxel in the treatment of both squamous cell carcinoma of the lung (HR = 0.59) and NSCLC (HR = 0.73).\(^2,3\) Additionally, nivolumab showed an approximate three-month improvement in median overall survival (OS) when compared with docetaxel. However, data are inconsistent with regards to the level of PD-L1 expression acting as a predictor of benefit with nivolumab.

Pembrolizumab, another PD-1 inhibitor, has also shown superiority over docetaxel in patients with NSCLC, with survival HRs ranging from 0.61 to 0.71 in patients with at least 1% programmed death-ligand 1 (PD-L1) expression, demonstrating a consistent benefit.\(^4\) A trend was observed in the pembrolizumab arm, where greater benefit was associated with higher PD-L1 expression.
Finally, atezolizumab, a PD-L1 inhibitor, was also superior to docetaxel in the POPLAR trial. It led to an improved median OS in patients with advanced NSCLC (HR = 0.73). Like pembrolizumab, atezolizumab exhibited a greater survival benefit in patients with higher PD-L1 expression.

Despite seemingly positive results, physicians who have examined the results from the CheckMate 057 trial, which compared nivolumab with docetaxel in patients with NSCLC, have varied in their interpretations of the data. The presentation of the CheckMate 057 data at ESMO Asia 2015 suggested that any expression of PD-L1 is associated with nivolumab benefit; however, some experts have challenged that perception. Patients with <1% PD-L1 expression did not appear to have any survival benefit with nivolumab when compared with docetaxel, whereas those with ≥1% PD-L1 expression had a significant survival benefit. While this finding shows that PD-L1 expression is predictive of nivolumab benefit at the lowest level of expression (1%), similar survival curves were also seen in the ≥5% vs. <5% and ≥10% vs. <10% subgroup comparisons. These findings demonstrate that the right level of PD-L1 expression at which nivolumab is beneficial is not clear, and one can argue that the true PD-L1 expression threshold for clinical benefit may well be more than 10%. Further studies are required in order to determine which group of patients could benefit from PD-1 inhibitors and if PD-L1 is indeed the right biomarker to test for in patients with NSCLC.

While PD-1 inhibitors have shown great potential in clinical trials, there are various challenges to implementing them in patient care. The biggest challenge is knowing who to treat with this class of drugs. Questions remain about whether treatment should be limited to patients with high PD-L1 expression or offered to those with any PD-L1 expression level, and whether a fresh tumour sample is required versus an archival one. It is important to remember that patients with ≥10% PD-L1 expression make up about one third of all patients, which is a large number. This forces physicians to think cautiously about what populations to use PD-1 inhibitors in, given the high costs of immunotherapies.

Additionally, the management of toxicities remains a challenge with PD-1 inhibitors. Gastrointestinal, respiratory, and endocrinology-related toxicities have often been associated with such therapies. Education is required at each institution, especially in the emergency department and intensive care units, to accurately identify and properly manage treatment-related toxicities.

Finally, deciding on how long to treat patients with PD-1 inhibitors is another big challenge. It is important to know whether patients are being treated for the right length of time. Such decisions could have a big impact in terms of resources and treatment-associated costs.

**Challenges to personalized medicine**

There are various challenges to personalized medicine in lung cancer in Canada. When discussing biomarker testing, one needs to consider both traditional individual tests and platform testing (such as next generation sequencing). Unfortunately, Canadian healthcare is not yet at a point where access to next generation sequencing is available to everyone across each province. Another challenge that needs to be addressed is when to test patients for specific mutations. Such testing can be performed at the time of diagnosis, relapse, or at every treatment decision point and can have large cost and resource implications. Pathology and diagnostic imaging are two specialties that would be impacted the most by a push for personalized medicine. Subsequently, an important question then arises: is the Canadian healthcare system fully capable and ready to implement these new testing procedures?

**Cost of treatment**

The cost of treatments for lung cancer is currently a hotly debated topic and for good reason. Using a hypothetical 70 kg patient, the cost of nivolumab, given at 3 mg/kg every two weeks, would be $4,110 per cycle, totalling $106,800 per year. Similarly, pembrolizumab given at 2 mg/kg every three weeks would cost $6,160 per cycle or $106,770 per year. If 10 mg/kg of pembrolizumab were to be given every three weeks, the cost would rise to $20,800 per cycle and $533,870 per year. It is clear that these costs have a huge impact on Canadian healthcare from a budgetary perspective. This becomes especially important when one considers data published by Cancer Care Ontario, which shows that the money being spent on new drugs has been rising rapidly for the past few years. Notably, since 2007, the cost of drugs has exceeded the budget set forth by the Ontario government. It is clear that these new drugs are having a financial impact on the Canadian healthcare system and stakeholders have not properly addressed their implications.

**Conclusions**

It is a very exciting time to be an oncologist specializing in lung cancer. One of the main priorities of the healthcare system should be to examine methods to simplify the process of biomarker assessment. The implementation of an immuno-oncology therapy program will require thought, planning, and further education of physicians on the management of the side effects associated with these drugs. Finally, the cost-effectiveness and budgetary impact of the new drugs are likely to be major impediments to implementing therapeutic advances in lung cancer.
References:


At the 2016 Canadian Lung Cancer Conference (CLCCO), New Evidence spoke with Dr. Arik Drucker, staff Medical Oncologist at the Nova Scotia Cancer Centre and Associate Professor of Medicine at Dalhousie University, about the LUX-Lung 7 study and the treatment landscape for non-small cell lung cancer (NSCLC) in Canada.

**New Evidence:** In the LUX-Lung 7 study that compared afatinib to gefitinib in untreated patients with epidermal growth factor receptor (EGFR) mutation-positive NSCLC, afatinib significantly improved progression-free survival (PFS) when compared with gefitinib. Can you comment on this finding?

**Dr. Drucker:** While I believe that PFS is an artificial metric, the LUX-Lung 7 study did show that afatinib was tolerable and demonstrated a survival benefit for a subset of patients with EGFR mutations.

**New Evidence:** What is the main take-home message from the results of LUX-Lung 7? Do you expect your practice to change as a result of these findings?

**Dr. Drucker:** The results of LUX-Lung 7 support the efficacy of afatinib over the earlier generations of EGFR tyrosine kinase inhibitors (TKIs) in the first-line treatment of NSCLC, with an improvement in some components of survival. Practices in our clinic will not likely change based on these results; if a patient is going to receive an EGFR TKI, I believe they should receive the most efficacious of these drugs.

**New Evidence:** What do you prescribe in the second line for patients with acquired EGFR TKI resistance mutations?

**Dr. Drucker:** At our clinic, we recommend patients, who are well enough, undergo a repeat biopsy. Newer drugs are available for patients carrying the exon 20 T790M resistance mutation (T790M) and based on the results of their repeat biopsy, patients progressing on a first-line EGFR TKI could be eligible for clinical trials using these newer agents. If patients are not motivated to undergo a repeat biopsy, or it is not feasible, chemotherapy may be another option. A third potential option could be nivolumab.

**New Evidence:** In your opinion, where do you see the treatment of NSCLC heading in the future in Canada?

**Dr. Drucker:** I believe directing therapy to those patients who have acquired resistance mutations (such as those who are positive for anaplastic lymphoma kinase mutations or T790M mutations) will become important in the future, as newer drugs that are specifically indicated for these subgroups of patients become available. Also, a number of immunotherapy agents will soon be available; they will need to be incorporated into the current treatment landscape and their funding will need to be established.

**New Evidence:** What do you think the role of immunotherapy drugs will be in the treatment of lung cancer?

**Dr. Drucker:** I think immunotherapy drugs will need to find their niche. Based on the current clinical trials, they are mainly beneficial for approximately one-quarter of patients, so a method will be needed to evaluate which patients are likely to benefit from these new drugs.

**New Evidence:** What are your thoughts on the anti programmed death-1 (PD-1) immune checkpoint inhibitors, nivolumab and pembrolizumab, as treatments for NSCLC?

**Dr. Drucker:** The proof of principle with nivolumab and pembrolizumab is excellent, and immuno-oncology has clearly shown superior efficacy and very durable responses in a proportion of patients. However, the majority of patients do not benefit from these drugs. For example, most patients in the CHECKMATE study comparing nivolumab to docetaxel progressed quite quickly. The minority of patients who did respond to nivolumab had a durable response at 18 months of follow-up. The challenge will be to identify the patients that will do well on nivolumab and pembrolizumab.

**New Evidence:** Nivolumab is approved in the United States for the treatment of squamous cell carcinoma of the lung. How do you see the treatment landscape changing if it were to be approved in Canada?

**Dr. Drucker:** Having nivolumab available and accessible in Canada would change practice. There are many patients who would tolerate nivolumab much better than they would tolerate taxane-based chemotherapies in the second line. Also, I think more patients would be eligible to receive nivolumab than chemotherapy because a lower performance status would probably be more acceptable when receiving nivolumab.

**References:**
Is the PD-L1 Biomarker Needed in Squamous Cell Carcinoma of the Lung?

A Summary of the Debate between Dr. Normand Blais and Dr. Charles Butts at CLCCO 2016

At the 2016 Canadian Lung Cancer Conference (CLCCO), Dr. Normand Blais from the Université de Montréal and Dr. Charles Butts from the University of Alberta debated the necessity for programmed death-ligand 1 (PD-L1) biomarkers in the treatment of squamous cell carcinoma (SCC) of the lung. Dr. Blais was asked to defend the ‘Yes’ side of the debate, while Dr. Butts was assigned to the ‘No’ side. Audience voting determined the winner of this light-hearted discussion. This article summarizes the two arguments and concludes with the results of the audience vote.

Is a PD-L1 biomarker needed in SCC of the lung? Yes!

Dr. Normand Blais

The treatment landscape for SCC of the lung is changing rapidly. At CLCCO 2015, immunotherapy was not considered the standard of care and was believed to be inferior to tyrosine kinase inhibitors; this is not true anymore. While PD-L1 biomarker testing may not be ready now, there will be a very important need for a biomarker in the future. This is true not only for SCC of the lung but also for all cancer therapies.

There are three main reasons why PD-L1 biomarker testing is needed: to prescribe immunotherapy drugs to patients who will most likely benefit, to save health care dollars by doing this, and to provide other treatments to patients who are not likely to benefit from immunotherapy.

Two key studies highlight the need to prescribe immunotherapy drugs to patients who are most likely to benefit from them: CHECKMATE-017 (which compared nivolumab to docetaxel in patients with advanced squamous non-small cell lung cancer [NSCLC]) and KEYNOTE-010 (which compared pembrolizumab to docetaxel in PD-L1-positive patients with advanced NSCLC).1,2 In these two studies, approximately 40–50% of patients had a very short progression-free survival (PFS).1,2 (Figure 1) It is very important to identify patients who are likely to respond to a targeted treatment because these patients tend to decline rapidly; if they do not respond to first-line therapy they are unlikely to receive another treatment. Therefore, by identifying patients who are not likely to respond to a drug, potentially better options can be given to them.

In terms of health economics, it is clear that the Canadian health care system will not be able to afford immunotherapy agents for every patient with lung cancer. The National Institute for Health and Care Excellence (NICE) in the U.K. has estimated that the actual cost increment to treat patients with nivolumab is approximately £109,000–£129,000 per quality-adjusted life year (QALY) gained. When translated into Canadian dollars, the incremental cost-effectiveness ratio per QALY is approximately $200,000 per year. This is not within the boundaries of a cost-effective treatment. For this reason, it is important that PD-L1 biomarker testing is conducted.

While PD-L1 is not yet ready to be used for testing, the current data suggest that it will be useful as a biomarker. In both CHECKMATE-017 and KEYNOTE-010, as PD-L1 expression increased, increased PFS and overall survival (OS) benefits from immunotherapy were observed.1,2 (Table 1) Also, as the percentage of PD-L1 expression required to receive immunotherapy is increased, the number of patients receiving this therapy decreased. A higher threshold would result in savings of health care dollars.

An interesting study that shows the potential impact of PD-L1 testing is the POPLAR study, which compared atezolizumab to docetaxel in previously treated patients with NSCLC.3 In this trial,
the only patient subgroup to have increased PFS benefit with docetaxel compared to atezolizumab was the group who did not express PD-L1 in tumour cells or immune cells.3,4 (Figure 2) This pattern was repeated in the OS data.3,4 (Figure 3) The PD-L1-negative group comprised 32% of the study population, suggesting that 32% of patients will not benefit from immunotherapy. PD-L1 testing would allow immunotherapy to be targeted to the remaining patients who could benefit.

Mutational burden is another method by which patients could be selected for immunotherapy treatment. In a study published in 2015, when patients treated with pembrolizumab were stratified by mutational burden, a significant separation of the PFS curve was observed (HR = 0.15, 95% CI = 0.06–0.39, \( p = 0.0001 \)).5 (Figure 4)

The history of biomarker development in Canada shows that acceptance of a biomarker takes time. Both epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) biomarkers were discussed for years before being accepted; now it is generally accepted practice in Canada to target EGFR and ALK treatments to appropriate patients. The development of PD-L1 as a biomarker is still in its early phases; history suggests that in time it too will be accepted in Canada. NICE has also examined the data for PD-L1 and stated that it is a biomarker to be considered for future development.

There is interest for PD-L1 testing in the medical community. In the U.S., the National Comprehensive Cancer Network has collaborated with the National Institutes of Health to conduct a broad analysis of PD-L1 testing with all of the current drugs being used, which will greatly increase the data available for PD-L1 testing. The Canadian ALK group has previously shown that large-scale collaborations are useful in biomarker development; this collaboration was instrumental in the evaluation of ALK throughout the world.6 The U.K. National External Quality Assessment Service has also demonstrated that with time, standardization and reproducibility of biomarker assays improve.

A PD-L1 biomarker may not be necessary at the present time but it will be needed in the near future because of economic issues. In his comment on the KEYNOTE-010 study, Dr. Mok said: “The cost-effectiveness of immune checkpoint inhibitors is particularly difficult to evaluate. The drugs are expensive and only some patients may benefit. Ideally, cost-effectiveness can be established if a robust biomarker for response is identified, thus limiting the use of treatment to patients who would benefit most.”7 Even Dr. Butts has acknowledged the need for an immune-related biomarker. The data are quite compelling to suggest that a biomarker will be developed in the future, and acknowledging the need for a biomarker will allow us to work on and ultimately accomplish this goal.
Table 1. Survival stratified by PD-L1 status in the CHECKMATE-017 and KEYNOTE-010 trials

<table>
<thead>
<tr>
<th>PD-L1 expression level</th>
<th>Percentage of patients (%)</th>
<th>HR for PFS</th>
<th>HR for OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nivolumab vs. Docetaxel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.62</td>
<td>0.59*</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>38</td>
<td>0.66</td>
<td>0.58</td>
</tr>
<tr>
<td>&gt;1%</td>
<td>44</td>
<td>0.67</td>
<td>0.69</td>
</tr>
<tr>
<td>&gt;5%</td>
<td>30</td>
<td>0.54</td>
<td>0.53</td>
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<tr>
<td>&gt;10%</td>
<td>25</td>
<td>0.58</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Pembrolizumab vs. Docetaxel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (&gt;1%, SCC)</td>
<td></td>
<td>0.86</td>
<td>0.74</td>
</tr>
<tr>
<td>1–50% (NSCLC)</td>
<td>59</td>
<td>0.76</td>
<td>0.76</td>
</tr>
<tr>
<td>&gt;50% (NSCLC)</td>
<td>41</td>
<td>0.59</td>
<td>0.53</td>
</tr>
</tbody>
</table>

HR = hazard ratio; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; SCC = squamous cell carcinoma

* Rejected by NICE.

**Figure 2. PFS stratified by PD-L1 expression in the POPLAR trial**

<table>
<thead>
<tr>
<th>Subgroup (% of enrolled patients)</th>
<th>Median PFS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3 (16)</td>
<td>Atezolizumab n = 144</td>
</tr>
<tr>
<td></td>
<td>Docetaxel n = 143</td>
</tr>
<tr>
<td>TC2/3 or IC2/3 (37)</td>
<td>7.8 (4.0–11.5)</td>
</tr>
<tr>
<td></td>
<td>3.9 (1.9–5.7)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3 (68)</td>
<td>4.0 (2.5–6.9)</td>
</tr>
<tr>
<td></td>
<td>2.8 (1.9–3.9)</td>
</tr>
<tr>
<td>TCO and IC0 (32)</td>
<td>3.3 (2.7–5.5)</td>
</tr>
<tr>
<td></td>
<td>3.0 (2.8–4.1)</td>
</tr>
<tr>
<td>ITT (N = 287)</td>
<td>1.9 (1.4–4.2)</td>
</tr>
<tr>
<td></td>
<td>4.1 (2.8–5.6)</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IC0 = immune cells with <1% PD-L1 expression; IC1 = immune cells with >1% and <5% PD-L1 expression; IC2 = immune cells with ≥5% and <10% PD-L1 expression; IC3 = immune cells with ≥10% PD-L1 expression; ITT = intent to treat; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; TC0 = tumour cells with <1% PD-L1 expression; TC1 = tumour cells with >1% and <5% PD-L1 expression; TC2 = tumour cells with ≥5% and <10% PD-L1 expression; TC3 = tumour cells with ≥10% PD-L1 expression

* Unstratified HR for subgroups and stratified HR for ITT. Data cut-off: Jan. 30, 2015. Adapted from Spira A, et al. ASCO 2015:8010.4
HR = hazard ratio; IC = immune cells; IC0 = immune cells with <1% PD-L1 expression; IC1 = immune cells with \( \geq 1\% \) and <5% PD-L1 expression; IC2 = immune cells with \( \geq 5\% \) and <10% PD-L1 expression; IC3 = immune cells with \( \geq 10\% \) PD-L1 expression; ITT = intent to treat; PD-L1 = programmed death-ligand 1; TC = tumour cells; TC0 = tumour cells with <1% PD-L1 expression; TC1 = tumour cells with \( \geq 1\% \) and <5% PD-L1 expression; TC2 = tumour cells with \( \geq 5\% \) and <10% PD-L1 expression; TC3 = tumour cells with \( \geq 10\% \) PD-L1 expression

* Unstratified HR for subgroups and stratified HR for ITT. Data cut-off: Jan. 30, 2015.
Adapted from Spira A, et al. ASCO 2015:8010.4

Figure 3. OS stratified by PD-L1 expression in the POPLAR trial

Figure 4. PFS stratified by mutational burden

PFS = progression-free survival
Adapted from Rizvi NA, et al. Science 2015.5
Is a PD-L1 biomarker needed in squamous carcinoma of the lung? No!

Dr. Charles Butts

It is generally accepted that there is a need for a biomarker in SCC of the lung; the question being posed in this debate is whether PD-L1 is that biomarker. To answer this question, we must determine if PD-L1 status is predictive of benefit in patients with squamous NSCLC.

The most relevant benefit for patients with NSCLC is OS; PFS is ultimately irrelevant for patients. While response was initially used to develop PD-L1 as a biomarker, this was done because there were no randomized trials or controls available to measure OS. The gold standard is randomized, phase III data, and there is only one randomized, phase III trial that measures the ability of PD-L1 to predict an OS benefit in patients with squamous NSCLC: the CHECKMATE-017 study.1,8 In this study, patients with NSCLC had been previously treated and PD-L1 status was determined retrospectively; OS was the primary endpoint. (Figure 5) This study found a significant improvement in OS with nivolumab compared to docetaxel.1,8 (Figure 6) However, the trial also showed that the benefit of nivolumab was independent of PD-L1 expression; at all thresholds of PD-L1 expression, for both OS and PFS, the interaction between nivolumab benefit and PD-L1 status was not significant. (Figure 7) In their paper, the authors of CHECKMATE-017 stated: “PD-L1 expression was neither prognostic nor predictive of any of the efficacy end points.”

Dr. Blais also mentioned the KEYNOTE-010 trial, but the data from this trial are not relevant to squamous NSCLC. Only 21% of patients in the KEYNOTE-010 study had squamous NSCLC, and there was no statistical benefit of pembrolizumab in the SCC population of this study.2 More importantly, this study excluded patients with tumours not expressing PD-L1; therefore, it is not possible to determine if PD-L1 status was predictive of benefit.2

While the KEYNOTE-010 study does not provide information about the usefulness of PD-L1 as a biomarker, it does provide information about the treatment strategy of selecting patients for immunotherapy based on PD-L1 status. In the KEYNOTE-010 study, 20% of patients were excluded because they did not have tissue to perform PD-L1 testing; another 45% were excluded because they were negative for PD-L1 expression.2,9 (Figure 8) In the remaining 38% of patients, a significant OS benefit was observed in patients treated with pembrolizumab.2,9 (Figure 9)

This provides an interesting counterpoint to the CHECKMATE-017 study, where patients were treated with immunotherapy regardless of PD-L1 status.1 It seems logical to conclude that if PD-L1 is an effective biomarker for predicting the benefit of immunotherapy, then the patient population that was selected for PD-L1 status should have a much greater benefit than the population that was not selected for PD-L1 status. However, this was not the case; the OS benefits in the CHECKMATE-017 and KEYNOTE-010 trials were quite similar.1,2 (Table 2) While it is problematic to compare between studies, these data at least suggest that PD-L1 is not an effective biomarker.

Dr. Blais quoted Dr. Mok’s comments on the KEYNOTE-010 trial, which highlighted his opinion on the need for a...
**Figure 6. OS in the CHECKMATE-017 trial**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Overall survival (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Nivolumab (n = 135)</td>
</tr>
<tr>
<td></td>
<td>Docetaxel (n = 137)</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
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<tr>
<td>3</td>
<td>80</td>
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<tr>
<td>6</td>
<td>70</td>
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<td>9</td>
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<td>30</td>
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<td>33</td>
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**Number of patients at risk**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>135</td>
<td>137</td>
</tr>
<tr>
<td>3</td>
<td>113</td>
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<tr>
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</tr>
<tr>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Median OS, months (95% CI)**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Nivolumab (n = 135)</th>
<th>Docetaxel (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.2 (7.33–12.62)</td>
<td>6.0 (5.29–7.39)</td>
<td></td>
</tr>
</tbody>
</table>

**Number of events**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>103</td>
<td>122</td>
</tr>
</tbody>
</table>

**HR = 0.62 (0.48–0.81); p = 0.0004**

CI = confidence interval; HR = hazard ratio; OS = overall survival

*Minimum follow-up for survival: 18 months.
Adapted from Reckamp K, et al. WCLC 2015:10:ORAL02.01.*
### Figure 7. Nivolumab benefit was independent of PD-L1 expression in the CHECKMATE-017 trial

<table>
<thead>
<tr>
<th>PD-L1 expression (%)</th>
<th>Patients, n</th>
<th>Unstratified HR (95% CI)</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab</td>
<td>Docetaxel</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>54</td>
<td>52</td>
<td>0.58 (0.37–0.92)</td>
</tr>
<tr>
<td>≥1</td>
<td>63</td>
<td>56</td>
<td>0.69 (0.45–1.05)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>75</td>
<td>69</td>
<td>0.70 (0.47–1.02)</td>
</tr>
<tr>
<td>≥5</td>
<td>42</td>
<td>39</td>
<td>0.53 (0.31–0.89)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>81</td>
<td>75</td>
<td>0.70 (0.48–1.01)</td>
</tr>
<tr>
<td>≥10</td>
<td>36</td>
<td>33</td>
<td>0.50 (0.28–0.89)</td>
</tr>
<tr>
<td>Not quantifiable</td>
<td>18</td>
<td>29</td>
<td>0.39 (0.19–0.82)</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>54</td>
<td>52</td>
<td>0.66 (0.43–1.00)</td>
</tr>
<tr>
<td>≥1</td>
<td>63</td>
<td>56</td>
<td>0.67 (0.44–1.01)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>75</td>
<td>69</td>
<td>0.75 (0.52–1.08)</td>
</tr>
<tr>
<td>≥5</td>
<td>42</td>
<td>39</td>
<td>0.54 (0.32–0.90)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>81</td>
<td>75</td>
<td>0.70 (0.49–0.99)</td>
</tr>
<tr>
<td>≥10</td>
<td>36</td>
<td>33</td>
<td>0.58 (0.33–1.02)</td>
</tr>
<tr>
<td>Not quantifiable</td>
<td>18</td>
<td>29</td>
<td>0.45 (0.23–0.89)</td>
</tr>
</tbody>
</table>

*CI = confidence interval; HR = hazard ratio; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival

Adapted from Reckamp K, et al. WCLC 2015;10:ORAL02.01."
* One patient excluded from efficacy analyses because of noncompliance with imaging guidelines for prebaseline scans.
† Patients who received the maximum number of docetaxel doses permitted per local guidelines.
Adapted from Herbst RS, et al. ESMO Asia 2015:LBA3.

$PD-L1 = \text{programmed death-ligand 1; q3w = every three weeks; TPS = tumour proportion score}$
**Table 2. Comparison of efficacy between the CHECKMATE-017 and KEYNOTE-010 trials**

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Median OS (months)</th>
<th>1-year OS (%)</th>
<th>ORR (%)</th>
<th>HR for survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab CHECKMATE-017</td>
<td>9.2</td>
<td>42</td>
<td>20</td>
<td>0.62</td>
</tr>
<tr>
<td>Pembrolizumab KEYNOTE-010 TPS ≥1%</td>
<td>10.4</td>
<td>43</td>
<td>18</td>
<td>0.71</td>
</tr>
</tbody>
</table>

*HR = hazard ratio; ORR = overall response rate; OS = overall survival; TPS = Tumour Proportion Score*
biomarker for immune checkpoint inhibitors. However, in the same article Dr. Mok also wrote: “At present, there appear to be no solid data to support the routine application of PD-L1 expression as a predictive biomarker before the use of immune checkpoint inhibitors.” He agrees with the authors of the CHECKMATE-017 study that while there is a need for a biomarker, PD-L1 is not the biomarker that is needed.

Another issue with the use of PD-L1 as a biomarker is the increased burden that will be placed on pathologists. There will be an increased number of biopsies performed with PD-L1 testing, and therefore increased analysis by pathologists. Also, at present the pathologist must identify one cell in 100 that is positive to determine if a patient will receive immunotherapy. We cannot ask pathologists to undertake this increased workload without solid evidence to support it.

A biomarker is needed in the treatment of SCC of the lung, particularly for expensive therapies or therapies associated with toxicity. However, PD-L1 is not the biomarker that is needed. By refraining from PD-L1 testing, the number of patients who might benefit will be maximized. This strategy will also save time, save tissue, save resources, and perhaps save our pathologists.

**Conclusion**

While the results of the audience vote were very close, the winner of the debate was Dr. Butts with 58% of the vote.

**References:**

New Evidence: What is the current state of mutation testing in non-small cell lung cancer (NSCLC) in Canada?

Dr. Raphael: Over the last few years, mutation testing has become more prevalent for patients with non-small cell lung cancer (NSCLC) in Canada. However, its significance is unfortunately less well known among some members of the general medical community. Given the high incidence and mortality of lung cancer, general physicians should be more educated on the significance of mutation testing and everyone should know that targeted treatments and mutation testing can offer hope to a sizeable portion of lung cancer patients.

The state of mutation testing in Canada currently varies from province to province. There is a great deal of uncertainty about who should organize the tests, what genes and tissues should be tested, at what stage to conduct testing, and so on. Given that the molecular pathology field is constantly and rapidly evolving, a greater effort must be made to keep up with the progress.

New Evidence: Have there been any major changes in mutation testing protocols in the recent past?

Dr. Raphael: The emergence of next-generation multiplex sequencing methods has greatly widened the number of abnormalities that we can detect. We are now beginning to look for less prevalent mutations in genes, such as proto-oncogene B-Raf (BRAF) and the ROS proto-oncogene (ROS). However, this raises the question of whether we should test a rare gene or not, given that mutations in BRAF and ROS occur in only a small percentage of patients with NSCLC.

In addition, multiplex testing, which has allowed us to test for several mutations at the same time instead of in a stepwise fashion, can significantly improve turnaround times. At present, multiplex testing is available in cancer centres throughout Toronto and is also becoming widespread in other up-to-date large cancer centres.

New Evidence: Could you elaborate on the new testing protocol you established at Sunnybrook Health Sciences Centre?

Dr. Raphael: Lung cancer has always been stigmatized and, to a degree, ignored. When the new targeted therapies came out, I recognized that they could really bring some hope to patients with lung cancer. My colleagues and I came to the agreement that pathologists are well suited for ordering mutation tests and handling the information. As pathologists, we make the diagnosis and it is easier for us to organize the transport and triage of tissue. All of these factors put us in a good position to organize mutation testing.

At Sunnybrook, I set up a dedicated email address for requesting mutation tests and made sure that this address was included in every patient report. Once the results came back, I relayed them to the clinician as an addendum to an already issued report.

For patients who were referred to Sunnybrook after they had been diagnosed, we trained intake clerks at the Odette Cancer Centre to read the referral reports and recognize key terms such as NSCLC, so that they could identify patients who needed the test on intake. Both of these simple steps sped up the process and had a significant positive effect on patients.

The whole process of getting everyone on board, implementing the email system, and training the intake clerks only took a couple of months and was not very difficult.

New Evidence: Could you tell us about the new reflex testing protocol that you introduced at North York General Hospital?

Dr. Raphael: By the time I came to North York General, mutation testing had been fully funded by Cancer Care Ontario (CCO) and was no longer funded by pharmaceutical companies. This was vital, given that funding is by far the biggest barrier to introducing any new test in a hospital lab. I was also quite familiar with epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) testing. As a result, the introduction of reflex testing was very easy.

In reflex testing, all patients diagnosed with NSCLC automatically undergo mutation testing, instead of a clinician individually ordering tests based on cancer stage. This eliminated the idea of using a dedicated email address to tell the Pathology Department when to order the test.

Convincing the pathologist in the department to make these changes was relatively straightforward, because we had data showing that reflex testing reduced the turnaround time for mutation tests; this is important for NSCLC patients because of their short life expectancy. I also think that being the chief of pathology certainly helped with convincing people. I certainly received a lot of positive feedback from other physicians about the changes.
New Evidence: Did you face any challenges while implementing these new mutation testing protocols?

Dr. Raphael: Every time there is a transition from one method to another that involves new responsibilities, there is always a bit of concern about how much more time the new approach will take, how much paperwork needs to be completed, or how many resources it will require. Given that the medical oncologists were the ones responsible for ordering mutation testing in the past, this was something new for the pathologists. The old idea was that a physician would need to be in direct contact with the patient in order to know who should be tested. I really had to convince people that this new system could be used just as well and could be even a bit faster. Naturally, a few people were less receptive than others and needed some convincing, but in the end everything worked out great.

New Evidence: Do you plan to implement the approaches you used at Sunnybrook Hospital and North York General Hospital at other institutions?

Dr. Raphael: I have visited a number of hospitals and spoken to many physicians, especially pathologists, about the approach and have tried to bring this system to other hospitals. It is important to recognize the differences between hospitals in how they do things and encourage each hospital to figure out the best way for them to implement mutation testing. More often than not, I find myself pleasantly surprised as to how slickly and efficiently each hospital is able to apply these methods. Often, I am the one who ends up learning something new from them.

I strongly advocate reflex testing. I believe that it is only a matter of time before reflex testing becomes the standard of care for lung cancer, and I see absolutely no reason to not test all patients with an NSCLC diagnosis.

I also like to advocate that pathologists be the major players in implementing these methods, given their role in the lab and advanced knowledge of the diagnosis. But it does not have to be only pathologists; the important thing is to choose individuals who are committed and who will feel that organizing this test is their job.

New Evidence: What is the importance of reflex testing in lung cancer?

Dr. Raphael: Reflex testing does not require a separate clinician order for each case and may help ensure expedited and consistent routing of specimens for molecular testing. Furthermore, reflex testing is desirable because eventually most lung cancer patients will require the mutation information at some point during their treatment.

I believe that we need to look at other cancers in order to learn from them, because the ideas are not that different. When we look at breast cancer, for example, there were a few decades of lead-in and lessons in terms of predictive markers of response to drugs that we can study and apply to lung cancer. Reflex testing for estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) receptors has been the standard of care in breast cancer for a long time. As such, great efforts are made to ensure the accuracy, quality, and turnaround speeds for this test; these parameters are very carefully regulated by CCO.

We aim to eventually make reflex testing for NSCLC as natural as mutation testing in patients with breast cancer. Mutation testing in lung cancer should never be the exception; it should be the rule.

New Evidence: How important is a multidisciplinary approach in implementing new testing protocols?

Dr. Raphael: A multidisciplinary approach is just as essential here as in any other area of complex cancer care. The most important thing is to have someone in the pathology lab, such as a pathologist, and someone on the clinical side work together. In reflex testing, it is important that there is good communication between the different specialists.

The pathologist is often the one making the decision to test, organizing the testing, and ensuring an accurate flow of information. The pathologist also has some other important jobs. One job would be deciding how the tissue will be triaged to answer some questions about the tumour: Is it malignant? Is it non-small cell? Is it EGFR-positive? Steps must be taken to avoid tests that would unnecessarily use up biopsied tissue. As an example, in the case of a clear adenocarcinoma, a positive thyroid transcription factor 1 (TTF1) stain is sufficient before sending the tissue away for EGFR testing.

Furthermore, it is important that referring pathologists send the tissue for sequencing as long as they are able to identify that it is malignant and non-small cell. Most of the time, the testing lab can provide an accurate answer with relatively small amounts of tissue. This will become especially true as we move into an era of next-generation sequencing. Our goal is to avoid unnecessary biopsies, which can be quite invasive and carry substantial morbidities.

In terms of tissue procurement, three specialists are involved: interventional radiologists, pulmonologists, and thoracic surgeons. Radiologists and pulmonologists have to get an adequate amount of tissue in the right format for testing. For cytologic samples from radiologists or pulmonologists, a cell block is very useful whereas smears are of much less or no use in mutation testing. They have to make sure that the collected sample is appropriate not only for tumour identification and staging, but also for mutation testing; for example, bony tissue is usually not useful in this context.
appropriate for EGFR testing.\(^9\)

In my experience, I have seen great multidisciplinary collaboration.

**New Evidence:** What are some other suggestions for implementing new testing protocols in hospitals?

**Dr. Raphael:** Given the complex organization of any hospital, simplicity, ease, and uniformity are important. Busy hospital employees tend to give up on things that are too complicated or involve too much paperwork and bureaucracy. The more uniform the approach — and that is why I advocate reflex testing — the more likely it is that you are going to get things done.

One simple and straightforward method to order testing is the use of obligatory synoptic reports. These are like advanced drop-down lists that require the pathologist to fill in information about various aspects of a diagnosis, including mutation status, before they can complete the case.\(^16\)

Another good practice is to organize the testing so that the pathologist can order it through one click in their lab information system or LIS, reducing ordering time to about 30 seconds. This approach has already been implemented at some Ontario hospitals.

Last, here at North York, we are exploring a new approach in which we remotely access the originators’ LIS and enter the test results. This means that we do not have to fax the results and they do not have to retype them. It is amazing how much hospital information is sent by fax — who uses faxes anymore? This way, if the mutation testing lab can put the report directly into the original institution’s LIS, errors are eliminated and the reporting happens on the same day.

**New Evidence:** Is it feasible to have a standard algorithm that can be used across Canada to reduce disparities between testing centres?

**Dr. Raphael:** I am an advocate of finding what works best at each institution. I do not believe it would be feasible to set a national standard for mutation testing in Canada, because healthcare is a provincial responsibility. However, I expect that within each province, the process will become more organized and more controlled.

What absolutely must be uniform are the expectations of how well and how quickly the test will be done. I believe that you have to adhere to certain parameters of accountability, accuracy, flow of information, and confidentiality, as with any other healthcare activity in a publicly funded system.

Mutation testing in lung cancer evolved in a peculiar environment. At first, the tests were sponsored only by pharmaceutical companies, allowing for little uniformity in the approach.\(^1\) We are now transitioning into a period where it is more regulated. Just as it is being done for mutation testing in breast cancer, I believe we will soon get there for lung cancer too — CCO will fund the tests, organize programs, and demand accountability from all involved.\(^17\)

The encouraging thing is that the introduction and the implementation of a uniform testing approach is happening faster in lung cancer than it did in breast cancer.

**New Evidence:** What are some benchmarks that all testing protocols should strive to meet?

Dr. Raphael: When discussing benchmarks, there are two things to consider: what genes to test for and how fast can results be made available.

The guideline from the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP), which was endorsed by the American Society of Clinical Oncology (ASCO), states that all individual mutations with an incidence rate of at least 1% in EGFR-mutated lung adenocarcinomas should be included in clinical EGFR mutation testing.\(^3\) The guideline also defines the order in which the genes should be tested.\(^3\) This will likely not be an issue in the near future with next-generation sequencing, which will allow for a larger number of exons to be tested routinely and all at once.\(^3\)

As for turnaround times, the current guideline recommends ten working days.\(^1\) I strongly believe that we can do better than that. Many patients diagnosed with lung cancer do not have two weeks to wait for their results to come back because of their short life expectancy, which is often in months or even weeks.\(^3\) Using the algorithms that we have submitted to CCO, which prioritize saving time, we hope to get the turnaround time down to eight days from the moment of sample collection.

As an example, when a hospital sends tissue to a reference centre for testing, the pathologist at the centre selects an area of the tumour for testing.\(^3\) We have proposed that the originating pathologist select the area, which means that the tissue can come in and be tested right away. If tests are batched optimally, the actual testing protocol can be completed in just 36 hours.

**New Evidence:** What is the role of advocacy in improving the state of mutation testing in lung cancer?

**Dr. Raphael:** Advocacy is important in closing some gaps. Organizations such as Lung Cancer Canada have been doing a great job raising awareness and funding conferences so that healthcare professionals can discuss disparities in testing.
Among the general public, there is a negative perception associated with lung cancer, as well as a misconception about the outcomes of diagnosed patients — more advocacy is required to raise awareness on these topics. There is an assumption that lung cancer is the patient’s fault because of their smoking habits. Furthermore, when I was a medical student, lung cancer was essentially a death sentence. Now at Sunnybrook, there is a clinic for long-term survivors of lung cancer. For someone of my generation, that is an oxymoron — who ever heard of a long-term survivor of lung cancer?

However, we now have the potential to change these misconceptions by highlighting the great advances that have been made recently in fighting this deadly disease. Everyone needs to know that there is now hope for patients with lung cancer, which is something you could not say a few decades ago.

**New Evidence:** What changes would you like to see in mutation testing in the near future?

**Dr. Raphael:** The number of mutations that must be tested will probably increase in the future, so I anticipate that we will have to widen our spectrum of testing.

As the cohort of patients who have been treated for a long time increases, things like mutation resistance will become more of an issue and we will have to work harder in order to deal with them. Ideally, labs will have to adjust to this rapidly changing field so that they can keep up with which mutations to test for and ensure that information is reported in a clinically comprehensible and meaningful manner.

I would also like to see more coherent funding for all genetic testing across each province. This must be a priority if we are to truly offer first-class healthcare to our patients. I anticipate that, as time goes on, testing technology will become more standardized, cheaper, faster, and easier, and I hope that eventually all thoracic centres will be able to do their own testing.

Last, I hope that my fellow pathologists will recognize that these tests are the future and that they will make these tests a part of their routine practice. They need to be as involved as possible in the organization of these methods so that we can provide patients with a complete picture of their cancer; in other words, truly personalized medicine.

**New Evidence:** How important is a repeat biopsy for patients with NSCLC who have progressed after EGFR tyrosine kinase inhibitor (TKI) therapy?

**Dr. Raphael:** Repeat biopsy is an evolving area where practice patterns are just being established in line with new advances in technologies and medicines. Although a repeat biopsy may be useful in identifying changes in tumour characteristics, it carries a risk of complications, which patients and their physicians usually want to avoid. In lung cancer, a repeat biopsy can be hindered by the location and accessibility of the lesion and, as a result, is not performed as often as it is in other cancers, such as prostate cancer. However, there is a need to establish whether a new mutation that may respond to new agents has occurred in a tumour. This need is bringing about a change in practice and leading to investigations into non-invasive procedures such as liquid biopsies. Another reason for performing a repeat biopsy after relapse on EGFR TKI therapy is the occurrence of phenotypic changes in the tumour, such as the presence of small cell carcinoma of epithelial mesenchymal transformation.

**New Evidence:** What are the advantages of liquid biopsy?

**Dr. Raphael:** Liquid biopsy in oncology is an exciting technology that I see playing a role in lung cancer as well as other tumours. Both circulating cell-free DNA and the genetic analysis of circulating tumour cells are being actively explored. In patients with NSCLC, liquid biopsy can provide the genetic landscape of all cancerous lesions present in the blood and may play a role in determining when they are in remission or in relapse. Additionally, during relapse, the technique allows us to determine what percentage of circulating tumour cells harbour a treatable resistance mutation and to decide when to initiate therapy. Finally, liquid biopsy may prove to be useful in cancer as it allows for the collection of a sample of only the type of tumour cells that are in circulation and may metastasize. It also gives us an idea of the tumour as a whole instead of just the biopsied section.

**New Evidence:** What are your thoughts on third-generation EGFR TKIs and how do you see them affecting healthcare in the future?

**Dr. Raphael:** Third-generation EGFR TKIs may offer new possibilities and alternatives to patients with NSCLC who have developed resistance to an earlier-generation EGFR TKI. They tend to have less toxicity and offer more inhibitory specificity when compared with previous-generation EGFR TKIs. Furthermore, third-generation EGFR TKIs may offer an alternative to traditional chemotherapy. Third-generation EGFR TKIs may lead to better prognosis and provide patients with advanced EGFR mutation-positive NSCLC with more tolerable therapy options.
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