Canadian consensus: oligoprogressive, pseudoprogressive, and oligometastatic non-small-cell lung cancer

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ABSTRACT

Background Little evidence has been generated for how best to treat patients with non-small-cell lung cancer (NSCLC) presenting with rarer clinical scenarios, including oligometastases, oligoprogression, and pseudoprogression. In each of those scenarios, oncologists have to consider how best to balance efficacy with quality of life, while maximizing the duration of each line of therapy and ensuring that patients are still eligible for later options, including clinical trial enrolment.

Methods An expert panel was convened to define the clinical questions. Using case-based presentations, consensus practice recommendations for each clinical scenario were generated through focused, evidence-based discussions.

Results Treatment strategies and best-practice or consensus recommendations are presented, with areas of consensus and areas of uncertainty identified.

Conclusions In each situation, treatment has to be tailored to suit the individual patient, but with the intent of extending and maximizing the use of each line of treatment, while keeping treatment options in reserve for later lines of therapy. Patient participation in clinical trials examining these issues should be encouraged.

Key Words Non-small-cell lung cancer, advanced; NSCLC, advanced; oligometastatic disease; oligoprogression; pseudoprogression

Curr Oncol. 2019 Feb;26(1):e81-e93

BACKGROUND

Little evidence has been generated for how best to treat patients with non-small-cell lung cancer (NSCLC) presenting with rarer clinical scenarios, including oligometastases, oligoprogression, and pseudoprogression. In each of those scenarios, oncologists have to consider how best to balance efficacy with quality of life, while maximizing the duration of each line of therapy and ensuring that patients are still eligible for later options, including clinical trial enrolment.

METHODS

An invited expert panel of thoracic oncology specialists in medical and radiation oncology and anatomic and molecular pathology was convened. Panellists were tasked to perform an evidence-based overview of specific topics related to oligometastatic and oligoprogressive NSCLC and to pseudoprogression on immuno-oncology agents. Case a With the exception of S.A. Laurie, the corresponding author, all other authors are listed in alphabetic order.
presentations were used to illustrate typical examples of those rare clinical situations, and after an overview of the evidence by all attendees, evidence-informed recommendations for practice were developed. The guideline presented here was drafted by the first author with the assistance of a medical writer, and all authors provided feedback. The final guideline was approved by all authors and submitted for publication.

RESULTS

Non–Central Nervous System Oligometastatic and Oligopersistent Wild-Type NSCLC

Case Description

An incidental left upper lobe mass found in a 59-year-old male ex-smoker during a coronary angiogram was followed by serial computed tomography (ct) imaging until slight growth prompted investigations. Combined positron-emission tomography and cr imaging in March 2016 identified a 2.3 cm left upper lobe mass (standardized uptake value 13.6), and biopsy showed an adenocarcinoma, which was EGFR- and ALK-negative (Figure 1, left panel). A positron-emission tomography–positive 1.8 cm mass was also noted in the left adrenal gland (Figure 1, right panel), and although an adrenal biopsy in April 2016 showed only rare atypical cells, there was some concern that this location might represent a single site of metastatic disease.

In June 2016, the patient had a left upper lobe lobectomy to remove a 2.3 cm node-negative invasive adenocarcinoma. Because the adrenal biopsy was non-diagnostic, benefit of the doubt led to planning for an adrenalectomy. However, before that surgery occurred, the patient developed a rapidly growing malignant right supraclavicular lymph node, and repeat imaging confirmed significant progression of his adrenal metastasis.

Carboplatin–gemcitabine chemotherapy was initiated, but by the 3rd cycle, the supraclavicular node had progressed, although the adrenal metastasis had shrunk to 6×5 cm from 8×7 cm. Because the patient was PD-L1 positive [≥50% tumour progression score by the Dako 28-8 pharmDx PD-L1 immunohistochemistry assay (Dako Corporation, Glostrup, Denmark)], he received 4 cycles of pembrolizumab. Initially, there appeared to be no clinical response, but after the 4th cycle, the patient experienced a rapid and excellent response such that the node in his neck was no longer palpable, and the adrenal metastasis had shrunk further to 2.9×1.5 cm by July 2017 (Figure 2). The patient continues on treatment and is doing well.

Panelist Presenters
Drs. J. Laskin and P. Cheung

Clinical Questions

- What is oligometastatic NSCLC, and proportionally, how many patients present in this fashion?
- Is oligometastatic NSCLC a distinct clinical entity?
- Which patients warrant aggressive, localized ablative therapy of all sites of metastatic disease, either as initial therapy or after induction chemotherapy?

Oligometastasis, a term first formally defined in 1995, refers to a minimal metastatic state in which patients have a low burden of metastatic disease with only a small number of metastatic sites at initial presentation of their illness. Given that metastatic burden is a continuum, some authors question the existence of the oligometastatic state. However, many believe that it represents a distinct group of patients who might have a more favourable outcome and in whom more aggressive therapy might be warranted. There are data to suggest that, compared with patients having more diffuse disease, those with fewer sites of metastases might experience longer survival. The recognition that different sites and numbers of metastases are associated with different prognoses has been integrated into the 8th edition of the staging system for NSCLC, in which malignant effusions or isolated contralateral lung metastases are considered M1a, a single site of extrathoracic metastatic disease is considered M1b, and more extensive extrathoracic metastatic disease is considered M1c. “Oligometastatic disease” is a closely related concept referring to an oligometastatic state, that, after systemic therapy, either persists or is induced from a more widely metastatic state.

It is known that patients with a solitary site of metastatic disease (most commonly brain or adrenal gland) who undergo surgical resection of both their primary and the metastasis can occasionally experience long-term survival or cure, and that dual resection is a generally accepted treatment strategy for such patients. Whether patients with wild-type NSCLC and more than a solitary site of distant metastatic spread should be considered for more aggressive localized therapy was the topic for discussion.
The development of increasingly sophisticated radiotherapy techniques [stereotactic body radiation (SABR), also called stereotactic ablative radiation (SABR)] allows for the delivery of radical doses of radiation safely in a very short treatment time to almost any body site\(^9\), thus making the local control option feasible for some patients with metastatic NSCLC.

The rationale for the treatment of oligometastatic and oligopersistent disease arises from the fact that, rather than develop metastases at new sites, many patients with advanced NSCLC treated with systemic therapy relapse at a site of pre-existing disease\(^11–13\). Hypothetically, those sites will harbour chemotherapy-resistant clones and can serve to seed other sites with metastases. There are data to suggest that the larger the tumour deposit, the greater the likelihood of residual resistant clones, and thus the greater the likelihood of benefit from local control of that lesion\(^14\). Thus, it might be possible to delay the onset of treatment resistance and the development of new sites of metastases by aggressive ablative local therapy to the oligometastatic sites.

The absolute number of metastatic sites that constitutes the upper limit of the oligometastatic state remains a subject of debate, ranging from 3 or fewer\(^7\) or 5 or fewer\(^15,16\) to 6 active extracranial lesions (3 each in liver and lung parenchyma)\(^17\). Estimates of its occurrence fall into the 26%–55% range\(^3,15,18,19\), with the variation likely representing definition differences. An individual patient analysis of 757 patients having 1–5 either synchronous or metachronous NSCLC metastases found that most oligometastases were either in brain (35.5%) or lung (33.6%), followed by adrenal gland (13.0%), bone (8.5%), other (7.8%), liver (2.4%), and lymph node (2.4%)\(^16\). The meta-analysis revealed that, in patients treated with ablation to all sites of disease, including the primary, median overall survival was 26 months, and survival at 1, 2, 5, and 8 years was 70.2%, 51.1%, 29.4%, and 23.4% respectively. The longest survival times were observed in patients with metachronous metastases and an absence of nodal disease, but the 5-year overall survival rate was still 13.8% in patients with synchronous metastases and N1–2 disease.

Data about whether the treatment of oligometastatic or oligopersistent disease alters the natural history of advanced NSCLC are limited, given that most of the published literature consists of retrospective case series or single-arm phase II trials and are thus subject to selection bias. Data suggest that, for treated patients, progression-free survival (PFS) or even overall survival might be prolonged in comparisons with historical controls\(^17,20\). The optimal sequencing of systemic therapy and local ablative therapy (LAT) remains unclear. Initial ablative treatment to all disease might delay the need for initiation of systemic therapy in selected patients. It might also be a useful strategy for those not felt to be suitable for systemic therapy because of poor performance status or comorbidities, or for patients who want to avoid the toxicities of systemic therapy. However, somewhat more data about the use of local ablative therapies as consolidation treatment after the use of systemic therapy are available.

In a small randomized phase II study, 49 patients with oligometastatic NSCLC (≤3 sites of metastatic disease) who had received at least 4 cycles of chemotherapy or 3 months of an appropriate targeted therapy and who had not progressed were randomized to maintenance systemic therapy or to SABR to all sites of disease, followed by maintenance therapy\(^7\). Most patients (88%) had wild-type EGFR. The trial was halted early because a significant improvement in PFS in favour of SABR was observed (11.9 months vs. 3.9 months; hazard ratio: 0.35; \(p = 0.0054\)), with no significant toxicities.

Since the consensus meeting, a second small (29 patients) single-centre randomized phase II study, enrolling only patients with wild-type EGFR and up to 5 sites of metastatic disease in addition to the primary lesion, has been published. It also revealed increased PFS (9.7 months vs. 3.5 months, \(p = 0.01\)) with no significant increase in toxic effects\(^21\). In that study (NCT02045446 at http://ClinicalTrials.gov/), patients who experienced stable disease or a partial response [by the Response Evaluation Criteria in Solid Tumors (RECIST)] after 4–6 cycles of first-line platinum-based chemotherapy were randomized to SABR plus maintenance chemotherapy or to maintenance chemotherapy alone. The results satisfied the hypothesis that using SABR prevented local failure at the original disease sites—the most likely sites of first recurrence. Based on the findings of that study, the use of radiation therapy after chemotherapy is being evaluated in a phase III setting for patients with limited metastatic NSCLC.

**Consensus Statement**

Overall, the current level of evidence does not support the routine use of LAT as the initial treatment in oligometastatic disease, for which systemic therapy remains the standard of care. Local treatment approaches could be considered for patients not suitable for, or who refuse or want to delay, systemic therapy.

Some available data suggest that the use of consolidative local ablative radiotherapy (SABR) to all sites of disease in patients without progression after first-line systemic therapy might lead to longer PFS without undue toxicity. Those data were obtained mostly in patients with EGFR wild-type NSCLC. We encourage the enrolment of such patients into ongoing clinical trials [such as NRG-LU002 (NCT03137771 at http://ClinicalTrials.gov)] that are examining this issue. Outside a clinical trial, such an approach could be considered in selected patients.

**Non–Central Nervous System Oligoprogressive Oncogene-Driven NSCLC**

**Case Description—Oligoprogressive Oncogene-Driven NSCLC, ALK Rearrangement**

A previously well 42-year-old male never-smoker first presented in 2009 with extensive pulmonary infiltrates, biopsy-proven to be adenocarcinoma. During the subsequent year, he received multiple therapies, including a platinum doublet, pemetrexed, and erlotinib.

By mid-2010, the patient was very symptomatic with progressive disease, and results of fluorescence in situ hybridization testing revealed that he had an ALK rearrangement. He started treatment with crizotinib in October 2010 and experienced a dramatic response [Figure 3(A–C)]. He continued on crizotinib for several years. However, in
March 2014, CT imaging showed a new nodule in the right lower lobe [Figure 3(D)]. Because the patient’s performance status was good and he remained asymptomatic, crizotinib was continued despite further progression in that nodule [Figure 3(E)].

One year later, in January 2016, imaging showed continued growth of the nodule in the right lung and a new area of tumour growth in the left upper lobe [Figure 3(F,G)]. Given a concern for the possible development of symptoms from the left lung tumour, treatment with SBRT was delivered to the right lung in June 2016 and to the left lung in August 2016. Follow-up CT imaging in April 2017 showed typical radiation-related changes in both lungs and ongoing disease control [Figure 3(H,I)]. The patient has experienced only those two isolated areas of progression. The bulk of his metastatic burden has remained under control, and he remains well while still taking crizotinib.

**Panelist Presenters**
Drs. J. Rothenstein, S. Brule, R. MacRae, S. Banerji, and D. Hao

**Clinical Questions**
- What is oligoprogression, and how often does it occur?
- When might treatment past progression with a tyrosine kinase inhibitor (TKI) be considered for patients with extracranial progressive disease?

Compared with standard platinum-based chemotherapy, targeted therapy for oncogene-driven (EGFR-mutated and ALK-translocated) NSCLC is associated with significantly improved outcomes. Most patients treated with an appropriate targeted therapy will experience some degree of tumour shrinkage. However, treatment resistance remains an inevitable occurrence, and at some point, all patients on targeted therapy will progress. Acquired resistance to first-line TKIs typically develops after 9–12 months on erlotinib, gefitinib, or afatinib and after approximately 11 months on crizotinib.

Acquired resistance can be attributed to a number of different mechanisms (concisely described elsewhere) that can either already exist at low frequency in subclones at diagnosis or that can develop under the selective pressure of drug exposure. Three different patterns of resistance can be observed with TKI therapy: isolated central nervous system (CNS) progression without extra-CNS progression (discussed in a later subsection), generalized disease progression requiring a change in therapy (extra-CNS with or without CNS progression), and oligoprogression.

Oligoprogressive disease describes a situation in which a patient develops disease progression in one or a limited number of sites after a targeted therapy has resulted in either a period of stable disease or a partial or complete response. Some definitions describe a specific number of lesions, such as “≤4 discrete lesions amenable to invasive/non-invasive ablation.” The frequency of oligoprogression during TKI treatment varies depending on the definition used and whether isolated CNS progression is included; however, estimates range from 15% to 47%. Oligoprogression is felt to arise as a consequence of tumour heterogeneity, and the development of an isolated resistant subclone at only 1 or a few metastatic sites.

An increasingly common method for treating oligoprogression in NSCLC patients with driver mutations is to continue the TKI that is controlling the greater proportion of the disease, while using LAT to eradicate the resistant clones in the area or areas of progression. Given its relatively few fractions and short treatment time, SBRT might be preferred to more extended radiation schedules or invasive surgery, both of which can be associated with longer interruptions of the TKI. Retrospective studies suggest that aggressive local treatment can eradicate TKI-resistant oligometastases and could have several theoretical benefits, including prevention or treatment of local symptoms and complications from a growing tumour; prevention of secondary seeding by the TKI-resistant clone or clones; and potential for ongoing maintenance with the current TKI, which might be providing overall clinical benefit despite oligoprogression. Retrospective data suggest that SBRT can permit continuation of the TKI and delay the time to a change in therapy. For example, in a review of 18 patients with EGFR mutation–positive disease treated with LAT, the median time to another progression event was 10 months, and the median time to a change in therapy was 22 months. In another cohort of 46 patients, the median time to another progression event was 7 months. Similar results were observed in a cohort of 33 patients with ALK-positive lung cancer who experienced progression while on crizotinib. In 14 patients with oligoprogression who were suitable for LAT, the median total duration of crizotinib was 28 months, compared with 10 months in those who progressed and were not suitable for LAT. Data suggest that higher...
radiation doses might lead to better local control of the oligoprogressive sites, although it is unclear whether doses as used for curative intent are required in this setting.\textsuperscript{24} Retrospective studies such as the foregoing are inherently susceptible to selection bias, and the lack of a control arm precludes definitive conclusions about the true value of \textsc{lat} in this setting. However, based on limited data, guidelines from the U.S. National Comprehensive Cancer Network currently recommend this strategy\textsuperscript{9}. Ongoing clinical trials conducted specifically in oligoprogressive oncogene-driven \textsc{nsclc} (summarized in Kim \textit{et al.},\textsuperscript{43}) will help to provide prospective evidence for the use of this strategy in this situation, and participation in such trials should be encouraged. Likewise, as in the case of \textit{egfr} wild-type \textsc{nsclc}, there is also a desire to evaluate the role of \textsc{lat} in oligopersistent disease after a period of time on a \textsc{tki} in oncogene-driven disease. Sites of residual tumour could be more likely to harbour resistant subclones that could lead to treatment failure. Ongoing trials are studying this strategy (see NCT02759835, NCT01941654, and NCT01573702 at http://ClinicalTrials.gov/).

**Consensus Statement**

Canadian oncologists believe that certain selected patients with limited extra-CNS oligoprogression, who are otherwise experiencing clinical benefit and good tolerance of their targeted therapy, could be considered for an approach that combines \textsc{lat} with continuation of their current targeted therapy. Generally, to avoid prolonged interruption of the targeted therapy, and because it is safe and effective, \textsc{sabr} or \textsc{sabr} is, when possible, preferred to more protracted radiation courses or surgery. Careful and close follow-up of treated patients is required, because additional progression events are expected.

**Case Description—Baseline CNS Oligometastatic Disease, Both Wild-Type and Oncogene-Driven**

In October 2014, an otherwise healthy 49-year-old male architect presented with an 18-month history of progressive fatigue; intermittent left chest pain; and retrosternal, back, and eye pain.

Staging investigations revealed a dominant left upper lobe mass, with widespread metastases to mediastinal lymph nodes, lung, pleura, and brain. Biopsy of the lung lesions confirmed adenocarcinoma. Molecular testing of the biopsy sample revealed the presence of the \textit{egfr} exon 21 L858R mutation.

In November 2014, the patient received whole-brain radiotherapy (\textsc{wbrt}). He then started gefitinib. In December 2014, after 6 weeks of gefitinib, the patient demonstrated a slight interval decrease in the left upper lobe mass, stable small pulmonary nodules, and stable or improved brain metastases (Figure 4). The patient continued with gefitinib and continued to show a decrease in enhancing brain lesions and stable disease in the chest.

In January 2016, after 14 months taking gefitinib, the patient began to experience some headaches, and magnetic resonance imaging of the brain showed an interval increase in a cerebellar lesion. The remainder of his disease burden was stable, and so the cerebellar lesion was treated with stereotactic radiosurgery (\textsc{srs}), and the patient was continued on gefitinib.

In May 2016, after 18 months on gefitinib, the patient was still clinically well, but chest \textsc{ct} imaging suggested early progression, with slightly more prominent pulmonary nodules, suggestive of possible lymphangitic carcinomatosis. The patient continued gefitinib with closer monitoring.

By the following month, June 2016, brain magnetic resonance imaging revealed that 6 enhancing lesions in the brain were starting to enlarge (Figure 5). The patient received further \textsc{srs} to all lesions and continued taking gefitinib.

In August 2016, the patient started to experience mild hemoptysis. Imaging by \textsc{ct} showed an increase in the size of the dominant left upper lobe mass, a bilateral increase in pulmonary nodules, appearance of new nodules, and worsening lymphangitic carcinomatosis (Figure 6(A,B)). The molecular analysis of a biopsy sample from the left upper lobe mass revealed that the patient had an \textit{egfr} T790M resistance mutation. The gefitinib was therefore stopped after 21 months, and treatment with osimertinib was started.

By September 2016, brain magnetic resonance imaging showed 2 enlarging brain metastases, which were treated by \textsc{srs}. The patient continued on osimertinib, and by December 2016, after 3 months on the drug, his best response was stable disease. Chest \textsc{ct} imaging showed a slight decrease in the size of the left upper lobe mass, with the remainder of his disease being stable (Figure 6(C)).

By March 2017, he had been treated with osimertinib for 7 months. A routine restaging \textsc{ct} showed that his pulmonary disease was completely stable, but a new paraaortic lymph node (1.8×2.2 cm) was visible. The nodule was irradiated (25 Gy in 5 fractions), and osimertinib treatment is ongoing.
How should patients with brain oligometastases be treated?

Patients who present with symptomatic brain metastases require appropriate treatment with corticosteroids and consultations with radiation oncology or neurosurgery (or both). There has been a shift away from the use of wbrt, because it has become clear that this therapy is associated with short-term effects of asthenia and longer-term neurocognitive toxicity. Many authors advocate that its use be avoided or postponed whenever possible. Thus, if radiation is felt to be required (either as definitive treatment or after resection), patients, whenever suitable, should be considered for srs. For patients with 1–4 metastases, srs is replacing wbrt, because srs is associated with improved cognitive outcomes.

Multiple randomized trials have compared wbrt and srs with srs alone or wbrt alone. In general, those studies have shown that overall survival is as good with srs alone as with strategies that use wbrt. At the time points studied, neurocognitive functioning has been better preserved with srs alone; however, cns recurrences are more common with srs than when wbrt is used. Strategies to decrease the neurocognitive effects of wbrt include the use of memantine, an N-methyl-d-aspartate receptor antagonist used in the treatment of dementia, and the concept of hippocampal avoidance, which is being studied in randomized trials.

For patients with surgically resected metastases, adjuvant srs, compared with wbrt, provides inferior intracranial control at 12 months (40.7% [95% confidence interval: 25.9% to 64.2%] vs. 81.5% [95% confidence interval: 68.1% to 97.5%])

Studies of gefitinib, erlotinib, and afatinib have revealed intracranial disease control rates of up to 89% in patients with NSCLC showing common EGFR mutations. In patients with measurable cns disease, response rates of up to 40% have been reported. Similarly, in ALK-translocated NSCLC, crizotinib leads to intracranial disease control in 56% of patients with previously untreated brain metastases and in 62% of patients with previously treated brain metastases, with an objective response rate in the range of 18%–33% depending on whether the patient has received prior treatment. Control of cns disease appears to be even higher with newer ALK inhibitors. In the phase III ASCEND-4 trial comparing ceritinib with chemotherapy as first-line therapy, ceritinib was associated with an intracranial response rate of 73% in patients with measurable disease, and at 24 weeks, a 70% rate of disease control in all 54 patients with brain metastasis (both measurable and non-measurable). In the more recently reported phase III ALEX trial, which compared crizotinib with alectinib as first-line treatment, analysis of patients with measurable disease found that alectinib was associated with longer pfs overall and with an 81% intracranial response rate (38% complete response rate) compared with crizotinib’s 50% intracranial response rate (5% complete response rate), with a median duration of intracranial response of 17.3 months compared with 5.5 months. Furthermore, the risk of cns progression was markedly reduced with alectinib, even in patients with baseline cns metastases.

Standard platinum doublet chemotherapy has also been shown to have intracranial activity in ALK-positive NSCLC. For example, in PROFILE 1014, disease control rates with chemotherapy, while less than those with crizotinib, were approximately 40% at 12 weeks and 20% at 24 weeks in patients with previously treated brain metastases. Similar results were seen for the chemotherapy arm of ASCEND-4, with an intracranial disease control rate of 55% at 24 weeks. Fewer data about the value of chemotherapy in the treatment of EGFR mutation–positive brain metastases are available. In a pooled analysis of patients enrolled to LUX-Lung 3 and 6, rates of cns progression with chemotherapy were similar to rates seen with afatinib in patients both with and without brain metastases at baseline.
Newer TKIs might result in even better outcomes for patients with brain metastases. Initial results of the phase III AURA3 trial showed a longer duration of PFS for osimertinib compared with platinum therapy plus pemetrexed in the subgroup of patients with CNS metastases. Independent radiologic assessment of all intracranial metastases for that trial is ongoing, and so intracranial response and disease control rates are not yet available. Preliminary data from the FLAURA trial comparing osimertinib with erlotinib or gefitinib as first-line therapy in NSCLC patients with common EGFR mutations were recently presented, demonstrating that osimertinib shows durable CNS control. Similarly, lorlatinib and brigatinib, next-generation ALK/ROS1 inhibitors, demonstrated substantial intracranial efficacy in phase II trials.

Although data are limited, response rates to chemotherapy in previously untreated brain metastases from EGFR wild-type lung cancer appear to approach response rates in extracranial disease—although response rates appear to be lower than those observed with targeted therapies in mutation-positive disease and could be lower than those observed with platinum-doublet chemotherapy in ALK-positive NSCLC, given data suggesting that ALK-positive cancers might be more susceptible to pemetrexed. Thus, any patient with wild-type NSCLC for whom local brain-directed therapy is delayed in favour of a trial of systemic therapy will have to be monitored very closely for CNS progression.

**Oligoprogression in the CNS in Patients Without Baseline CNS Metastases and With Oncogene-Driven NSCLC:** In some patients, the CNS will be the sole site of progression, while extracranial disease remains completely or mostly controlled; in others, CNS progression will be just one component of more generalized disease progression. In NSCLC, CNS metastases are a frequent occurrence, affecting 21%–64% of patients, with one third of patients presenting with brain metastasis at baseline. The rates of CNS progression with first-line TKI are 20%–46% for NSCLC patients with ALK-positive translocations and 22%–52% for NSCLC patients with EGFR mutations. Treatment decisions will depend on the degree of progression both intracranially and extracranially, and on the systemic treatment options remaining for the patient. Regardless, patients with symptomatic CNS metastases require the approach described earlier: corticosteroids and a referral to radiation oncology or neurosurgery (or both).

In patients with oncogene-driven asymptomatic CNS progression in the setting of more widespread progression, a change of systemic therapy is usually warranted. If another targeted agent with CNS activity is available, treatment with that agent and careful CNS surveillance can be considered. In patients with CNS oligoprogression alone, consideration could be given to local brain treatment and continuation of the current targeted therapy that is controlling the extra-CNS disease. Alternatively, if another targeted agent is available that has CNS activity, withholding local therapy and switching to the other targeted agent, with careful brain surveillance, could also be considered.

In patients with ALK-positive NSCLC in whom oligoprogressive CNS disease develops during crizotinib treatment, some data suggest that both ceritinib and alectinib (both available in Canada) can lead to an intracranial response, at rates of 45% and 52%–67% respectively. Osimertinib has been approved by Health Canada for patients with an acquired EGFR T790M resistance mutation after first- or second-generation TKIs. A subset analysis of the AURA 3 trial demonstrated that patients with 1 or more measurable or non-measurable CNS metastases on baseline brain imaging experienced a significantly longer median PFS with osimertinib than with chemotherapy: 11.7 months compared with 5.6 months (p = 0.004). The CNS objective response rate was 70% with osimertinib and 31% with chemotherapy for those with evaluable disease in the brain.

**Asymptomatic Oligoprogression in the CNS in Wild-Type NSCLC Without Baseline CNS Metastases:** In this situation, greater consideration should be given to local therapy (srs, if feasible), given that data about the role of systemic therapies, either further cytotoxic chemotherapy or immunotherapy, are limited. Responses in the CNS with immunotherapy have been reported, but the relevant data are too preliminary to routinely support the use of immunotherapy specifically for the treatment of CNS metastases. If a local therapy is deferred in this situation, very careful CNS monitoring is recommended.

**Consensus Statement**
If clinically appropriate and possible, wbrt should be deferred in favour of srs. With small-volume asymptomatic brain metastases, consideration might be given to starting with systemic therapy, particularly if the patient has an oncogenic driver. Careful brain surveillance is vital to ensure disease control in the CNS.

**Pseudoprogression with Immuno-oncology Agents in NSCLC**

**Case Description**
In February 2016, a fit 80-year-old woman with EGFR- and ALK-negative adenocarcinoma of the lung was started on therapy with a PD-1 inhibitor. Originally diagnosed with metastatic NSCLC in 2013, her previous treatments had included carboplatin doublet chemotherapy and single-agent pemetrexed in addition to stereotactic radiation to liver and brain.

At restaging in June 2016 after several months of a PD-1 inhibitor, the patient’s liver lesions had grown in size, as had her paratracheal lymph node [Figure 7(A)]. Because she remained fit, with an Eastern Cooperative Oncology Group performance status of 0 and good tolerance to treatment save for a mild rash and hypothyroidism, the patient was continued on the PD-1 inhibitor. After 4 more doses, she was restaged, with clear evidence of improvement [Figure 7(B)], thus demonstrating that the original imaging was indicative of pseudoprogression. The patient was therefore continued on therapy. By February 2017, she was experiencing clinical deterioration, with increased pain and worsening performance status. At that point, imaging confirmed significant disease progression [Figure 7(C)] and immunotherapy was discontinued.
FIGURE 7 Changes in computed tomography imaging over time. (A) In June 2016, compared with an earlier image, liver metastases have increased to 2.0 cm and 1.4 cm; the paratracheal node has increased to 1.2 cm; the right upper lung mass measures 3.7 cm (stable), but has changed in shape and decreased in attenuation. (B) In August 2016, liver metastases have decreased to 0.9 cm and 0.9 cm; the paratracheal node has decreased to 6 mm; the right upper lung mass has decreased to 2.6 cm. (C) In February 2017, the liver metastasis has increased to 1.7 cm; the paratracheal node is stable; and the right upper lung mass has increased to 9.3 cm, with invasion of the mediastinum.

Panelist Presenters
Drs. G. Nicholas, P.K. Cheema, N. Daaboul, M.S. Tsao, R. Juergens, and N. Blais

Clinical Questions
- What is pseudoprogression?
- How is it determined?
- How often is it observed in NSCLC?
- How should a patient who manifests radiologic disease progression while on an immuno-oncology agent be treated?

Immunotherapy can be effective in NSCLC: approximately 20% of patients with advanced disease experience durable responses with immune checkpoint inhibitor therapy\(^76\). Multiple anti–PD-1 and –PD-L1 antibodies have become standard therapies in the first- or second-line treatment of patients with advanced NSCLC\(^74,77–80\), and still others are in various phases of clinical development. In contrast to cytotoxic chemotherapy and targeted agents, immunotherapy is associated with a number of response patterns, including delayed response to therapy, disease regression that continues even after therapy is discontinued, and pseudoprogression. Pseudoprogression has to be differentiated from hyperprogression—very rapid disease progression associated with clinical deterioration that has been described with immuno-oncology agents\(^81\) and which is not discussed here.

Definitions of pseudoprogression vary, but generally describe apparent tumour growth arising from a treatment effect rather than true disease progression. Distinguishing between pseudo and true disease progression is crucial to avoid prematurely discontinuing an effective therapy, while at the same time not continuing an ineffective, costly, and potentially toxic treatment and losing an opportunity to move on to another therapy if the patient deteriorates clinically from true disease progression.

In the initial clinical trials of immuno-oncology agents, it was clear that patients were occasionally manifesting radiologic disease progression that met RECIST 1.1 criteria for progressive disease, but were felt to be clinically benefiting from treatment. Those patients were continued on study therapy, and some subsequently went on to experience either a radiologic response or more prolonged stabilization of disease after the initial progression. After this “atypical” or “unconventional” response pattern was recognized, attempts were made to standardize its measurement using either international consensus (for example, immune-related response criteria\(^82\)) or agent- and protocol-specific criteria (for example, in clinical trials of nivolumab\(^74,78\)). More recently, the immunotherapy RECIST (iRECIST) criteria, based on RECIST 1.1\(^83\), have been published\(^84\). The iRECIST framework standardizes tumour response evaluation in clinical trials of immunotherapy agents, but it requires further validation and is not meant for decision-making in routine clinical practice. However, aspects of iRECIST are helpful in defining pseudoprogression.

Pseudoprogression might manifest as temporary tumour growth or development of new lesions (or both) on imaging, subsequently followed by disease stabilization or a disease response\(^85\). The cause of the apparent tumour growth is unclear, but might possibly be related to infiltration of the tumour with immune effector cells and inflammation.

Table 1 summarizes differences between disease progression and pseudoprogression. Although changes in tumour size over time as measured on serial radiologic imaging will eventually distinguish the two, the patient’s clinical status at any given time is crucial. With true disease progression, the patient is more likely to experience a deterioration in performance status and worsening of disease-related symptoms. With pseudoprogression, the patient’s performance status usually remains stable or improves, systemic symptoms might or might not improve, and symptoms of tumour enlargement might or might not be present.

In clinical trials, some cancer patients treated beyond RECIST disease progression with immuno-oncology agents appear to do well\(^86\). However, in NSCLC, pseudoprogression is uncommon; data from clinical trials in NSCLC reveal that such “unconventional” responses occur much less than 10% of the time (Table 1). Thus, although many patients have been treated past response in the clinical trials of immune agents, many received only a few additional cycles of therapy, suggesting that the greatest proportion
of those patients were experiencing true disease progression (Table III). Those observations highlight the rarity of pseudoprogression and the rarity of long-term benefit resulting from treating past progression. Given current uncertainty about the role of PD-L1 status in selecting patients for immuno-oncology therapy, no data of which we are aware correlate baseline PD-L1 status and the likelihood of experiencing pseudoprogression. Given that genuine pseudoprogression is uncommon, the panel recommends close follow-up imaging in patients who continue treatment beyond progression to ascertain whether ongoing benefit is being achieved.

**Consensus Statement**

Canadian oncologists emphasize that pseudoprogression is uncommon in patients with NSCLC treated with PD-1/PD-L1 inhibitors. In patients showing clinical evidence of deterioration at radiologic progression, therapy should be discontinued, and the patient should be switched to another line of therapy, if appropriate. When selecting patients to continue on immunotherapy past RECIST progression, oncologists should use clinical judgment and take the patient’s clinical characteristics and burden of illness into consideration. Patients who continue immunotherapy must be in stable clinical condition, have no signs of rapid disease progression, and be tolerating the treatment. Patients who continue immunotherapy have to be continually monitored and re-imaged by CT at 4–8 weeks to ensure that they are not on a trajectory of true disease progression. No biomarkers are currently available to delineate between pseudo and true disease progression.

**ACKNOWLEDGMENTS**

This initiative was funded by an unrestricted educational grant from Pfizer Canada. Pfizer did not have representation at meetings, did not provide input into the content at any point, and did not review the consensus document before submission. The authors thank Chrystal Palaty PhD, from Metaphase Health Research Consulting Inc., for assistance with manuscript writing and submission.

**CONFLICT OF INTEREST DISCLOSURES**

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests:

- SAL has received honoraria from Pfizer, AstraZeneca, Boehringer Ingelheim, and Novartis; SB has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Bristol–Myers Squibb, Eli Lilly, Novartis, Pfizer, and Roche, and has received research funding from AstraZeneca and Merck; NB has served on advisory boards for Amgen, AstraZeneca, Merck, Bayer, Boehringer Ingelheim, Bristol–Myers Squibb, Celgene, Eli Lilly, Novartis, Pfizer, Sanofi, and Roche; SB has received honoraria from AstraZeneca, Boehringer Ingelheim, Bristol–Myers Squibb, Eisai, and Merck; PKC has served as an advisor for AstraZeneca, Boehringer Ingelheim, Hoffmann–La Roche, Pfizer, Novartis, Takeda, Eli Lilly, and Bristol–Myers Squibb, and has received research funding from Boehringer Ingelheim and Hoffmann–La Roche; PC has received grants for investigator-initiated research projects from AbbVie,
TABLE III  Characteristics of treatment past progression with immunotherapy

<table>
<thead>
<tr>
<th>Reference (trial name)</th>
<th>Treatment past progression</th>
<th>Unconventional responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts treated</td>
<td>Median weeks</td>
</tr>
<tr>
<td>Borghaei et al., 2015&lt;sup&gt;78&lt;/sup&gt; (CheckMate 057, nonsquamous)</td>
<td>71/287</td>
<td>24.7</td>
</tr>
<tr>
<td>Brahmer et al., 2015&lt;sup&gt;74&lt;/sup&gt; (CheckMate 017, squamous)</td>
<td>28/135</td>
<td>21</td>
</tr>
<tr>
<td>Garon et al., 2015&lt;sup&gt;80&lt;/sup&gt;, and Hui et al., 2017&lt;sup&gt;91&lt;/sup&gt; (KEYNOTE-001)</td>
<td>32/101</td>
<td>4–9 Weeks</td>
</tr>
<tr>
<td>Fehrenbacher et al., 2016&lt;sup&gt;79&lt;/sup&gt; (POPLAR)</td>
<td>121/535</td>
<td>23</td>
</tr>
<tr>
<td>Kazandjian et al., 2017&lt;sup&gt;89&lt;/sup&gt; (3 pooled trials, unidentified)</td>
<td>243/609</td>
<td>40</td>
</tr>
</tbody>
</table>

Pts = patients.

Pfizer, and Sanofi–Aventis; DH has served as an advisor or consultant for AstraZeneca/MedImmune, Bristol–Myers Squibb, Merck, Pfizer, and Roche; RJ has served as an advisor or consultant for AstraZeneca/MedImmune, Bristol–Myers Squibb, Merck, Pfizer/Sero, and Roche; 99/144; 10/535; 1.9; 121/535. 23 Not stated; 1.9 3 Cycles (range: 1–34 cycles) 5/144; Not published; Not published; Not published; Not published.

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