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REVIEW ARTICLE

Rapidly changing treatment algorithms for metastatic nonsquamous non-small-cell lung cancer

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ABSTRACT

Background The treatment paradigm for metastatic nonsquamous non-small-cell lung cancer (NSCLC) continues to change. Algorithms published only 6 months ago are outdated today and are dramatically different from those published a few years ago. New driver mutations continue to be identified, and the development of therapies to inhibit oncogenic addiction is ongoing. Patient survival is improving as treatments become more personalized and effective.

Methods This review looks at the outcomes of recent trials and discusses treatment options for patients with metastatic NSCLC of nonsquamous histology. Algorithms continue to change quickly, and an attempt is made to keep the paradigm current and applicable into the near future.

Results Treatment algorithms for NSCLC tumours with *EGFR* mutations, *ALK* rearrangements, and *ROS1* rearrangements, and for wild-type tumours are presented. A future algorithm based on new immunotherapy data is proposed.

Conclusions The treatment algorithm for *EGFR* mutation is changing with the proven efficacy of osimertinib for the acquired T790M mutation. All patients taking first- or second-generation epidermal growth factor receptor tyrosine kinase inhibitors must be tested. The treatment algorithm for *ALK* rearrangement has changed with the proven superiority of alectinib compared with crizotinib in the first-line setting. The approval of crizotinib for *ROS1* rearrangements now means that patients also must be tested for that mutation. The biomarker for checkpoint inhibitors continues to be PD-L1 by immunohistochemistry stain, but whether testing will be necessary for patient selection if chemotherapy combinations are implemented will be determined soon.

Key Words Metastatic nonsquamous NSCLC, algorithms, chemotherapy, targeted therapy, *EGFR*, *ALK*, immunotherapy

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INTRODUCTION

In the past, the standard of care for metastatic non-small-cell lung cancer (NSCLC) was to treat patients with a platinum doublet for 4–6 cycles and to offer second-line therapy upon progression[1]. Patients who have genetic alterations in the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and Ros1 proto-oncogene receptor tyrosine kinase benefit from targeted therapies in the first-line setting and in subsequent lines. In patients with no known driver mutations or with wild-type tumours, immunotherapy with checkpoint inhibitors has revolutionized treatment.

Tumour mutation testing allows patients to be divided into four categories: those whose tumours are *EGFR*-positive (10%–30%)[2]; those who have tumours with *ALK* rearrangements (4%–7%)[2]; those who have tumours with *ROS1* rearrangements (1%); and those whose tumours either have no *EGFR*, *ALK*, or *ROS1* mutations[3] or have an unknown mutation status. As mutation testing expands to include new targets, including *BRAF* V600E, *HER2*, *RET*, and *CMET* exon 14 splice mutations, we can expect the

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number of patient subcategories to grow. The continued development of effective therapies means that treatment algorithms will increase in complexity[4].

Algorithms that were published less than a year ago are already out of date and continue to change. This paper presents new treatment algorithms for each of the four current patient categories and proposes an immune checkpoint treatment algorithm for the future. It also discusses treatments for patients with nonsquamous histology only.

EGFR-MUTATION POSITIVE

First-Line Therapies: Tyrosine Kinase Inhibitors

The first line of treatment for patients with metastatic nonsquamous NSCLC whose tumours harbour an *EGFR* mutation is a tyrosine kinase inhibitor (TKI) that inhibits the EGFR protein. That approach is the global standard of care (Figure 1). As demonstrated in numerous trials[6–14], patients experience a superior objective response rate (ORR) and progression-free survival (PFS) when treated with EGFR TKIs compared with chemotherapy in the first line[6–14].

In clinical practice, EGFR-directed TKIs can include gefitinib, erlotinib, afatinib, and dacomitinib. Although dacomitinib is not yet approved for use in Canada, it is discussed here because many insights can be gained from its use in clinical trials. Gefitinib and erlotinib are first-generation EGFR TKIs; afatinib and dacomitinib are second-generation TKIs. Second-generation TKIs block more members of the human *EGFR* family than the first-generation TKIs do, and unlike the first-generation EGFR TKIs, they are non-competitive inhibitors, conferring a longer period of resistance[15]. The adverse events associated with the second-generation EGFR TKIs are greater, with more diarrhea, rash, paronychia, and stomatitis occurring. Thus, the patient's performance status, comorbidities, age, and communication abilities factor into decision-making when choosing the appropriate TKI. None of the randomized trials comparing chemotherapy with the first-generation EGFR TKIs in *EGFR*-mutant NSCLC have shown a statistically significant improvement in overall survival (OS) for the overall population of patients with *EGFR*-mutant tumours, likely because of a high rate of crossover at progression.

The specific *EGFR* mutation subtype is important to consider when selecting a first-line TKI. The common *EGFR* mutation subtypes, which make up approximately 90% of activating mutations, are either a deletion in exon 19 or point mutations in exon 21 (L858R). The other 10% of mutations are considered uncommon. Subgroup analysis from randomized trials has shown that an exon 19 deletion is predictive of better efficacy than the exon 21 L858R mutation, which could be important to consider when selecting therapy[16]. The preplanned mutation subgroup analysis of the LUX-Lung 3 and 6 trials underlined that consideration: patients whose tumours had an exon 19 deletion and who were treated with afatinib, compared with their peers treated with chemotherapy, experienced statistically significant OS improvements[14].

Two recent trials have compared first- and second-generation EGFR TKIs in the first-line setting, demonstrating that efficacy is superior for the second-generation TKIs compared with the first-generation TKIs. The LUX-Lung 7 phase IIB randomized trial compared afatinib with gefitinib in patients having advanced NSCLC and common *EGFR* mutations[17]. The co-primary endpoint of PFS was met [hazard ratio (HR): 0.73; $p = 0.0165$], favouring afatinib. Response rate, a secondary endpoint, was 70% compared with 56%, also favouring afatinib (HR: 1.873; $p = 0.0083$). The OS duration was 3.0 months longer with afatinib than with gefitinib (27.9 months vs. 24.5 months), but did not reach statistical significance. The main adverse events reported for afatinib were diarrhea and rash; transaminitis was reported for gefitinib.

The ARCHER 1050 phase III randomized trial compared dacomitinib with gefitinib in patients with advanced NSCLC and common *EGFR* mutations in the first-line setting[18]. The primary endpoint of PFS was met, favouring dacomitinib over gefitinib (14.7 months vs. 9.2 months, $p < 0.0001$), although the response rates were not statistically different (74.9% vs. 71.6%). The duration of response was impressively longer in the patients treated with dacomitinib (14.8 months vs. 8.3 months, $p < 0.0001$). Adverse events were as expected for a second-generation EGFR TKI, and more than 66% of patients treated with dacomitinib required a dose reduction. The results of ARCHER 1050 demonstrate that dacomitinib is superior to gefitinib in the first-line treatment of NSCLC patients with common *EGFR* mutations.

Other approaches being investigated for first-line therapy include dual inhibition of the EGFR and angiogenesis pathways. A randomized phase II trial illustrated a PFS benefit for the erlotinib–bevacizumab combination compared with erlotinib alone, the medium PFS being 16.0 months for the combination compared with 9.0 months for erlotinib monotherapy[19]. No statistical differences in the response rate or OS were observed. In June 2016, the European Commission approved the combined use of erlotinib–bevacizumab for the first-line treatment of patients with *EGFR*-positive NSCLC. The ongoing BEVERLY trial, a larger phase III trial of this EGFR TKI–bevacizumab combination, is aiming to confirm and quantify the benefit[20].

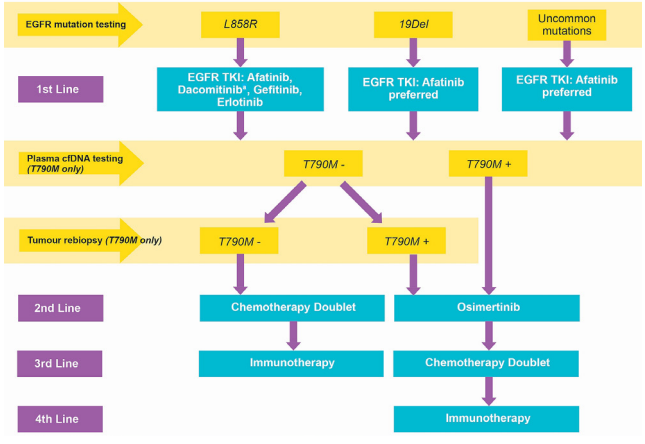

FIGURE 1 Treatment algorithm for advanced nonsquamous non-small-cell lung cancer with *EGFR* mutation. Adapted with permission from Melosky *et al.*, 2018[5]. EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor; cfDNA = cell-free DNA.

Testing for the EGFR *T790M Resistance Mutation on Progression*

All patients treated with first- or second-generation TKIs will eventually progress. During treatment with first- or second-generation EGFR TKIs, up to 60% of patients will acquire the T790M mutation in *EGFR* exon 20, which leads to TKI resistance[21]. All patients clinically progressing on first-line treatment must be tested for the presence of this mutation. Testing for cell-free DNA in plasma is suggested as an alternative to repeat biopsy. Various testing platforms are being developed and validated, and the concordance between cell-free DNA and tumour tissue is improving[22–25]. A tumour rebiopsy is recommended to confirm T790M status in patients who initially test negative for the presence of a T790M mutation by cell-free DNA testing.

Second-Line Therapy

For patients with *EGFR* T790M–positive disease, the third-generation EGFR TKI osimertinib is now a treatment option. The AURA3 phase III trial randomized, to either osimertinib or standard platinum-based doublet chemotherapy, 419 patients in whom a first-line EGFR TKI had failed and who had acquired the T790M mutation[26]. In that trial, the PFS duration favoured osimertinib: 10.4 months compared with 4.4 months for the chemotherapy group ($p < 0.001$). The adverse event profiles for osimertinib and platinum-based doublet chemotherapy in AURA3 were consistent with those in previous trials.

A subset analysis was conducted for patients in the AURA3 trial who had 1 or more measurable or non-measurable central nervous system (CNS) metastases on baseline brain imaging. In those patients, the median PFS was significantly longer with osimertinib (11.7 months) than with chemotherapy (5.6 months, $p = 0.004$). Among patients who were evaluable for response in brain, the CNS ORR was 70% with osimertinib and 31% with chemotherapy ($p = 0.015$)[27].

Osimertinib is now a standard of care for patients who progress on first- and second-generation EGFR TKIs and whose tumours have an acquired *EGFR* T790M resistance mutation. After progression on osimertinib, a chemotherapy doublet could be considered, followed by a clinical trial, if the patient is eligible. Given that the response rates to immunotherapy for *EGFR*-mutated lung cancer are low, and PD-L1 expression might not necessarily be associated with response to immunotherapy in those patients, immunotherapy, if tried, should be the last line[28].

Recently released results from the FLAURA trial show that osimertinib has a superior PFS duration at 18.9 months compared with 10.2 months for a first-generation EGFR TKI (HR: 0.46; 95% confidence interval: 0.37 to 0.57; $p < 0.0001$); OS results are pending[29]. How that result will affect the choice of first-line therapy is still unknown, because sequence superiority has yet to be addressed by the interim analysis of the first PFS. Data will be forthcoming.

For patients without a T790M mutation, the choice for second-line therapy is a chemotherapy doublet. Patients who are T790M-negative and who progress on chemotherapy have few other options and could consider a clinical trial. Again, immunotherapy can be considered only for last line[28].

ALK MUTATION–POSITIVE NSCLC

First-Line Therapy with ALK TKIs: Crizotinib, Ceritinib, and Alectinib

Rearrangements in the *ALK* gene are found in 4%–7% of lung cancers, specifically in tumours of adenocarcinoma histology[2]. Lung cancer tumours found to be positive for an *ALK* rearrangement should be treated with an ALK TKI. In the past, crizotinib was the only option for first-line therapy in patients harbouring such tumours[30]. Crizotinib has a modest degree of CNS activity, but its efficacy is better in systemic disease[31]. Several recent studies have demonstrated the efficacy of ceritinib or alectinib in the first-line setting, and those agents have been added to the algorithm (Figure 2). Because brain is a frequent site of metastasis for patients with *ALK*-positive tumours, the intracranial activity of the ALK TKIs is important to consider.

Ceritinib, a second-generation ALK inhibitor, was first approved in the second-line setting, but was compared with chemotherapy in the first-line setting in the ASCEND-4 phase III trial[32]. In that trial, 376 patients with *ALK*-positive NSCLC were randomized to either ceritinib or chemotherapy. The median PFS was 16.6 months in the ceritinib group and 8.1 months in the chemotherapy group ($p < 0.00001$). As a result of this positive trial, the European Medicines Agency approved ceritinib in the first-line setting in May 2017. Health Canada can be expected to follow. Ceritinib was shown to have activity against intracranial disease, with the best intracranial response rate in measurable disease ranging from 36% to 58.8% in early trials[33–35]. The ongoing phase III ASCEND-5 trial included 119 patients (51.5%) with brain metastasis at baseline, but the data are not yet mature[36].

Alectinib, a second-generation ALK inhibitor, was tested in the first-line setting in the J-ALEX randomized phase III trial[37]. That trial compared alectinib with crizotinib, and for patients randomized to alectinib, PFS at 24.0 months was not reached; it was 10.2 months with crizotinib ($p < 0.0001$). The J-ALEX trial was conducted in Japan, where limitations on the use of sodium lauryl sulfate meant that the alectinib dose tested (300 mg orally, twice daily) was low.

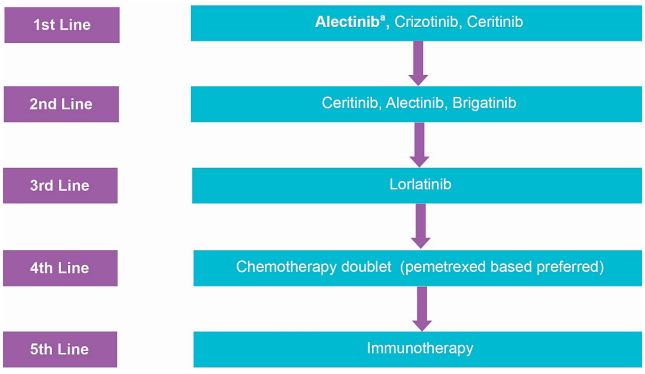

FIGURE 2 Treatment algorithm for advanced nonsquamous non-small-cell lung cancer with *ALK* rearrangement. [a]Because of central nervous system penetration, alectinib is the preferred agent for first-line therapy.

The efficacy of alectinib in first-line NSCLC was confirmed with the results of the global ALEX randomized phase III trial, presented at the 2017 meeting of the American Society of Clinical Oncology[38]. In that trial, 303 patients were randomized to alectinib (600 mg orally, twice daily) or to crizotinib. The primary endpoint of PFS by independent review was not reached for alectinib. However, the secondary endpoint, PFS by investigator review, was more than 26.0 months for alectinib and 10.4 months for crizotinib ($p < 0.0001$). The adverse event profile favoured alectinib. Patients with brain metastases were stratified, and the cumulative incidence of CNS progression at 12.0 months was 9.4% for alectinib compared with 42.4% for crizotinib. That reduction to less than one quarter the incidence of brain metastases is an outstanding clinical benefit for patients. Alectinib will likely become the preferred option for first-line therapy in patients with *ALK*-rearranged NSCLC.

Second-Line Therapy with Ceritinib, Alectinib, or Brigatinib

Because the first-line treatment paradigm will likely change given the results of the ALEX study, second-line treatment will reflect the change as well.

Ceritinib is the first ALK inhibitor to be approved in the second-line setting in patients with *ALK*-positive NSCLC who have progressed on crizotinib. The ASCEND-5 randomized phase III trial compared ceritinib with chemotherapy (pemetrexed or docetaxel) in 231 patients with *ALK*-positive NSCLC after progression on crizotinib[36]. Median PFS was significantly improved with ceritinib, at 5.4 months, compared with chemotherapy, at 1.6 months. Moreover, the ORR was increased with ceritinib (39.1% vs. 6.9% with chemotherapy). The study confirmed the efficacy of ceritinib as shown in earlier trials[33–35] and established the sequence of crizotinib followed by ceritinib as the standard treatment for patients with metastatic *ALK*-positive lung cancer.

Alectinib was shown to be efficacious and safe in patients with crizotinib-refractory *ALK*-positive NSCLC—attributes first demonstrated in a phase I/II study[39] and confirmed in two large phase II North American and global trials[40,41]. In the global study, an ORR of 50.8% was observed, and the CNS ORR in patients with measurable CNS metastases was 58.8%, with 20.6% complete responses[40]. Similar results were seen in the North American trial, which reported an ORR of 52.2%, a CNS ORR in patients with measurable CNS metastases of 75%, and 25% complete responses[41]. In both studies, grade 3 or greater adverse events were rare. The phase III ALUR trial confirmed the benefit of alectinib compared with second-line chemotherapy using either docetaxel or pemetrexed[42]. In ALUR,107 patients were randomized 2:1 to alectinib or to chemotherapy. The median PFS by investigator assessment was 9.6 months for alectinib and 1.4 months for chemotherapy (HR: 0.15; 95% confidence interval: 0.08 to 0.29; $p < 0.001$).

Brigatinib is a second-generation ALK inhibitor that received accelerated approval from the U.S. Food and Drug Administration on 28 April 2017 for use in patients with crizotinib-refractory *ALK*-positive NSCLC. The approval was based on the results of the ALTA phase II trial, which tested two doses of brigatinib in the second-line setting and demonstrated that patients who received the higher dose achieved an impressive PFS of 12.9 months[43]. A phase III trial that is comparing brigatinib with crizotinib is currently underway. The trial has completed accrual, and results are awaited. In addition, a phase II trial of brigatinib in patients for whom ceritinib or alectinib has failed is also underway.

It is important to note that all of the second-line studies described here were conducted in post-crizotinib patient populations. Efficacy data from prospective trials for a second-generation ALK TKI after failure of an initial second-generation ALK TKI have yet to be published.

Third Line and Beyond

For patients with *ALK*-positive NSCLC who progress after second-line therapy, advanced lines of therapy include a chemotherapy doublet (pemetrexed-based preferred), clinical trials, or new agents such as lorlatinib.

Lorlatinib is a third-generation ALK inhibitor that has broad-spectrum activity against most known *ALK* resistance mutations, including G1202R[44]. Lorlatinib demonstrated efficacy in a phase I study in heavily pretreated patients. The ORR (46%) and PFS (11.4 months) were impressive, given that most patients had received 2 or more prior lines of therapy[45]. In April 2017, lorlatinib received breakthrough status from the U.S. Food and Drug Administration.

As new agents such as lorlatinib are approved and moved into the algorithm, the current third-line options, such as a chemotherapy doublet, will be pushed back to a later line of therapy.

ROS1 MUTATION–POSITIVE NSCLC

The *ROS1* oncogene encodes a tyrosine kinase receptor that is related to the ALK tyrosine kinase receptor. *ROS1* rearrangements occur in approximately 1% of NSCLCs with nonsquamous histology.

In the expansion cohort of the phase I study of crizotinib, 50 patients with *ROS1* rearrangements were enrolled. Patients were treated with crizotinib and assessed for safety, pharmacokinetics, and response to therapy[3]. The PFS was 19.2 months, the ORR was 72%, and the responses were durable, with a median duration of response of 17.6 months. In May 2016, crizotinib was approved in the United States for first-line therapy in patients with *ROS1*-rearranged NSCLC[46] (Figure 3). A *ROS1* rearrangement is now recognized as a standard biomarker for testing in patients with nonsquamous histology in the advanced NSCLC setting.

Second-line options for patients with *ROS1* rearrangements who progress on crizotinib are being investigated.

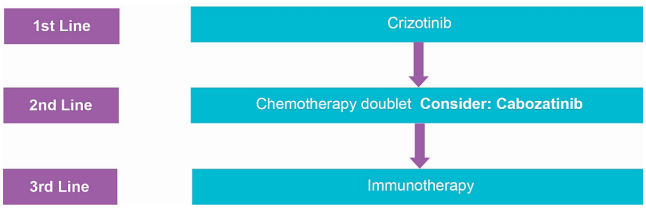

FIGURE 3 Treatment algorithm for advanced nonsquamous non-small-cell lung cancer with *ROS1* rearrangement.

In those patients, the second-line treatment is a chemotherapy doublet, because alectinib has no activity, and ceritinib is unlikely to provide benefit because its potency to inhibit *ROS1* is similar to that with crizotinib[47]. Cabozantinib has been shown to be a useful second-line agent, but data are restricted to case reports only[48].

MUTATION STATUS–NEGATIVE (WILD-TYPE) NSCLC

First-Line Therapy: Platinum Doublet

The term "wild-type" is used to describe advanced NSCLC in which patients have tumours without *EGFR* mutations or *ALK* or *ROS1* rearrangements. The well-established standard of care for such patients is a platinum doublet (pemetrexed-based preferred) for 4–6 cycles (see Figure 4)[49,50], which remains the treatment choice for patients who do not express high levels of PD-L1 (to be described shortly).

Maintenance Therapy

Maintenance therapy involves the continuation of chemotherapy, which could involve continuing the original agent or switching to a different one. The PARAMOUNT trial demonstrated that, compared with placebo, pemetrexed maintenance after first-line chemotherapy significantly reduced disease progression for patients with nonsquamous tumour histology[51]. A pemetrexed doublet improves both PFS and OS when administered as maintenance therapy[52].

Checkpoint Inhibitors in First-Line Treatment for Patients with High PD-L1 Expression

The success of PD-1 (or PD-L1) immune checkpoint inhibitors has been the most important change in the NSCLC treatment paradigm. Trials evaluating 3 immunotherapy agents targeting the PD-1 receptor pathway in patients with NSCLC have demonstrated durable clinical activity and manageable toxicities[53–56]. Found on T lymphocytes, PD-1 is an inhibitory receptor that binds the PD-L1 and PD-L2 ligands, which then suppress the immune response. Monoclonal antibodies targeting PD-1 or PD-L1 can lead to reactivation of T lymphocytes.

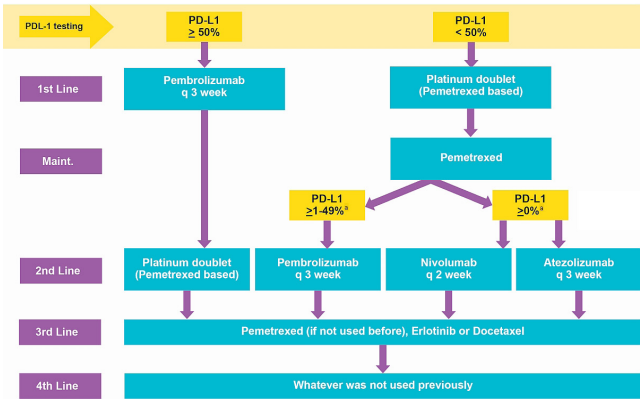

FIGURE 4 Treatment algorithm for advanced nonsquamous non-small-cell lung cancer, wild type. [a]Based on results of initial PD-L1 testing.

Biomarker testing for PD-L1 is imperfect and somewhat complex. Patients tested for levels of PD-L1 overexpression can be categorized into PD-L1 expressers (≥1% expression) and non-expressers (<1% expression). To make matters more complicated, threshold levels of PD-L1 expression are used to determine who can be treated, and PD-L1 might not correctly identify the patients most likely to respond and—importantly—not respond to immune checkpoint inhibitors.

Recently, these agents were tested in the first-line setting for treatment-naïve patients. The KEYNOTE-024 trial randomized patients whose tumours expressed high levels of PD-L1 (≥50%) to either pembrolizumab, a monoclonal antibody against PD-1, or to platinum doublet chemotherapy for 4–6 cycles[57]. Patients were excluded if their tumours were positive for an *EGFR* mutation or an *ALK* translocation. The ORR favoured pembrolizumab, at 45% compared with 28% for chemotherapy ($p = 0.001$). The primary endpoint was met, with a PFS favouring pembrolizumab (10.3 months vs. 6.0 months for chemotherapy, $p < 0.001$). Crossover was allowed, and at the time of analysis, the median OS was not reached in either group. The 12-month survival favoured pembrolizumab, with a 40% reduction in deaths ($p = 0.005$). As a result of the KEYNOTE-024 outcomes, pembrolizumab has moved into the first-line setting for patients whose tumours express PD-L1 at 50% or greater.

Those results contrast with the results of the CheckMate 026 first-line trial of nivolumab, a monoclonal antibody against PD-1. CheckMate 026 randomized patients whose tumours expressed PD-L1 (≥1%) to either nivolumab or a platinum doublet. The primary endpoint was PFS in patients whose tumours expressed PD-L1 at 5% or greater. That endpoint was not met, with the PFS favouring chemotherapy at 5.9 months compared with 4.2 months for nivolumab ($p = 0.2511$). The response rate also favoured chemotherapy. Although the trial was not powered to look at the subgroup of patients with high PD-L1 expression (≥50%), that subgroup also did not experience an improvement in efficacy[58].

Additional or alternative biomarkers are needed. An exploratory analysis of tumour mutational burden was recently presented and showed that, in patients having tumours with a high tumour mutational burden, OS was significantly improved in the group given nivolumab compared with the group given chemotherapy (PFS: 9.7 months vs. 5.8 months)[59]. Whether future trials confirm tumour mutational burden as a more appropriate biomarker to guide treatment decisions remains to be seen.

Immune Checkpoint Inhibitors in Second- or Third-Line Therapy: Pembrolizumab, Nivolumab, and Atezolizumab

Access to first-line pembrolizumab is limited to patients with high expression of PD-L1 (≥50%) and has not yet been accepted by all regulatory bodies, but this agent is also used in the second- and third-line settings. For patients with high PD-L1 expression (≥50%) who have been exposed to pembrolizumab in the first-line setting, second-line treatment will be a platinum doublet. For other patients, several immune checkpoint inhibitors are available. The decision about which antibody to use in the second line depends on

many factors, including biomarker testing results done in the first line, scheduling of drug administration (every 2 or every 3 weeks), drug cost, and availability.

Pembrolizumab was compared with docetaxel in the second-line NSCLC setting in the KEYNOTE-010 trial. The trial was positive for OS, favouring pembrolizumab: 10.4 months compared with 8.5 months with docetaxel ($p = 0.0008$)[60]. The trial enrolled a broader range of patients than the first-line trials did, and it included patients whose tumours were positive (≥1%) for PD-L1 expression.

Nivolumab was the first checkpoint inhibitor to show efficacy in a randomized phase III trial in a second-line setting, contrasting with the previously discussed results of CheckMate 026. The CheckMate 057 randomized phase III trial compared nivolumab with docetaxel for efficacy in the second-line treatment of patients with nonsquamous NSCLC. Results showed OS benefits favouring nivolumab, at 12.2 months compared with 9.4 months for docetaxel ($p = 0.0015$)[61]. Although survival was independent of whether the PD-L1 biomarker was present, a positive relationship was observed between the degree of positivity of the biomarker and the level of benefit of the drug.

Atezolizumab is a monoclonal antibody directed against PD-L1 that was shown in the OAK trial to be efficacious[62]. The trial randomized 850 patients with previously treated NSCLC to atezolizumab or to docetaxel. Although patients were stratified for PD-L1 expression, they did not have to express PD-L1 to be enrolled. Overall survival was improved in the group treated with atezolizumab (13.8 months) compared with the group treated with docetaxel (9.6 months, $p = 0.0003$). Overall survival was significantly increased regardless of PD-L1 status or histology.

Next Line and Beyond

Now that checkpoint inhibitors are used in the second line, the former second-line therapies have become third-line options for patients whose tumours are wild-type or mutation unknown. Further-line therapies might include the agents that were not administered in earlier lines. Options include docetaxel[63], erlotinib[64], and pemetrexed[65]—although the latter can be prescribed only if it was not used in first-line or maintenance therapy.

A significant limitation of therapy selection is that no trials have tested these various agents in later lines of therapy. Patients with satisfactory performance status can be considered for clinical trials.

FUTURE ALGORITHM

With many investigational agents in development, it is enticing to speculate on future treatment algorithms for patients with nonsquamous NSCLC wild-type or unknown mutation status (Figure 5).

A mention of KEYNOTE-021 is important here, because it is the first randomized trial to investigate combinations of chemotherapy and immune checkpoint inhibitors. The study included a cohort of 123 previously untreated patients with metastatic nonsquamous wild-type NSCLC who expressed PD-L1 at any level. Patients were randomized to either a pembrolizumab–carboplatin–pemetrexed triplet for 4 cycles or a carboplatin–pemetrexed doublet[66]. The response rate for the pembrolizumab triplet was nearly twice that for the doublet (55% vs. 29%). All responses were partial. In addition, patients treated with the pembrolizumab triplet experienced an improvement in median PFS (13.0 months vs. 8.9 months for patients treated with pemetrexed–carboplatin). In the trial, patients received maintenance pembrolizumab for 24 months or maintenance pemetrexed indefinitely. The triplet has now been approved and fast-tracked by the U.S. Food and Drug Administration. The confirmatory KEYNOTE-189 phase III trial finished accrual in April 2017 (see NCT02578680 at https://ClinicalTrials.gov). If the latter trial is positive and confirms the results of KEYNOTE-021, patient selection based on the PD-L1 biomarker could become obsolete.

While speculating on the future of targeted therapy, it is worth asking whether PD-1 and -L1 checkpoint inhibitors will be prescribed for patients whose tumours are driven by *EGFR* mutations or *ALK* arrangements. None of the immunotherapy agents tested in the CheckMate 057[58], KEYNOTE-010[60], or OAK[67] trials showed efficacy in those patients. The first-line KEYNOTE-024 and CheckMate 026 trials excluded patients with *EGFR* and *ALK* mutations. Tumours with driver mutations have a low mutational load and are unlikely to respond to immunotherapy even if PD-L1 levels are high[28]. Immunotherapy for patients with driver mutations should be considered a last-line therapy option only.

SUMMARY

Over the last few years, treatment algorithms for NSCLC have changed dramatically.

For patients with *EGFR*-driven tumours, first-line options include gefitinib, erlotinib, afatinib, and now dacomitinib. All patients clinically progressing should be tested for an acquired T790M mutation and, if positive, treated with osimertinib. For patients with *ALK*-driven tumours, the impressive results in the ALEX trial will move alectinib into the first-line setting. For patients progressing on crizotinib, treatment options to improve survival include the second-generation inhibitors ceritinib, alectinib, and brigatinib. Patients found to have *ROS1* rearrangements should be treated with crizotinib. For patients without driver mutations or who have an unknown tumour mutation status, PD-L1 status should be measured; for those

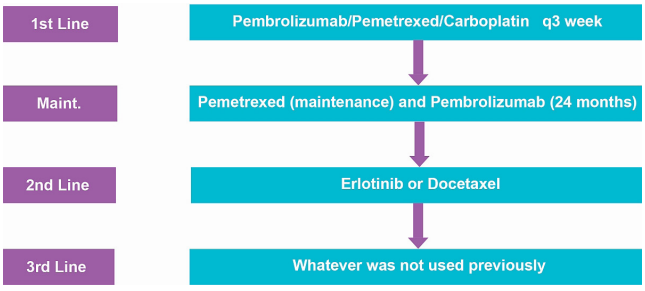

FIGURE 5 Possible future treatment algorithm for advanced nonsquamous non-small-cell lung cancer based on data from recent immunotherapy trials.

with high PD-L1 expression (≥50%), pembrolizumab is the treatment of choice. For patients who have low or unknown PD-L1 expression (<50%), chemotherapy remains the standard first-line treatment.

The combination of chemotherapy with immune agents is a development to look forward to. The phase III KEYNOTE-189 trial results are eagerly awaited. If they confirm the added benefit of combination therapy, the PD-L1 biomarker will change in its importance to patient selection, although it could still play a role in physician management decisions. Studies looking at the potential of tumour mutational burden as a biomarker are awaited, but in the meantime, PD-L1 is still important.

The treatment paradigms for NSCLC with nonsquamous histology continue to change rapidly. Those changes add a level of increased decision-making for the treating physician, but ultimately lead to increase survival and quality of life for patients.

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CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and I declare the following interests: I am a co-editor of this supplement, and I have received honoraria from Boehringer Ingelheim, Eli Lily, Pfizer, Roche, Merck, Bristol–Myers Squibb, Novartis, and AstraZeneca. I have a consulting/advisory role with Boehringer Ingelheim, and my institution has received research funding from Roche and Bayer. I have received travel, or accommodation, or expenses from Boehringer Ingelheim, AstraZeneca, Novartis, and Pfizer.

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