ASCO special articles

Therapy for Stage IV Non–Small-Cell Lung Cancer With Driver Alterations: ASCO and OH (CCO) Joint Guideline Update

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abstract

PURPOSE To provide evidence-based recommendations updating the 2017 ASCO guideline on systemic therapy for patients with stage IV non–small-cell lung cancer (NSCLC) with driver alterations. A guideline update for systemic therapy for patients with stage IV NSCLC without driver alterations was published separately.

METHODS The American Society of Clinical Oncology and Ontario Health (Cancer Care Ontario) NSCLC Expert Panel updated recommendations based on a systematic review of randomized controlled trials (RCTs) from December 2015 to January 2020 and meeting abstracts from ASCO 2020.

RESULTS This guideline update reflects changes in evidence since the previous update. Twenty-seven RCTs, 26 observational studies, and one meta-analysis provide the evidence base (total 54). Outcomes of interest included efficacy and safety. Additional literature suggested by the Expert Panel is discussed.

RECOMMENDATIONS All patients with nonsquamous NSCLC should have the results of testing for potentially targetable mutations (alterations) before implementing therapy for advanced lung cancer, regardless of smoking status recommendations, when possible, following other existing high-quality testing guidelines. Most patients should receive targeted therapy for these alterations: Targeted therapies against *ROS*-1 fusions, *BRAF* V600e mutations, *RET* fusions, *MET* exon 14 skipping mutations, and *NTRK* fusions should be offered to patients, either as initial or second-line therapy when not given in the first-line setting. New or revised recommendations include the following: Osimertinib is the optimal first-line treatment for patients with activating epidermal growth factor receptor mutations (exon 19 deletion, exon 21 L858R, and exon 20 T790M); alectinib or brigatinib is the optimal first-line treatment for patients with anaplastic lymphoma kinase fusions. For the first time, to our knowledge, the guideline includes recommendations regarding *RET, MET, and NTRK* alterations. Chemotherapy is still an option at most stages.

Additional information is available at www.asco.org/thoracic-cancer-guidelines.

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The purpose of this guideline update is to revise the ASCO guideline on the systemic treatment of patients with stage IV non–small-cell lung cancer (NSCLC), specifically, the portions on patients whose NSCLC has driver alterations. The update is a result of potentially practice-changing evidence published since the last update. ASCO published the last full clinical practice guideline update on systemic therapy for patients with stage IV NSCLC that included those with driver alterations in 2017.[1] The current guideline update includes targeted therapy for patients whose NSCLC has epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), proto-oncogene receptor tyrosine kinase (*ROS1*), or *BRAF* alterations that were covered in the 2017 update, as well as emerging driver alteration targets. ASCO published a complementary guideline update on systemic therapy without driver alterations in January 2020.[2]

Approximately 60% of patients with lung cancer tumors have driver alterations.[3] Over the past few decades, advances in the treatment of stage IV NSCLC resulted from using cytotoxic chemotherapy agents and nontargeted biologic agents, such as bevacizumab, which improved survival by a median of a few weeks to a few months. Previous ASCO guidelines for the treatment of patients with advanced NSCLC have largely focused on chemotherapy strategies. The

THE BOTTOM LINE

Therapy for Stage IV Non–Small-Cell Lung Cancer with Driver Alterations: ASCO and OH (CCO) Joint Guideline Update

Guideline Question

What systemic therapy treatment options should be offered to patients with stage IV non–small-cell lung cancer (NSCLC) with driver alterations, depending on the specific alteration of the patient's cancer?

Target Population

Patients with stage IV NSCLC with driver alterations in epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), *ROS*-1 fusions, *BRAF* V600e mutations, *RET* fusions, *MET* exon 14 skipping mutations, and *NTRK* fusions (with known marker status test results available to the clinician).

Target Audience

Oncology care providers (including primary care physicians, specialists, nurses, social workers, and any other relevant member of a comprehensive multidisciplinary cancer care team), patients, and their caregivers in North America and beyond.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Summary of Key Recommendations

Recommendation 1.1. For patients with stage IV NSCLC and driver alterations in *EGFR*

- In the first-line setting, for patients with T790M, L858R, or exon 19 deletion mutations, osimertinib should be offered (Evidence quality: high; Strength of recommendation: strong).

Recommendations 1.2, 1.3, 1.4, and 1.5. For patients with stage IV NSCLC and driver alterations in *EGFR*—if osimertinib is not available:

- In the first-line setting, if osimertinib is not available, gefitinib with chemotherapy may be offered or dacomitinib may be offered (Evidence quality: high; Strength of recommendation: moderate).
- Other options that may be offered include afatinib or erlotinib/bevacizumab or erlotinib/ramucirumab or gefitinib, erlotinib, or icotinib (Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.6. For patients with stage IV NSCLC and driver alterations in *EGFR*

- In the first-line setting, for patients with a performance status (PS) of 3, an EGFR tyrosine kinase inhibitor (TKI) may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 1.7. For patients with stage IV NSCLC and driver alterations in *EGFR*

- In the first-line setting, for patients with *EGFR* mutations other than exon 20 insertion mutations, T790M, L858R, or exon 19 deletion alterations, afatinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or osimertinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak) or treatments outlined in the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.8. For patients with stage IV NSCLC and driver alterations in *EGFR*

- In the first-line setting, for patients with any activating *EGFR* mutation (including exon 20 insertion mutations), regardless of programmed death ligand-1 (PD-L1) expression levels, single-agent immunotherapy should not be used (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.9. For patients with stage IV NSCLC and driver alterations in *EGFR* causing resistance to first- and second-generation EGFR TKIs

- In the first-line setting, for patients with *EGFR* exon 20 insertion mutation causing resistance to first- and second-generation EGFR TKIs, doublet chemotherapy with or without bevacizumab or standard treatment outlined in the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendations 2.1 and 2.2. For patients with stage IV NSCLC and driver alterations in *EGFR*

- In the second-line setting, for patients who did not receive osimertinib and have a T790M mutation at the time of progressive disease, osimertinib should be offered (Evidence quality: high; Strength of recommendation: strong).
- In the second-line setting, for patients with any *EGFR* mutation who have progressed on EGFR TKIs with no T790M mutation OR whose disease has progressed on osimertinib, treatment based on the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

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Recommendation 3.1. For patients with stage IV NSCLC and driver alterations in *ALK*

- In the first-line setting, alectinib or brigatinib should be offered (Evidence quality: high; Strength of recommendation: strong).
- In the first-line setting, if alectinib and brigatinib are not available, ceritinib or crizotinib should be offered (Evidence quality: high; Strength of recommendation: strong).

Recommendations 4.1, 4.2, and 4.3. For patients with stage IV NSCLC and driver alterations in *ALK*

- In the second-line setting, if alectinib or brigatinib was given in the first-line setting, lorlatinib may be offered (Type: informal consensus; Evidence quality: low; Strength of Recommendation: moderate).
- In the second-line setting, if crizotinib was given in the first-line setting, then alectinib, brigatinib, or ceritinib should be offered (Evidence quality: intermediate; Strength of recommendation; strong).
- In the third-line setting, if crizotinib was given in the first-line setting and alectinib, brigatinib, or ceritinib in the second-line setting, then lorlatinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or standard treatment based on the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendations 5.1, 5.2, and 5.3. For patients with stage IV NSCLC and driver alterations in *ROS1*

- In the first-line setting, crizotinib or entrectinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or standard treatment based on the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or ceritinib or lorlatinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendations 6.1 and 6.2. For patients with stage IV NSCLC and driver alterations in *ROS1*

- In the second-line setting, if ROS1-targeted therapy was given in the first-line setting, standard treatment based on the ASCO/OH nondriver mutation guideline should be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- In the second-line setting, if nontargeted therapy was given in the first-line setting, crizotinib, ceritinib, or entrectinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendations 7.1 and 7.2. For patients with stage IV NSCLC and driver alterations with *BRAF* V600E mutation

- In the first-line setting, dabrafenib/trametinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or standard first-line treatment based on the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendations 8.1, 8.2, 8.3, and 8.4. For patients with stage IV NSCLC and driver alterations with *BRAF* V600E mutation

- In the second-line setting, if previous BRAF/MEK-targeted therapy (dabrafenib/trametinib) was given in the first-line setting, standard treatment based on the ASCO/OH nondriver mutation guideline should be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- In the second-line setting, if BRAF-targeted therapy was not given in the first-line setting, dabrafenib/trametinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or dabrafenib or vemurafenib alone may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).
- If previous chemotherapy, immunotherapy, and/or BRAF-targeted therapy were given in the first- or subsequent-line setting, standard treatment based on the ASCO/OH nondriver mutation guideline should be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 8.4. For patients with stage IV NSCLC and driver alterations with *BRAF* mutations other than V600E

- In the second-line setting, standard treatment based on the ASCO/OH nondriver mutation guideline should be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendations 9.1 and 9.2. For patients with stage IV NSCLC and *MET* exon 14 skipping mutation

- In the first-line setting, for patients with an *MET* exon 14 skipping mutation, MET-targeted therapy with capmatinib or tepotinib may be offered or standard treatment based on the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of Recommendation: moderate).

Recommendations 10.1 and 10.2. For patients with stage IV NSCLC and *MET* exon 14 skipping mutation

- In the second-line setting, for *MET* abnormalities other than exon 14 skipping mutations or if MET-targeted therapy was given in the first-line setting, standard treatment based on the ASCO/OH nondriver mutation guideline should be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

- In the second-line setting, patients with an *MET* exon 14 skipping mutation who previously received or were ineligible for first-line chemotherapy with or without immunotherapy (ie, if MET-targeted therapy was not given in the first-line setting), capmatinib or tepotinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendations 11.1, 11.2, and 11.3. For patients with stage IV NSCLC and driver alterations in *RET*

- In the first-line setting, selpercatinib may be offered or standard treatment based on the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or pralsetinib* may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendations 12.1, 12.2, and 12.3. For patients with stage IV NSCLC and driver alterations in *RET*

- In the second-line setting, if RET-targeted therapy was given in the first-line setting, standard treatment based on the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of Recommendation: moderate).
- In the second-line setting, if RET-targeted therapy was not given in the first-line setting, selpercatinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or pralsetinib* may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendations 13.1 and 13.2. For patients with stage IV NSCLC and driver alterations in *NTRK*

- In the first-line setting, entrectinib or larotrectinib may be offered or standard treatment based on the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendations 14.1 and 14.2. For patients with stage IV NSCLC and driver alterations in *NTRK*

- In the second-line setting, if NTRK-targeted therapy was given in the first-line setting, standard treatment based on the ASCO/OH nondriver mutation guideline may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- In the second-line setting, if NTRK-targeted therapy was not given in the first-line setting, entrectinib or larotrectinib may be offered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Note: Unless otherwise listed, recommendations apply to patients with a PS of 0-2.

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

Note: Unless otherwise noted, type of recommendation is evidence-based.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

*Provisionally included pending confirmatory data.

past guidelines focused on the optimal use of carboplatin versus cisplatin, platinum versus nonplatinum doublets, three-drug chemotherapy combinations versus two-drug combinations, the use of bevacizumab, and the incorporation of maintenance therapy strategies. Decision making for the optimal treatment of patients with NSCLC in 2021 focuses on the molecular signatures of tumors and programmed death ligand-1 (PD-L1) score. In 2017, updated guidelines introduced the use of immunotherapy into clinical practice and provided guidance on treating patients with some driver alterations, for example, *EGFR*-activating mutations and *ALK* fusions. Since 2017, substantial progress has been made in the development of therapeutics targeting a variety of lung cancers, partially reliant on dominant oncogenic drivers. Therefore, in 2020, ASCO and Ontario Health (Cancer Care Ontario) (OH [CCO]) published the first part of the updated guidelines, for patients without driver alterations. This manuscript is the second part of the updated ASCO and OH (CCO) guidelines for the treatment of patients with advanced NSCLC with oncogenic-driven tumors.

Many oncogenic drivers of cancer were identified over the last several decades, but little progress occurred in therapeutically targeting these disturbed molecular pathways in the clinic setting. The epidermal growth factor was discovered in 1962, and its receptor pathway in 1975. Activated *RAS* mutations were first reported in 1982. The oncogene *MET* was discovered in 1985, and a cell line

harboring an *MET* exon 14 splice mutation was reported in 2003. *ROS1* was discovered in 1986, and *ROS1* fusion proteins in 2007. *RET* was discovered in 1985, the *RET*-fusion proteins in 1990, and its role in lung cancer in 2012. *ALK* was discovered in a rare subset of patients with lymphoma in 1994, and the *EML4-ALK* fusion was reported in lung cancer in 2007. The *BRAF* V600e mutation was initially reported in 2002. The scientific elucidation of these oncogenes, their pathways, and molecular signaling was paramount to the successful therapeutic targeting of patients with these molecular abnormalities in lung cancer in the decades to follow. Collectively, patients with NSCLC and known targetable alterations, including emerging targets such as *KRAS* G12C and *HER2* exon 20 insertion mutations, comprise about 1/3 of patients, regardless of smoking history, and are seen in the majority of patients who are never or remote smokers with adenocarcinoma.

Initial attempts at incorporating molecularly targeted therapy in patients with advanced NSCLC produced modest results, because of either the inability to effectively inhibit the pathway or failure to identify an enriched population most likely to benefit. The targeting of *KRAS* mutations is an example of the former, and the use of gefitinib in unselected patient populations is an example of the latter. The first breakthrough in identifying a population of patients with lung cancer likely to respond to molecularly targeted therapy was in 2004 with the identification of activating mutations in *EGFR*. The field of personalized medicine in lung cancer has rapidly advanced since. As of this writing, the US Food and Drug Administration (FDA) has approved therapeutics to treat patients with *EGFR*, *ALK*, *ROS1*, *BRAF* V600e, *RET*, *MET*, and *NTRK* molecular alterations. This guideline will focus on these seven targets. Therapeutics have demonstrated promising activity against several other molecular targets; additional advances are likely to come soon.

The results from phase III clinical trials provide enough evidence to recommend the optimal first-line treatment of patients with *EGFR*-activating mutations in exon 19 (deletion), exon 21 L858R, and exon 20 T790M mutations, plus those with *ALK* fusions. The Expert Panel provides evidence-based recommendations with a rating of high for the strength of evidence and strong for the strength of recommendation in some instances. However, recommendations of other targetable mutations covered in this guideline rely on phase II single-arm data only. In the absence of phase III trials evaluating the targeted agent to the standard-of-care recommendations based on the nondriver alterations guidelines, the Expert Panel used informal consensus to provide the best current guidance for current clinical practice for the majority of other recommendations. For example, the Expert Panel recommended targeted therapy for the treatment of patients with *RET* fusions; however, no direct comparisons of targeted therapy with nondriver mutation treatment are available. The efficacy of nondriver mutation treatment is unknown in most populations with targetable mutations such as *ROS1*, *BRAF* V600e, *RET*, *MET*, and *NTRK*. Presumably, previous phase III trials of chemotherapy included these populations in studies evaluating chemotherapy, immunotherapy, antivascular endothelial growth factor (VEGF) therapy, and combination therapies, but the relative benefits of these therapies in these rare subgroups are unknown.

Because of these limitations, the Expert Panel provides clinicians multiple options they may use to treat patients with these molecular targets in the first- and second-line settings. It is unknown if improved outcomes would be seen when comparing standard nondriver mutation treatment with using the targeted therapy in the first- or second-line setting. It is crucial that studies comparing targeted therapy with standard therapy for lung cancer continue to provide evidence to move from informal consensus to true evidence-based strategies. In most instances, US FDA approval of these targeted agents does not specify line of therapy because of the inclusion of multiple lines of therapy in most phase II studies. Sometimes, the number of patients treated in the first-line setting is limited, but response rates (RRs) are similar regardless of line of therapy used, presuming patients received no prior targeted therapy. Furthermore, these guidelines do not provide recommendations for further lines of therapy beyond the use of targeted agents and one line of standard nondriver alteration–targeted treatment.

GUIDELINE QUESTIONS

This clinical practice guideline addresses three overarching clinical questions: For patients with stage IV NSCLC with driver alterations: (1) What is the most effective first-line therapy? (2) What is the most effective second-line therapy? (3) Is there a role for a third-line therapy or beyond? The guideline addresses patients with NSCLC in the following histologic or subgroups: *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET*, *HER2*, and *NTRK*.

The update does not apply to patients with stage IV NSCLC without known driver alterations. The guideline also does not apply to patients with stage IV NSCLC with rarer histologies, for example, large cell, neuroendocrine, etc.

METHODS

Guideline Update Development Process

ASCO uses a signals approach to facilitate guideline updating. This approach identifies new, potentially practice-changing data (signals) that might translate into revised practice recommendations. The approach relies on targeted literature searching and the expertise of ASCO guideline panel members to identify signals. This systematic review–based guideline update was developed by a multidisciplinary Expert Panel, which included two patient representatives and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel also included representatives from OH (CCO) in an effort to

avoid duplication of guidelines on topics of mutual interest (Appendix Table A1, online only). The Expert Panel, co-chaired by N.H. and G.M, met via teleconference and/or webinar and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. In addition to the ASCO approval process, OH (CCO) provided approval through its Program in Evidence-Based Care (PEBC) approval internal and external processes. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed using a systematic review. ASCO guidelines staff updated the literature search that was conducted to inform its recommendations on systemic therapy for patients with stage IV NSCLC with driver alterations.[1] MEDLINE was searched from December 2015 to January 2020, for ASCO Abstracts 2018, 2019, and 2020, and ESMO 2019. The updated search was restricted to articles published in English and to systematic reviews, meta-analyses, randomized controlled trials (RCTs), and phase II prospective trials. Articles were selected for inclusion in the systematic review of the evidence, based on the following criteria:

- Population: Patients with stage IV NSCLC (many studies also include patients with stage IIIB) and known actionable target/biomarker status (ie, clinician already has testing results)
- Fully published or recent meeting presentations of English-language reports of phase II or III RCTs, rigorously conducted systematic reviews, or meta-analyses. Trials with a population with stage IV NSCLC that compared targeted therapy with standard treatment
- Minimal sample size of 20 or 1% of target population required to have the actionable driver alteration of total participants
- Included actionable targets were *EGFR*, *ALK*, ROS, *BRAF*, *NTRK*, *RET*, *MET*, *HER2*, and *KRAS*.

Articles were excluded from the systematic review if they were (1) meeting abstracts without presentations or full posters; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.[4] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date. The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 54 studies met eligibility criteria and form the evidentiary basis for the updated guideline recommendations. Specific studies applicable to the update's clinical questions are narratively summarized here (n = 40). A list of all publications is in the Data Supplement (online only).

The identified trials were published and/or presented between December 2015 and January 2020, plus a search of abstracts of the ASCO Virtual Meeting of May 2020. The randomized trials compared similar interventions. The primary outcome for all trials was therapeutic efficacy, although it was framed in a variety of ways such as progression-free survival (PFS), RR, and overall survival (OS). Few of the studies used OS as the primary outcome. The randomized trials compared a variety of interventions. Table 1 presents the articles that were particularly pertinent to the development of the recommendations. Characteristics of the studies' participants are in the Data Supplement.

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed (see Table 2 for RCTs and Table 3 for observational studies). Refer to the Data Supplement and Methodology Manual for more information on and for definitions of ratings for overall potential risk of bias.

As seen in Table 2, study quality was formally assessed for the RCTs, and Table 3 for the single-arm studies identified. Other studies' quality assessments are in the Data Supplement. Design aspects related to the individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc, generally indicating a low to intermediate potential risk of bias for most of the identified evidence. Follow-up times varied between studies, lowering the comparability of the results. Refer to Methodology Manual for definitions of ratings for overall potential risk of bias.

Additional data on key outcomes of interest and key adverse events (AEs) are reported in Tables 4 and 5 and in the Data Supplement. Data analysis regarding unchanged recommendations is reviewed in the 2017 guideline update.[1]

RECOMMENDATIONS

First-Line Treatment

Clinical question 1. For patients with a sensitizing (L858R/exon 19 deletion) *EGFR* mutation with stage IV NSCLC and a performance status (PS) of 0-2 who have not had previous systemic therapy, what is the optimal first-line treatment?

EGFR First-Line

Recommendation 1.1. For patients with a sensitizing (L858R/exon 19 deletion, with or without a concomitant T790M mutation) *EGFR* mutation with stage IV NSCLC and a PS of 0-2 who have not had previous systemic therapy, clinicians should offer osimertinib monotherapy (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statement. Although Recommendation 1.1 addresses many patients in the target population, the guideline manuscript presents additional options that may be reasonable, based on the evidence reviewed. This statement applies to all recommendations with the word should. In addition, the use of osimertinib in patients previously treated with adjuvant or consolidation tyrosine kinase inhibitors (TKIs) is not part of this guideline.

Literature review update and analysis. For osimertinib, new evidence identified by the systematic review consisted of one randomized trial (FLAURA) for patients with sensitizing *EGFR* mutations (L858R/exon 19 deletion with or without a concomitant T790M mutation). In this trial, participants were randomly assigned to either osimertinib or a standard first-line EGFR TKI therapy (erlotinib or gefitinib).[5] A majority of patients' cancers in both arms had exon 19 deletions (see Patient Characteristics, Data Supplement). The primary outcome was duration of PFS, and the investigator-

TABLE 1. Study Characteristics

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
Carter et al[65]	RCT		CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Selumetinib plus erlotinib	Selumetinib		*KRAS* mut + or *KRAS* WT	*KRAS* WT and *KRAS* mutation PS 0-2	Arm 1: KRAS mut S: 11, KRAS WT E: 19 Arm 2: KRAS mut E + S: 30, KRAS WT E + S: 19	
Park et al[15]	RCT	LUX-Lung 7	CQ 1. 1st line	Afatinib	Gefitinib		Activating *EGFR* mut	Activating *EGFR* mut PS 0-1	Arm 1: 160 Arm 2: 159	Arm 1: 160 Arm 2: 159
Yang et al[26]	RCT		CQ 1. 1st line, CQ 2. 2nd line	Gefitinib	Erlotinib		Exon 19 deletion or exon 21 mutations	Stage IIIB or IV Exon 19 deletion or exon 21 mut PS 0-2	Arm 1: 128 Arm 2: 128	Arm 1: 128 Arm 2: 128
Kim et al[42]	RCT	ALTA (note older search)	CQ 2. 2nd line	Brigatinib 90 mg daily	Brigatinib 180 mg daily with 7-day lead-in 90 mg		*ALK*	Disease progression during crizotinib tx ECOG PS ≤ 2 ≥ 1 measurable lesion 0 or greater prior chemotherapy	Arm 1: 112 Arm 2: 110	Arm 1: 112 Arm 2: 110
Shaw et al[41]	RCT	ASCEND-5	CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Ceritinib	Chemotherapy		*ALK*+ rearrangement	Documented *ALK* rearrangement 1-2 prior therapies, prior crizotinib with DP PS 0-2	Arm 1: 115 Arm 2: 116	Arm 1: 115 Arm 2: 116
Soria et al[5,6]	RCT	FLAURA	CQ 1. 1st line	Osimertinib	Standard *EGFR*-TKI		Exon 19 deletion or Leu858Arg mut	No prior treatment Local or central confirmation of *EGFR* exon 19 deletion or L858R (p.Leu858Arg)	Arm 1: 279 Arm 2: 277	Arm 1: 279 Arm 2: 277
An et al[8]	RCT		CQ 1. 1st line	Gefitinib and placebo	Gefitinib and pemetrexed		Common mutation	Nonsquamous cell carcinoma *EGFR* (common mutation) Stage III or IV		Arm 1: 45 Arm 2: 45
Cheng et al[9]	RCT		CQ 1. 1st line	Gefitinib and pemetrexed	Gefitinib		Primarily exon 19 deletion or exon 21 L858R point mutation	Patients from East Asia with stage IV or recurrent histologically or cytologically confirmed NSCLC	Arm 1: 129	Arm 1: 126

(continued on following page)

TABLE 1. Study Characteristics (continued)

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
								Activating *EGFR* mutations (primarily exon 19 deletion or exon 21 L858R point mut)	Arm 2: 66	Arm 2: 65
								Age ≥ 18 years (≥ 20 years in Japan and Taiwan)		
								ECOG PS 0-1		
								Measurable disease documented by CT or MRI		
Soria et al[34]	RCT	ASCEND-4	CQ 1. 1st line	Ceritinib	Chemotherapy		*ALK*+ rearrangement	Locally advanced or metastatic nonsquamous	Arm 1: 189	Arm 1: 189
								ALK-rearranged NSCLC, untreated with any systemic anticancer therapy (except NACT or adjuvant systemic therapy [if relapse had occurred > 12 months from the end of therapy])	Arm 2: 187	Arm 2: 187
								Measurable disease as per RECIST 1.1 criteria		
								WHO PS 0-2		
								Asymptomatic or neurologically stable brain metastases (for ≥ 2 weeks)		
Lim et al[49]	Obs		CQ 2. 2nd line	Ceritinib			*ROS1* rearrangement	*ROS1*-rearranged NSCLC	Arm 1: 32	Arm 1: 32
								Age 20+		
								Locally advanced or metastatic NSCLC that had progressed despite standard therapy		
								ECOG PS of 0-2		
								Adequate organ function and laboratory results		
								At least one measurable lesion at baseline according to the RECIST 1.1		
Shi et al[25]	RCT	CONVINCE	CQ 1. 1st line	Icotinib	Cisplatin/pemetrexed plus pemetrexed maintenance		Exon 19 deletion or L858R mutation in exon 21	Histologically confirmed stage IIIB or IV lung adenocarcinoma (AJCC TNM V. 7) with activating *EGFR* mutations (exon 19 deletion or L858R mut in exon 21)	Arm 1: 148	Arm 1: 148
								18+ years old	Arm 2: 148	Arm 2: 137
								No history of chemotherapy for metastatic disease		
								Measurable lesion according to RECIST 1.1		
								ECOG PS of 0-2		
								Adequate organ function		

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TABLE 1. Study Characteristics (continued)

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
Wu et al[45]	Obs		CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Oral crizotinib			*ROS1* rearrangement and *ALK*-negative	18+ years of age Histologically or cytologically confirmed locally advanced or metastatic NSCLC *ROS1* rearrangement +, *ALK*-negative ≤ 3 lines of prior systemic therapies for advanced-stage disease 1+ measurable tumor lesions as assessed by RECIST 1.1 that were not irradiated ECOG PS of 0 or 1 Patients with brain mets were eligible if asymptomatic or were neurologically stable for 2+ weeks if treated	Arm 1: 127	Arm 1: 127
Camidge et al[33]	RCT	ALTA-1L	CQ 1. 1st line	Brigatinib, 180 mg once daily with a 7-day lead-in at 90 mg	Crizotinib 250 mg twice daily		*ALK*+	18+ years of age Locally advanced or metastatic NSCLC with ≥ 1 measurable lesion according to RECIST 1.1 Had not previously received *ALK*-targeted therapy	Arm 1: 137 Arm 2: 138	Arm 1: 137 Arm 2: 138
Wu et al[12]	RCT	ARCHER 1050	CQ 1. 1st line	Dacomitinib	Gefitinib		Exon 19, Leu858A4g	Stage IIIB or IV or recurrent *EGFR*+ PS 0-1	Arm 1: 227 Arm 2: 225	Arm 1: 227 Arm 2: 225
Mok et al[13]								Documented *EGFR* mutation (exon 19 deletion or the Leu858Arg mutation, with or without the Thr790Met mutation)		
Solomon et al[40]	Obs		CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Lorlatinib			*ALK* or *ROS1* gene rearrangement	Histologically or cytologically confirmed diagnosis of metastatic NSCLC *ALK* or *ROS1* gene rearrangement ≥ 1 target extracranial lesion by RECIST 1.1.	Arm 1: 276 enrolled (with both *ALK* and ROS1)[a]	Arm 1: 228 *ALK*-positive (1st line: 30, 2nd line anti-*ALK*: 27, crizotinib plus chemotherapy: 32, 2nd gen anti-*ALK* ± chemo.: 28, 3rd line anti-*ALK* ± chemo.: 65, 4th gen anti-*ALK* ± chemo.: 46), ROS1: 47[b]

(continued on following page)

TABLE 1. Study Characteristics (continued)

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
Imai et al[14]	Obs		CQ 1. 1st line	Afatinib			Exon 19 deletion or L858R point mutation in exon 21	Chemotherapy-naïve patients with NSCLC harboring sensitive mutations of *EGFR* (exon 19 deletion or L858R point mutation in exon 21) Age 70 years or older with an ECOG-PS of 0-2 Histologically or cytologically confirmed NSCLC Stage IIIB-IV or postoperative relapsed NSCLC Presence of a measurable lesion according to RECIST 1.1 Adequate organ function Written informed consent	Arm 1: 40	Arm 1: 40
Peters et al[72]	Obs		CQ 2. 2nd line, CQ 3. 3rd line, and beyond	T-DM1			HER2+ (IHC 2+ or 3+)	Age 18+ HER2-positive (IHC 2+ or 3+) locally advanced or metastatic NSCLC previously treated with ≥ 1 prior platinum-based chemotherapeutic regimen ECOG PS 0-1 Measurable disease (per RECIST 1.1) Adequate organ function Left ventricular ejection fraction ≥ 50%	Arm 1: 49	Arm 1: 49
Reck et al[30]	RCT	IMpower150 subgroup analyses	CQ 1. 1st line	ABCP	BCP	ACP	*EGFR*—Exon 19 deletion, L858R, exon 20 insertion, T790M, S768I, and others	Non-SCC ECOG PS 0-2 Any PD-L1 IHC status Patients who had received previous adjuvant or NACT were eligible if the last treatment was at least 6 months before random assignment Patients with *EGFR* alterations were included if they had had disease progression with or unacceptable side effects from treatment with at least one approved TKI		Arm 1: ABCP 34, arm 2: ACP 45, arm 3: BCP 45

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TABLE 1. Study Characteristics (continued)

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
Michels et al[44]	Obs	EUCROSS	CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Crizotinib			*ROS1*	≥ 18 years of age *ROS1* ECOG PS 0-2 ≥ 1 measurable lesion per RECIST	Arm 1: 34	Arm 1: 30[c]
Landi et al[48]	Obs	METROS	CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Crizotinib with ROS1-positive	Crizotinib with MET-positive		*ROS1* rearrangements or MET deregulation (amplification, ratio MET/CEP7), ie, either MET amplification or exon 14 mutation	Histologically confirmed diagnosis of locally advanced or metastatic NSCLC Availability of archival tissue for biomarker analyses ECOG PS ≤ 2 ≥ 1 previous chemotherapy line At least one measurable tumor lesion according to RECIST 1.1 Adequate bone marrow and organ functions	Arm 1: 26 Arm 2: 26	Arm 1: 26 Arm 2: 26
Shaw et al[46]	Obs		CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Lorlatinib 100 mg one time daily (in Ph 2)			*ROS1* rearrangement	≥ 18 years Histologically or cytologically confirmed metastatic NSCLC *ROS1* rearrangement ECOG PS ≤ 2 (≤ 1 for phase I only). ≥ 1 measurable target extracranial per RECIST 1.1. Asymptomatic treated or untreated CNS metastases were permitted Treatment-naïve or ≥ 1 *ROS1* inhibitor (for phase I) or any no. of prior therapy or *ROS1* inhibitor (phase II)		Arm 1: 69[d]

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TABLE 1. Study Characteristics (continued)

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
Drilon et al[47]	Obs	*ALK*A-372-001, STARTRK-1, STARTRK-2	CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond, Others: all	Entrectinib (at least 600 mg)			*ROS1*+	*ROS1*+		Arm 1: 53[e]
Subbiah et al[50]	Obs	VE-BASKET	CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Vemurafenib (960 mg twice a day)			*BRAF* V600 mutation–positive	≥ 16 years Histologically confirmed, measurable, *BRAF* V600 mutation–positive, cancers that were refractory to standard therapy or for which standard or curative therapy did not exist or was not considered appropriate by the investigator Patients with solid tumors were required to have adequate hematologic, renal, and liver function		Arm 1: 62
Drilon et al[62]	Obs		CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Larotrectinib (orally, 100 mg twice daily for adults or children BSA ≥ 1 m^2)			*NTRK*	Locally advanced or metastatic *NTRK* fusion–positive tumors—4 months to 76 years of age Previously treated with therapy other than kinase inhibitors (where available) ECOG PS 0-2 (ECOG PS 0-3 were eligible)		Arm 1: 55[f]
Doebele et al[63]	Obs	ALKA-372-001, STARTRK-1, and STARTRK-2	CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Entrectinib daily at least 600 mg/m^2			*NTRK*	Locally advanced or metastatic *NTRK* fusion–positive solid tumors ECOG PS 0-2 Minimum life expectancy of 3 months (*ALK*A or STARTRK-1) or 4 weeks (STARTRK-2) Adequate organ function		Arm 1: 54 (10 NSCLC)
Furuya et al[18]	RCT	NEJ 026	CQ 1. 1st line	Erlotinib and bevacizumab (150 mg daily and 15 mg/kg every 3 weeks)	Erlotinib (150 mg daily)		Exon 19 deletion or exon 21 L858R *EGFR* mutations	Non-SCC Chemotherapy-naïve Stage IIIB or IV or postop recurrence Exon 19 deletion or exon 21 L858R *EGFR* mutations Asymptomatic CNS metastases allowed	Arm 1: 114 Arm 2: 114	Arm 1: 112 Arm 2: 112

(continued on following page)

TABLE 1. Study Characteristics (continued)

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
Ahn et al[29]	Obs	KCSG-LU15-09	CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Osimertinib (80 mg once daily)			Activating *EGFR* mutations other than exon 19 deletion, L858R, T790M, and insertion in exon 20	Stage IV Activating *EGFR* mutations other than exon 19 deletion, L858R, T790M, and insertion in exon 20 ≥ 19 years ECOG PS 0-2 Adequate hematologic/liver/kidney function	Arm 1: 36	Arm 1: 36
Gao et al[71]	Obs		CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Pyrotinib 400 mg			HER2 exon 20	Stage IIIB or IV NSCLC ECOG PS 0-1 Centrally confirmed HER2 exon 20 progression during or after prior therapy ≥ 1 prior platinum-based		Arm 1: 60
Wolf et al[53,54]	Obs	GEOMETRY	CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Capmatinib (400 mg daily)			MET Δ ex14 alteration–positive	Stage IIIB or IV NSCLC Met delta ex14 alteration–positive PS 0-1 ≥ 1 measurable lesion Neurologically stable or asymptomatic brain metastases allowed	Arm 1: 69 (cohort 4), 28 (cohort 5)	Arm 1: 69 (cohort 4), 28 (cohort 5)
Paik et al[55]	Obs	VISION	CQ 1. 1st line, CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Tepotinib (500 mg)			MET Δ ex14 alteration–positive	Adults MET Δ ex14 alteration–positive PS 0-1 *EGFR*– and *ALK*– Patients with brain metastases whose condition was neurologically stable and whose glucocorticoid dose was being tapered were eligible to participate, as were patients with untreated asymptomatic brain metastases measuring 1 cm or less in the longest diameter	Arm 1: 152	Arm 1: 99

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TABLE 1. Study Characteristics (continued)

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
Gadgeel et al[66]	Obs		CQ 2. 2nd line, CQ 3. 3rd line, and beyond	Trametinib (2 mg daily) and docetaxel (75 mg/m^2 every 3 weeks)			*KRAS*+	*KRAS*+ 1 or 2 prior regimens (prior IO allowed) PS 0-1 Neutrophil count ≥ 1,500/mcL, platelets ≥ 100,000/mL, and hemoglobin ≥ 9 g/dL Bilirubin ≤ 1.5 × ULN; AST and ALT 2.5 × ULN, if liver Mets 5 × ULN Creatinine 1.5 × ULN or calculated creatinine clearance ≤ 40 mL/min LVEF ≥ LLN; QTc ≤ 480 ms (Bazett's formula) No evidence of retinopathy as determined by ophthalmologist or history of retinal vein occlusion Patients with treated brain metastases	Overall: 54, Note: G12C = 19 and non-G12C = 35	Overall: 54, Note: G12C = 19 and non-G12C = 35
Cortot et al[16]	RCT	IFCT-1503 ACE-Lung	CQ 1. 1st line	Afatinib (40 mg daily)	Afatinib (40 mg daily) plus cetuximab (500 mg/m^2 every 2 weeks)		Exon 19 deletion or L858R, G719X, L861Q, and S768I mutations or exon 19 insertion	Advanced NSCLC *EGFR*: common mutations (exon 19 deletion or L858R, G719X, L861Q, and S768I mutations or exon 19 insertion) No prior treatment (chemotherapy or TKI) PS 0-1 Allowed untreated brain metastases	Arm 1: 59 Arm 2: 59	Arm 1: 59 Arm 2: 58
Noronha et al[10]	MA		CQ 1. 1st line	Gefitinib (250 mg per day)	Gefitinib plus pemetrexed plus carboplatin ((250 mg per day + 500 mg/m^2 + AUC 5 every 3 weeks) plus maintenance pemetrexed)		Exon 19, 21, or 18 mutations	≥ 18 years *EGFR* exon 19, 21, or 18 mutations PS 0-2 Stage locally advanced IIIB[E] or stage IV, measurable disease Adequate organ function	Arm 1: 176 Arm 2: 174	Arm 1: 176 Arm 2: 174

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TABLE 1. Study Characteristics (continued)

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
Nakagawa et al[19]	RCT	RELAY	CQ 1. 1st line	Erlotinib and ramucirumab (150 mg daily + 10 mg/kg) every 2 weeks	Erlotinib and placebo (150 mg daily + 10 mg/kg) every 2 weeks		Exon 19 deletion or Leu858Arg mutation	≥ 18 years of age (≥ 20 in Japan/ Taiwan) Stage IV Documented exon 19 deletion or Leu858Arg mutation (previously documented by local testing) PS 0-1 Life expectancy ≥ 3 months Able to tolerate ≥ 2 cycles	Arm 1: 224 Arm 2: 225	Arm 1: 224 Arm 2: 225
Zhou et al[17]	RCT	ARTEMIS (CTONG 1509)	CQ 1. 1st line	Erlotinib plus bevacizumab (150 mg daily and 15 mg/kg every 3 weeks)	Erlotinib (150 mg daily)		Exon 19 deletion or L858R mutation in exon 21	Chemo-naïve *EGFR* + exon 19 or exon 21 L858R ECOG PS 0-1 Bevacizumab eligible	Arm 1: 157 Arm 2: 154	Arm 1: 157 Arm 2: 154
Goto et al[57] Drilon et al[60]	Obs		CQ 1 1st line and CQ 2. 2nd line	Selpercatinib (LOXO-292)			RET fusion	Age ≥ 18 yrs or ≥ 12 years if regulator permits Advanced or met solid tumor ECOG PS 0-2 QTc of ≤ 470 ms Adequate organ function		Arm 1: 105 (prior platinum-based chemo) also 39 treatment-naïve
Peters et al[35]	RCT	ALEX	CQ 1. 1st line	Alectinib (600 mg twice daily)	Crizotinib (250 mg twice daily)		*ALK*+	Confirmed advanced NSCLC that was *ALK*-positive ≥ 18 years ECOG PS 0-2 No prior tx Adequate hepatic, renal, and bone marrow function Asymptomatic brain or leptomeningeal metastases were eligible; previous CNS radiotherapy was allowed if completed ≥ 14 days before enrollment.		Arm 1: 152 Arm 2: 151
Nakagawa et al[37] Hida et al[36]	RCT	J-ALEX	CQ 1. 1st line	Alectinib 300 mg	Crizotinib 250 mg		*ALK*+	*ALK*-positive No prior treatment or 1 prior chemotherapy regimen PS 0-2 *ALK* positivity confirmed centrally by IHC and FISH or RT-PCR		Arm 1: 103 Arm 2: 104

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TABLE 1. Study Characteristics (continued)

Reference	Study Design	Study Name	Clinical Question	Arm 1—Intervention(s)	Arm 2—Intervention(s)	Arm 3—Intervention(s)	Subalteration	Inclusion	n Randomly Assigned	n Analyzed
Gainor et al[58,59]	Obs	ARROW	CQ 1. 1st line, CQ 2. 2nd line	Pralsetinib BLU-667 400 mg			RET+	RET+ ECOG 0-1		ITT: 132 all (92 2nd line, 29 1st line), Response evaluable population: 116 (80 2nd line, 26 1st line)

Abbreviations: ABCP, atezolizumab/bevacizumab/carboplatin/paclitaxel; ACP, atezolizumab/carboplatin/paclitaxel; AJCC, American Joint Committee on Cancer; *ALK*, anaplastic lymphoma kinase; BCP, bevacizumab/carboplatin/paclitaxel; BSA, body surface area; chemo, chemotherapy; CT, computed tomography; CQ, clinical question; del, deletion; DP, disease progression; E, erlotinib; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; f/u, follow-up; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IO, immunotherapy; ITT, intention to treat; LLN, lower limit of normal; LVEF, left ventricle ejection fraction; MRI, magnetic resonance imaging; mets, metastases; mut, mutation; NACT, neoadjuvant chemotherapy; NSCLC, non–small-cell lung carcinoma; NTRK, neurotrophic tropomyosin receptor kinase; Obs, observational; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression free survival; PS, performance status; QTc, QT interval corrected for heart rate; RCT, randomized controlled trial; RT-PCR, reverse transcriptase-polymerase chain reaction; S, selumetinib; SCC, squamous cell carcinoma; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor; Tx, treatment; ULN, upper limit of normal; WT, wild type.

[a]275 enrolled and ≥ 1 dose.

[b]*ALK*+ in 5 cohort, EXP1-EXP5.

[c]"…if an adequate baseline tumor assessment was performed, eligibility criteria were fulfilled, and at least 1 dose of crizotinib was administered. The ITT included all patients who received at least 1 dose of crizotinib."

[d]All patients with ROS1 alteration (with different prior treatments and at different doses, in various parts of study). Sample size not predefined or based on power calculations.

[e]≥ 1 dose entrectinib and ≥ 12 months of f/u patients with ROS1 fusion–positive NSCLC, who were ROS1 inhibitor-naïve, had measurable disease at baseline, and ≥ 12 months follow-up from the onset of treatment; patients were not assessable if they did not have measurable disease at baseline.

[f]55 (8 adults and 12 pediatric patients from phase I trial and 35 adults and adolescents from the phase II trial); four patients with lung cancer.

[g]Not amenable to radical therapy.

[h]Long-term OS follow-up ongoing.

TABLE 2. Quality RCTs

Bibliography	Study Design	Adequate Random Assignment	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-Up	ITT	Insignificant COIs	Overall Risk of Bias (RCTs)
Carter et al[65]	RCT	Unclear	Unclear	Yes, Note: for exclusion	Yes	No	Partially	Yes	Yes	Yes	Intermediate
Park et al[15]	RCT	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	No	Low, intermediate
Yang et al[26]	RCT	Unclear	Unclear	Yes[a]	Yes	Unclear	Yes	Yes	Yes	Yes	High[b]
Kim et al[42]	RCT	Unclear	Unclear	Yes	Yes	No	Partially	Yes	Yes	No	Intermediate
Shaw et al[41]	RCT	Yes	Yes	Yes	Partially	Partially	Yes	Yes	Yes	No	High
Soria et al[5,6]	RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Intermediate
An et al[8]	RCT	Unclear	Unclear	Unclear	Yes	Yes	Partially	Unclear	Yes	Unclear	High[c]
Cheng et al[9]	RCT	Yes	Unclear	Yes	No	No	Yes	Yes	Yes	No	Intermediate
Soria et al[34]	RCT	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	High
Shi et al[25]	RCT	Yes	Unclear	Yes	Yes	No	Partially	Yes	No[d]	No	Intermediate
Camidge et al[33]	RCT	Yes	Unclear	Yes	Yes	Partially	Partially	Partially	Yes	No	Intermediate, high
Wu et al[12]	RCT	Yes	Yes	Yes	Yes	Yes	Partially	Yes	Yes	No	Intermediate
Reck et al[30]	RCT	Yes	Unclear	Partially	Yes	No	Yes	Yes		No	Intermediate[e]
Furuya et al[18]	RCT	Unclear	Unclear	Yes	Yes	No	Yes	Unclear	No[f]	No	High
Cortot et al[16]	RCT	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes: all treated	No	Intermediate[g]
Noronha et al[10]	RCT	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Low[h]
Nakagawa et al[19]	RCT	Yes	Partially	Yes	Yes	Yes	Yes	Yes	Yes	No	Low
Zhou et al[17]	RCT	Yes	No	Yes	Yes	No	Partially	Yes	Yes	No	Intermediate[i]
Peters et al[35]	RCT	Yes	Yes	Yes	Yes	No	Yes	Partially	Yes	No	Intermediate
Hida et al and Nakagawa et al[36,37]	RCT	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Intermediate

Abbreviations: COI, conflict of interest; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; RCT, randomized controlled trial.

[a]Authors wrote that larger sample size needed because of not meeting primary end point.

[b]Authors note potential enrollment bias because patients had to pay for agents and imaging self (not industry sponsored).

[c]Several variables not assessable.

[d]11 not treated and not included in control arm.

[e]Some end points exploratory.

[f]Two participants from each arm excluded from analysis, four in total.

[g]Some elements required for quality assessment were not reported in poster.

[h]ECOG 3/4. OS is positive. Only real drawback compared with osimertinib is toxicity.

[i]Moderate, also not published fully yet, OS not reported, QOL not reported.

assessed PFS result was 18.9 (95% CI, 15.2 to 21.4) versus 10.2 (95% CI, 9.6 to 11.1) months for osimertinib versus the standard arm, respectively. OS also favored osimertinib.[6] RRs were similar and not statistically significantly different. AEs were similar, although rash was greater in the control arm (Table 4).

Clinical interpretation. In 2017, osimertinib was recommended only in the second-line and only for those with T790M mutations. In this update, the Expert Panel favored the use of osimertinib in the first-line setting, given the demonstration of improvement in PFS and OS, with fewer side effects, compared with the first-generation EGFR-TKI comparators. Previous trials indicated first-generation EGFR TKIs, such as gefitinib or erlotinib, and improved PFS compared with platinum-based doublet chemotherapy in the first-line for patients with activating *EGFR* mutations. These trials established a first-generation EGFR-TKI as a reasonable comparator arm for the FLAURA trial. In addition, a clinical trial demonstrated improved PFS of osimertinib compared with chemotherapy in patients with T790M mutations.[7] No trials have been conducted to demonstrate the efficacy of platinum-based doublets plus bevacizumab or programmed death-1 (PD-1)/PD-L1 inhibitors in the first-line setting of patients with *EGFR* mutations. Despite this limitation, the Expert Panel still favors the use of osimertinib, if available, as first-line treatment of patients with *EGFR* exon 19 deletion or L858R mutations. Although Recommendation 1.1 addresses many patients in the target population, the guideline manuscript presents additional options, based on the evidence reviewed. This statement applies to all recommendations with the word should. However, the use of osimertinib in patients

TABLE 3. Quality Observational

Bibliography	Appropriate Study Design	Sufficient Sample Size	Validated and Reliable Measures	Adequate Follow-Up	Insignificant COI	Overall Risk of Bias
Lim et al[49]	Unclear[1]	Yes	Partially[c]; ITT, yes	Yes	No	Medium
Wu et al[45,a]	Yes	Yes	Yes	Yes	No	Medium
Solomon et al[40,a,g]	Unclear	Partially[d]	Partially	Partially	No	Medium
Imai et al[14,e]	Partially	Yes	Yes	Yes	Unclear	Low
Peters et al[72]	Partially[f]	Partially[h]	Partially	Yes	No	High
Michels et al[44]	Yes	Yes	Partially	Yes	Partially	Medium
Landi et al[48]	Partially	Partially[i]	Partially	Yes	No	Medium
Shaw et al[46,a]	Partially[j]	Partially[i]	Partially	Yes	No	Medium
Drilon et al[47,a]	Unclear	Yes	Yes	Yes	No	High
Subbiah et al[50]	Yes[a]	No[l]	Partially	Yes	No	Low
Drilon et al[62,b]						Certainty of the evidence (quality of evidence) was very low to low
Doebele et al[63,b]						Certainty of the evidence (quality of evidence) was very low to moderate
Ahn et al[29]	Yes	Unclear	Partially	Yes	No	Medium
Gao et al[71]	Unclear	Partially	Partially	Yes	Unclear	Medium
Wolf et al[53,54]	Yes[k]	Unclear[i]	Partially	Unclear	No	Medium[m]
Paik et al[55,a]	Partially	Partially[i]	Partially	Yes	No	Medium
Gadgeel et al[66]	Unclear	Partially[i]	Partially	Unclear	Yes	Medium
Goto et al[57,a] Drilon et al[60]	Partially[k]	Yes	Yes	Unclear	No	Medium
Gainor et al[59,a,c,f,k,m]	Unclear	Unclear	Unclear	Unclear	No	High

Abbreviations: COI, conflict of interest; NSCLC, non–small-cell lung cancer; PFS, progression-free survival.
[a]Study is ongoing.
[b]See Pancreatic Cancer guideline: Sohal et al.[64]
[c]Simon's two-stage minimax design.
[d]No power calculations and no hypothesis.
[e]Elderly specific.
[f]Phase II expansion cohort.
[g]PFS immature for several of the cohorts.
[h]Exploratory study.
[i]Target not specified.
[j]Included phase I, small percentage of patients whose NSCLC had *ROS1* alterations.
[k]Included phase I.
[l]Trial did not require centrally confirmed BRAF V600 mutation(s).
[m]Not published as of closing date parameter.

previously treated with adjuvant or consolidation TKIs is not in this guideline's purview. Notably, these (and other recommendations regarding *EGFR*) are limited to the mutations described. *EGFR* by IHC testing or fluorescence in situ hybridization (FISH) testing is not actionable for these guidelines.

Recommendations 1.2 and 1.3

Recommendation 1.2. For patients with a sensitizing (L858R/exon 19 deletion) *EGFR* mutation with stage IV NSCLC and a PS of 0-2, previously untreated with systemic therapy, and for whom osimertinib is not available, clinicians may use combination of gefitinib with doublet chemotherapy (platinum/pemetrexed with maintenance pemetrexed) (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate).

Recommendation 1.3. For patients with a sensitizing (L858R/exon 19 deletion) *EGFR* mutation with stage IV NSCLC and a PS of 0-2, previously untreated with systemic therapy, and for whom osimertinib is not available, clinicians may use dacomitinib monotherapy (Type: evidence-

TABLE 4. Results

Bibliography	Study Design	Which Study	Interventions			Primary Outcome	OS, Months	PFS, Months (95% CI Unless Otherwise Specified)	RR	1-Year Survival	Others	Overall Risk of Bias
			Arm 1	Arm 2	Arm 3							
Carter et al[65]	RCT		Selumetinib plus erlotinib	Selumetinib		PFS/TTP: *KRAS* WT, RR: *KRAS* mutation	Arm 1: KRAS mut S: 10.5 (95% CI, 5.7 to undefined); KRAS WT E: 6.3 (2.6 to 19.5) Arm 2: KRAS mut E + S: 21.8 (95% CI, 5.7 to undefined); KRAS WT E + S: 12.9 (95% CI, 3.5 to 25.4), Statistic and significance: NS	Arm 1: KRAS mut S: 4.0 (95% CI, 2.9 to 7.8); KRAS WT E: 2.4 (1.3 to 3.7) Arm 2: KRAS mut E + S: 2.3 (95% CI, 2.0 to 4.6); KRAS WT E + S: 2.1 (95% CI, 1.8 to 5.1), Statistic and significance: NS	Arm 1: KRAS mut S: 0 (95% CI, 0 to 33.6); KRAS WT E: 1 (5%) (95% CI, 0 to 26) Arm 2: KRAS mut E + S: 3 (10%) (95% CI, 2.1 to 26.3); KRAS WT E + S 2 (12%) (95% CI, 1.5 to 36.4)			Intermediate
Park et al[15]	RCT	LUX-Lung 7	Afatinib	Gefitinib		OS, PFS/TTP: PFS/TTF	Arm 1: 27.9 (95% CI, 25.1 to 32.2) Arm 2: 25.0 (95% CI, 20.6 to 29.3) HR 0.87 (95% CI, 0.66 to 1.15), $P = .33$[a]	Arm 1: 11.0 (95% CI, 10.6 to 12.9) Arm 2: 10.9 (95% CI, 9.1 to 11.5), HR: 0.73 (95% CI, 0.57 to 0.95), $P = .017$	Arm 1: 112/160, 70% Arm 2: 89/159, 56%, OR 1.87 (95% CI, 1.18 to 2.99), $P = .0083$		Type: TTF, arm 1: 13.7 months (95% CI, 11.9 to 15.0), arm 2: 11.5 months (95% CI, 10.1 to 13.1), HR 0.73 (95% CI, 0.58 to 0.92), $P = .0073$	Low, intermediate
Yang et al[26]	RCT		Gefitinib	Erlotinib		PFS/TTP: revised phase III, RR: original phase II version	Arm 1: 20.1 Arm 2: 22.9 HR = 0.84 (0.63 to 1.13), $P = .25$	Arm 1: 10.4 Arm 2: 13.0 HR = 0.81 (0.62 to 1.05), $P = 1.08$	Arm 1: 52% Arm 2: 56% $P = .53$		22.1 months f/u. Exploratory end point exon 19 and exon 21: OS: exon 19: 22.9 mo (erl) *v* 17.8 mo (gef), $P = .022$. PFS 11.4 mo *v* 11.2 mo, $P = .160$	High[b]
Kim et al[42]	RCT	ALTA (note older search)	Brigatinib 90 mg daily	Brigatinib 180 mg daily with 7-day lead-in 90 mg		RR[u]		Arm 1: 9.2 (7.4 to 15.6) Arm 2: 12.9 (11.1 to NR), HR 0.55 (95% CI, 0.35 to 0.86)u	Arm 1: 45% (97.5% CI, 34 to 56%) Arm 2: 54% (97.5% CI, 43 to 65)	Arm 1: 71% (60 to 79) Arm 2: 80% (67 to 88)[c]	ORR[v]: arm 1: 48% (95% CI, 39 to 58), arm 2: 53% (95% CI, 43 to 62) Median DOR 13.8 months (95% CI, 7.4 to NR) and 13.8 months (95% CI, 9.3 to NR). PFS[v]: 9.2 (7.4 to NR) *v* 15.6 (11.0 to NR)	Intermediate
Shaw et al[41]		ASCEND-5	Ceritinib	Chemotherapy		PFS/TTP	Arm 1: 18.1 (13.4 to 23.9), Arm 2: 20.1 (11.9 to 25.1), HR 1.0 (95% CI, 0.67 to 1.49), $P = .50$[d]	Arm 1: 5.4 (4.1 to 6.9) Arm 2: 1.6 (1.4 to 2.8), HR 0.49 (95% CI, 0.36 to 0.67), $P < .0001$[v]	Arm 1: 45 (39.1% [30.2 to 48.7]) Arm 2: 8 (6.9% [3.0 to 13.1])[v]		Disease control: arm 1: 88 (76.5% [67.7 to 83.9]), arm 2: 42 (36.2% [27.5 to 45.6])	High

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TABLE 4. Results (continued)

Bibliography	Study Design	Which Study	Interventions			Primary Outcome	OS, Months	PFS, Months (95% CI Unless Otherwise Specified)	RR	1-Year Survival	Others	Overall Risk of Bias
			Arm 1	Arm 2	Arm 3							
Soria et al[5,6]	RCT	FLAURA	Osimertinib	Standard EGFR-TKI		PFS/TTP: duration of PFS[u]	12-month OS rate: 89% *v* 83%	Arm 1: 18.9 (95% CI, 15.2 to 21.4)	Arm 1: 80% (95% CI, 75 to 85)	Arm 1: 89% (85 to 92)	Median DOR: arm 1: 17.2 (13.8 to 22.0), arm 2: 8.5 (7.3 to 9.8);	Intermediate
							38.6 months (95% CI, 34.5 to 41.8)	Arm 2: 10.2 (95% CI, 9.6 to 11.1)	Arm 2: 76% (95% CI, 70 to 81),	Arm 2: 82% (77 to 86)	PFS subgroup analysis exon 19 deletion 0.43 (0.32 to 0.56), L858R 0.51 (0.36 to 0.71)	
							31.8 months (95% CI, 26.6 to 36)	HR: 0.46 (95% CI, 0.37 to 0.57), $P <$ .001[u]	OR: 1.27 (95% CI, 0.85 to 1.90), $P = .024$			
							HR for death, 0.80; 95% CI, 0.64 to 1.00; $P = .046$)	No. of events 136 osimertinib, 206 control				
An et al[8]	RCT		Gefitinib and placebo	Gefitinib and pemetrexed		OS, PFS/TTP, RR, AEs[e]	Arm 1: 32 (26.7 to 37.2)	Arm 1: 14 (11.8 to 16.2)	Arm 1: 33 (73.33%)		2-year PFS rates:	High[f]
							Arm 2: 34 (28.7 to 39.2),	Arm 2: 18 (15.7 to 16.2),	Arm 2: 36 (80%)		Arm 1: 8.89%,	
							$P > .05$	$P < .05$			Arm 2: 20%	
											$P < .05$	
Cheng et al[9]	RCT		Gefitinib and pemetrexed	Gefitinib		PFS/TTP	Immature	Arm 1: 15.8 (95% CI, 12.6 to 18.3)	Arm 1: 101 (80%)		TtPD: arm 1: 16.2 (12.6 to 18.7), arm 2: 10.9 (9.7 to 12.8), $P = 0.018$	Intermediate
								Arm 2: 10.9 (95% CI, 9.7 to 13.8), HR 0.69 (0.49 to 0.96), $P = .029$	Arm 2: 48 (74%),			
								Note: Exon 21 L585R 12.6 (8.5 to 21.2) *v* 10.9 (8.2 to 12.5), HR 0.58 (0.33 to 1.01), $P = .054$	Median DOR: 15.4 (10.9 to 16.8) *v* 11.3 (8.3 to 15.4), $P = .74$ (0.5 to 1.08)			
Soria et al[34]	RCT	ASCEND-4	Ceritinib	Chemotherapy		PFS/TTP[v]	Arm 1: NE (29.3 to NE)	Arm 1: 16.6 (95% CI, 12.6 to 27.2)	Arm 1: 137 (72.5% [95% CI, 65.5 to 78.7])		PFS[u]: arm 1: 16.8 months (95% CI, 13.5 to 25.2), arm 2: 7.2 months (95% CI, 5.8 to 9.7), HR 0.49 (95% CI, 0.37 to 0.64), $P <$ .00001 by stratified log-rank test	High
							Arm 2: 26.2 (22.8 to NE),	Arm 2: 8.1 (95% CI, 5.8 to 11.1)	Arm 2: 50 (26.7% [20.5 to 33.7])			
							HR 0.73 (0.50 to 1.08), $P = .056$	HR 0.55 (95% CI, 0.42 to 0.73), $P <$ .00001 by stratified log-rank test				
Lim et al[49]	Obs		Ceritinib			RR: ORR	Arm 1: 24 months (95% CI, 5 to 43 months)	Arm 1: 9.3 months (95% CI, 0 to 22 months),	Arm 1: 62% (95% CI, 45 to 77)	Arm 1: 56% (95% CI, 39 to 72)	DoR: arm 1: 21.0 months (95% CI, 17 to 25 mo)	

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TABLE 4. Results (continued)

Bibliography	Study Design	Which Study	Interventions			Primary Outcome	OS, Months	PFS, Months (95% CI Unless Otherwise Specified)	RR	1-Year Survival	Others	Overall Risk of Bias
			Arm 1	Arm 2	Arm 3							
								For crizotinib-naïve patients, 19.3 months (95% CI, 1 to 37 months)			DCR: 81% (95% CI, 65 to 91)	
Shi et al[25]	RCT	CONVINCE	Ccotinib	Cisplatin/ pemetrexed plus pemetrexed maintenance		PFS/TTP	Arm 1: 30.5 months (95% CI, 24.1 to 38.3) Arm 2: 32.1 months (95% CI, 27.0 to 38.5), Log rank P = .885	Arm 1: 11.2 months (95% CI, 9.2 to 12.6) Arm 2: 7.9 months (95% CI, 6.5 to 10.2), HR, 0.61 (95% CI, 0.43 to 0.87), P = .006 PFS assessed by IREC				Intermediate, high
Wu et al[45]	Obs		Oral crizotinib			RR: ORR by IRR	Arm 1: 32.5 (95% CI, 32.5 months to NR)[g]	Arm 1: 15.9 (95% CI, 12.9 to 24.0)	Arm 1: 71.7% (95% CI, 63.0 to 79.3)[v]	Arm 1: 83.1% (95% CI, 75.2 to 88.6)	Arm 1: TTR: 1.9 months (range, 1.6 to 15.8); DOR: 19.7 months (95% CI, 14.1 to NR); DCR:88.2% of patients (95% CI, 81.3 to 93.2) at week 8 and 80.3% of patients (95% CI, 72.3 to 86.8) at week 16	
Camidge et al[33]	RCT	ALTA-1L	Brigatinib, 180 mg once daily with a 7-day lead-in at 90 mg	Crizotinib, 250 mg twice daily		PFS/TTP	NR	Arm 1: 12-month PFS, 67% (95% CI, 56 to 75) Arm 2: 12-month PFS 43% (95% CI, 32 to 53), HR for progression or death, 0.49 (95% CI, 0.33 to 0.74); P < .001 by the log-rank test[v]	Arm 1: 76% (95% CI, 68 to 83) Arm 2: 73% (95% CI, 65 to 80), note: overall objective response rate	Arm 1: 85% (95% CI, 76 to 91) Arm 2: 86% (95% CI, 77 to 91)	Intracranial overall objective response rate: arm 1: 83% (95% CI, 59 to 96), arm 2: 33% (95% CI, 15 to 57),	Intermediate, high
Wu et al[12]	RCT	ARCHER 1050	Dacomitinib	Gefitinib		PFS/TTP[v]	Arm 1: 34.1 (29.5 to 37.7) Arm 2: 26.8 (23.7 to 32.1), HR 0.76 (0.58 to 0.99), P = 0.044	Arm 1: 14.7 months (11.1 to 16.6) Arm 2: 9.2 (9.1 to 11)	Arm 1: 170/227 (75% [69 to 80]) Arm 2: 161/225 (72% [65 to 77])		Median DOR, arm 1: 14.8 (12.0 to 17.4), arm 2: 8.3 (7.4 to 9.2) HR 0.4 (0.31 to 0.53), P < .0001	Intermediate
Mok et al[13]								HR 0.59 (0.47 to 0.74), P < .0001[h]	P = .423		TTF: 11.1 (9.2 to 14.6) v 9.2 (7.6 to 9.4), HR 0.67 (0.54 to 0.83), P = .0001[v]	

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TABLE 4. Results (continued)

Bibliography	Study Design	Which Study	Interventions			Primary Outcome	OS, Months	PFS, Months (95% CI Unless Otherwise Specified)	RR	1-Year Survival	Others	Overall Risk of Bias
			Arm 1	Arm 2	Arm 3							
Solomon et al[40]	Obs		lorlatinib			RR, Objective tumor response and intracranial tumor response		EXP1: NR (11.4 to NR), EXP2-3A: NR (12.5 to NR), EXP3B: 5.5 (2.7 to 9.0), EXP4-5: 6.9 (5.4 to 9.5), Pooled EXP2-5 7.3 (5.6 to 11.0)	Arm 1: EXP1: 27 (90.0%; 95% CI, 73.5 to 97.9), EXP2-3A: 41 (69.5%; 95% CI, 56.1 to 80.8), EXP3B: 9 (32.1%; 95% CI, 15.9 to 52.4), EXP4-5: 43 (38.7%, 95% CI, 29.6 to 48.5) pooled EXP2-5: 93 (47.0%; 95% CI, 39.9 to 54.2),		Median DOR, months: (95% CI)[i], arm 1: NR (10.0 to NR), NR (11.1 to NR), NR (4.1 to NR), NR (5.5 to NR), NR (11.1 to NR), Intracranial tumor response (confirmed, %; 95% CI): 2/3 (66.7%; 9.4 to 99.2), 20/23 (87.0%; 66.4 to 97.2), 5/9 (55.6%; 21.2 to 86.3), 26/49 (53.1%; 38.3 to 67.5), 51/81 (63.0%; 51.5 to 73.4)[j,m]	
Imai et al[14]	Obs		Afatinib			PFS/TTP	Arm 1: median OS was NR	Arm 1: 12.9 (95% CI, 8.8 to 19.3)	Arm 1: 72.5% (95% CI, 58.6% to 86.3%)	Arm 1: 87.4%	DCR: arm 1: 100%	
Peters et al[71]	Obs		T-DM1			RR: objective	Arm 1: 12.2 (95% CI, 4.7 to 23.6)	Arm 1: 2.6 (95% CI, 1.4 to 2.8)	Arm 1: IHC 2+ = 0% (95% CI, 0.0 to 11.9); IHC 3+ = 20% (95% CI, 5.7 to 43.7)[n]		DoR: arm 1: (HER2 mutant cohort) = 4 months (95% CI, 2 to 9 months); CBR: arm 1: IHC 2+, 7% (2/29, 95% CI, 1 to 23) and IHC 3+, 30% (6/20; 95% CI, 12 to 54)	
Reck et al[30]	RCT	IMpower150	ABCP	BCP	ACP	12-month OS, PFS/TTP	Arm 1 (ABCP): 78.9%, months: NE (95% CI, 17 to NE) Arm 2 (BCP): 68.9%, months: 18.7 (95% CI, 13.4 to NE) HR 0.61 (95% CI, 0.29 to 1.28) Arm 3 (ACP): 75%, 21.4 (95% CI, 13.8 to NE) HR *v* Arm 2: 0.93 (95% CI, 0.51 to 1.68)	Arm 1: 10.2 (95% CI, 7.9 to 15.2) Arm 2: 6.9 (95% CI, 5.7 to 8.5) HR 0.61 (95% CI, 0.36 to 1.03), ABCP *v* BCP Arm 3: 6.9 (95% CI, 5.7 to 8.2) HR 1.14 (95% CI, 0.73 to 1.78), ACP *v* BCP	Arm 1: proportion of patients with OR 70.6% (95% CI, 52.5 to 84.9) Arm 2: 35.6% (95% CI, 21.9 to 52.1) Arm 3: 41.9% (95% CI, 27.0 to 57.9)		Median DoR (range): arm 1: 11.1 (2.8 to 18.0), arm 2: 5.6 (2.6 to 15.2), arm 3: 4.7 (2.6-13.5)	Intermediate, Note: some end points exploratory
Michels et al[44]	Obs	EUCROSS	Crizotinib			RR: ORR at the time of data cutoff by local assessment	Arm 1: not met (95% CI, 17.1 to NR)	Arm 1: 20 (95% CI, 9.6 to NR), By local assessment 20 (95% CI, 10.1 to NR)	Arm 1: independent 22/30, 73%, (95% CI, 54 to 88)[v]; 21/30, 70% (95% CI, 51 to 85)[u], DCR 27/30 90% (95% CI, 74 to 98) by. Both by local assessment. DCR 25/30 83% (95% CI, 65 to 94) IRR	Arm 1: 83% (95% CI, 69 to 97)	DoR: arm 1: 19 (95% CI, 8.3 to NR), Note: By local assessment 19 (95% CI, 9.1 to NR) by local assessment[o]	High

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TABLE 4. Results (continued)

Bibliography	Study Design	Which Study	Interventions			Primary Outcome	OS, Months	PFS, Months (95% CI Unless Otherwise Specified)	RR	1-Year Survival	Others	Overall Risk of Bias
			Arm 1	Arm 2	Arm 3							
Landi et al[48]	Obs	METROS	Crizotinib with ROS1-positive	Crizotinib with MET-positive		RR	Arm 1: NR Arm 2: 5.4 months (95% CI, 4.2 to 6.5), note: results by cohort	Arm 1: 22.8 months (95% CI, 15.2 to 30.3) Arm 2: 4.4 months (95% CI, 3.0 to 5.8), NOTE: results by cohort	Arm 1: 65% (95% CI, 44 to 82) Arm 2: 27% (95% CI, 11 to 47)[p]	Arm 1: 79.2% Arm 2: 26.3%	DCR/TTR/DOR: arm 1: 85%/7.9 weeks (IQR, 7.4 to 10.3)/21.4 months (95% CI, 12.7 to 30.1), arm 2: 69%/7.4 weeks (IQR 6.4 to 9.3)/3.7 months (95% CI, 1.1 to 6.3)	
Shaw et al[46]	Obs		Lorlatinib 100 mg one time daily (in Ph 2)			RR, Other: Objective tumor response and intracranial tumor response—central reviewed		Arm 1: 21.0 months (95% CI, 4.2 to 31.9) in TKI-naïve patients and 8.5 months (4.7 to 15.2) in crizotinib-treated patients	Arm 1: 28/69 (41% [95% CI, 29 to 53]) TKI-naïve: 13/21 (62% [95% CI, 38 to 82]). Prior crizotinib only: 14/40 (35% [95% CI, 21 to 52])		DoR: arm 1: TKI-naïve: 25.3 (95% CI, 7.3 to 31.9). Prior crizotinib only: 13.8 (95% CI, 9.7 to NR) months, patients with confirmed extracranial objective response 13/21 (62% [95% CI, 38 to 82]), prior: 14/40 (35% [95% CI, 21 to 52]), patients with confirmed intracranial objective response TKI-naïve 7/11 (64% [95% CI, 31 to 89]); prior crizotinib only 12/24 (50%, [95% CI, 29 to 71])	
Drilon et al[47]	Obs	ALKA-372-001, STARTRK-1, STARTRK-2	Entrectinib (at least 600 mg)			RR, other: DoR[v]	Arm 1: NE (95% CI, 15.1 to NE),	Arm 1: 19 (95% CI, 12.2 to 36.6)	Arm 1: 41/53, 77% (95% CI, 64 to 88)		Median DoR: arm 1: 24.6 (95% CI, 11.4 to 34.8) Intracranial 11/20, 55 (95% CI, 32 to 77) patients with baseline CNS mets[v] Median DoR in 20 patients with CNS disease[v] was 12.9 months (95% CI, 5.6 to NE). Median intracranial PFS: 7.7 months (95% CI, 3.8 to 19.3)	
Subbiah et al[50]	Obs	VE-Basket Study	Vemurafenib (960 mg twice a day)			RR[u]	Arm 1: 15.4 (95% CI, 9.6 to 22.8)	Arm 1: 6.5 (95% CI, 5.2 to 9.0)	Arm 1: 37.1 (95% CI, 25.2 to 50.3)		CBR %: arm 1: 48.4 (95% CI, 35.5 to 61.4)	
Drilon et al[62]	Obs		Larotrectinib (orally, 100 mg twice daily for adults or children with a BSA $\geq$ 1 m^2)			RR: ORR (complete and partial)		Arm 1: NR progression–free at 1 year: 55%; progression-free at 6 months: 73%	Arm 1: 75% (95% CI, 61 to 85) and exceeded a pre-established lower boundary of 30%			
Doebele et al[62]	Obs		Entrectinib daily at least 600 mg/m^2			RR: objective response rate, median duration of response	Arm 1: 21 months (95% CI, 14.9 to NE)	Arm 1: 11.2 months (95% CI, 8.0 to 14.9)	Arm 1: ORR: 31/54 (57%, 95% CI, 43.2 to 70.8), CR: 4 (7%), PR: 27 (50%), SD: 9 (17%)		Median DoR (co-primary end point), arm 1: 10.4 months (95% CI, 7.1 to NE)[v]	

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TABLE 4. Results (continued)

Bibliography	Study Design	Which Study	Interventions			Primary Outcome	OS, Months	PFS, Months (95% CI Unless Otherwise Specified)	RR	1-Year Survival	Others	Overall Risk of Bias
			Arm 1	Arm 2	Arm 3							
Furuya et al[18]	RCT	NEJ 026	Erlotinib and bevacizumab (150 mg daily and 15 mg/kg every 3 weeks)	Erlotinib (150 mg daily)		PFS/TTP[v]	NR	Arm 1: 16.9 Arm 2: 13.3, HR 0.605 (95% CI, 0.417 to 0.877), P = .016, nominal significance level, 0.02398[k]	Arm 1: 72.3% Arm 2: 66.1%, P = .311, DCR 94.6% *v* 96.4%, P = .518		PFS[u]: Arm 1: 16.6, arm 2: 12.4, HR 0.563 (95% CI, 0.394 to 0.804), P = .00057, median follow-up 12.5 months PFS stratified by EGFR-mutation subtype: Exon 19 del: 16.6 *v* 12.4 (HR 0.69 [95% CI, 0.41 to 1.16]), NS Exon 21: 17.4-13.7 (HR 0.57 [95% CI, 0.33 to 0.97]), P?	High
Ahn et al[29]	Obs	KCSG-LU15-09	Osimertinib (80 mg once daily)			RR: ORR		Arm 1: 9.5 (range 1.0 to 20.1)	Arm 1: PR: 18 (50%), SD: 14 (38.9%), PD: 4 (11.1%), DCR: 88.9% (95% CI, 78.1 to 99.7). Median DOR: 7.0 months (95 CI, 4.7 to 9.3)			
Gao et al[71]	Obs		Pyrotinib 400 mg			RR	Arm 1: NR, others: 20 (33.3%) deaths at data cutoff	Arm 1: 6.8 (95% CI, 4.1 to 8.3), Others: 40 (66.7%) events, note: TTR median 6.1 (range: 5.9 to 24.3) weeks	Arm 1: 19/60, 31.7 (95% CI, 20.3 to 45)[u]		Median DoR: arm 1: 7 (95% CI, 5.5 to 11) months, others: 12 (20%) patients CNS mets. Similar ORR/DoR with or without (ORR 33.3% *v* 31.3%, DoR 7 *v* 8.3) months Subtypes of HER2 mutation, commonality a. A775_G776insYVMA or M774_A775insAYVM (73.3%) b. G776>VC, G776R, and G776C (10%) c. P780_Y781insGSP (8.3%) d. L755P (6.7%) e. V777L (1.7%)	

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TABLE 4. Results (continued)

Bibliography	Study Design	Which Study	Interventions			Primary Outcome	OS, Months	PFS, Months (95% CI Unless Otherwise Specified)	RR	1-Year Survival	Others	Overall Risk of Bias
			Arm 1	Arm 2	Arm 3							
Wolf et al[53,54]	Obs	GEOMETRY monostudy	Capmatinib (400 mg daily)			RR[v]		Arm 1: 5.42 (95% CI, 4.17 to 6.97) prior treatment, arm 2: 12.4 (95% CI, 8.2 to NE) no prior). Event-free rate at 12 months: 25.8% (95% CI, 15.9 to 36.9), arm 2: 9.69 (95% CI, 5.52 to 13.86), event-free rate at 12 months: 49.7% (95% CI, 29.3 to 67.1), PFS[u]: arm A: 4.8 (95% CI, 4.11 to 7.75), arm B: 11.14 (95% CI, 5.52 to 15.24)	Arm 1: ORR Cohort A 40.6 (95% CI, 28.9 to 53.1), arm 2: Cohort B 67.9 (95% CI, 47.6 to 84.1), ORR[u] arm 1: 42 (95% CI, 30.2 to 54.5), arm 2: 60.7 (95% CI, 40.6 to 78.5)	DOR: arm 1: 9.72 (95% CI, 5.55 to 12.98), event-free, 31.8% Arm 2: 11.14 (95% CI, 5.55 to NE), event-free rate at 12 months: 47.3%		
Paik et al[65]	Obs	VISION	Tepotinib 500 mg			RR[v]	Arm 1: 17.1 months (95% CI, 12.0 to 26.8)[l]	Arm 1: 8.5 months (95% CI, 6.7 to 11.0)	Arm 1: 46% (95% CI, 36 to 57), Arm 1[u]: 56% (95% CI, 45 to 66)		DoR: arm 1: 11.1 (95% CI, 7.2 to NE)	Intermediate, high
Gadgeel et al[66]	Obs	SWOG 1507	Trametinib (2 mg daily) and docetaxel (75 mg/m^2 every 3 weeks)			RR	Arm 1: (months 95% CI) 10.9 (8 to 16.3), G12C 8.8 (4.9 to 12.1), non-G12C 12.2 (8.0 to 18.8), HR G12C *v* non-G12C 1.57 (95% CI) 0.79 to 3.13)	Arm 1: PFS (months, 95% CI): Total 4.1 (3.1 to 5.1), G12C 3.3 (1.5 to 4.3), non-G12C 4.1 (3.4 to 5.6), HR G12C *v* non-G12C 1.82 (95% CI) 1.0 to 3.28)	Arm 1: RR (95% CI)—total: 33 (21 to 47), G12C 26 (9 to 51), non-G12C 37 (21 to 55), note: DoR (months, 95% CI) 5.0 (2.8 to 5), G12C 4.1 (1.4 to 5), and non-G12C 5.6 (2.8 to 5.6)			
Cortot et al[16]	RCT	IFCT-1503 ACE-Lung	Afatinib (40 mg daily)	Afatinib (40 mg daily) plus cetuximab (500 mg/m^2 every 2 weeks)		TTF at 9 months	Arm 1: NR (95% CI, 20.7 to NR) Arm 2: NR (95% CI, 20.4 to NR)	Arm 1: 12.1 (95% CI, 9.1 to 15.0) Arm 2: 12.9 (95% CI, 9.5 to 13.8). Note: 9-month PFS 66.2 (95% CI, 51.7 to 77.3) *v* 74.9 (95% CI, 59.9 to 84.9)	Arm 1: 69.5 Arm 2: 65.5	Arm 1: 92.3 (95% CI, 80.6 to 97.0) Arm 2: 88.0 (95% CI, 75.2 to 94.5)	TTF (response after 2 cycles): arm 1: 11.1 (95% CI, 8.7 to 14.1), arm 2: 11.5 (95% CI, 7.6 to 13.8) 9-Month TTF 62.1 (95% CI, 47.9 to 73.4) *v* 63.2 (95% CI, 49.3 to 74.2)	Intermediate[q]

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TABLE 4. Results (continued)

Bibliography	Study Design	Which Study	Interventions			Primary Outcome	OS, Months	PFS, Months (95% CI Unless Otherwise Specified)	RR	1-Year Survival	Others	Overall Risk of Bias
			Arm 1	Arm 2	Arm 3							
Noronha et al[10]	MA		Gefitinib (250 mg per day)	Gefitinib plus pemetrexed plus carboplatin (250 mg per day + 500 mg/m^2 + AUC 5 every 3 weeks) plus maintenance pemetrexed		PFS/TTP[u]	Arm 1: 17 months (95% CI, 13.5 to 20.5) Arm 2: NR, HR (unadjusted), 0.45 (95% CI, 0.31 to 0.65), P <.001	Arm 1: 8 (95% CI, 7 to 9) Arm 2: 16 (95% CI, 13.5 to 18.5) HR (unadjusted) 0.51 (95% CI, 0.39 to 0.66), P <.001[u]	Arm 1: 62.5% (95% CI, 55.1 to 69.3) Arm 2: 75.3% (95% CI, 68.3 to 81.1) P = .01		PFS2[r] arm 1: 14 months (95% CI, 12 to 16), arm 2: 23 months (95% CI, 19.3 to 26.8), HR 0.69 (95% CI, 0.53 to 0.92), P <.001	Low, intermediate
Nakagawa et al[19]	RCT	RELAY	Erlotinib and ramucirumab (150 mg/d + 10 mg/kg) every 2 weeks	Erlotinib and placebo (150 mg/d + 10 mg/kg) every 2 weeks		PFS/TTP	Arm 1: NR Arm 2: NR Statistic and significance: 0.83 (0.53 to 1.30), P = NS. Note: immature at data cutoff	Arm 1: 19.4 (95% CI, 15.4 to 21.6) Arm 2: 12.4 (95% CI, 11.0 to 13.5), HR 0.59 (95% CI, 0.46 to 0.76), P < .0001[u] 16.5 months (95% CI, 13.7 to 19.3) *v* 11.1 months (95% CI, 9.7 to 12.7), (stratified HR 0.671 (95% CI, 0.52 to 0.87)[v]	Arm 1: 76% (95% CI, 71 to 82) Arm 2: 75% (95% CI, 69 to 80), P = .741, note: Disease control 95% (95% CI, 92 to 98) *v* 96% (95% CI, 93 to 98), P = 1	Arm 1: 93% (95% CI, 89 to 96) Arm 2: 94% (95% CI, 90 to 96)	DoR: arm 1: 18.0 (13.9 to 19.8), arm 2: 11.1 (9.7 to 12.3), Unstratified HR 0.62 (0.48 to 0.81), P = .0003	Low[s]
Zhou et al[17]	RCT	ARTEMIS (CTONG 1509)	Erlotinib 150 mg daily plus bevacizumab 15 mg/kg every 3 weeks	Erlotinib 150 mg daily		PFS/TTP[v]		Arm 1: 18.0 months (95% CI, 15.2 to 20.7) Arm 2: 11.3 months (9.8 to 13.8) Statistic and significance: 0.55 (95% CI, 0.41 to 0.75), P < .001[v]	Arm 1: 86.3% Arm 2: 84.7%, Statistic and significance: 0.74 to NS[v]		DCR: arm 1: 95.9%, arm 2: 96.5%, and statistic and significance: > 0.999, NS, DoR: arm 1: 16.6 months (13.8 to 18.1), arm 2: 11.1 months (8.6 to 12.5), 0.59 (0.42 to 0.82)	Intermediate

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TABLE 4. Results (continued)

Bibliography	Study Design	Which Study	Interventions			Primary Outcome	OS, Months	PFS, Months (95% CI Unless Otherwise Specified)	RR	1-Year Survival	Others	Overall Risk of Bias
			Arm 1	Arm 2	Arm 3							
Goto et al[57] Drilon et al[60]	Obs		Selpercatinib (LOXO-292)			RR[v]		Arm 1: 16.5 months (13.7 to NE) Prior Tx	Arm 1: 64% (95% CI, 54 to 73), prior Tx	Type: DoR, srm 1: 17.5 months (12 to NE), prior tx		Moderate
								Others: NE (13.8 to NE), no prior Tx	Other: 85% (95% CI, 70 to 94), no prior Tx	Other: NE (12 to NE), no prior tx		
Peters et al[35]	RCT		Alectinib (600 mg twice daily)	Crizotinib (250 mg twice daily)		PFS/TTP[u]	Arm 1: NE	Arm 1: NR (95% CI, 17.7 to NE)	Arm 1: 82.9 (95% CI, 76.0 to 88.5)	Arm 1: 84.3% (95% CI, 78.4 to 90.2)	PFS[v]: arm 1: 25.7 (95% CI, 19.9 to NE)	Intermediate
							Arm 2: NE	Arm 2: 11.1 (95% CI, 9.1 to 13.1), 12-mo event-free survival 68.4 (95% CI, 61.0 to 75.9) *v* 48.7% (95% CI, 40.4 to 56.9)	Arm 2: 75.5 (95% CI, 67.8 to 82.1)[u]	Arm 2: 82.5% (95% CI, 76.1 to 88.9)	Arm 2: 10.4 (95% CI, 7.7 to 14.6)	
							HR, 0.76 (95% CI, 0.48 to 1.20), $P = .24$	HR 0.47 (95% CI, 0.34 to 0.65), $P < .001$[u]			HR 0.50 (95% CI, 0.36 to 0.70); $P < .001$	
Nakagawa et al[37]	RCT	J-ALEX	Alectinib 300 mg	Crizotinib 250 mg		PFS/TTP	Arm 1: NR	Arm 1: 34.1	Arm 1: 92 (85.6 to 97.5)			Intermediate
Hida et al[36]							Arm 2: 43.7	Arm 2: 10.2	Arm 2: 79 (70.5 to 87.3)			
							HR 0.8 (99.88% CI, 0.35 to 1.82), $P = .3860$ NS[t]	HR 0.37 (0.26 to 0.52)				
Gainor et al[58,59]	Obs	ARROW	Pralsetinib (BLU-667) 400 mg			RR	N/R	N/R	2020 ITT, all 58% (95% CI, 49 to 67), prior platinum 55 (95% CI, 45 to 66), no prior treatment 66 (95% CI, 46 to 82)			Not assessable
									2020 response-evaluable, all 65 (95% CI, 55 to 73), prior plat 61 (95% CI, 50 to 27), note: includes two results awaited confirmation, no prior treatment 73 (95% CI, 52 to 88)			

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine transaminase; AST, aspartate transaminase; AUC, area under the curve; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; E, erlotinib; EGFR, epidermal growth factor receptor; f/u, follow-up; HR, hazard ratio; IHC, immunohistochemistry; IRC, independent review committee; mut, mutation; NE, not estimable; NR, not reached; NS, not significant; obs, observational; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RR, response rate; S, selumetinib; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure; TTP, time to progression; TtPD, time to progressive disease; Tx, treatment; WT, wild type.

[a]OS results immature.

[b]Authors note potential enrollment bias because patients had to pay for agents and imaging self (not industry sponsored).

[c]Preliminary one-year OS probability.

[d]Preplanned interim overall analysis data at the time of the primary PFS analysis were not mature.

[e]Unclear which is primary outcome.

[f]Several variables not assessable.

[g]59.8% of patients were still in follow-up at data cutoff, so OS data are considered to be immature.

[h]Similar for masked independent and investigator assessments.

[i]Using Brookmeyer and Crowley method.

[j]Using exact method based on binomial distribution, EXP1, EXP2-3A, EXP3B, EXP4-5, and EXP2-5.

[k]Preplanned analysis for PFS; median follow-up, 12.4 months.

[l]Immature results.

[m]By cohort ALK+: EXP1, EXP2-3A, EXP3B, EXP4-5, EXP2-5, and ROS1 EXP6. All cohorts EXP1-6.

[n]Divided between cohorts IHC 2+ and IHC 3+.

[o]Publication also reported by subgroups of response-evaluable (n = 30) and DNA sequencing plus population (n=18).

[p]Results by cohort. Authors did not list % for CI for response.

[q]Some elements required for quality assessment were not reported in poster.

[r]An exploratory unplanned analysis, we evaluated PFS2, which is defined as the time from random assignment to the second PD event (second progression or death, whichever occurred first) as determined by the investigator.

[s]One of the few blinded studies.

[t]Per protocol OS follow-up ongoing.

[u]Investigator-assessed.

[v]Independent review committee-assessed.

TABLE 5. Adverse Events

Bibliography	Overall AEs	Hematologic AEs	GI Plus Other AEs	Other AEs
Carter et al[65]			Grade 3	Grade 3
			Diarrhea: arm 1: S 11%, arm 2: E 11%, arm 3: S + E 37%	Rash: arm 1: S 11%, arm 2: E 0%, arm 3: S + E 13%
			Nausea: arm 1: S 11%, arm 2: E 0%, arm 3: S + E 10%,	Lymphocyte (decrease): arm 1: S 11%, arm 2: E 0%, arm 3: S + E 18%
			Dehydration: arm 1: S 0%, arm 2: E 0%, arm 3: S + E 22%	Fatigue arm 1: S 11%, arm 2: E 5%, arm 3: S + E 20%
Park et al[15]	Grade ≥ 3: arm 1: 57%, arm 2: 52%		Grades 3-4	Grades 3-4
	SAEs: arm 1: 11%, arm 2: 4%		Diarrhea: arm 1: 20/160 (13%), arm 2: 2/159 (1%)	Rash or acne: arm 1: 15/160 (9%), arm 2: 2/159 (1%)
			Nausea: arm 1: 2/160 (1%), arm 2: 0	
Yang et al[26]	Grade ≥ 3: arm 1:1.6%, arm 2: 5.4%, no significant difference between arms			Grade ≥ 3
				Rash: arm 1: 0, arm 2: 2.3%
				Bilirubin increase: arm 1: 0%, arm 2: 2.3%
Kim et al[42]			Grade ≥ 3 AEs	Grade ≥ 3
			Nausea: arm 1: 1%, arm 2: 1%,	Rash: arm 1: 1%, arm 2: 3%
			Dyspnea: arm 1: 3%, arm 2: 2%	Grade ≥ 3 TEAEs
				Hypertension: arm 1: 6%, arm 2: 6%
				Increased blood creatine phosphokinase: arm 1: 3%, arm 2: 9%
				Pneumonia: arm 1: 3%, arm 2: 5%
				Increased lipase: arm 1: 4%, arm 2: 3%
Shaw et al[41]	SAEs: arm 1: 43% (11% Tx-related), arm 2: 32% (11%)	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3
		Neutropenia: arm 1: 1%, arm 2: 15%,	Diarrhea: arm 1: 4%, arm 2: 1%,	Fatigue: arm 1: 5%, arm 2: 4%,
		ALT concentration increased: arm 1: 21%, arm 2: 2%	Nausea: arm 1: 8%, arm 2: 2%,	AST concentration increased: arm 1: 14%, arm 2: 1%
			Vomiting: arm 1: 8%, arm 2: 2%	Asthenia: arm 1: 5%, arm 2: 6%
				Increased γ glutamyltransferase concentration: arm 1: 21%, arm 2: 1%
				Dyspnea: arm 1: 5%, arm 2:6%
Soria et al[5]	Grade 3-5: arm 1: 34%, arm 2: 45%	Cardiac events, all grades: arm 1: 10%, arm 2: 5%	Diarrhea: arm 1: 2%, arm 2: 2%	Rash: arm 1: 1%, arm 2: 7%,
		Cardiac events, grade ≥ 3: arm 1: 2%, arm 2: 1%		Dry skin: arm 1: < 1%, arm 2: 1%
				Prolonged QT interval on ECG: arm 1: 2%, arm 2: 1%
				AST elevation: arm 1: 1%, arm 2: 4%
An et al[8]		Neutropenia: arm 1: 9 (20%), arm 2: 10 (22.2%)	Diarrhea: arm 1: 1 (2.22%), arm 2: 2 (4.44%)	Fatigue: arm 1: 1 (4.44%), arm 2: 2 (4.44%)
		Leukopenia: arm 1: 4 (8.89%), arm 2: 5 (11.11%)		AST: arm 1: 4 (8.88%), arm 2: 5 (11.11%)

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TABLE 5. Adverse Events (continued)

Bibliography	Overall AEs	Hematologic AEs	GI Plus Other AEs	Other AEs
				ALT: arm 1: 5 (11.11%), arm 2: 6 (13.33%)
				Infection: arm 1: 5 (11.11%), arm 2: 6 (13.33%)
				Pneumonitis: arm 1: 1 (2.22%), arm 2 (4.44%)
Cheng et al[9]	Overall: patients ≥ 1 grade 3-4 TEAE: 53 (42%) *v* 12 (19%),	Grade ≥ 3 AEs	Grade ≥ 3 AEs	Grade ≥ 3 AEs
	SAEs: patients ≥ 1 SAE: 11 (9%) *v* 1 (2%)	Neutropenia: arm 1: 6 (5%), arm 2: 1 (2%)	Diarrhea: arm 1: 1 (1%), arm 2: 1 (2%)	Rash: arm 1: 2 (2%), arm 2: 1 (2%)
		Anemia: arm 1: 4 (3%), arm 2: 0		Fatigue: arm 1: 7 (6%), arm 2: 0
				Dry skin: arm 1: 1 (1%), arm 2: 0
				Increased ALT: arm 1: 20 (16%), arm 2: 5 (8%),
				Increased AST: arm 1: 7 (6%), arm 2: 2 (3%),
				Stomatitis: arm 1: 5 (4%), arm 2: 0
Soria et al[34]	Study drug–related grade ≥ 3 AEs: arm 1: 123 (65%), arm 2: 70 (40%)	Grade ≥ 3 AEs	Grade ≥ 3 AEs	Grade ≥ 3 AEs
		Neutropenia: arm 1: 1 (1%), arm 2: 19 (11%)	Diarrhea: arm 1: 10 (5%), arm 2: 2 (1%)	Gamma-glutamyltransferase increased: arm 1: 54 (29%), arm 2: 3 (2%)
		Anemia: arm 1: 4 (2%), arm 2: 13 (7%)	Nausea: arm 1: 5 (3%), arm 2: 9 (5%)	Asthenia: arm 1: 5 (3%), arm 2: 6 (3%)
		ALT increased: arm 1: 58 (31%), arm 2: 5 (3%)	Vomiting: arm 1: 10 (5%), arm 2: 10 (6%)	
		AST increased: arm 1: 32 (17%), arm 2: 3 (2%)		
Lim et al[49]	Any grade: 100% (irrespective of study drug association), grade ≥ 3: 37%	Grade 3	Grade 3	Fatigue: arm 1: 5 (16%)
	SAEs: 50% (22% suspected to be related to the drug)	Superior vena cava syndrome: arm 1: 1 (3%)	Nausea: arm 1: 1 (3%)	Pneumonia: arm 1 grade 3: 2 (6%), arm 1 grade 5: 2 (6%)
		Anemia: arm 1: 2 (6%)	Anorexia: arm 1: 1 (3%)	Infection: arm 1 grade 3: 1 (3%)
			Abdominal discomfort: arm 1: 1 (3%)	Dry mouth: arm 1 grade 3: 1 (3%)
				Pleural effusion: arm 1 grade 3: 1 (3%)
				Acute hepatitis: arm 1 grade 4: 1 (3%)
Shi et al[25]	Any grade: arm 1: 79.1%, arm 2: 94.2%; $P < .001$	Grade 3-4 AEs:	Diarrhea: arm 1: 7.4%, arm 2: 4.4%, *P* value for any grade = .108	Rash: arm 1: 14.9%, arm 2: 1.5%,
	Grades 3-4: arm 1: 9.5%, arm 2: 4.7%	Neutropenia: arm 1: 0%, arm 2: 10.9%	Nausea: arm 1: 2.7%, arm 2: 46.0%, *P* value for any grade = < .001	*P* value for any grade = < .001
		P value for any grade = < .001	Vomiting: arm 1: 1.4%, arm 2: 29.2%, *P* value for any grade = < .001	
Wu et al[45]	TRAEs: 96.1% (all grades), 25.2% (grades 3-4)	Neutropenia: arm 1: 10.2%	Diarrhea: arm 1: 0.8%	
		Leukopenia: arm 1: 2.4%	Nausea: arm 1: 1.6%	
		Elevated transaminases: arm 1: 5.5%		

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TABLE 5. Adverse Events (continued)

Bibliography	Overall AEs	Hematologic AEs	GI Plus Other AEs	Other AEs
Camidge et al[33]	Overall: 97% *v* 100% (any grade); 61% *v* 55% (grade ≥ 3 AEs)	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3
		Neutropenia: arm 1: 0%, arm 2: 4%,	Diarrhea: arm 1: 1%, arm 2: 2%,	Hypertension: arm 1: 10%, arm 2: 3%
		Increased blood creatine kinase level: arm 1: 16%, arm 2: 1%	Nausea: arm 1: 1%, arm 2: 3%	Interstitial lung disease or pneumonitis: arm 1: 3%, arm 2: 0.7%
		Increased lipase level: arm 1: 13%, arm 2: 5%		
Wu et al[12]	Arm 1: 63%, arm 2: 41%	Hypokalaemia: arm 1: 5%, arm 2: 2%	Grade ≥ 3 AEs	Rash: arm 1: 4%, arm 2: 0
	SAEs: arm 1: 27%, arm 2: 22%		Diarrhea: arm 1: 9%, arm 2: 1%	Dermatitis acneiform: arm 1: 14%, arm 2: 0
				ALT increased: arm 1: 1%, arm 2: 8%,
				Maculopapular rash: arm 1: 4%, arm 2: < 1%
				Pustular rash: arm 1: 4%, arm 2: 0
				Dermatitis: arm 1: 2%, arm 2: < 1%
				Dyspnea: arm 1: 2%, arm 2: 3%
				Stomatitis: arm 1: 4%, arm 2: 0
				Paronychia: arm 1: 7%, arm 2: 1%
Solomon et al[40]	SAEs[a] (Tx-related): arm 1: 19/275 (7%)	Grade 3-4 AEs:		Cognitive effects: arm 1: 3/275 (1%)
		Hypercholesterolaemia[b]: arm 1: 16%		No Grade 5 Tx–related AEs
		Hypertriglyceridaemia[b]: arm 1: 16%		
Imai et al[14]			Grade 3	Grade 3
			Diarrhea: arm 1: 12.5%	Rash: arm 1: 5%
Peters et al[72]	Any grade: arm 1: 92%	Grade 3		Grade 3
	Grade ≥ 3: arm 1: 22%	Infusion-related reaction: arm 1: 2%		Fatigue: arm 1: 4%
		Thrombocytopenia: arm 1: 2%		
Michels et al[44]	SAEs, TAEs with frequency ≥ 10%, grade 3: arm 1: 8 (24%), grade 5: arm 1: 1 (3%)[c]	Neutropenia: arm 1: L/K 3/34 (15%)	Nausea: arm 1: 1/34 (3%)	Grade 1 or 2
		ALT: arm 1: 1/34 (3%)	Vomiting: arm 1: 1/34 (3%)	Sinus bradycardia: arm 1: 16 (47%)
Landi et al[48]	All grades, TRAEs: arm 1: 100%, arm 2: 81%	Neutropenia: arm 1: 4%, arm 2: 4%	Nausea: arm 1: 8%, arm 2: 8%	Peripheral edema: arm 1: 4%, arm 2: 0%
	SAEs: 13 reported; 2 related to study drug	Anemia: arm 1: 0, arm 2: 4%	Possibly nausea TEAEs: arm 1: 8%, arm 2: 4%[d]	Fatigue: arm 1: 8%, arm 2: 0
		Transaminase elevation, arm 2: 8%		Respiratory symptoms: arm 1: 4%, arm 2: 4%
Shaw et al[46]	Overall: 49% (grade 3/4 TRAEs), SAEs: 7% (Tx-related SAEs)	Thrombocytopenia: arm 1: 1%		Hypertriglyceridaemia: arm 1: 13 (19%)
				Hypercholesterolaemia: arm 1: 10 (14%)
				Weight increased: arm 1: 7%
				Lipase increased: arm 1: 6%
				Hypophosphataemia: arm 1: 6%
				Dizziness: arm 1: 3%
Drilon et al[47]	Overall: on-target treatment-emergent AEs, grade 3 = 31%, grade 4 = 4%	Neutropenia: arm 1: 4%	Diarrhea: arm 1: 2%	
		AST increase: arm 1: 2%	Weight increase: arm 1: 7%	
		ALT increase: arm 1: 2%		

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TABLE 5. Adverse Events (continued)

Bibliography	Overall AEs	Hematologic AEs	GI Plus Other AEs	Other AEs
Subbiah et al[50]	Grades 3-4: 77%.	Anemia: arm 1: 10%[e]	Nausea: arm 1: 5%	AEs leading to tx interruption
	≥ Grade 3[e]: 81%		Nausea (leading to tx interruption): arm 1: 3%	Sepsis: 5% (Tx-related SAE: 2%)
	SAEs: 63%		Vomiting: arm 1: 2%	Bronchitis: 3%
	Tx-related SAEs: 40%			Pneumonia: 3%
				Dyspnea: 3%
				Grade ≥ 3 AEs
				Dyspnea: 8%[e]
				Cachexia: 8%[e]
				Fatigue: 5%[e]
				Asthenia: 5%[e]
				Arthralgia: 5%[e]
Furuya et al[18]	Grade 3-4 AEs: arm 1: 56.3%, arm 2: 37.7%	Hypertension: arm 1: 25/112 (22.3%), arm 2: 0/114 (0%)	Diarrhea: arm 1: 6/112 (5.4%), arm 2: 2/114 (1.8%)	Rash: arm 1: 23/112 (20.5%), arm 2: 24/114 (21.2%)
	SAEs: arm 1: 8.0%, arm 2: 4.4%	Proteinuria: arm 1: 8/112 (7.1%), arm 2: 0/114 (0%)		Hepatic dysfunction: arm 1: 9/112 (8%), arm 2: 6/114 (5.3%)
				Hemorrhage (PH excluded): arm 1: 2/112 (1.8%), arm 2: 1/114 (0.9%)
Ahn et al[29]				Grade 4
				Elevated AST/ALT: arm 1: 2 (5.6%)
Gao et al[71]	TRAE grade 3: 26.7%		Diarrhea: arm 1: ≥ 10% grade 3-4 12/60 (20%)	AST increased: 1/60 (1.7%)
	TRAE SAEs: 2/60 (3.3%)		Vomiting: arm 1: 1 (1.7%)	
Wolf et al[53,54]	Grade 3-4: 119 (35.6%)	Peripheral edema: arm 1: 25/334 (7.5%)[f]	Diarrhea: arm 1: 1/334 (0.3%)	Fatigue: arm 1: 10 (3%)
	Grade 4 AEs with capmatinib: 5 (4.5%)		Nausea: arm 1: 6/334 (1.8%)	Decreased appetite: arm 1: 3/334 (0.9%)[f]
	SAEs: 43 (12.9%)[f]		Vomiting: arm 1: 6 (1.8%)[f]	
Gadgeel et al[66]		Grade ≥ 3	Diarrhea: arm 1: 5/54	Rash: arm 1: 11/54
		Neutropenia: arm 1: 4/54 (neutrophil count decreased)	Nausea: arm 1: 3/54	Fatigue: arm 1: 8/54
		Anemia: arm 1: 4/54		
		Leukopenia: arm 1: 3/7		
Cortot et al[16]	Overall TRAE grade 3: arm 1: 37.3%, arm 2: 51.7%, grade 4: arm 1: 5.1%, arm 2: 0		Diarrhea: arm 1: grade 3: 15.3%, grade 4: 3.4%; arm 2: grade 3: 12.1%, grade 4: 0	Sepsis/infection: 11/54
			Vomiting: arm 1: grade 3: 3.4%, grade 4: 1.7%, arm 2 grade 3-4: 0	Paronychia: arm 1: grade 3, 1.7% + grade 4, 1.7% *v* arm 2: grade 3: 3.4%. Asthenia: arm 1: grade 3: 0% *v* arm 2: grade 3: 6.9%
				Stomatitis: arm 1: grade 3: 3.4% *v* arm 2: grade 3 8.6%

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TABLE 5. Adverse Events (continued)

Bibliography	Overall AEs	Hematologic AEs	GI Plus Other AEs	Other AEs
Noronha et al[10]	Overall: grade ≥ 3: 49.4% (95% CI, 42 to 56.9) *v* 75% (95% CI, 67.8 to 81), SAEs: grade ≥ 3: 25.3% (95% CI, 19.4 to 32.4) *v* 50.6% (95% CI, 43 to 58.2), *P* < .001	FN: arm 1: 0, arm 2: 11%	Diarrhea: arm 1: 8%, arm 2: 14%,	Rash: arm 1: 5%, arm 2: 5%
			Nausea plus vomiting: arm 1: 2%, arm 2: 6%	Discontinuation because of toxicity: G: ILD, n = 1; non-neutropenic infection, n=1
				G + C: n = 30: discontinued pemetrexed (continued on gefitinib)
Nakagawa et al[19]	Overall: TEAEs 72% *v* 54% safety population	Grade 3-4 Tx–related AEs ≥ 20%	Grade 3-4 Tx–related AEs ≥ 20%	Grade 3-4 Tx–related AEs ≥ 20%
	SAEs: Treatment-related SAEs any grade 15% *v* 12%	Hypertension: arm 1: 52 (24%), arm 2: 12 (5%).	Diarrhea: arm 1: 16 (7%), arm 2: 3 (1%),	Dermatitis acneiform: arm 1: 33 (15%), arm 2: 20 (9%),
				Rash: arm 1: 2 (1%), arm 2: 5 (2%)
				ALT: arm 1: 17 (8%) + 2 (1%), arm 2: 14 (6%) + 3 (1%)
				AST: arm 1: 5%, arm 2: 4%
				Proteinuria: arm 1: 6 (3%), arm 2: 0
				Decreased appetite: arm 1: 6 (3%), arm 2: 4 (2%)
				ILD: arm 1: 1 (< 1%), arm 2: 2 (1%)
Zhou et al[17]	Overall: TEAE Grade ≥ 3: 53.5% *v* 25.5%, SAEs: 22.3% *v* 13.1%	Anemia: arm 1: 1.3%, arm 2: 2.0%	Diarrhea: arm 1: 2.5%, arm 2: 0	Rash: arm 1: 5.1%, arm 2: 3.3%
		Hypertension: arm 1: 18.5%, arm 2: 3.3%		Proteinuria: arm 1: 8.3%, arm 2: 0%
				Grade ≥ 3: ALT increased: arm 1: 2.5%, arm 2: 3.3%
				AST increased: arm 1: 1.9%, arm 2: 3.3%
				Hypokalemia: arm 1: 1.3%, arm 2: 2.0%
Peters et al[35]	Overall: grade ≥ 3: 63 (41%) *v* 76 (50%), differed by ≥ 5% in frequency, SAEs: 28% *v* 29%	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3
		Anemia: arm 1: 7 (5%), arm 2: 1 (1%)	Diarrhea: arm 1: 0, arm 2: 3 (2%)	ALT increased: arm 1: 7 (5%), arm 2: 22 (15%)
		Increased blood bilirubin: arm 1: 0, arm 2: 3 (2%)	Nausea: arm 1: 1 (1%), arm 2: 5 (3%)	AST increased: arm 1: 8 (5%), arm 2: 16 (11%)
			Vomiting: arm 1: 0, arm 2: 5 (3%)	
Reck et al[30]	Overall grade 3-4: 63.6 *v* 68.2 *v* 63.6			Immune-related AEs and infusion-related reactions: arm 1: 55%, arm 2: 52%, arm 3: 23%
	Treatment related: 57 *v* 43 *v* 49			
	SAEs: 36.4 *v* 34.1 *v* 20.5			
Goto et al[60]		Grade 3-4 TRAE	Grade 3-4 TRAE	Grade 3-4 TRAE
		Hypertension: arm 1: < 12%[g]	Diarrhea: arm 1: 2%	QT prolonged: arm 1: 3%
			Nausea: arm 1: < 1%	
			Fatigue: arm 1: < 1%	
Drilon et al[62]		Grade 3		
		Anemia: arm 1: 11%		
Doebele et al[63]		Anemia: arm 1: 12%		Fatigue: arm 1: 7%
				Increased weight: arm 1: 10%

(continued on following page)

TABLE 5. Adverse Events (continued)

Bibliography	Overall AEs	Hematologic AEs	GI Plus Other AEs	Other AEs
Paik et al[55]	Grade ≥ 3: 28% Tx-related SAEs: 15%	Peripheral edema: arm 1: 7%		
Nakagawa et al[36]	Grade ≥ 3: arm 1: 36.9%, arm 2: 60.6% (in Hida et al, arm 1: 26, arm 2: 52) Treatment-related SAEs: 13.6 *v* 25	Neutropenia: arm 1: 2%, arm 2: 14% Anemia: arm 1: 1%, arm 2: 0	Diarrhea: arm 1: 0, arm 2: 2% Nausea: arm 1: 0, arm 2: 2% Visual impairment: arm 1: 0, arm 2: 0	ILD: arm 1: 5%, arm 2: 3%
Gainor et al[58,59]	NR	Anemia, hypertension, and neutropenia increased in multiple tumor types results[h]		

Abbreviations: AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; E, erlotinib; FN, febrile neutropenia; S, selumetinib; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events; Tx, treatment.

[a]Reported for safety population—includes ROS1 ≥ 10% of patients.

[b]Cluster term comprising AEs that represent similar clinical symptoms or syndromes.

[c]Publication also reported by subgroups of response-evaluable (n = 30) and DNA sequencing plus population (n = 18). All AEs reported are treatment-related AEs.

[d]Inconsistency: article states nausea present in 4%/8% of patients in arm 2.

[e]In ≥ 20%.

[f]From a different dataset cohort, n = 334.

[g]Denominator, 531 patients.

[h]Safety population, 354 patients with multiple tumor types (including 179 with NSCLC).

based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate).

Literature review update and analysis. The updated systematic review identified three RCTs and one systematic review for patients with sensitizing *EGFR* mutations L858R/exon 19 deletion mutations on interventions other than osimertinib.[8–10] One relatively small RCT and a larger RCT compared the interventions of gefitinib and pemetrexed versus control for those with common *EGFR* mutations.[8] In a study reported by Noronha et al,[10] 350 patients were randomly assigned to receive gefitinib plus carboplatin plus pemetrexed versus gefitinib monotherapy. The primary outcome was investigator-assessed PFS. The combination of gefitinib plus chemotherapy resulted in a superior PFS of 16 (95% CI, 13.5 to 18.5) versus 8 (95% CI, 7 to 9) months, a hazard ratio (HR) (unadjusted) of 0.51 (95% CI, 0.39 to 0.66), $P < .001$, and OS (not reached [NR] *v* 17 months, HR, 0.45; $P < .001$), although more side effects are reported in the combination arm.[11]

The results of the ARCHER 1050 RCT support the use of dacomitinib monotherapy in which 462 participants with exon 19 deletions or Leu858Arg mutations received either dacomitinib monotherapy or gefitinib.[12,13] The primary outcome was PFS by masked IRC review, which was longer in the dacomitinib arm compared with the gefitinib arm with 14.7 (95% CI, 11.1 to 16.6) versus 9.2 (95% CI, 9.1 to 11) months, HR 0.59, and $P < .0001$. OS also favored dacomitinib (34.1 *v* 26.8 months, $P = .44$). Some AEs were higher with dacomitinib, including stomatitis, rash, diarrhea, nausea, and paronychia.

Clinical interpretation. The Expert Panel recognizes that osimertinib may not be available to all clinicians and patients around the world. If osimertinib is not available, clinicians have several other options that improve PFS and OS compared with a control arm of first-generation EGFR-TKI monotherapy. Although dacomitinib demonstrated an improved PFS and OS compared with gefitinib, the Expert Panel favored the use of osimertinib over dacomitinib, because of reports of increased side effects associated with dacomitinib. Similarly, the combination of carboplatin plus pemetrexed plus gefitinib results in improved PFS and OS compared with gefitinib alone; however, the use of chemotherapy in this regimen results in increased side effects for patients compared with receiving osimertinib alone.

Recommendation 1.4. For patients with a sensitizing (L858R/exon 19 deletion) *EGFR* mutation with stage IV NSCLC and a PS of 0-2, who have not had previous systemic therapy and do not have access to osimertinib, clinicians may use monotherapy with afatinib or erlotinib/bevacizumab or erlotinib/ramucirumab (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review update and analysis. The use of afatinib is supported by the Lux-Lung 3, 6, and 7 trials. The Lux-Lung trials published before 2016 were reviewed in prior versions of this guideline and will not be re-reviewed here. The current systematic review found two RCTs (LUX-Lung 7 and IFCT-1503 ACE-Lung), one publication, one presentation (in one, afatinib was the control arm), and an observational study including afatinib. Since phase III trials

are available, the observational one is reported in the results table only. Imai et al,[14] a single-arm trial of afatinib, for patients with common mutations and included patients who are chemotherapy-naïve. The primary outcome was PFS with a result of 12.9 months. The RR was 73%, and the OS was NR. The most common AE was diarrhea: 12.5% (grade 3). In the LUX-Lung 7 RCT, patients were randomly assigned to receive afatinib or gefitinib.[15] The primary outcome was PFS, which was statistically significantly better with afatinib (11 *v* 10.9 months). Although PFS favored afatinib over gefitinib, immature OS data indicated no difference (27.9 *v* 25 months, $P = .26$).

Another study used afatinib as the control arm versus afatinib with cetuximab; this study (IFCT-1503 ACE-Lung) included some patients with rarer *EGFR* (G719X, L861Q, and S768I) mutations, with a primary outcome of time to treatment failure (TTF) at 9 months.[16] The TTF (by 0.8 months) and PFS at 9 months (by 8.7 months) were longer with afatinib alone. The RR and 1-year survival were higher with the combination. Serious adverse events (SAEs) (11% *v* 4%) were higher with afatinib (*v* gefitinib), the first study.[15] In the other study, diarrhea was higher with the combination.

The third set of nonosimertinib options for patients with these mutations under Recommendation 1.4 is erlotinib/bevacizumab, reported in two RCTs, one published, the other a meeting presentation,[17,18] and in one RCT on erlotinib/ramucirumab.[19] The primary outcome was PFS in all three studies. Like with afatinib, in trials comparing erlotinib plus bevacizumab with erlotinib alone, PFS, but not OS, was improved with the combination, at the expense of more side effects. In a phase III trial, 228 patients received erlotinib plus bevacizumab versus erlotinib alone.[18] Median PFS favored the combination (16.9 *v* 13.3 months, HR 0.605, $P = .016$). OS was a secondary outcome and not reported. More patients in the combination arm had SAEs. In the presentation of Zhou et al of erlotinib/bevacizumab versus erlotinib, the PFS result was 18 *v* 11.3 months, HR 0.55 (95% CI, 0.41 to 0.75), and OS was not reported. Treatment-related AEs were higher with the intervention.[17] A phase III trial comparing 449 patients treated with erlotinib plus ramucirumab versus erlotinib plus placebo[19] demonstrated a PFS of 19.4 versus 12.4 months, favoring the ramucirumab arm ($P < .0001$). At the time of publication in October 2019, OS data were immature with median survival NR in either arm. Rates of hypertension and bleeding were higher in the ramucirumab arm.[19]

Clinical interpretation. If osimertinib and dacomitinib are not available and gefitinib plus carboplatin plus pemetrexed is not an option, clinicians may offer patients afatinib monotherapy or the combination of erlotinib with a VEGF inhibitor (bevacizumab or ramucirumab). These options improve PFS but have not reported an improvement in OS compared with a first-generation EGFR-TKI alone. These options also result in more side effects compared with gefitinib or erlotinib monotherapy. Clinicians may discuss these options in special circumstances in which improved PFS may have a clinical impact on the patient's quality of life (eg, highly symptomatic disease).

Recommendation 1.5. For patients with a sensitizing (L858R/exon 19 deletion) *EGFR* mutation with stage IV NSCLC and a PS of 0-2, who have not had previous systemic therapy and do not have access to other regimens, clinicians may use monotherapy with gefitinib, erlotinib, or icotinib (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review update and analysis. If clinicians do not treat patients with any of the options listed in recommendations 1.1-1.4, they may choose to use gefitinib, erlotinib, or icotinib monotherapy, where available. Evidence supporting these options comes from comparisons between the EGFR-TKI and chemotherapy in the first-line setting or a head-to-head comparison of icotinib with gefitinib. Trials on these agents published before the opening date parameters and reviewed in previous versions will not be re-reviewed (eg, Mok et al,[20] Han et al,[21] and Maemondo et al[22]). Based on higher RR and PFS with gefitinib compared with chemotherapy, these trials established gefitinib monotherapy as a reasonable option for the first-line treatment of patients with *EGFR*-mutated lung cancer. Trials such as Zhou et al[23] and the EURTAC trial[23] established erlotinib as an option in the first-line setting. In addition, icotinib was compared with gefitinib.[24] In the new systematic review,[25] CONVINCE was an RCT of icotinib versus cisplatin/pemetrexed with pemetrexed maintenance for patients with common *EGFR* mutations. The primary outcome was PFS, and the result was 11 versus 8 months, HR 0.61, and $P = .006$. OS was similar.

Another RCT[26] compared gefitinib versus erlotinib with 128 participants in each arm, exon 19 deletion or exon 21 mutations, and the primary outcome in the revised phase III was PFS (RR was the primary outcome in the original phase II version). PFS with HR = 0.81 (0.62 to 1.05) was not statistically significantly different, nor was OS nor RR. In addition, there was no significant difference in AEs. The authors state that there may have been potential enrollment bias in this study.

Two RCTs compared the interventions of gefitinib and pemetrexed versus gefitinib for those with common *EGFR* mutations.[5,8,9] In the first, < 70 patients received gefitinib alone, and PFS was the primary outcome.[9] The PFS was 15.8 versus 10.9 months; the RRs were similar, and duration of response was longer with the combination. The second RCT of interventions of gefitinib and pemetrexed versus gefitinib for those with common *EGFR* mutations included 90 participants.[8] The primary outcomes for efficacy were mixed; OS and RR were not significantly (NS) different, and PFS was better in the combination arm; there were not many differences in AEs.

Clinical interpretation. The Expert Panel recognizes that not all therapies recommended in these guidelines are available to all patients. Although osimertinib, dacomitinib, and the combination of carboplatin plus pemetrexed plus gefitinib all demonstrated improved OS compared with first-generation EGFR-TKI alone, and afatinib or the combination of erlotinib plus a VEGF inhibitor improves PFS over first-generation EGFR-TKIs alone, the use of erlotinib, gefitinib, or icotinib is also a reasonable option, if other therapies are not available. Goals of therapy, side effects, and availability of therapies may drive therapeutic decisions. EGFR monotherapy generally doubles the RR and improves PFS by about 30% compared with chemotherapy in this patient population. In addition, EGFR-TKIs are generally better tolerated and more convenient to take than chemotherapy. Few, if any, patients would not be considered medically eligible, unless their PS is > 3, to receive at least a brief course of these drugs to assess tumor response, which can be rapid in many instances; however, data are insufficient to recommend specific regimens.

Recommendation 1.6. For patients with a sensitizing (L858R/exon 19 deletion) *EGFR* mutation with stage IV NSCLC and a PS of 3, who have not had previous systemic therapy, monotherapy with an EGFR TKI may be given, with the choice dependent on access and toxicity profile of each agent (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and analysis. Trials evaluating patients with *EGFR* mutations generally exclude patients with an Eastern Cooperative Oncology Group (ECOG) PS of 3 or higher. Therefore, there are insufficient data to inform clinicians on the benefits of these agents in that patient population.

Clinical interpretation. The Expert Panel determined that in special circumstances, EGFR-TKI monotherapy could be discussed in this patient population; however, the choice of agent would depend on access and toxicity profile. Although osimertinib, erlotinib, or gefitinib might be tolerable to this patient population, the Expert Panel would have reservations about recommending dacomitinib or afatinib because of toxicity concerns. For some patients whose ECOG PS is 3 because of cancer, it would be reasonable to offer EGFR monotherapy to assess for a rapid response and possible improvement in PS.

Recommendation 1.7. For patients with an activating *EGFR* mutation other than exon 20 insertion mutations, T790M, L858R, or exon 19 deletion (eg, G719X, L861Q, and S768I), and a PS of 0-2, who have not had previous systemic therapy, clinicians may offer afatinib monotherapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or osimertinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak) or standard treatment based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; evidence quality; low: Strength of Recommendation: moderate).

Literature review update and analysis. For patients with activating mutations other than exon 20 insertion, T790M, L858R, or exon 19 deletion (eg, G719X, L861Q, and S761I), clinicians may offer afatinib or osimertinib monotherapy. Although most studies evaluating EGFR inhibitors included patients only with *EGFR* L858R or deletion in exon 19 mutations, 32 patients enrolled onto three clinical trials (Lux-Lung 2, Lux-Lung 3, and Lux-Lung 6) harbored mutations in S768I, L861Q, and/or G719X, demonstrating an RR of 66% with a response duration of > 1 year in 52% of patients. In a database of 693 patients from randomized trials (not included in the systematic review), expanded-access programs, or compassionate-use programs, afatinib was used in 62 treatment-naïve patients with G719X, 55 treatment-naïve patients with L861Q, and ten treatment-naïve patients with S768I, resulting in the RR of 63%, 59%, and 62%, respectively.[27] Similar results were reported with osimertinib in a phase II trial by Cho et al[28] in which 37 patients were identified with these mutations. The treatment achieved an RR of 50% with a median duration of response of 11.2 months.[29]

Clinical interpretation. Little data are available to estimate the activity of afatinib and osimertinib in this patient population. Given the infrequency of these activating mutations, it would be difficult to conduct larger-scale trials. The patient and disease characteristics of patients with these less common *EGFR*-activating mutations are like those with exon 19 deletion and L858R mutations. Randomized trials in these subsets are unlikely to occur, and clinicians will be left with limited data to make these clinical decisions.

Qualifying statement for recommendation 1.7. Although *EGFR*-sensitizing mutations such as L858R and exon 19 deletions were explicitly excluded from clinical trials of chemotherapy/immunotherapy and immunotherapy-alone trials, they did not explicitly test for expanded *EGFR* mutations, and these patients may have been included. It is unlikely that a significant number of patients were included to make a recommendation. Doublet chemotherapy with or without bevacizumab is also a reasonable option as is the regimen of carboplatin plus paclitaxel plus bevacizumab plus atezolizumab, since patients with EGFR were allowed in the IMpower150 study evaluating this regimen.

Literature review and analysis. This statement was based on a subgroup of the IMpower150 study of patients with cancers with *EGFR* mutations.[30] Note that this study was also discussed in the nondriver alterations guideline update (January 2020). It compared atezolizumab/bevacizumab/carboplatin/paclitaxel (ABCP) versus atezolizumab/carboplatin/paclitaxel (ACP) versus bevacizumab/platinum combination (BCP) (the first regimen is recommended). The subgroup of patients with *EGFR* mutations was 34 with ABCP, 45 with ACP, and 45 with BCP and had disease progression or unacceptable treatment-related side effects from prior TKI therapy (Table 4). The primary outcomes were interim OS and PFS. For the comparisons for ABCP versus BCP, the PFS was 10.2 (ABCP) versus 6.9 (BCP) months;

however, the difference was nonsignificant. The OS was not estimable (NE) (95% CI, 17 to NE) ABCP versus 18.7 (95% CI, 13.4 to NE) BCP, and the HR difference was NS. For patients with sensitizing mutations (58 who received either ABCP or BCP), the median PFS was statistically significant for ABCP 0.41 (95% CI, 0.23 to 0.75); the OS for the same sample was also 0.31 (95% CI, 0.11 to 0.83). Immune-related events were highest with ABCP.

Recommendation 1.8. For patients with any activating *EGFR* mutation, regardless of PD-L1 expression levels (including exon 20 insertion mutations), single-agent immunotherapy should not be used as first-line therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review update and analysis. The Expert Panel recommends against the use of single-agent immunotherapy as first-line treatment for patients with any activating *EGFR* mutation, regardless of PD-L1 score. This recommendation is based on a meta-analysis of CheckMate 057, KEYNOTE 010, POPLAR, and OAK trials evaluating the use of single-agent nivolumab, pembrolizumab, or atezolizumab in cohorts of patients with *EGFR*-activating mutations.[31]

Clinical interpretation. The benefits of immunotherapy given in combination with chemotherapy with or without bevacizumab are undefined. There is insufficient information to make detailed recommendations on these options; however, growing evidence indicates that single-agent immunotherapy (with PD-1 or PD-L1 inhibitors) appears to result in low RRs, regardless of PD-L1 score. Therefore, clinicians are encouraged to use EGFR-TKIs in the first-line setting. Once EGFR therapy is exhausted, consideration may be given to chemotherapy alone or with immunotherapy, bevacizumab, or the combination.

Recommendation 1.9 For patients with an exon 20 insertion mutation causing resistance to first- and second-generation EGFR TKIs, clinicians may offer platinum doublet chemotherapy with or without bevacizumab (Type: informal consensus: Evidence quality: low; Strength of recommendation: moderate) or standard treatment based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Clinical interpretation. The Expert Panel recommends that clinicians may offer standard therapy with platinum-based doublets with or without bevacizumab or standard treatment based on the nondriver mutation guideline for patients with *EGFR* exon 20 insertion mutations. RRs with currently available EGFR-TKIs in patients with exon 20 insertion mutations are low. Although this is an area of substantial clinical interest, no data are available to guide clinicians on which strategy is optimal or preferred. Several investigational agents have demonstrated higher RRs than reported with currently available agents, but also with significant toxicities.

SECOND-LINE

Clinical Question 2: *EGFR* Second-Line

What is the optimal second-line therapy for patients with stage IV NSCLC with a tumor EGFR–sensitizing mutation and PS 0-2?

Recommendation 2.1. For patients with a sensitizing (L858R/exon 19 deletion) *EGFR* mutation with stage IV NSCLC and a PS of 0-2, who have had previous EGFR targeted therapy (who did not receive osimertinib) and subsequently have an *EGFR* T790M resistance mutation at the time of progressive disease, clinicians should offer osimertinib (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. Clinicians should use osimertinib in patients with an *EGFR* T790M mutation who have received a prior EGFR-TKI (except osimertinib). This recommendation is unchanged from 2017.[1]

Clinical interpretation. Osimertinib, if available, is the preferred first-line EGFR-TKI for patients with *EGFR* exon 19 deletion, L858R, or T790M mutations. However, some patients remain on first-generation EGFR-TKIs, including gefitinib or erlotinib. At the time of disease progression on these first-generation EGFR-TKIs, approximately 50%-60% of patients' cancers will be expected to have an *EGFR* exon 20 T790M mutation.[20] For patients with a confirmed *EGFR* T790M resistance mutation, clinicians should offer osimertinib. Retesting *EGFR* status is, therefore, essential to identify these patients who would benefit from osimertinib. A number of potential resistance mechanisms have been reported, in addition to T790M, including transformation to small-cell lung cancer. The Expert Panel suggests discussion of a repeat tissue biopsy.

Recommendation 2.2. For patients with any *EGFR* mutation whose disease has progressed on EGFR TKIs with no T790M mutation OR whose disease has progressed on osimertinib, clinicians may treat based on ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. A preplanned subset analysis of IMpower150 (also discussed under Qualifying Statement 1.7), which randomly assigned patients with carboplatin plus paclitaxel plus bevacizumab (BCP) or atezolizumab or both (ABCP), the population evaluated the 50 patients in ABCP and the BCP arms together who received prior EGFR-TKI therapy. The OS HR was 0.39, NE versus 17.5 (95% CI, 0.14 to 1.07), suggesting improved OS for patients receiving the four-drug combination compared with carboplatin plus paclitaxel plus bevacizumab alone. The PFS was 0.42 (95% CI, 0.22 to 0.8), 9.7 versus 6.1 months.[30,32]

Clinical interpretation. The preferred treatment approach to this patient population is undefined. Options include chemotherapy alone, chemotherapy with bevacizumab, or chemotherapy with bevacizumab and atezolizumab. IMpower150 included this patient population in its design as an exploratory set, whereas other chemotherapy/immunotherapy combination studies reported at this writing have excluded this patient population. Approximately 10% of the patients on IMpower150 had an *EGFR* or *ALK* mutation, and as an exploratory analysis, conclusions on this regimen's efficacy in this patient population are limited and should be considered hypothesis-generating only.

ALK First-Line

Recommendation 3.1. For patients with an *ALK* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong). If alectinib and brigatinib are not available, clinicians should offer ceritinib or crizotinib (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. Clinicians should offer brigatinib or alectinib to patients with previously untreated NSCLC with an *ALK* rearrangement. In 2017, the recommendation was for crizotinib. The systematic review found three RCTs on *ALK*-rearrangement treatments (alectinib, ceritinib, and brigatinib).[33,34] The changed recommendation is based on the results of these head-to-head comparator trials of brigatinib versus crizotinib and alectinib versus crizotinib. Camidge et al[33] reported the results of a phase III trial of 275 patients with advanced NSCLC for patients with no prior ALK-targeted therapy and an *ALK* rearrangement who were randomly assigned to receive brigatinib or crizotinib. The primary outcome was PFS, and it favored brigatinib. The 12-month PFS was 67% (95% CI, 56 to 75) versus PFS 43% (95% CI, 32 to 53); HR for progression or death, 0.49; and $P < .001$ for brigatinib and crizotinib, respectively. Overall objective RRs were not different. The intracranial RR was also higher for those receiving brigatinib (78% *v* 29%).

Two randomized trials support the use of alectinib in the front-line setting.[35] Peters et al reported a phase III trial comparing treatment with alectinib versus crizotinib in 303 patients with *ALK*-positive advanced NSCLC. The primary outcome was investigator-assessed PFS and was NE. Twelve-month PFS was significantly higher for those receiving alectinib 68.4% (95% CI, 61 to 75.9) versus 48.7% (95% CI, 40.4 to 56.9), HR 0.47 (95% CI, 0.34 to 0.65), and $P < .001$. These results are consistent with similar results reported by Hida et al and Nakagawa et al in a phase III trial of 207 patients[36] of Japanese participants.[36,37] The primary outcome, PFS, was statistically significantly improved. There was not an OS improvement.

If brigatinib or alectinib is not available, clinicians should offer ceritinib or crizotinib. This recommendation is based on phase III trials demonstrating the superiority of the targeted agent over chemotherapy in the first-line setting of this patient population. Soria et al[34] reported the results of a phase III trial of first-line ceritinib versus platinum-based chemotherapy in 376 patients with *ALK*-positive NSCLC. Patients receiving ceritinib had a median PFS of 16.6 versus 8.1 months in the chemotherapy group (HR 0.55, $P < .00001$).[34] There was more hypertension with ceritinib as well as increased blood creatine kinase levels and increased lipase levels.[34]

Clinical interpretation. The Expert Panel recommends the use of either brigatinib or alectinib. Each of these agents demonstrated superior PFS compared with crizotinib. Alectinib is supported by the results of two randomized trials, whereas brigatinib is supported by the results of one randomized trial. Both these agents have superior CNS activity compared with crizotinib. Brain metastasis and leptomeningeal disease are common problems in patients with adenocarcinoma harboring an *ALK* fusion. The side effect profiles of these two agents are similar. To reduce the risk of pulmonary toxicity, brigatinib must be administered at 90 mg daily for 1 week as a lead-in to the 180 mg daily dose. Alectinib is administered at 600 mg twice daily in the United States, whereas it is administered at 300 mg twice daily in Japan. Crizotinib has inferior PFS and CNS activity compared with alectinib or brigatinib against *ALK*-positive NSCLC.

If brigatinib or alectinib is not available, the Expert Panel recommends the use of either ceritinib or crizotinib. There are no head-to-head comparisons of ceritinib with crizotinib in the first-line setting at the time of this publication. Each of these agents have proven to have superior PFS compared with chemotherapy in the first-line setting.

The authors became aware of data presented after the closing date parameter and will discuss these data in future updates when more data are published to assess the study's quality and the final results. The data concerned a study on patients with *ALK*-positive, first-line lorlatinib versus crizotinib.[38,39]

ALK Second-Line

Recommendation 4.1. For patients with an *ALK* rearrangement, a PS of 0-2, and who have previously received alectinib or brigatinib, clinicians may offer lorlatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. This recommendation that clinicians may offer lorlatinib for patients with an *ALK* rearrangement whose cancer has progressed on previous treatment with alectinib or brigatinib is based on phase II data reported by Solomon et al (ongoing).[40] A total of 215 patients with *ALK*-positive disease were enrolled. Positivity of *ALK* rearrangement was confirmed by FISH or IHC (local). The 215 included cohorts of 30 patients who were treatment-naïve, 59 who received prior crizotinib with or

without prior chemotherapy, 28 who received one prior non-crizotinib ALK inhibitor with or without chemotherapy, and 112 who received two or three prior ALK inhibitors with or without chemotherapy. RRs were 32%-39% in the latter two groups. Serious treatment-related AEs occurred in 7% of patients. The most common side effects were hypercholesterolemia and hypertriglyceridemia.

Clinical interpretation. There are no trials comparing lorlatinib with chemotherapy in this patient population. Ceritinib had demonstrated superior PFS to chemotherapy in a population treated with prior crizotinib, but not prior alectinib or brigatinib. In contrast, lorlatinib demonstrated significant activity in a heavily pretreated patient population with one, two, or three prior ALK inhibitors. Therefore, clinicians may offer lorlatinib in this setting.

Recommendation 4.2. For patients with an *ALK* rearrangement, a PS of 0-2, and who have previously received crizotinib in the first-line setting, clinicians should offer alectinib, brigatinib, or ceritinib in the second-line setting (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation; strong).

Literature review and analysis. Clinicians may offer ceritinib, alectinib, or brigatinib to patients with *ALK*-positive NSCLC who previously received crizotinib as their first-line ALK therapy. The support for using ceritinib comes from a phase III trial reported by Shaw et al in which 231 patients with *ALK*-positive advanced NSCLC who previously received chemotherapy and crizotinib were randomly assigned to ceritinib versus docetaxel or pemetrexed. Ceritinib showed a significant improvement in median PFS compared with chemotherapy (5.4 *v* 1.6 months). OS was not statistically significantly improved. Among side effects, neutropenia was higher with chemotherapy and nausea was higher with ceritinib.[41]

The option of brigatinib or alectinib in this setting is derived from the results of phase II trials. Kim et al[42] reported an RR of 45%-54% in patients previously treated with crizotinib who received 90 mg daily or 180 mg daily of brigatinib, respectively. The median PFS was 9.2-12.9 months in the two dose levels, respectively. Similarly, alectinib was reported to have an RR of 48% in 87 patients with advanced NSCLC and *ALK* rearrangements previously treated with crizotinib.[43]

Clinical interpretation. Ceritinib demonstrated superior PFS compared with chemotherapy in a phase III trial of patients previously receiving chemotherapy and crizotinib. Alectinib and brigatinib each demonstrated an RR of approximately 50% in this population. Head-to-head comparisons of these agents in this clinical setting have not been reported. However, alectinib and brigatinib have each demonstrated superior PFS to crizotinib in the first-line setting, whereas no comparator trials are available for ceritinib. Each of these agents have significant CNS activity, and the side effect profiles are similar.

Recommendation 4.3. For patients with an *ALK* rearrangement, a PS of 0-2, and who have received prior crizotinib in the first-line setting and alectinib, brigatinib, or ceritinib in the second-line setting, clinicians may offer lorlatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or clinicians may offer standard therapy based on the ASCO/OH nondriver mutation guideline in the third-line setting (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and analysis. The recommendation stated that clinicians may offer lorlatinib for patients with an *ALK* rearrangement whose disease has progressed on previous treatment with crizotinib in the first-line setting and alectinib, brigatinib, or ceritinib in the second-line setting. This recommendation is based on the same data reviewed under Recommendation 4.1. Clinicians may also offer standard therapy based on the ASCO/OH nondriver mutation guideline. The Expert Panel gave a moderate strength of recommendation for lorlatinib and a weak recommendation for nondriver therapy based on the known activity of lorlatinib in this setting and the lack of data for nontargeted therapy in this population.

Clinical interpretation. There are little data on the activity of chemotherapy with or without bevacizumab with or without immunotherapy (PD-1 or PD-L1 inhibitors) in this clinical setting. Some patients treated on IMpower150 had *ALK* fusions; in a combined analysis of patients with *EGFR* mutations, the combination of carboplatin plus paclitaxel plus atezolizumab plus bevacizumab had superior OS compared with carboplatin plus paclitaxel plus bevacizumab alone. However, the Expert Panel believes that these data must be interpreted as hypothesis-generating only. The relative risk or benefit of lorlatinib compared with nondriver treatment recommendations is undefined. The reported high activity of lorlatinib in this patient population led to the higher strength of recommendation for lorlatinib over nondriver treatment options.

ROS1 First-Line

Recommendation 5.1. For patients with *ROS1* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer crizotinib or entrectinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 5.2. For patients with *ROS1* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer standard therapy based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 5.3. For patients with *ROS1* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer ceritinib or lorlatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and analysis. For the first option, two studies investigated crizotinib in the systematic review.

EUROCROSS included 34 patients with *ROS1*, crizotinib for all lines, and the primary outcome was RR with a 73% result.[44] *ROS1* positivity was confirmed by FISH. Sinus bradycardia occurred in 47% of patients. The second was a single-arm, ongoing, study in which 127 patients received three or fewer prior treatment lines, 98% of whom had nonsquamous cell carcinoma. *ROS1* positivity was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR). The primary outcome of RR was 72%.[45] The PFS was 15 months, and the OS data were immature. 25% of participants had grade 3-4 AEs.

The systematic review found no new evidence in first-line ceritinib since the 2017 guideline. Shaw et al[46] published the results of an ongoing study on lorlatinib in multiple lines. Positivity of *ROS1* was determined by FISH or RT-PCR or next-generation sequencing. There were 47 patients in the phase II portion (of 69 total). The sample size was not predefined or based on power calculations. The primary outcome was RR: 62% in the 21 patients who had not received prior treatment and 35% in those with prior crizotinib. The AEs with the highest rates were hypertriglyceridemia and hypercholesterolemia.

Investigators conducted a pooled analysis of patients with *ROS1* rearrangements in the ALKA-372-001, STARTRK-1, and STARTRK-2 studies of entrectinib (included phase I studies).[47] There were 53 patients with lung cancer, and the primary outcome was RR, which was 77% (95% CI, 64 to 88); the PFS was 19 months. 35% of patients experienced grade 3 and grade 4 treatment–related AEs (authors described as on-target treatment-emergent adverse events).[47(p266)]

ROS1 Second-Line

Recommendations 6.1 and 6.2. **Recommendation 6.1.** For patients with *ROS1* rearrangement and a PS of 0-2, previously treated with ROS1-targeted therapy, clinicians should offer standard therapy based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 6.2. For patients with *ROS1* rearrangement and a PS of 0-2, and previously treated with nontargeted therapy first-line, clinicians may offer crizotinib or entrectinib or ceritinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The EUROCROSS trial,[44] Wu et al,[45] and Shaw et al[46] studies discussed under *ROS1* first-line also included patients who received prior therapy. Two studies were found that included patients with prior treatment. The first,[48] METROS, was a single-arm study of crizotinib, with cohorts of 26 patients (each) with *ROS1* or *MET* alterations who had received one or more prior regimens of chemotherapy. *ROS1* rearrangement and *MET* amplification were tested with FISH centrally. At the study's end, the investigators confirmed *MET* mutation by direct sequencing. The RR, the primary outcome, was 65% (of those with *ROS1*), and the PFS for patients in the *ROS1* cohort was 22.8 (95% CI, 15.2 to 30.3) months. SAEs were reported in 50% of the patients.

Another study included 32 patients receiving second-line ceritinib.[49] The results for the primary outcome of RR were 62%. The PFS was 9.3 months for all patients on study and 19.3 months for the subgroup of patients who had not received prior crizotinib. The OS was 24 months. Fifty percent of patients had SAEs (as investigators defined).

Clinical interpretation. Approximately 1%-2% of patients with nonsquamous, NSCLC may have *ROS1* translocation, although the actual incidence may vary and depends on the population under study. This mutation is more common in nonsmokers/remote smokers. Patients with *ROS1* rearrangements were not explicitly excluded from chemotherapy or most immunotherapy/combination chemotherapy-immunotherapy studies, but the number of patients with *ROS1* rearrangements on any of these studies is likely extremely low.

The systematic review did not identify any RCTs comparing targeted agents such as crizotinib, entrectinib, ceritinib, or lorlatinib with either chemotherapy or chemotherapy/immunotherapy, and no RCTs were identified that compared two ROS1 inhibitor therapies with each other. The 2017 guidelines recommended crizotinib in the first- or second-line setting. Since that time, further phase II data were published with crizotinib, including the cohort in the 2017 guidelines described by Goto et al and subsequently published by Wu et al and a separate European cohort of 34 patients published by Michels et al. The consistency of an over 70% RR, a median PFS $>$ 12 months, and a 1-year OS of more than 80% in separate phase II trials was felt by the Expert Panel to represent a very high likelihood of a clinically meaningfully benefit for these patients.[44,45] Similar high RRs were found with entrectinib on an ongoing pooled analysis of three studies (77%), with a median PFS of 19 months. Ceritinib had an RR of 62%, and all patients were pretreated with chemotherapy, whereas lorlatinib had an RR of 62% in noncrizotinib pretreated patients. Although comparing phase II data regarding toxicity is a challenge, there are sufficient toxicity data to reasonably conclude that lorlatinib has more side effects.

In patients whose disease progresses on targeted therapy—typically crizotinib—there was a paucity of data, as only two patients in the ceritinib study received prior crizotinib. The lorlatinib study included 40 patients pretreated with crizotinib, with an RR of 35% and a median PFS of 8.5 months.[46] These data were insufficient to recommend this therapy in this setting, and not clearly better than chemotherapy or chemotherapy/immunotherapy.

BRAF First-Line

Recommendations 7.1 and 7.2. **Recommendation 7.1.** For patients with a *BRAF* V600E mutation, clinicians may offer dabrafenib/trametinib as first-line treatment (Type: informal

consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 7.2. For patients with a *BRAF* V600E mutation, clinicians may offer standard first-line therapy based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

There was no new evidence found in the systematic review, and therefore, the 2017 recommendations (now numbered Recommendations 7.1 and 7.2) are unchanged.[1]

BRAF Second-Line

Recommendations 8.1-8.4. **Recommendation 8.1.** For patients with a *BRAF* V600E mutation who have had previous BRAF/MEK-targeted therapy (dabrafenib/trametinib), clinicians should offer standard first-line therapy based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 8.2. For patients with a *BRAF* V600E mutation, if BRAF-targeted therapy was not given in the first-line setting, clinicians may offer dabrafenib/trametinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or dabrafenib alone (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak) or vemurafenib (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Recommendation 8.3. For patients with a *BRAF* V600E mutation who have had previous chemotherapy, immunotherapy, and/or BRAF-targeted therapy in the first- or subsequent-line setting, clinicians should offer standard treatment based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 8.4. For patients with *BRAF* mutations other than *BRAF* V600E mutations, clinicians should offer standard therapy based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low, Strength of recommendation: moderate).

Literature review and analysis. In the VE Basket trial of vemurafenib for patients with *BRAF* V600 mutation–positive NSCLC, the primary outcome, investigator-assessed RR, was 37%.[50] The PFS was 6.5 months. Grade 3-4 AEs were 77%; those that were treatment-related were 40%.

Clinical interpretation. According to My Cancer Genome, 4.75% of patients with NSCLC have *BRAF* alterations and *BRAF* V600 alterations, specifically in 1.24% of all NSCLC.[51,52] There are no RCTs comparing vemurafenib with standard-of-care chemotherapy in first-line or with dabrafenib or dabrafenib/trametinib (latter recommended in 2017). Therefore, the 2017 recommendations including standard-of-care chemotherapy or dabrafenib/trametinib remain as options in the first-line for these patients. In addition to the 2017 recommendations for *BRAF* V600, clinicians may discuss vemurafenib as another option for second-line therapy compared with standard-of-care chemotherapy, although the occurrence of significant AEs is somewhat greater (note: in 2017, "If patients with *BRAF* mutations received immunotherapy in the second-line, clinicians may offer patients dabrafenib alone or in combination with trametinib in the third-line" [Type: informal consensus]).

MET First-Line and Second-Line

Recommendations 9.1-9.2, 10.1-10.2. **Recommendation 9.1.** For patients with an *MET* exon 14 skipping mutation, a PS of 0-2, and previously untreated NSCLC, clinicians may offer MET-targeted therapy with capmatinib or tepotinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 9.2. For patients with an *MET* exon 14 skipping mutation, a PS of 0-2, and previously untreated NSCLC, clinicians may offer standard first-line therapy based on the ASCO/OH nondriver mutations guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 10.1. Patients with *MET* abnormalities other than exon 14 skipping mutations, a PS of 0-2, or those previously treated with MET-targeted therapy, clinicians should offer standard therapy based on the ASCO/OH nondriver mutations guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 10.2. For patients with an *MET* exon 14 skipping mutation, a PS of 0-2, and who have previously received or been ineligible for first-line chemotherapy with or without immunotherapy, clinicians may offer MET-targeted therapy with capmatinib or tepotinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The investigators of the GEOMETRY phase II cohort study of capmatinib for patients with *MET* Δ exon 14 alteration–positive NSCLC presented the results of two of the cohorts at ASCO 2019 (subsequently published after closing date parameter).[53,54] 28 participants received capmatinib in the first-line setting, and 69 had received previous treatment. The primary outcome was investigator-assessed overall response rate (ORR); for first-line, the investigator-assessed ORR was 68% (cohort 5b untreated), n = 28, and the second-line was 41% (cohort 4, pretreated). All responses were partial. The median PFS was 12.4 months in the first-line and 5.4 months for patients who received prior treatment. The event-free rate at 12-month result was 26%; in second-line, it was 50% (reported at ASCO). Safety was assessed in data set of 364 participants. Sixty-seven percent of participants had grade 3-4 AEs; 13% had SAEs. Peripheral edema occurred in 9% of patients.

The ongoing VISION study is a phase II cohort study of tepotinib in the same population.[55] Central testing for mutations was performed centrally on circulating free DNA from plasma using next-generation sequencing or on RNA from

fresh or archival biopsy tissue. Patients had prior treatment regimens of 0 to ≥ 2. The primary study outcome was investigator-assessed ORR, and the result was 46%. All responses were partial. The median duration of response was 11.1 months. The median duration of OS was immature; it was reported at 17.1 months (95% CI, 12.0 to 26.8). Twenty-eight percent of patients had treatment-related AEs (investigator-determined), and SAEs occurred in 15%. Peripheral edema occurred in 7% of patients.

The METROS single-arm study[48] involved crizotinib, with 26 patients (each) in two cohorts who had *ROS1* or *MET* rearrangements and had received one or more prior regimens of chemotherapy. *ROS1* rearrangement and *MET* amplification were centrally tested using FISH. At study's end, the investigators confirmed *MET* mutation by direct sequencing. The primary study outcome was RR and was 27% (of those with *MET*), the PFS was 4.4 months, and SAEs were reported in 13 of the patients (50%). (The *ROS1* results are discussed in the *ROS1* section.)

Clinical interpretation. Somatic *MET* exon 14 alterations are present in approximately 3%-4% of patients with NSCLC.[56] Multiple mutations in *MET*, in introns and exons, can lead to *MET* exon 14 alterations. Beyond typical next-generation sequencing, *MET* exon 14 alterations can be detected using diagnostic approaches that use RNA sequencing. Evaluation of the clinical and pathologic characteristics of patients with *MET* exon 14 alterations suggests that these molecular aberrations are more common in patients who are older and are often present in tumors with sarcomatoid alterations, although they also happen in adenocarcinoma and squamous cell carcinoma.

Both capmatinib and tepotinib have been studied in prospective clinical trials that enrolled no control group. Crizotinib was evaluated in a much smaller single-arm study, enrolling ten patients with *MET* exon 14 alterations. In these single-arm studies, for groups of patients previously treated for metastatic NSCLC and those without prior therapy, the RRs suggest that MET inhibitors may be superior to chemotherapy in the first-line setting, but the low quality of evidence precluded the guideline from recommending that MET inhibitors should be used as initial therapy for patients with NSCLC with *MET* exon 14 alterations. There are other early data in patients whose tumors harbor *MET* amplification (without *MET* exon 14 alterations), suggesting that these patients may benefit from MET inhibitors. However, the data were too low quality to make a recommendation for patients with *MET* amplification in the absence of *MET* exon 14 alterations.

RET Rearrangement First-Line and Second-Line

Recommendations 11.1-11.2, 12.1-12.2. **Recommendation 11.1.** For patients with an *RET* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer selpercatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 11.2. For patients with an *RET* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer standard therapy based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 11.3. For patients with an *RET* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer pralsetinib* (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

See the Literature Review Analysis and Clinical Interpretation sections regarding first-line options.

Recommendation 12.1. For patients with *RET* rearrangement who have had previous RET-targeted therapy, clinicians may offer treatment based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 12.2. For patients with *RET* rearrangement, if RET-targeted therapy was not given in the first-line setting, clinicians may offer selpercatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 12.3. For patients with *RET* rearrangement, if RET-targeted therapy was not given in the first-line setting, clinicians may offer pralsetinib* (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

*Provisionally included pending confirmatory data.

Literature review and analysis. The systematic review included a phase II study of selpercatinib (LOXO-292) for patients with *RET* fusion and prior platinum-based treatment.[57] Positivity of *ROS1* was determined by FISH or PCR or next-generation sequencing. There were 105 participants in the primary analysis and also a cohort of 39 who had not received prior treatment. The primary outcome was independent review committee–assessed RR; for those with prior treatment, the result was 64%; for those with no prior treatment, it was 85%. The PFS was 17 months for those with prior treatment and NE (14 to NE) for those with no prior treatment.

At the ASCO 2020 (and 2019) meeting, investigators presented data from ARROW, an ongoing noncomparative phase I or II trial of pralsetinib.[58,59] The primary outcome was RR; 132 patients who received pralsetinib, regardless of prior treatment that had 58% (95% CI, 49 to 67) ORR. For 92 patients who had prior platinum-based treatment, the ORR was 55% (95% CI, 45 to 66), and for 29 patients without prior treatment, it was 66% (95% CI, 46 to 82). In the response-evaluable population, 116 in the total population had 65% (95% CI, 55 to 73) ORR and 80 patients in the second-line had 61% ORR (95% CI, 50 to 27) (the investigators noted that two patients' results awaited confirmation). The results of twenty-six patients in first-line are in Table 4. Neither PFS nor OS was reported. AEs were presented in patients with

multiple tumor types. Study methods have not been published; therefore, study quality was not assessable.

Clinical interpretation. Approximately 1% of patients with nonsquamous, NSCLCs harbor an *RET* translocation, with a variety of fusion partners. Like with *ROS*, these patients tend to be younger and more likely to be light or never smokers than patients with nondriver mutation NSCLCs. Patients with *RET* translocation were not explicitly excluded from chemotherapy or most immunotherapy/combination chemotherapy-immunotherapy studies; however, the number of patients with *RET*-positive results on any of these studies is likely extremely low.

Standard treatment has been doublet chemotherapy, as these patients were not identified as a unique subset. The added value of immunotherapy is uncertain, because of the limited number of patients likely enrolled on immunotherapy clinical trials, although given the typical clinical presentation (nonsmoker), it is probable that immunotherapy without concurrent chemotherapy would have a low likelihood of benefit.

The phase II study of selpercatinib reported by Goto et al (with an August 2020 publication after the systematic review was completed) had a primary end point of RR in a platinum-pretreated population, and the results are under the Literature Review and Analysis section.[57,60] The Expert Panel concluded that these RRs and PFS, although in an ongoing phase II trial, were sufficient to conclude that the significant activity of selpercatinib would make it a reasonable option for first- or second-line therapy and likely provide a significant benefit to patients. A phase III trial is underway to confirm whether first- or second-line use is more appropriate, as there is clinical equipoise.

In addition, investigators in the ARROW study presented some data on another RET-targeted agent, pralsetinib. Some patients' result, all final results, and most methods await confirmation and publication. The US FDA gave pralsetinib accelerated approval on September 4, 2020.[61] The data and the methods of the study were not fully published at this guideline's writing, and final confirmed information is pending. There are no comparative data between treatments for *RET*-fusion NSCLC. ASCO awaits final published evidence, and study methods and, if appropriate, will update the guideline.

NTRK

Recommendations 13.1-13.2, 14.1-14.2. **Recommendation 13.1.** For patients with an *NTRK* fusion, a PS of 0-2, and previously untreated NSCLC, clinicians may offer entrectinib or larotrectinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 13.2. For patients with an *NTRK* fusion, a PS of 0-2, and previously untreated NSCLC, clinicians may offer standard therapy based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 14.1. For patients with an *NTRK* fusion, if NTRK-targeted therapy was not given in the first-line setting, clinicians may offer standard therapy based on the ASCO/OH nondriver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 14.2. For patients with an *NTRK* fusion previously treated NSCLC who have not received an NTRK inhibitor, clinicians may offer entrectinib or larotrectinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis.* The systematic review found a publication of a pooled analysis of ALKA-372-001, STARTRK-1, and TARTRK-2.[62] Drilon et al studied TRK fusion inhibitor larotrectinib in 55 patients, including four patients with lung cancer, age 4 months-76 years, with *TRK* fusion–positive locally advanced or metastatic tumors who had previous treatment with therapy other than kinase inhibitors (where available). Twelve different tumor disease sites were represented, including the four patients with lung cancer, and 51% of patients had received at least two prior systemic chemotherapies. Genes included *NTRK*1 (45%), *NTRK*2 (2%), and *NTRK*3 (53%). *TRK* fusions were identified by next-generation sequencing (50 patients) or by FISH (five patients) as routinely obtained by each participating site. The primary study outcome was ORR, which was 75% (95% CI, 61 to 85), for the entire population, and exceeded a preestablished lower boundary of 30%. Thirteen percent of all patients experienced complete response, and 62% experienced partial response. Three of the four patients with lung cancer had responses. In addition, 73% of all trial participants were progression-free at 6 months and 55% were progression-free at 1 year. AEs were most commonly grade 1 or 2. The most frequent grade 3 AE was anemia (15%).

Doebele et al[63] studied entrectinib in patients with advanced or metastatic *NTRK* fusion–positive solid tumors. Data from patients in the STARTRK-1 and ALKA-1-372-011 trial who had solid tumors (10 of 54 with NSCLC) and *NTRK* molecular alterations were considered phase II eligible, that is, had solid tumors, RECIST measurable disease, no prior TKI treatment targeting the fusion of interest, and treatment consistent with the established phase II dose of 600 mg/m^2 of entrectinib daily, were combined in an analysis with 51 patients from the STARTRK-2 phase II trial. The objective RR, the primary end point, was 57% (95% CI, 43.2 to 70.8), including four complete and 27 partial responses. Six of 10 patients with NSCLC had responses. The outcome in the overall study population exceeded the prespecified lower clinically meaningful boundary of 30%. The second primary end point, median duration of response, was 10 months. The median PFS and OS were 11 (95% CI, 8.0 to 14.9) months and 21 (95% CI, 14.9 to NE) months, respectively.

Analyses were also conducted in a safety population that included 68 patients with *NTRK* fusion–positive cancer who had received at least one dose of entrectinib. Within this population, most treatment-related AEs were grade 1-2 and reversible; 10% of patients reported SAEs. In addition, the study authors' results reported a larger safety population that included patients with any gene rearrangement and tumor type and at least one dose of entrectinib. Overall, the results in this larger safety population were consistent with the safety profile of the *NTRK* fusion–positive safety population.

Clinical interpretation. *NTRK* rearrangements lead to fusion genes and occur across a broad range of tumor types but are rare in patients with NSCLC (identified in < 0.5%). Despite the rarity of these alterations, the data from prospective single-arm trials of patients with multiple histologies but a demonstrated *NTRK* rearrangement show a high RR and long duration of response when the NTRK-targeted kinase inhibitors larotrectinib and entrectinib are used. The RRs from these trials suggest that NTRK inhibitors may be superior to chemotherapy in the first-line setting, but the low quality of evidence precluded the Expert Panel from recommending that NTRK inhibitors should be used as initial therapy for patients with NSCLC with *NTRK* rearrangements.

* *Adapted from* Sohal et al.[64]

SPECIAL COMMENTARY

Emerging Targets

In addition to the list of targets and relevant therapies reviewed, there are several emerging targets in lung cancer with active targeted therapies anticipated soon. These include, but are not limited to, aberrations in *KRAS, HER2,* and *NRG-1*. The first two targets were included in the systematic review.

KRAS

Literature review and analysis. The ASCO systematic review found two studies, one published RCT and the second, a single-arm study, including those with *KRAS* mutations (the study by Carter et al also included patients with *KRAS* wild type) and previous treatment.[65,66] The study by Carter et al investigated erlotinib versus selumetinib plus erlotinib versus selumetinib. The primary outcome was RR, and the results were minimal. Both the OS and PFS results were nonsignificant. The participants in the study by Gadgeel et al received trametinib and docetaxel, for whom RR was 33%. In the selumetinib study, the highest AE rates were in the combination arm, for example, diarrhea, nausea, and rash. Other results are in the Data Supplement.

Clinical interpretation. The incidence of oncogenic *KRAS* mutations in lung adenocarcinoma is approximately 30% in western countries and 10% in Asia[67] and is more common in smokers and uncommon in squamous cell lung carcinoma (27% on My Cancer Genome).[68] Mutations are most seen in codons 12 and 13, with the $KRAS^{G12C}$-mutant allele identified in approximately 40% of patients with cases of *KRAS*-mutant lung cancer. Despite historical challenges in targeting *KRAS* directly, small molecules that inactivate the $KRAS^{G12C}$-mutant protein have now been developed. For example, AMG510 (proposed name: sotorasib, Amgen; ClinicalTrials.gov identifier: NCT03600883) has demonstrated partial responses in seven of the 13 patients with advanced NSCLC with a $KRAS^{G12C}$ mutation, and six achieved stable disease (disease control rate, 100%) at 960 mg once daily dosing.[69] The US FDA has granted this agent fast-track designation (September 2019), with updated data anticipated shortly. Other agents are also in development for patients with $KRAS^{G12C}$-mutant lung cancer (ClinicalTrials.gov identifier: NCT03785249, NCT03745326, and NCT03101839). The activity of these agents against other subtypes of *KRAS*-mutant lung cancer such as $KRAS^{G12D}$ remains under investigation. Recent studies suggesting potential lack of benefit with anti-PD-1 therapy based on the presence of co-alterations in *TP53*, *STK11*, and *KEAP1* should not be used to withhold standard therapy from patients at this time.[70]

HER2

Literature review and analysis. The systematic review found two publications/presentations, both observational. Gao et al[71] presented the results at ASCO 2019 on pyrotinib including 60 patients, and the other study on trastuzumab emtansine (T-DM1) included 49 patients[72]; the patients had received at least one prior platinum-based regimen. The study by Gao et al required *HER2* exon 20 positivity, centrally confirmed (specific tests not reported). The primary outcome was RR. The exploratory study by Peters et al required *HER2* positivity (IHC 2þ or 3þ), and *HER2* status was determined retrospectively or prospectively by IHC. The primary outcome was objective RR. Gao et al reported results of 32% RR and a PFS of 7 months. AEs occurred in 27% of patients, and 3.3% were considered treatment-related. Peters et al divided the analysis between cohorts IHC 2+ and IHC 3+; IHC 2+ = 0% (95% CI, 0.0 to 11.9); and IHC 3+ = 20% (95% CI, 5.7 to 43.7). The PFS was 2.6 months, and the OS was 12.2 months. Ninety-two percent of patients had AEs, and 4% had grade 3 fatigue.

Clinical interpretation. *ERBB2* alterations occur in 3.97% of NSCLC.[73] No RCTs compared therapy for patients with *HER2*-positive NSCLC with chemotherapy. There appear to be some responses for some subgroups of patients with *HER2*-positive disease, but it is not clear how clinicians can generalize this information into a treatment plan. Currently, the guideline does not make a recommendation for or against the use of either pyrotinib or trastuzumab emtansine because of the low level of evidence.

Other Emerging Targets

Other emerging targets in lung cancer include *Neuregulin 1* (*NRG1*) gene fusions, leading to activation of ErbB-

mediated signaling. These have been described in lung and other cancers, with multiple fusion partners reported, most commonly CD74. The incidence is uncommon, estimated at approximately 0.2% of lung cancers (both adenocarcinoma and squamous subtypes), and may be higher in patients with invasive mucinous adenocarcinoma, who are never smokers and who are female. Afatinib, an irreversible pan-ErbB inhibitor, has demonstrated activity in a small number of patients (4 of 12 partial responses; median PFS, 3.5 months; range, 0.6-16.5).[74] Other agents are also under investigation in this population (ClinicalTrials.gov identifier: NCT02912949, NCT02912949, and NCT04383210).

Although there are insufficient data to recommend targeted therapy in these and other subgroups at the time of this guideline update, we anticipate rapid evolution of the evidence and availability of targeted therapies in these subgroups of patients soon. ASCO guidelines are regularly updated and monitor literature for relevant publications for future systematic reviews for this guideline.

PATIENT AND CLINICIAN COMMUNICATION

For recommendations and strategies to optimize patient-clinician communication, see the Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline[75] and previous versions of this guideline update.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited and/or fragmented access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented and/or poor quality care than other Americans.[76–79] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and healthcare providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of the results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and co-insurance.[80,81] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[82,83]

Discussion of cost can be an important part of shared decision making.[84] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease, and there are two or more treatment options that are comparable in terms of benefits and harms.[84]

The following table (Table 6) shows estimated prices for the available treatment options addressed in this guideline. Of note, medication prices may vary markedly, depending on negotiated discounts and rebates.

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[84]

TABLE 6. CMS Reimbursement and Oral Drug Prices Table

Agent, Route, and Treatment Setting	HCPCS Code	Dose	Schedule	2020 Medicare Drug Prices (Part D), Price (USD) for Monthly Dose	Schedule
Erlotinib		150 mg	Daily	4,215	150 mg daily
Osimertinib		80 mg	Daily	16,597	80 mg daily
Gefitinib		250 mg	Daily	8,110	250 mg daily
Dacomitinib		45 mg	Daily	14,155	45 mg daily
Afatinib		40 mg	Daily	10,282	40 mg daily
Icotinib		125 mg × 3	Three times daily	N/A	125 mg 3 times daily
Crizotinib		250 mg	Daily	10,179	250 mg daily
Ceritinib		150 mg × 5	Daily	21,107	750 mg daily
Alectinib		150 mg × 8	Twice daily	15,789	600 mg twice daily
Brigatinib		90 mg	Daily	16,779	90 mg daily
Lorlatinib		100 mg	Daily	17,288	100 mg daily
Entrectinib		200 mg × 3	Daily	18,380	600 mg daily
Dabrafenib		75 mg × 4	Twice daily	11,600	150 mg twice daily
Trametinib		2 mg	Daily	9,748	2 mg daily
Vemurafenib		240 mg × 8	Twice daily	11,852	960 mg twice a day
Capmatinib		200 mg × 2	Daily	10,559	400 mg daily
Tepotinib		500 mg	Daily	N/A	500 mg daily
Selpercatinib		80 mg × 2	Daily	11,310	160 mg daily
Larotrectinib		100 mg	Daily	17,493	100 mg daily
Atezolizumab Injection[a]	J9022	10 mg	Every 3 weeks	77.759	1,200 mg (flat dose) every 3 weeks (in combination with bevacizumab and chemotherapy doublet)
Bevacizumab Injection[a]	J9035	10 mg	Every 3 weeks	81.18	15 mg/kg every 3 weeks
Pemetrexed[a] Injection	J9305	10 mg		68.12	500 mg/m^2 every 3 weeks
Ramucirumab	J9308	5 mg/kg × 2	Every 2 weeks	60.71	10 mg/kg every 2 weeks

NOTE: Regimens and prices for treatment of stage IV NSCLC with driver alterations. Source for prices of oral drugs: Prices per dose from CMS, Medicare Part D, Drug Coverage (part D), 2020 Medicare. For orally administered drugs reinforced through Medicare Part D were identified through ref. 85. For a beneficiary in zip code 63101.

For nonoral regimens, a patient with BSA of 2.082 m2 (weight, 88.7 kg; height, 175.9 cm) from July 2020 reimbursement data for Medicare plan B (from Medicare for 88.7 kg and 15 mg/kg). Source for prices: Prices per dose from CMS Payment Allowances for Med Part B Drugs…doc: October 2020 ASP Pricing File 091520' Effective October 1, 2020-December 31, 2020. Weight and height from ref. 86.

Payment Allowances for Med Part B Drugs…doc: July 2020 ASP Pricing File 061520' Effective July 1, 2020-September 30, 2020.[87]

Males ≥ 20 yrs, all racial and ethnic groups (US sample), mean weight 88.7 kg (Table 5), and mean height 175.9 cm; Females, all racial and ethnic groups (US sample), ≥ 20 years, mean weight 75.4 kg (Table 3), and mean height 162.1 cm (Table 9). BSA calculator[88]: Men 2.082 m^2, Women 1.843 m^2, BSA male 2, height, 176 cm, 88 kg results in 4.15 mg Medscape: Mosteller.

Female BSA 2; height, 162 cm, 75 kg results in 3.67.[89]

Note from 2009: drug costs may vary by plan and by pharmacy where a prescription is filled (eg, preferred or nonpreferred pharmacies. Drug prices are dynamic, and the prices listed in the table may not reflect current prices). In some cases, the recorded out-of-pocket price per dose is equivalent to the price per cycle. This may represent a minimum price per fill set by the health plan. Drug costs may vary by plan and by pharmacy where a prescription is filled (eg, preferred or nonpreferred pharmacies). Does not include costs of administration or facility charges.

Abbreviations: BSA, body surface area; CMS, Centers for Medicare & Medicaid Services; HCPCS, Healthcare Common Procedure Coding System; NSCLC, non–small-cell lung cancer; USD, US dollars.

[a]According to nondriver alteration guideline.[2]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effectiveness analyses that lack contemporary cost data and agents that are not currently available in either the United States or Canada and/or are industry-sponsored. No cost-effectiveness analyses were identified to inform the topic.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from September 4 through September 18, 2020. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with six written comments received. A total of 84% of the six respondents either agreed or agreed with slight modifications to the recommendations, and one (16%) of the respondents disagreed with a subset of recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before CPGC review and approval.

The draft was submitted to external reviewers that OH CCO PEBC selected. Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All healthcare professionals with an interest in lung cancer in the PEBC database, in Ontario, were contacted by e-mail to inform them of the survey, which included one hundred eighteen professionals. Eighteen (15%) responses were received; 15 clinicians with content expertise participated.

It was rated as high quality, and it was agreed that it would be useful in practice. Review comments such as a request for clarification on the Qualifying Statement for Recommendation 1.7 were reviewed by the Expert Panel and integrated into the final manuscript before approval by the CPGC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative in the guideline panel is not only to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the Journal of Clinical Oncology.

LIMITATIONS OF THE RESEARCH AND FUTURE RESEARCH

- Insufficient data on targeted therapy in very rare (in Emerging Targets section) patient populations
- Previous phase III trials of chemotherapy, chemotherapy with immunotherapy, bevacizumab, or the combination presumably included patients with a variety of targetable mutations such as *RET* and *MET* populations; however, the relative benefits of this therapy compared with targeted therapy in these patient populations are unknown.
- The limited number of these patient populations with targetable mutations likely enrolled on immunotherapy clinical trials provides insufficient data to define optimal therapy and sequencing of therapeutic strategies.
- Only phase II data reporting RR and PFS are available for many of these targeted agents in targeted populations.
- For several of the targets, no direct comparisons of targeted therapy with nondriver mutation treatment are available.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update[2] (https://ascopubs.org/doi/10.1200/JCO.19.03022)
- Molecular Testing for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors Guideline Endorsement[90] (http://ascopubs.org/doi/10.1200/JCO.2017.76.7293)
- Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitors[91] (http://ascopubs.org/doi/10.1200/JCO.2017.77.6385)
- Integration of Palliative Care into Standard Oncology Practice[92] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[75] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This ASCO/Ontario Health (Cancer Care Ontario) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/thoracic-cancer-guidelines.

EQUAL CONTRIBUTION

N.H.H. and G.M. were Expert Panel co-chairs, and N.H.H., A.G.R., and G.M. were Writing Subcommittee members.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Therapy for Stage IV Non–Small-Cell Lung Cancer With Driver Alterations: ASCO and OH (CCO) Joint Guideline Update

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APPENDIX

TABLE A1. Therapy for Stage IV NSCLC With Driver Alterations: ASCO and OH (CCO) Joint Guideline Update Expert Panel Membership

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Abbreviations: OH (CCO), Ontario Health (Cancer Care Ontario); PGIN, Practice Guidelines Implementation Network.