A CME-Certified Supplement to JNCCN

PROGRAM OVERVIEW/STATEMENT OF NEED

While the majority of patients with epidermal growth factor receptor (*EGFR*) mutated non-small cell lung cancer (NSCLC) carry “common” *EGFR* mutations that are easily targeted with standard tyrosine kinase inhibitors (TKIs), up to 20% of these patients have uncommon mutations that are more difficult to treat. Uncommon *EGFR* mutations, including the G719X, S768I, and L861Q point mutations and exon 20 insertions, are more difficult to treat, have fewer treatment options, and are associated with a poorer prognosis. In recent years, novel treatments with efficacy against uncommon *EGFR* mutations have emerged. The *EGFR* TKI afatinib has been specifically approved for the treatment of G719X, S768I, and L861Q point mutations, and 2 novel *EGFR* targeted therapies—amivantamab and mobocertinib—have recently demonstrated efficacy against exon 20 insertions.

Hitting the Right Spot: Advances in the Treatment of NSCLC With Uncommon *EGFR* Mutations, will provide oncology clinicians with information on the biology and challenges associated with uncommon *EGFR* mutations, the latest guidance on identifying patients with these mutations, and safety and efficacy data for novel treatment options for patients who carry these mutations.

TARGET AUDIENCE

The intended audience for this educational initiative is oncologists, oncology nurses, and other members of the care team involved in the management of patients with NSCLC.

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This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of USF Health and Rockpointe. USF Health is accredited by the ACCME to provide continuing medical education for physicians.

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FEE INFORMATION

There is no fee for this educational activity.

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Discuss the biology of uncommon *EGFR* mutations found in NSCLC and the role of these mutations in treatment resistance
- Utilize guideline-recommended molecular testing to identify patients with NSCLC who carry uncommon *EGFR* mutations
- Evaluate current and emerging targeted therapies for the treatment of uncommon *EGFR* mutations based on safety and efficacy data
- Develop patient personalized treatment plans for patients with NSCLC who carry uncommon *EGFR* mutations

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Hitting the Right Spot: Advances in the Treatment of NSCLC With Uncommon *EGFR* Mutations

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ABSTRACT

An understanding of the biology of uncommon epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer (NSCLC) is evolving. These mutations are important for the selection of targeted therapy and the development of resistance. The advent of genomic profiling has led to guideline-recommended molecular testing to identify patients with NSCLC who carry uncommon *EGFR* mutations to aid in the selection of appropriate targeted therapy. This article discusses the efficacy and safety of current and emerging targeted therapies for the treatment of uncommon *EGFR* mutations in NSCLC to aid in developing patient-specific treatment plans.

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Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths, accounting for 18.4% of all cancer deaths.¹ The most common lung cancer is non-small cell lung cancer (NSCLC), which occurs in 85% of patients with lung cancer, and the most common NSCLC is adenocarcinoma, which represents 40% of all lung cancer diagnoses. A large proportion of NSCLC adenocarcinoma is mutation-driven, and genomic profiling of these tumors revolutionized the treatment of NSCLC by improving identification of genetic alterations and providing options for targeted molecular therapies to individualize treatment.

Because of the number of mitogenic driver mutations present in NSCLC, these tumors are now classified into molecular subsets on the basis of mutation status.^{2,3} The most frequently altered genes in NSCLC are *EGFR* (10%–35%), *KRAS* (25%–30%), *FGR* (20%), *ALK* (3%–7%), *MET* (2%–4%), *BRAF* (1%–3%), *ROS1* (1%–3%), and *RET* (1%–3%).^{2,3} For many of the molecular subsets, including *EGFR*, *ROS1*, *ALK*, *NTRK*, *KRAS*, *BRAF*, *MET*, and *RET*, there are approved targeted therapies available for treatment. In addition, there are several investigational therapies in development for other molecular subsets, including *EGFR* exon 20 insertions, exon 18 alterations, and *HER2*-amplified NSCLC.

EGFR Mutations

The *EGFR* signaling pathways influence angiogenesis and the activation and regulation of cellular proliferation, underscoring the importance of *EGFR* mutations in NSCLC.⁴ Upregulation of *EGFR* signaling due to kinase-activating mutations or increased *EGFR* expression results in powerful proto-oncogenic functions, causing rapid and uncontrolled proliferation and expansion of mutated tumor cells.⁵ Identified in 20% to 30% of patients with NSCLC worldwide, *EGFR* mutations are more common in adenocarcinomas, never-smokers, women, and Asians.^{6,7} *EGFR* mutations are located primarily in the tyrosine kinase domain at exons 18 to 21, with exon 19 deletions and exon 21 L848R mutations representing the majority of *EGFR* mutations. It is important to identify the specific *EGFR* mutation, including sensitive mutations,

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primary resistance mutations, and de novo and acquired resistance mutations. Molecular testing of *EGFR* mutations is the standard of care for the diagnostic evaluation of NSCLC, and the presence or absence of *EGFR* mutations greatly influences treatment selection.⁸

Studies have shown that 12% to 34% of patients with NSCLC with *EGFR* mutations carry atypical or uncommon *EGFR* mutations.^{9–11} Uncommon *EGFR* mutations are diverse and include a variety of point mutations and insertions on exons 18 through 21. The most common of these are exon 20 insertions (9%) and the point mutations G719S/A/C (collectively known as G719X; 11.5%) on exon 18, S768I (5.5%) on exon 20, and L861Q (5.85%) on exon 21. Although therapy with tyrosine kinase inhibitors (TKIs) has been shown to benefit patients with NSCLC with some of these uncommon mutations, such as the G719X, A768I, and L861Q point mutations, other uncommon *EGFR* mutations often are not sensitive to TKI treatment.¹² For example, patients with *EGFR* exon 20 insertions, which account for approximately 9% of *EGFR* mutations, are often resistant to standard *EGFR* TKIs. Patients who carry these alterations have poor responses to early TKIs, with objective response rates (ORRs) ranging from 11% with afatinib to 0% with gefitinib/erlotinib and median progression-free survival (PFS) of ≤ 2 months.¹¹ Additionally, similar to patients who carry other NSCLC driver mutations, such as *ALK*, *KRAS*, and common *EGFR* mutations, patients with uncommon *EGFR* mutations have poor outcomes on immune checkpoint inhibitor therapy (immunotherapy). The median PFS for patients with known NSCLC driver mutations receiving immunotherapy is 2.8 months, and the median PFS is 2.7 months in patients with *EGFR* exon 20 insertions.^{13,14} It is important, therefore, to identify therapeutically relevant oncogenic drivers to determine which targeted treatments the mutations may be sensitive to, identify primary resistance mechanisms, or identify de novo and acquired resistance mutations.^{6,8}

Molecular Testing for Rare *EGFR* Mutations

Biomarker testing is recommended to determine the specific *EGFR* mutation for guiding the selection of targeted therapy. The NCCN Clinical Practice Guidelines in

Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer recommend biomarker testing in eligible patients with metastatic NSCLC once the histologic subtype is identified (Table 1).¹⁵ The NCCN Guidelines recommend testing for a broad array of biomarkers, including *EGFR*, *ALK*, *ROS1*, *KRAS*, *BRAF*, *RET*, *MET* exon 14 skipping, *NTRK* 1/2/3, and PD-L1 in patients with nonsquamous histology.¹⁵ ASCO also recommends performing mutation testing in any patient with nonsquamous NSCLC, any tissue with an adenocarcinoma component, and/or clinical/demographic features suggestive of the presence of a biomarker-driven malignancy (eg, age ≤ 50 years, never or light smoker).¹⁶ The initial recommended biomarker testing is for *EGFR*, *ALK*, *ROS1*, and *BRAF*, and if these are negative then the next step is a broad biomarker testing panel that includes *KRAS*, *RET*, *MET*, and *HER2*.¹⁶ However, use of a broad biomarker panel for initial testing is preferred, because this allows for identification of less-common *EGFR* variants.

Testing for *EGFR* mutations may be performed using either tissue or blood, although there are advantages and disadvantages for both approaches. Testing of biopsy tissue from patients with NSCLC is highly sensitive, although sensitivity does not reach 100%, and these tests can often be done in-house. Additionally, for newly diagnosed patients, biopsy tissue is often readily available. Ideally, a full next-generation sequencing panel should be ordered because it can detect rare and previously uncharacterized alterations in the sequenced genes, whereas a request for a single gene test may only determine common *EGFR* mutations. The disadvantages of tissue testing are that the tissue sample may be inadequate or not demonstrate cellularity, tissue samples are often not reflective of tumor heterogeneity, and it can take 2 to 4 weeks to perform a complete DNA sequencing panel once the tissue is received. Mutation testing of blood samples is a rapid and noninvasive way to evaluate patients for *EGFR* mutations. A major advantage of this approach is that it can easily detect both common and uncommon mutations. The major disadvantages of blood testing are that it is less sensitive than tissue testing, it is dependent on DNA shedding into the peripheral

Table 1. NCCN Guidelines for Biomarker Testing in Metastatic NSCLC

Nonsquamous (including adenocarcinoma; large-cell); NSCLC Not Otherwise Specified	Squamous Cell Carcinoma
<ul style="list-style-type: none"> Minimum testing: <i>EGFR</i>, <i>ALK</i>, <i>KRAS</i>, <i>ROS1</i>, <i>BRAF</i>, <i>RET</i>, <i>MET</i> exon 14, <i>NTRK</i> 1/2/3 <ul style="list-style-type: none"> Recommended: broad next-generation sequencing panel PD-L1 	<ul style="list-style-type: none"> Test never-smokers, mixed histologies, small specimens <ul style="list-style-type: none"> Consider testing all patients with squamous NSCLC for <i>EGFR</i>, <i>ALK</i>, <i>KRAS</i>, <i>ROS1</i>, <i>BRAF</i>, <i>RET</i>, <i>MET</i> exon 14, <i>NTRK</i> 1/2/3 Recommended: broad next-generation sequencing panel PD-L1

The NCCN Clinical Practice Guidelines in Oncology for NSCLC¹⁵ provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories. Abbreviation: NSCLC, non–small cell lung cancer.

circulation, and it can be costly and there are often barriers to full insurance coverage.

Liquid biopsy testing offers an alternative to standard procedures when tissue biopsy specimens are insufficient or cannot be obtained. It also provides a rapid assessment of emerging resistance mechanisms. A panel convened by the International Association for the Study of Lung Cancer (IASLC) developed a set of guidelines for using liquid (blood/plasma) testing for determining therapeutic targets in treatment-naïve patients with advanced NSCLC.¹⁷ The guidelines recommend testing a surgical specimen (biopsy) if available and treating with standard-of-care therapy based on the presence or absence of oncogenic drivers. In testing tissue specimens, it is strongly suggested to use a tissue-sparing approach. If the tissue biopsy specimen is not sufficient for molecular testing, the molecular analysis should be performed on a liquid biopsy for circulating tumor cell DNA. A full next-generation sequencing panel is preferred if available, but if not, the IASLC recommends that testing should include *EGFR*, *ALK*, *ROS1*, and *BRAF* at a minimum.¹⁷ If the therapeutic target is positive, the patient should be treated with standard-of-care therapy based on the presence or absence of oncogenic drivers. Due to a higher rate of false-negatives associated with liquid biopsies, if the therapeutic target is negative, the tissue should be rebiopsied and the molecular analysis performed on the biopsy specimen. It is recommended that all NSCLC tissue specimens be tested for PD-L1 by immunohistochemistry.

Advances in Targeted Therapy for Rare *EGFR* Mutations

An understanding of the biology of rare *EGFR* mutations in NSCLC has ushered in the development of targeted therapy for specific types of mutations. Three generations of TKIs that target *EGFR* point mutations (G719X, S768I, and L861Q) are available or in development, as well as treatments for exon 20 insertions. Treatments that target exon 18 and *HER2* mutations are also in development. Clinical data for the newer *EGFR*-targeted therapies are discussed.

EGFR Point Mutations

Afatinib

Afatinib is a second-generation irreversible ErbB blocker that was initially approved by the FDA for patients with *EGFR* exon 19 deletions or exon 21 substitutions that have progressed after platinum-based chemotherapy. In January 2018, this approval was broadened to include treatment of 3 atypical *EGFR* point mutations (S768I, L861Q, and/or G719X) in patients with metastatic NSCLC.^{18,19} The approval was based on a pooled analysis

from studies that included 32 patients with the following mutations: G719X with S, A, C, D substitutions; S768I; and L861Q, which also can present in combination with other point mutations.¹⁸ The patients, who were treated with afatinib at 40 mg or 50 mg daily, had a confirmed ORR of 66% (95% CI, 47–81). Among the 21 responders, 52% had a response duration of ≥ 12 months and 33% had a response duration ≥ 18 months.

A post hoc analysis of the phase II LUX-Lung 2 and the randomized phase III LUX-Lung 3 and LUX-Lung 6 clinical trials of afatinib treatment of *EGFR* mutation–positive advanced (stage IIIb–IV) lung cancers found that 12% (75/600 patients) had uncommon *EGFR* mutations.¹⁰ Uncommon *EGFR* mutations detected in patients in group 1 (n=38) included point mutations or duplications in exons 18 to 21 (L861Q, G719S, G719A, G719C, S768I) alone or in combination. Uncommon *EGFR* mutations in group 2 patients (n=14) included de novo T790M mutations in exon 20 alone or in combination with other mutations, and exon 20 insertions were the uncommon mutation in group 3 patients (n=23). Group 1 patients showed the most active response to afatinib treatment: ORR, 71.1% (23/38 patients); median PFS, 10.7 months; and median overall survival (OS), 19.4 months.

A later pooled analysis assessed the clinical efficacy of afatinib in 693 patients with NSCLC harboring uncommon *EGFR* mutations treated in randomized clinical trials, compassionate use and expanded access programs, phase IIIb or noninterventional trials, and case series.²⁰ The analysis found that afatinib showed strong activity against major uncommon (G719X, L861Q, S768I) and compound *EGFR* mutations in patients who were *EGFR* TKI-naïve. The ORRs were 60% in patients with major uncommon mutations (n=110) and 77% in those with compound mutations (n=35). The respective time to treatment failure was 10.8 and 14.7 months.

Osimertinib

Osimertinib is a third-generation irreversible *EGFR* TKI that is approved by the FDA for multiple indications for the treatment of NSCLC. It is approved in patients with *EGFR*-mutated metastatic NSCLC whose tumors have developed T790M mutations after initial *EGFR* inhibitor treatment, and it is approved for both first-line metastatic treatment and adjuvant therapy after tumor resection in patients with NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations. The ASCO and Ontario Health (Cancer Care Ontario) guidelines recommend osimertinib for first-line treatment of patients with exon 19 deletion, exon 21 L858R, and exon 20 T790M *EGFR* mutations.²¹

The phase I AURA trial included immunohistochemical analyses to assess key pathways and tumor markers, including phospho-*EGFR*, phospho-S6, phospho-AKT,

PD-L1, and CD8.²² The AURA trial showed that osimertinib modulated key EGFR signaling pathways and led to increased immune cell infiltration. The phase III AURA3 trial compared osimertinib versus platinum-pemetrexed chemotherapy in 419 patients with metastatic NSCLC whose tumors had developed *EGFR* T790M mutations following first-line treatment with an EGFR TKI.²³ Osimertinib resulted in a significant improvement in median PFS, from 4.4 months with chemotherapy to 10.1 months with osimertinib (hazard ratio [HR], 0.30; $P < .001$). The ORR was also better in patients treated with osimertinib versus chemotherapy (71% vs 31%; $P < .001$). Importantly, osimertinib was associated with an improvement in median PFS in patients with central nervous system metastases. Rates of grade ≥ 3 adverse events were lower in patients treated with osimertinib versus platinum-pemetrexed chemotherapy.

The phase III, double-blind FLAURA trial of osimertinib randomized 556 patients with previously untreated, *EGFR* mutation-positive (exon 19 deletion or L858R) advanced NSCLC to treatment with osimertinib at 80 mg/d orally or to a standard EGFR TKI (gefitinib, 250 mg/d orally or erlotinib, 150 mg/d orally).^{24,25} Median PFS was significantly longer with osimertinib than with the comparator standard TKI therapy (18.9 vs 10.2 months; HR for disease progression or death, 0.46; 95% CI, 0.37–0.57; $P < .001$).²⁴ The ORR was similar for osimertinib and the comparator group (80% and 76%, respectively), and the respective median durations of response were 17.2 and 8.5 months. The median duration of treatment exposure was 20.7 and 11.5 months in the osimertinib and comparator groups, respectively, at the time of data cutoff, and 22% of patients treated using osimertinib versus 5% of those treated using the comparator continued to receive their assigned treatment.²⁵ Median OS, a secondary endpoint, was 38.6 months (95% CI, 34.5–41.8) in the osimertinib group and 31.8 months (95% CI, 26.6–36.0) in the comparator group (HR for death, 0.80; 95% CI, 0.64–1.00; $P = .046$). OS rates and the number of patients continuing to receive first-line trial therapy were consistently higher with osimertinib at 12, 24, and 36 months. Grade ≥ 3 adverse events occurred less frequently with osimertinib (42% vs 47%).

Based on its efficacy against multiple *EGFR* mutations, osimertinib is currently being evaluated as a potential treatment option for patients with uncommon *EGFR* point mutations. A phase II study of 36 patients with metastatic or recurrent NSCLC harboring uncommon *EGFR* mutations was conducted in Korea.²⁶ The study evaluated outcomes in patients with the G719X ($n = 19$), L861Q ($n = 9$), and S768I ($n = 8$) mutations treated using osimertinib. The ORRs were 53%, 78%, and 38% with the G719X, L861Q, and S768I mutations, respectively, and the respective PFS were 8.2, 15.2, and 12.3 months.

Exon 20 Insertions

EGFR exon 20 insertions, the second most common *EGFR* mutation after classic mutations, account for 10% to 12% of all observed *EGFR* mutations.^{11,27} They are largely resistant to first-, second-, and third-generation *EGFR* TKIs, because exon 20 insertion mutations induce steric hindrance of the drug-binding pocket. Insertions at the C-terminal end of p shift it into the drug-binding pocket, forcing a rigid placement of the α -C helix in the inward, activated position. In addition, the phosphate-binding loop is shifted into the drug-binding pocket of both receptors.¹¹ These findings indicate that small, flexible quinazoline derivatives (eg, afatinib) may be capable of inhibiting exon 20 insertions because they have the ability to fit into the sterically hindered binding pocket, whereas drugs with a large, inflexible group (eg, erlotinib) cannot reach the C797 residue and cannot inhibit exon 20 insertions.¹¹

Patients with NSCLC with exon 20 insertions have a worse prognosis compared with those with other *EGFR* mutations, and current TKI targeted therapies are less effective for exon 20 insertions than for classic *EGFR* mutations.^{28,29} A phase II study evaluated the third-generation EGFR TKI osimertinib at 160 mg/d in 21 patients with NSCLC with exon 20 insertions.³⁰ The study showed that osimertinib had some activity against exon 20 insertions, with an ORR of 25% and a median PFS of 9.7 months (95% CI, 4.07–NA). Exon 20 mutations are associated with superior outcomes from immune checkpoint inhibitors compared with classic *EGFR* mutations on exons 19 and 21.³¹ However, the role for immunotherapy in patients with exon 20 insertions is limited because the benefit associated with these therapies is small (a median PFS of approximately 2 months) and the risk of treatment-related adverse events is high.

Although numerous treatments have been evaluated in patients with exon 20 insertions, until recently the standard of care for front-line treatment of NSCLC with exon 20 insertions remained platinum-based chemotherapy.²⁹ Improved understanding of the biology surrounding these mutations has led to the development of numerous targeted therapies that have efficacy against exon 20 insertions, leading to the approval of the first exon 20 insertion-targeted therapy, amivantamab, which has been approved as second-line therapy.³²

Amivantamab

Amivantamab, a fully humanized, bispecific IgG1 antibody targeting EGFR and cMET receptors, is the first treatment approved by the FDA as second-line therapy for adult patients with exon 20 insertion mutation NSCLC. It is an EGFR-targeted therapy with immune cell-directing activity that is associated with a significant clinical benefit in *EGFR*-driven NSCLC, including TKI-

resistant tumors. Amivantamab targets activating and resistant *EGFR* and *cMET* mutations and amplifications through an Fc-dependent monocyte/macrophage-mediated antitumor mechanism, with trogocytosis contributing to tumor cell receptor degradation.^{33,34}

Amivantamab monotherapy has shown antitumor activity in patients with diverse *EGFR* mutation disease, including *EGFR* exon 19 deletions; L858R, T790M, and C797S mutations; exon 20 insertions; and *MET* amplification.^{35,36} A phase I study reported that 30% of patients (32/108) with *EGFR*-mutant NSCLC had a best response of partial response across diverse *EGFR* mutations, including exon 20 insertions, T790M, C797S, and *cMET* amplification.³⁵ The ongoing phase I/II CHRYSALIS study is evaluating amivantamab treatment in patients with metastatic/unresectable NSCLC with exon 20 insertion mutations whose disease has progressed on platinum-based chemotherapy (Figure 1).³⁷ In the dose-escalation portion of the study, the intravenous monotherapy recommended phase II doses (RP2D) of 1,050 mg in patients <80 kg and 1,400 mg in patients ≥80 kg were established. The safety and efficacy of the RP2D doses are currently being established in the dose expansion phase. The primary efficacy endpoint is the ORR per RECIST 1.1.

The efficacy population for the CHRYSALIS study comprises 81 patients with a median time from initial diagnosis to study entry of 17 months who were previously treated with platinum-based doublet chemotherapy, and 25% of whom had received *EGFR* TKI therapy.³⁷ Among this cohort, the median age is 62 years, 59% are female, and the patients are predominantly Asian (49%) or White (37%). Initial results from this study have indicated the efficacy of amivantamab in this population. The ORR determined by blinded independent review was 40% (95% CI, 29–51), and the median duration of response was 11.1 months (95% CI, 6.9–not reached). The clinical benefit rate, defined as complete response, partial response, or stable disease for at least 2 disease assessments, was 74% (95% CI, 63–83).

Amivantamab has shown activity for all of the 25 distinct exon 20 insertion variants identified by next-generation sequencing from 63 evaluable patient samples (Figure 2).³⁷ At the time of data cutoff, 15 of 32 patients remained on amivantamab treatment and 20 of 32 had responses lasting ≥6 months. The median PFS was 8.3 months (95% CI, 6.5–10.9), and the median OS was 22.8 months (95% CI, 14.6–not reached). The safety profile of amivantamab was consistent with the inhibition of the *EGFR* and *MET* pathways. Treatment-related adverse reactions related to *EGFR* inhibition included rash (86%), paronychia (42%), stomatitis (18%), pruritus (17%), and diarrhea (10%). Rash caused 2% of patients to discontinue treatment. Grade ≥3 adverse reactions were reported in 39% of patients, with the most common being diarrhea (3.5%), rash (3%), and infusion-related reactions (2%). Infusion-related reactions that were considered treatment-related occurred in 65% of patients; 94% of these reactions occurred with the first infusion and rarely impacted the ability of patients to continue treatment.

Mobocertinib

Mobocertinib (TAK-788) is an oral, selective *EGFR*/*HER2* TKI with selective preclinical activity against activating *EGFR* and *HER2* mutations, including exon 20 insertions, without inhibiting wild-type *EGFR*.^{38–40} A phase I/II study reported a confirmed ORR of 43% in 28 evaluable patients with advanced NSCLC refractory to standard therapy and ECOG performance status 0–1 who were treated with mobocertinib at 160 mg/d during dose escalation.^{38,39} The median (range) best percentage change in target lesion measurements was –32.6% (–100% to 26.3%), and the median PFS was 7.3 months (95% CI, 4.4–15.6).⁴⁰

The design and patient cohorts for the ongoing 3-part open-label, multicenter study of mobocertinib (phase I, dose escalation; phase II, dose expansion; EXCLAIM extension cohort) are shown in Figure 3.⁴¹ Approximately two-thirds of patients were of Asian descent and female, and the median number of prior

Figure 1. CHRYSALIS study design: post-platinum exon 20 insertion patient population.³⁷

Abbreviations: C1, cycle 1; C2+, cycle 2 and beyond; Exon20ins, exon 20 insertions; NSCLC, non-small cell lung cancer; RP2D, recommended phase II dose.

Figure 2. Best ORR by insertion region of exon 20 (detected by ctDNA).³⁷

Abbreviations: CBR, clinical benefit rate; ctDNA, circulating tumor cell DNA; ORR, objective response rate; SoD, sum of diameters.

^aOne patient in the efficacy population discontinued before any disease assessment and is not included in the plot.

systemic anticancer regimens was 2 for the platinum pre-treated patient (PPP) cohort and 1 for the EXCLAIM cohort. The confirmed ORR per an independent review committee for mobocertinib was 26% (95% CI, 19–35) in the PPP cohort and 23% (95% CI, 15–33) in the EXCLAIM cohort. The median duration of response to mobocertinib treatment per an independent review committee was 17.5 months (95% CI, 8.3–not estimable) in the PPP and not estimable in the EXCLAIM cohorts. More than 50% of responses were ongoing in both cohorts at the time of data cutoff. Median PFS per an independent review committee was 7.3 (95% CI, 5.5–10.2) in both patient cohorts. Other results showing meaningful clinical benefit from mobocertinib treatment are shown in Table 2.⁴¹ A similar proportion of patients in each cohort had a reduction

from baseline in the sum of the target lesion diameter: 82% (94/114) and 80% (77/96) in the PPP and EXCLAIM cohorts, respectively. Treatment-related adverse events occurring in $\geq 30\%$ of patients were diarrhea (90% of patients; grade ≥ 3 in 21% of PPP and 16% of EXCLAIM cohort patients), rash (45%), paronychia (35%), decreased appetite ($\sim 30\%$), nausea ($\sim 30\%$), and dry skin (30%).

Poziotinib

Poziotinib, a novel EGFR TKI inhibitor, is smaller and more flexible than first- and second-generation TKIs, which allows it to bind to the sterically hindered drug-binding pocket of exon 20 insertion mutants.^{11,42} In

Figure 3. Design and patient cohorts in the phase I/II and EXCLAIM extension study of mobocertinib in patients with NSCLC previously treated with platinum.⁴¹

Locations: United States only for phases I and II; United States, European Union, and Asia for phase II extension cohort.

Abbreviations: CNS, central nervous system; NSCLC, non-small cell lung cancer; ORR, overall response rate; PK, pharmacokinetics; PS, performance status; TKI, tyrosine kinase inhibitor.

^aActive or measurable (but not both) CNS metastases permitted. Active CNS metastases: untreated or treated and progressing; measurable CNS metastases: ≥ 10 mm in longest diameter by contrast-enhanced MRI.

Table 2. Meaningful Clinical Benefit of Mobocertinib in PPP and EXCLAIM Extension Cohorts⁴¹

Parameter	PPP Cohort	EXCLAIM Cohort
Total, n	114	96
Median time on treatment (range), mo	7.0 (0–31)	6.5 (0–14)
% confirmed ORR per IRC [95% CI] (n)	26 [19–35] (30)	23 [15–33] (22)
% confirmed ORR per INV [95% CI] (n)	35 [26–45] (40)	32 [23–43] (31)
Median DoR per IRC [95% CI], ^a mo	17.5 [8.3–NE]	NE [8.3–NE]
Median DoR per INV [95% CI], ^a mo	13.9 [5.6–NE]	NE [5.5–NE]
% DCR per IRC [95% CI] ^b (n)	78 [69–85] (89)	76 [66–84] (73)
% DCR per INV [95% CI] ^b (n)	78 [69–85] (89)	75 [65–83] (72)
Median PFS per IRC [95% CI], mo	7.3 [5.5–10.2]	7.3 [5.5–10.2]
Median PFS per INV [95% CI], mo	7.3 [5.5–8.1]	7.1 [5.6–7.8]

^aDoR per Kaplan-Meier estimates.

^bDCR defined as confirmed complete response or partial response, or best response of stable disease for at least 6 weeks after initiation of study drug. Abbreviations: DCR, disease control rate; DoR, duration of response; INV, investigator; IRC, independent review committee; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PPP, platinum pretreated patients.

genetically engineered mouse models of NSCLC driven by exon 20 insertion, poziotinib-treated mice had an 80% reduction in tumor volume, whereas afatinib treatment resulted in a 35% increase in tumor volume. In a phase II study with 44 evaluable patients who had *EGFR* exon 20–NSCLC, poziotinib showed efficacy with an ORR (best response) rate of 55% and an ORR (confirmed) of 43%.⁴³

A phase II study evaluated the safety and efficacy of oral poziotinib at 16 mg/d in 115 previously treated patients with NSCLC and *EGFR* exon 20 insertion mutations (ZENITH20).⁴⁴ The median age of patients was 61 years, and the median number of lines of prior therapy was 2. Results for the total population and the evaluable patients are shown in Table 3. In the evaluable patients, the ORR was 19.3% (95% CI, 11.7–29.1), the median duration of response was 7.4 months (95% CI, 3.7–9.7), and the median PFS was 4.1 months (95% CI, 3.7–5.5). The most common treatment-related grade ≥ 3 adverse events were rash (28%), diarrhea (26%), stomatitis (9%), and paronychia (6%).

Management of Adverse Events

In addition to indicating efficacy in the treatment of patients with NSCLC harboring uncommon *EGFR* mutations, newer targeted therapies have shown a manageable toxicity profile.^{37,41,44,45} The most frequent treatment-related adverse events of grade ≥ 3 severity associated with these agents are diarrhea and rash. In clinical trials of these novel targeted therapies, <20% of patients discontinued treatment because of an adverse event, and many adverse events were managed by a reduction in the drug dose.

Management of the rash associated with *EGFR* TKI targeted therapies (mobocertinib, poziotinib, afatinib, osimertinib) includes topical emollients, topical steroids, and early referral to dermatology. Early and aggressive use of antidiarrheal agents (eg, loperamide, diphenoxylate hydrochloride-atropine sulfate) and hydration are useful to manage diarrhea. In addition, monitoring of serum electrolytes (potassium, sodium), renal function (serum creatinine), and liver function tests are recommended. Dose reductions decrease the risk of treatment-related adverse events, particularly with afatinib.⁴⁶

Table 3. Clinical Activity of Poziotinib in Patients With NSCLC Harboring *EGFR* Exon 20 Insertions: ZENITH20 Study⁴⁴

Parameter	Total Patients	Evaluable Patients
Total, n	114	96
% ORR [95% CI] (n)	14.6 [8.9–22.6] (17)	19.3 [11.7–29.1] (17)
% Unconfirmed ORR [95% CI] (n)	19.1 [12.4–27.5] (22)	25.0 [16.4–35.4] (22)
% DCR [95% CI] (n)	68.7 [59.4–77.0] (79)	80.7 [70.0–88.3] (71)
Median DoR [95% CI], mo	7.4 [3.7–9.7]	7.4 [3.7–9.7]
Median PFS [95% CI], mo	4.2 [3.7–6.6]	4.1 [3.7–5.5]

Abbreviations: DCR, disease control rate; DoR, duration of response; NSCLC, non–small cell lung cancer; ORR, objective response rate; PFS, progression-free survival.

The most common adverse event with the EGFR antibody amivantamab is an infusion-related reaction, which is characterized by dyspnea, flushing, chills, and nausea.³⁷ It occurs in 65% of patients, but grade 3 reactions occur in <2% of patients. The vast majority (94%) of infusion-related reactions occur on cycle 1, day 1 of therapy, have a median time to onset of 44 minutes, and occur after cycle 2, day 1 of therapy in <1% of patients. Infusion-related reactions may be mitigated by holding the drug infusion and reinitiating it at a reduced rate.⁴⁷ Administration of steroids, analgesics, and/or antihistamines can lessen the risk and severity of an infusion-related reaction.

Future Directions in EGFR-Targeted Therapy

Although exon 20 insertions and point mutations in exons 18 to 21 are the best studied of the uncommon *EGFR* mutations, several other *EGFR* and *EGFR/ERBB* family mutations occur less frequently, and effective targeted therapies are needed for these. Currently, ongoing studies are evaluating therapies for both exon 18 mutations and *HER2* mutations and amplifications in patients with NSCLC. Of the major uncommon *EGFR* mutations in NSCLC, exon 18 mutations account for up to 5% of the variants. Limited clinical evidence suggests that the EGFR TKIs afatinib and osimertinib have modest activity against exon 18 mutations.⁴⁸ Mutations of the *ERBB2/HER2* gene, another member of the *ERBB/EGFR* family, occur most frequently in the kinase domain exons 18 to 21.⁴² Response to HER2-targeted TKIs and HER2 monoclonal antibodies are variable by both cancer type and mutation. In nonsquamous NSCLC, *HER2* mutations occur in approximately 2.3% of patients, and an additional 1.4% of patients carry *HER2* amplifications.²

Exon 18 Mutations

In an in vitro study, NSCLC *EGFR* exon 18 mutations were highly sensitive to neratinib, an irreversible pan-HER TKI, in contrast to first-generation TKIs.⁴⁹ The phase II SUMMIT basket trial is evaluating neratinib monotherapy in these patients. Patients in this study are receiving oral neratinib at 240 mg/d in addition to mandatory loperamide prophylaxis for the first 8 weeks.⁵⁰ Of the initial 11 evaluable patients, the median age is 67 years, 55% are male, 91% are White, and 55% have an ECOG performance status of 1. Patients had received a median of 2 prior lines of therapy, and most had complex G719X mutations. The first best response was partial response in 6 patients, stable disease in 4, and progressive disease in 1. Responses were noted regardless of single or complex G719X mutations. The confirmed ORR was 40%, the duration of response was 7.5 months, and the median PFS was 9.1 months. No grade 3 diarrhea was reported.

The neratinib SUMMIT trial is continuing to enroll patients with *EGFR* exon 18-mutant NSCLC.

HER2 Mutations

Although *HER2* mutations and amplifications are common in breast and gastric cancers, they are relatively uncommon in NSCLC.⁵¹ And while numerous *HER2*-targeted therapies have been approved in other cancer types, none have yet been approved in NSCLC, although several studies are ongoing evaluating these agents.

Ado-trastuzumab emtansine is an HER2-targeted antibody-drug conjugate that was initially studied for the treatment of *HER2* metastatic breast cancers.⁵¹ A phase II trial evaluated ado-trastuzumab emtansine (3.6 mg/kg intravenously every 21 days) in a cohort of 18 patients (median age, 64 years) with *HER2*-mutant lung cancer who were followed for a median of 10 months. The median number of prior systemic therapies was 2, and 50% of patients had received prior HER2-targeted therapy. The ORR was 44%, and the median PFS was 5 months.⁵¹ The longest PFS was >11 months in a patient with stable disease as the best response with ~27% tumor shrinkage. Adverse events, including infusion reactions, thrombocytopenia, elevated liver enzymes, fatigue, and nausea, were grade 1 or 2. The results of this study were positive.

In a phase I trial, 11 patients with *HER2*-mutated NSCLC who received trastuzumab deruxtecan, an antibody-drug conjugate, had a confirmed ORR of 72.7%.⁵² An ongoing phase II trial, DESTINY-Lung01, is evaluating trastuzumab deruxtecan (6.4 mg/kg intravenously every 3 weeks) in patients with nonsquamous NSCLC overexpressing HER2 or containing a HER2-activating mechanism.⁵³ Early results from 42 patients (median age, 63 years; median number of prior therapies, 2) with *HER2* mutations primarily in the kinase domain (90.5%) showed a confirmed ORR of 61.9% and a disease control rate of 90.5% with trastuzumab deruxtecan treatment. The estimated median PFS was 14 months; median OS had not been reached. All patients had treatment-emergent adverse events (64.3% were grade ≥3), which led to dose interruption in 59.5% of patients, dose reduction in 38.1%, and discontinuation of therapy in 23.8%. Trastuzumab deruxtecan showed promising clinical activity.

In addition to *HER2*-directed therapies, trials are ongoing evaluating other EGFR-targeted TKIs in patients with *HER2* mutations. Poziotinib at 16 mg/d orally showed activity in *HER2* exon 20 insertion NSCLC in a phase II clinical trial.^{11,42} The confirmed ORR in the first 12 evaluable patients was 42%, and the median PFS was 5.6 months. The multinational, phase II ZENITH20 study included a patient cohort with *HER2* exon 20 insertion mutations (ZENITH20-2, n=90) who were treated with poziotinib at 16 mg/d orally.⁵⁴ The cohort had a median

age of 60 years, 64% were female, and 66% were non-smokers, and patients had received a median of 2 prior therapies. In the 74 evaluable patients, the confirmed ORR was 35.1% (27.8% in all 90 patients) and median PFS was 5.5 months. Tumor reduction was noted in 74% (67/90) of patients, and the median tumor reduction was 22%. Pozitotinib met efficacy expectations in this cohort, and further study of the drug is ongoing.

Summary

Mutations in the *EGFR* signaling pathway are common in NSCLC, the most common lung cancer. *EGFR* mutations are primarily located in the tyrosine kinase domain at exons 18 to 21. Some of the mutations, particularly exon 20 insertion mutations, do not respond well to TKIs and are therefore difficult to treat. The advent of genomic profiling has identified many of the mitogenic driver mutations in NSCLC and improved the selection of

targeted therapy. Biomarker testing using either tissue or blood is recommended as standard practice to guide the selection of therapy to target the specific mutation. The TKIs afatinib and osimertinib have shown activity in the treatment of 3 atypical *EGFR* point mutations (G719X, S768I, and L861Q), and several novel therapies, including the IgG1 antibody amivantamab and the *EGFR* TKIs mobocertinib and pozitotinib, are being studied for the treatment of exon 20 insertion mutations. Other uncommon *EGFR* mutations for which targeted therapies are being investigated include exon 18 mutations (neratinib) and *HER2* mutations (ado-trastuzumab emtansine and trastuzumab deruxtecan). As the understanding of the biology of genetic mutations in NSCLC and molecular testing for mutations evolve, options for targeted therapy to individualize NSCLC treatment will be better defined and lead to improved outcomes.

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Posttest Questions

- Which of the following statements regarding uncommon *EGFR* mutations is most accurate?
 - G719X mutations are resistant to erlotinib
 - G719X mutations are sensitive to immunotherapy
 - Exon 20 insertions are resistant to erlotinib
 - Exon 20 insertions are sensitive to immunotherapy
- Your patient is a 47-year-old woman of Asian descent with stage IV adenocarcinoma and no history of smoking. Which of the following steps would you take next?
 - Initiate *EGFR* therapy
 - Perform IHC for *EGFR*
 - Test for *EGFR* via FISH
 - Order a multiplex genetic sequencing panel
- Your patient is a 59-year-old man with newly diagnosed stage IV lung adenocarcinoma with brain metastases. He is a smoker of 20 pack-years and quit smoking 9 months prior to diagnosis. Genetic testing reveals a G719S mutation in exon 18.

Which of the following treatment options would you consider for this patient?

 - Erlotinib
 - Afatinib
 - Osimertinib
 - Mobocertinib
- Which of the following results was seen with amivantamab in the phase I CHRYSLIS study?
 - The overall response rate was 40%
 - Best responses were seen in Asian patients
 - The median overall survival was 15.8 months
 - The most common cause of treatment discontinuation was infusion reactions
- Which of the following patient populations would be most appropriate for treatment with the *EGFR* TKI mobocertinib?
 - Patients with T790M mutations
 - Patients with *EGFR* exon 18 insertions
 - Patients with *EGFR* exon 20 insertions
 - Patients with HER2 amplification