

# OPTIMIZING THE USE OF MOLECULAR TESTING IN LUNG CANCER

AN AJMC<sup>®</sup> STAKEHOLDER INTERCHANGE REPORT

With the advent of next-generation sequencing (NGS), molecular testing has substantially advanced the treatment paradigm and improved overall outcomes for oncogene-driven non-small cell lung cancer (NSCLC). However, universal molecular testing of the population of patients who may benefit has been limited by issues related to insurance coverage, long turnaround times with commercial platforms, and lack of adequate tissue for analysis. A recent stakeholder interchange from *The American Journal of Managed Care*<sup>®</sup> included practitioners from the academic and community oncology settings to discuss the role of molecular testing for treatment of NSCLC, evidence to support molecular testing for oncogenic drivers, practice-level challenges related to molecular testing, and opportunities to improve the utility of molecular testing. Joshua Bauml, MD of the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, Pennsylvania, led this discussion.

## ROLE OF MOLECULAR TESTING

### Types of Biomarkers

Biomarkers for lung and other types of cancer are generally classified as predictive, prognostic, or diagnostic. Predictive biomarkers predict the response to a therapeutic intervention (eg, *KRAS*-activating mutations predict resistance to *EGFR*-targeted therapy in colorectal cancer). Prognostic biomarkers provide information on the risk for a clinical outcome, including disease recurrence or progression; one example is the 21-gene recurrence score in breast cancer. Diagnostic biomarkers determine whether a patient has a specific condition (eg, measurement of stool DNA for surveillance of colorectal cancer).<sup>1</sup> Most molecular testing for lung cancer currently focuses on biomarkers that predict response to targeted therapy with small molecule tyrosine kinase inhibitors (TKIs) or immunotherapy with PD-L1 checkpoint inhibitors. However, molecular testing continues to evolve to include other potentially targetable gene aberrations and to increase sensitivity to identify additional patients who may benefit from these therapies.<sup>2</sup>

### Testing Modalities for Molecular Testing

The complexity of testing modalities for molecular profiling of tumors varies widely, from the detection of a single type of mutation in 1 gene to the detection of mutations across the entire genome. The most

complex molecular profiling tests identify all major types of gene alterations simultaneously, including substitutions, duplications, insertions, deletions, indels, gene variations, and structural variants such as inversions and translocations.<sup>3</sup>

Testing for most genetic variants can be performed in a molecular genetics or molecular pathology laboratory certified by the Clinical Laboratory Improvement Amendments (CLIA) using technologies such as allele-specific polymerase chain reaction (PCR), Sanger dideoxy sequencing, pyrosequencing, multiplex ligation-dependent probe amplification, or mass spectrometry. Testing for gene copy number and structural variants generally involves fluorescence in situ hybridization and is performed in a separate CLIA-certified cytogenetics laboratory. Key advantages of these technologies include rapid turnaround time (usually a few days, or in some cases, a few weeks, depending on complexity of the assay) and the ability to identify predefined gene aberrations of interest. However, the range of mutations detected is relatively limited, and some tests, such as pyrosequencing and mass spectroscopy, require additional specific instrumentation.<sup>3</sup>

NGS technologies have vastly improved the efficiency and breadth of tumor molecular profiling and are increasingly used in the clinical setting. NGS technologies involve whole-genome sequencing (WGS), which analyzes protein-coding and noncoding regions, and whole-exome sequencing (WES), which analyzes all protein-coding regions in the human genome. While these can simultaneously identify alterations across the entire genome or exome, these types of NGS technologies are generally impractical for clinical use. Most genomic alterations found on WGS and WES are of unknown clinical significance and the depth of coverage is relatively low, which reduces the detection sensitivity for low-abundance mutations. WGS and WES may also detect non-tumor-specific germline variants associated with disease, and the clinical implications of many genomic alteration findings from WES are unclear.<sup>3</sup>

By contrast, NGS technologies that use custom panels are more practical for detecting gene alterations of interest in a clinical scenario because they amplify specific regions of interest prior to NGS. In the amplicon method, regions of interest are amplified by multiplexed PCR amplification, and these tests are custom-designed to identify mutations in specific genes (typically 1-100). Tests using the hybridization capture method are designed to identify a larger number of mutations than the amplicon method (from 50 up to several thousand) and

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IN METASTATIC EGFR<sup>m</sup> NSCLC

# CHECK OUT THESE FIRST-LINE TAGRISSO DELIVERS

## MEDIAN PROGRESSION-FREE SURVIVAL NEARLY DOUBLED

Median PFS

**18.9 vs 10.2**

months for TAGRISSO vs erlotinib/gefitinib<sup>1</sup>

HR=0.46 (95% CI: 0.37, 0.57); P<0.0001

## MEDIAN OVERALL SURVIVAL BEYOND 3 YEARS

Median OS

**38.6 vs 31.8**

months for TAGRISSO vs erlotinib/gefitinib<sup>2</sup>

HR=0.799 (95.05% CI: 0.641, 0.997); P=0.0462

## INDICATION

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

## SELECT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc >500 msec, and 3.6% of patients had an increase from baseline QTc >60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF)  $\geq 10\%$  from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of



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# RESULTS: UNPRECEDENTED EFFICACY<sup>1,2</sup>

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Or scan code with your phone.

**FLAURA study design:** Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR-TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg orally, once daily). All US patients in the comparator arm received erlotinib. Crossover was allowed for patients in the EGFR-TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v1.1). Secondary endpoints included: OS, ORR, CNS PFS, and DoR.<sup>1,3-5</sup>

## SELECT SAFETY INFORMATION (cont'd)

- keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose

- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

**References:** **1.** TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. **2.** Ramalingam SS, Gray JE, Ohe Y, et al. Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): final overall survival analysis [oral presentation]. Presented at: European Society for Medical Oncology; September 27-October 1, 2019; Barcelona, Spain. Abstract LBA5. **3.** Soria JC, Ohe Y, Vansteenkiste J, et al; FLAURA Investigators. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-125 [protocol]. **4.** Soria JC, Ohe Y, Vansteenkiste J, et al; FLAURA Investigators. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-125. **5.** Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol.* 2018. doi:10.1200/JCO.2018.78.3118. [Epub ahead of print.]

Please see Brief Summary of Prescribing Information including Patient Information on adjacent pages.

 **TAGRISSO**<sup>®</sup>  
osimertinib

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involves hybridization of genomic DNA fragments to sequence-specific capture probes that correspond to target regions of the genome.<sup>3</sup>

NGS that uses customized panels can be designed to have a high depth of coverage, which enables detection of low-abundance mutations. However, an extremely high level of sensitivity may detect low-level mutations that are clinically insignificant or unknown, and some NGS platforms have platform-specific articles such as false-positive insertions, deletions, and indel calls. Therefore, optimizing the bioinformatics analysis is essential to ensure identification of clinically relevant variants. Furthermore, turnaround time for tests can range from several days to weeks depending on the complexity of the assay, although a stakeholder noted that the turnaround times offered by many commercial platforms have decreased as the competition in the NGS space has increased.<sup>3</sup>

Digital droplet PCR (ddPCR) and BEAMing (beads, emulsification, amplification, and magnetics) are used to detect known mutations in circulating tumor DNA (ctDNA). The ddPCR method involves isolation of cell-free DNA (cfDNA) from the blood plasma, followed by mixing extracted DNA with PCR reaction mechanisms, primers for genes of interest, and fluorescent hydrolysis probes that target mutation (or wild-type) sequences. The mixture is emulsified into droplets, with each droplet containing the PCR reagents, probes, and 1 copy of template DNA. Emulsion PCR is performed, during which hydrolysis of the probes releases the fluorophores. The post-PCR sample is reinjected, followed by measurement of the fluorescence of individual droplets.<sup>4</sup> Multiplex readouts that use fluorescence color and intensity have also been developed to simultaneously detect multiple targets of a single base extension assay.<sup>3</sup>

BEAMing involves extraction of cfDNA from blood plasma and use of PCR to pre-amplify the gene of interest using specific primers attached to tag sequences. Beads coated with primers that target the tag sequences are mixed with the amplified DNA, and emulsion PCR is performed, resulting in each emulsion droplet containing a bead coated with thousands of copies of the original DNA molecule. Fluorescent probes for mutations of interest are hybridized to the amplified DNA, and detection is performed using magnetic flow recovery methods. Although both ctDNA-based tests have a short turnaround time and high sensitivity and specificity, ddPCR and BEAMing are limited in that they can

detect only a limited number of mutations per assay and cannot detect all types of gene aberrations.<sup>3</sup>

### RNA-based NGS Techniques: Improving Identification of Targetable Kinase Fusions in Lung Cancer

Despite the significant progress made in molecular testing with NGS technologies, DNA-based NGS assays have limited capabilities for identifying targetable kinase fusions. Large-panel, hybrid capture-based NGS assays are able to detect only gene fusions that occur in short introns, because coverage of long introns compromises coverage of the remaining genes on the panel. Additionally, introns may have repetitive sequence elements that are also present in other parts of the genome, and short-read NGS is unable to uniquely map these reads. This leads to gaps in coverage of some introns and blind spots in identification of rearrangement breakpoints. Furthermore, a rearrangement detected in DNA sequencing assays may not necessarily lead to a fusion at the RNA level.<sup>5</sup>

RNA-based NGS panels have been investigated as an additional tool to overcome some of the limitations of DNA-based testing. A retrospective sequencing analysis evaluated a customized RNA-based sequencing panel, which targeted exons in 62 genes that are known to be involved in chromosomal rearrangements, to determine if RNA-based sequencing could identify additional targetable kinase fusions in tumor samples from patients with lung adenocarcinoma previously profiled by DNA sequencing.<sup>5</sup> Of the 232 successfully sequenced samples, 196 samples remained driver negative by both DNA and RNA sequencing; 36 tested positive for a mitogenic driver alteration. Of these 36 samples, 33 had actionable in-frame fusions, and the gene fusion recognized a diverse collection of fusion partners, some previously undetected in lung adenocarcinoma, highlighting the possibility of RNA-based NGS to detect a larger variety of potentially targetable gene fusions and rearrangements.<sup>5</sup> One stakeholder stated that all patients with metastatic, nonsquamous NSCLC at his academic institution receive a DNA-based NGS profile and an RNA-based fusion panel, and that the RNA-based panel has caught a couple of cases of *ALK*-rearranged NSCLC that were not detected on DNA-based NGS. However, other stakeholders noted that RNA-based panels are not available from all companies, and the selection of the NGS testing is often dictated by which test is covered by the patient's insurance, particularly in community-based practices.

### Recommendations for Molecular Testing in NSCLC

The most recently updated National Comprehensive Cancer Network (NCCN) guidelines for NSCLC recommend broad molecular testing for gene alterations known to affect therapeutic selection.<sup>2</sup> The minimum testing recommended includes testing for *EGFR* mutations, *ALK* rearrangements, *ROS1* rearrangements, *BRAF* point mutations, *KRAS* point mutations, *NTRK* gene fusions, and PD-L1 status.<sup>2</sup> The guidelines also advise testing for other emerging biomarkers for which targeted therapy could be effective for metastatic disease, including high-level *MET* amplification or *MET* exon 14 skipping mutation, *RET* rearrangements, *ERBB2* (ie, *HER2*) mutations, and tumor mutational burden.<sup>2</sup> The guidelines also recommend that when possible, molecular testing should be performed in a broad, panel-based approach, typically by NGS, and that RNA-based NGS should be considered to maximize detection of fusion events for patients (particularly never smokers) who do not have identifiable driver oncogenes on DNA-based NGS.<sup>2</sup>

The NCCN guidelines recommend molecular testing only for patients with advanced or metastatic NSCLC, and the stakeholders agreed that the testing is most useful for stage IV disease and possibly for stage III disease that is too extensive for chemoradiation therapy alone.<sup>2</sup> However, they also discussed the potential value of upfront testing for patients with stage II and less-extensive stage III disease to identify potential treatment targets ahead of time, in case the patient develops stage IV disease.

## VALUE OF TESTING: ONCOGENIC DRIVERS AND TARGETED THERAPIES

Molecular testing has been instrumental in the identification of oncogenic drivers of NSCLC and the development of targeted therapies for these drivers, providing additional therapeutic options beyond chemotherapy or radiation therapy for patients with advanced or metastatic NSCLC that harbors a targetable mutation. The most common oncogenic drivers for which targeted therapies are available include *EGFR*-activating mutations, *ALK* rearrangements, *ROS1* rearrangements, *BRAF* point mutations, and *NTRK* gene fusions.<sup>2</sup> (No targeted therapies have been shown to be effective against *KRAS* point mutations, the most common oncogenic driver mutation in NSCLC, although some data indicate that *KRAS*-mutated disease is associated with poorer response rate to chemotherapy and shorter progression-free survival [PFS] and overall survival [OS] in NSCLC compared with *KRAS* wild-type disease).<sup>6</sup>

### EGFR

Results from the IPASS trial published in 2009 showed that, compared with chemotherapy, the *EGFR* TKI gefitinib was associated with a significantly longer PFS in the subgroup of patients with *EGFR* mutation-positive disease and significantly shorter PFS in the subgroup with *EGFR* mutation-negative disease.<sup>7</sup> These findings introduced the concept of using molecular testing to identify mutational status. Subsequent trials showed improvements in PFS over chemotherapy

with the first-generation *EGFR* TKIs gefitinib<sup>8-10</sup> and erlotinib<sup>11-13</sup> and the second-generation *EGFR* TKI afatinib.<sup>14,15</sup>

The third-generation *EGFR* TKI osimertinib was shown to significantly improve PFS over platinum/pemetrexed in patients with T790M-positive advanced NSCLC after progression on first-line *EGFR* TKI therapy.<sup>16</sup> Additionally, results from the FLAURA trial showed that frontline osimertinib was associated with a significant improvements in duration of response<sup>17</sup> and OS<sup>18</sup> compared with first-generation *EGFR* TKI therapy (gefitinib or erlotinib) in patients with untreated, advanced, *EGFR* mutation-positive NSCLC. Osimertinib has also demonstrated stronger central nervous system (CNS) activity than its first-generation counterparts, further strengthening its role in the frontline setting. A primary analysis of the FLAURA trial showed a significantly higher objective response rate with osimertinib than with a first-generation *EGFR* TKI in the full-analysis set (66% vs 43%;  $P = .011$ ).<sup>19</sup> Additionally, 23% of the patients who received osimertinib had a complete CNS response, versus 0% of the patients who received a comparator TKI.<sup>19</sup>

The high CNS activity of osimertinib (and other newer-generation TKIs for other targets) may have particular clinical relevance for patients with oligometastasis in the brain.

The stakeholders noted that the high CNS activity of osimertinib (and other newer-generation TKIs for other targets) may have particular clinical relevance for patients with oligometastasis in the brain. One stakeholder referred to a couple of specific cases in his practice in which patients with oligometastatic *EGFR*-mutated NSCLC that had spread to the CNS were able to avoid radiation therapy or surgical resection with upfront osimertinib. He also noted that progression in the CNS generally did not occur even though disease progression eventually did occur with osimertinib as the tumor developed resistance.

### ALK

Over the past decade, molecularly targeted therapy has also substantially improved outcomes for patients with advanced or metastatic NSCLC with an *ALK* rearrangement. Crizotinib was approved based on results from an open-label phase 3 trial showing a significantly improved objective response rate and median duration of response with first-line crizotinib compared with chemotherapy in patients with *ALK*-positive, advanced nonsquamous NSCLC.<sup>20</sup> However, subsequent studies showed significant improvements in PFS and CNS response rate with alectinib<sup>21</sup> and brigatinib<sup>22</sup> compared with crizotinib in the frontline setting.

Lorlatinib is a third-generation TKI targeting ALK and ROS1 that was structurally designed to penetrate the blood–brain barrier, to target ALK resistance mutations that may develop after treatment with first- and second-generation ALK TKIs. However, lorlatinib also demonstrated activity in the frontline setting in a subgroup analysis of a phase 2 trial, with an objective response observed in 27 of 30 patients (90%) with treatment-naïve, ALK-rearranged NSCLC.<sup>23</sup> Among patients who had previously received 1 or more ALK TKIs with or without chemotherapy, the objective response rate was 47%, and the intracranial objective response rate was 63% of those patients with CNS metastases at baseline.<sup>23</sup> A phase 3 trial (NCT03052608) comparing lorlatinib and crizotinib in the frontline setting is currently ongoing and may further support a role for lorlatinib as first-line therapy for ALK-rearranged NSCLC.<sup>23</sup>

### ROS1

Crizotinib also targets ROS1 and has shown efficacy in ROS1-rearranged disease. A phase 1 study showed that crizotinib led to an overall response rate of 72% and a median duration of response of 17.6 months in patients with advanced ROS1-rearranged NSCLC.<sup>24</sup> These findings prompted the FDA approval of crizotinib in 2016 for ROS1-rearranged advanced NSCLC.<sup>25</sup>

However, the stakeholders suggested that entrectinib, an inhibitor of ROS1, TRKA/B/C, and ALK, may be a better option than crizotinib because of its strong CNS activity.<sup>26,27</sup> A combined analysis of the phase 1 ALKA-372-001 and STARTRK-1 trials assessed responses to entrectinib in a “phase 2-eligible population,” which included 25 patients with an advanced solid tumor harboring a gene fusion in *NTRK1/2/3*, *ROS1*, or *ALK*. An overall response rate of 86% was observed in the group of patients with ROS1-rearranged tumors (n = 14; 13 patients with NSCLC and 1 patient with melanoma).<sup>27</sup> Of the 8 patients with primary or metastatic disease that involved the brain prior to entrectinib treatment, 5 patients (including 2 patients with ROS1-rearranged NSCLC) had a CNS response.<sup>27</sup>

Responses were also durable, with a median duration of response of 17.4 months for ROS1- and ALK-rearranged tumors.<sup>27</sup> An updated analysis of this study population, presented at the International Association for the Study of Lung Cancer’s 18th World Conference on Lung Cancer, showed that 24 of 32 patients (75%) with treatment-naïve ROS1-rearranged NSCLC had an objective response to entrectinib, and 5 of 7 patients (71%) with evaluable CNS lesions had RECIST intracranial responses as evaluated by blinded independent central review.<sup>28</sup> Based on these data, the FDA approved entrectinib for treatment of adult patients with metastatic ROS1-rearranged metastatic NSCLC.<sup>29</sup>

In addition to its efficacy in ALK-rearranged NSCLC, lorlatinib has also demonstrated promising outcomes in TKI-naïve and -exposed patients with ROS1-rearranged disease as well as in patients with CNS metastases. An open-label, phase 1/2 trial of lorlatinib in patients with advanced, ROS1-rearranged NSCLC demonstrated an objective response in 13 of 21 (62%) and 14 of 40 (35%) patients with TKI-naïve and crizotinib-treated disease, respectively.<sup>26</sup> Intracranial responses to lorlatinib were observed in 7 of 11 (64%) of TKI-naïve patients and 12 of 24 (50%) patients with prior exposure to crizotinib.<sup>26</sup>

However, a stakeholder mentioned that repotrectinib (TPX-0005), a next-generation TKI with activity against ROS1, TRK1/2/3, and ALK, is the only TKI active against the most common mechanism of resistance in ROS1 translocation and could target resistance mutations to ROS1 TKIs, much like osimertinib targets the *EGFR* T790M resistance mutation. A preclinical study showed that repotrectinib had potent activity in Ba/F3 cells expressing fusion proteins with solvent-front substitution mutations in ROS1 that commonly occur after exposure to crizotinib (*ROS1* G2032R and *ROS* D2033N), and these cells demonstrated resistance to crizotinib, entrectinib, ceritinib, brigatinib, and ensartinib.<sup>30</sup> The study also showed that repotrectinib led to tumor regression in SCID/beige mice bearing Ba/F3 *CD74-ROS1* wild-type or *CD74-ROS1* G2032R xenograft tumors, and a female patient with *CD74-ROS1* G2032R NSCLC who had progressed on crizotinib had a confirmed partial response (duration of 7.4 months) and CNS response (duration of 9 months) with repotrectinib.<sup>30</sup> A first in-human dose-escalation phase 1/2 clinical trial (NCT03093116) is currently studying repotrectinib in patients with advanced solid tumors that harbor an *ALK*, *ROS1*, or *NTRK1/2/3* rearrangement.<sup>30,31</sup>

### BRAF

The BRAF V600E point mutation accounts for more than half of BRAF point mutations in NSCLC, and it has been shown to be independently associated with shorter median disease-free survival and OS in NSCLC (non-V600E mutations in BRAF were not shown to be associated with reduced survival).<sup>32</sup> Thus, finding effective therapies that target the BRAF V600E mutation has been of interest to improve outcomes in these patients. However, studies have shown modest outcomes with single-agent BRAF-targeted therapies, with confirmed response rates of 37% to 45% and median PFS of 5.2 to 6.5 months with vemurafenib<sup>33,34</sup> and an overall response rate and median PFS of 33% and 5.5 months, respectively, with dabrafenib.<sup>35</sup>

However, the stakeholders noted that the addition of trametinib, a MEK inhibitor, to dabrafenib likely results in numerically better response rates and longer median PFS. A phase 2 trial showed an overall response rate of 63.2% and median PFS of 9.7 months with dabrafenib plus trametinib in previously treated patients with BRAF V600E-mutated NSCLC,<sup>36</sup> and an overall response rate of 64% and median PFS of 10.9 months in the cohort of untreated patients with BRAF V600E-mutated NSCLC.<sup>37</sup>

### NTRK

The combined results from the ALKA-372-001 and STARTRK-1 trials showed that 3 patients (1 each diagnosed with NSCLC, mammary analogue secretory carcinoma, and colorectal cancer) with *NTRK1/2/3* gene fusions responded to entrectinib, and a patient with *SQSTM1-NTRK*-rearranged NSCLC and 15 to 20 brain metastases at baseline achieved a complete intracranial response that was ongoing 15 months later at the data cutoff date.<sup>27</sup> Additionally, combined data from the ALKA372001, STARTRK-1, and STARTRK-2 trials that focused on a cohort of 10 patients with NSCLC showed an overall response rate of 70% and an intracranial response in 4 of the 6 patients with CNS

metastases at baseline.<sup>38</sup> Larotrectinib, an inhibitor of *TRK1/2/3*, also led to reductions in tumor burden in all 8 patients with *NTRK* gene fusions (including 1 patient with NSCLC) in a study of patients with metastatic solid tumors refractory to standard therapies.<sup>39</sup> Based on these studies, larotrectinib and entrectinib have been approved by the FDA for adult and pediatric patients with any tumor harboring an *NTRK* gene fusion with no known resistance mutation, metastatic disease or disease in which surgical resection is predicted to cause severe morbidity, and progression following treatment or where no satisfactory standard therapy exists.<sup>29,40</sup>

## ctDNA AND LIQUID BIOPSY

While molecular testing of tumor tissue provides valuable information about potential therapies, the stakeholders noted that they are unable to obtain adequate tissue samples from “a significant proportion” of patients in their respective practices. Obtaining adequate DNA from tissue samples can be challenging, particularly from metastatic sites, and assessing the dynamic changes in molecular characteristics of tumors over time (eg, from the up-front to metastatic setting) in serial tissue biopsies is often impractical. Therefore, ctDNA in liquid biopsies may provide a more convenient, minimally invasive way to assess for clinically actionable mutations and tumor behavior in a serial fashion.

A prospective cohort study included patients with metastatic NSCLC who underwent plasma testing as part of their clinical management. Plasma NGS was accomplished using a 73-gene commercial platform, and 128 of 323 patients had adequate tissue DNA that was obtained within 24 weeks of the plasma sample. The concordance rate between tissue and plasma NGS was 81.3%. Therapeutically targetable mutations were identified in 113 patients (35.0%), and the mutation was detected in the plasma only for 66 (58.4%) of those patients (8 patients had negative concurrent tissue results). In addition, 31 of 94 (33.0%) of patients who had plasma NGS only (at the discretion of the treating physician or due to patient preference) had a therapeutically targetable mutation and were able to avoid an invasive biopsy.<sup>41</sup>

Furthermore, 67 patients were given targeted therapy based on results of plasma NGS alone or concurrent plasma and tissue NGS, and of the 42 patients evaluable by RECIST, 36 achieved complete response (n = 1), partial response (n = 19), or stable disease (n = 16).<sup>41</sup> The stakeholders concluded that these results indicate that plasma-based NGS could predict the efficacy of targeted therapy across multiple targetable mutations, including *EGFR*, *ALK*, and *BRAF*.

Another prospective study obtained pretreatment blood samples for comprehensive cfDNA analysis from 282 patients with newly diagnosed metastatic NSCLC who were undergoing physician-directed, standard-of-care tissue genotyping. The primary objective of the study was to demonstrate noninferiority of the cfDNA-based genotyping, compared with tissue-based methods, to identify guideline-recommended biomarkers in patients with untreated metastatic NSCLC. The results showed that comprehensive cfDNA NGS identified 1 of the 8 guideline-recommended biomarkers in 77 patients, whereas the tissue-based NGS identified these biomarkers in only 60

patients ( $P < .0001$  for noninferiority). The study also found that using cfDNA in addition to tissue-based testing increased detection of the guideline-recommended biomarkers by 48%, including in cases with “negative,” “not assessed,” or “insufficient quantity of tissue” results. A comparison of the incremental addition of each test showed that using cfDNA genotyping as the primary test would have recognized 87% of the 89 patients with a guideline-recommended biomarker, with the outstanding 13% identified with reflex tissue-based testing. By contrast, using tissue-based genotyping as the primary modality would have identified 67% of the 89 patients, with the remaining 33% identified with reflex cfDNA testing. Furthermore, the mean turnaround time was significantly shorter with cfDNA testing than with tissue genotyping (9 days vs 15 days;  $P < .0001$ ).<sup>42</sup>

**Clonal hematopoiesis of indeterminate potential (CHIP) may be a particularly significant barrier to the optimization of cfDNA-based testing.**

According to the stakeholders the study suggests that performing the plasma NGS early could identify a greater proportion of therapeutically relevant molecular targets than tissue-based NGS, particularly in cases in which the tissue biopsy is inadequate or the patient has already undergone tissue testing at another institution and is seeking a second opinion. Although the NCCN guidelines state that plasma cfDNA testing should not be used in place of a histologic tissue diagnosis, they state that it can be considered in specific circumstances, such as for patients medically unfit for invasive tumor sampling and in the initial diagnostic setting for patients who do not have sufficient tissue for molecular analysis after pathologic confirmation of NSCLC.<sup>2</sup>

### Limitations of Liquid Biopsy–Based Molecular Testing

However, cfDNA-based NGS currently has some shortcomings. The cfDNA-based method is less sensitive than tissue-based methods for detecting mutations and thus cannot be used alone to rule out the presence of a molecular alteration. Additionally, the recent development of multiple commercial-based plasma platforms has introduced issues such as a lack of standardization of preanalytic workflows and analytic validations across assays; even a test that is analytically validated with reproducible results is not guaranteed to be clinically valid or useful.<sup>2</sup>

Furthermore, the stakeholders explained that cfDNA in liquid biopsies may originate from sources other than the tumor, such as white blood cells, germline, fetal, post organ transplantation, or concomitant malignancies. Clonal hematopoiesis of indeterminate potential (CHIP) may be a particularly significant barrier to the optimization

of cfDNA-based testing. CHIP occurs as a result of the acquisition of somatic mutations that drive clonal expansion of hematopoietic stem cells over an individual's lifetime.<sup>2</sup> The stakeholders explained that although CHIP is not a major issue for most of the key targetable mutations in NSCLC, KRAS mutations can originate from CHIP, and detection of a KRAS mutation on a cfDNA-based assay does not reliably indicate that the lung tumor has this mutation. They added that sequencing the white blood cells in addition to the plasma sample could help identify the origin of the cfDNA, and a liquid biopsy purveyor that chooses to employ this with their samples would have a key advantage over its commercial competitors.

Despite their convenience and noninvasiveness, many of the stakeholders in the exchange use liquid biopsies only as a backup method, when the tissue biopsy is inadequate. Some stakeholders also said that they may consider using liquid biopsies to identify resistance mutations for patients on targeted therapy, although one panelist noted that the sensitivity can vary based on the test used, population evaluated, and size and location of the metastases.

## PRACTICE-LEVEL CHALLENGES AND UNMET NEEDS

In the last part of the interchange, the stakeholders discussed key practice-level challenges that may prevent the implementation of molecular testing in clinical practice. They focused on 2 studies that indicate the lack of education about molecular testing among community and academic oncologists in the United States.

Data from the National Survey of Precision Medicine in Cancer Treatment, which was distributed to a nationally representative sample of oncologists in 2017, showed that 75.6% of oncologists reported using NGS tests in the past 12 months to influence treatment decisions, with higher rates of use reported among younger physicians as well as among those oncologists with a faculty appointment, access to a tumor board, or training in genomics, or who see fewer than 50 patients per month with cancer. Use of NGS tests to guide use of an FDA-approved therapy and to determine eligibility for clinical trials were reported in 33.5% and 29.1% of oncologists, respectively.<sup>43</sup> Although the stakeholders perceived the rates of use to be lower than expected, they pointed out that some patients in oncology practices are not eligible for treatment (and would thus likely not receive molecular testing) or have histories (eg, heavy smoking) that suggest a low probability of oncogene-driven NSCLC, thereby reducing the clinical utility of molecular testing.

Another study that used polls from audience response systems at case-based research events and chart reviews to evaluate community and academic oncologists, respectively. The study data showed that molecular profiling was ordered by 33% of community- and 74% of academic-based oncologists. In this poll community oncologists marked unknown or incorrectly matched the molecular alteration to the targeted therapy in up to 69% of cases, which "reflects a large knowledge gap among community oncologists with regard to the correct application of molecular profiling to current FDA-approved

targeted therapies," according to the study authors.<sup>44</sup> However, the stakeholders pointed out that these results likely do not reflect what occurs in clinical practice, because oncologists would typically check resources, such as the NCCN guidelines, Up-to-Date, or another reputable online source, to guide management decisions if necessary.

## CLOSING REMARKS/CONCLUSIONS

At the end of the interchange, the stakeholders concluded that molecular testing has been key in the dramatic shift in the ability to target a patient's disease and personalize care. Moving forward, they stated that clarifying the optimal role for RNA-based NGS and reflex testing with liquid and tissue biopsies, identifying the appropriate sequence of molecularly targeted therapies, and expanding accessibility of molecular testing to more patients who may benefit will be instrumental in improving patient care. •

## REFERENCES

- Goossens N, Nakagawa S, Sun X, Hoshida Y. Cancer biomarker discovery and validation. *Transl Cancer Res.* 2015;4(3):256-269. doi: 10.3978/j.issn.2218-676X.2015.06.04.
- NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer, version 2.2020. National Comprehensive Cancer Network website. [nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](http://nccn.org/professionals/physician_gls/pdf/nscl.pdf). Published December 23, 2019. Accessed January 13, 2020.
- Vnencak-Jones CL, Berger MF, Pao W. Types of molecular tumor testing. My Cancer Genome website. [mycancergenome.org/content/page/molecular-testing/](http://mycancergenome.org/content/page/molecular-testing/). Updated April 3, 2019. Accessed January 13, 2020.
- Hindson BJ, Ness KD, Masquelier DA, et al. High-throughput droplet digital PCR system for absolute quantitation of DNA copy number. *Anal Chem.* 2011;83(22):8604-8610. doi: 10.1021/ac202028g.
- Benayed R, Offin M, Mullaney K, et al. High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with no mitogenic driver alteration detected by DNA sequencing and low tumor mutation burden. *Clin Cancer Res.* 2019;25(15):4712-4722. doi: 10.1158/1078-0432.CCR-19-0225.
- Campos-Parra AD, Zuloaga C, Manriquez ME, et al. KRAS mutation as the biomarker of response to chemotherapy and EGFR-TKIs in patients with advanced non-small cell lung cancer: clues for its potential use in second-line therapy decision making. *Am J Clin Oncol.* 2015;38(1):33-40. doi: 10.1097/JCO.0b013e318287bb23.
- Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361(10):947-957. doi: 10.1056/NEJMoa0810699.
- Maemondo M, Inoue A, Kobayashi K, et al; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med.* 2010;362(25):2380-2388. doi: 10.1056/NEJMoa0909530.
- Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol.* 2011;29(21):2866-2874. doi: 10.1200/JCO.2010.33.4235.
- Mitsudomi T, Morita S, Yatabe Y, et al; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol.* 2010;11(2):121-128. doi: 10.1016/S1470-2045(09)70364-X.
- Rosell R, Carcereny E, Gervais R, et al; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012;13(3):239-246. doi: 10.1016/S1470-2045(11)70393-X.
- Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* 2011;12(8):735-742. doi: 10.1016/S1470-2045(11)70184-X.
- Wu YL, Zhou C, Liang CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol.* 2015;26(9):1883-1889. doi: 10.1093/annonc/mdv270.
- Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol.* 2013;31(27):3327-3334. doi: 10.1200/JCO.2012.44.2806.
- Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014;15(2):213-222. doi: 10.1016/S1470-2045(13)70604-1.
- Mok TS, Wu Y-L, Ahn M-J, et al; AURA3 Investigators. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med.* 2017;376(7):629-640. doi: 10.1056/NEJMoa1612674.
- Soria JC, Ohe Y, Vansteenkiste J, et al; FLAURA Investigators. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-125. doi: 10.1056/NEJMoa1713137.

18. Ramalingam SS, Vansteenkiste J, Planchard D, et al; FLAURA Investigators. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50. doi: 10.1056/NEJMoa1913662.
19. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer [published online August 28, 2018]. *J Clin Oncol*. doi: 10.1200/JCO.2018.78.3118.
20. Solomon BJ, Mok T, Kim DW, et al; PROFILE 1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371(23):2167-2177. doi: 10.1056/NEJMoa1408440.
21. Peters S, Camidge DR, Shaw AT, et al; ALEX Trial Investigators. Alelectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829-838. doi: 10.1056/NEJMoa1704795.
22. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2027-2039. doi: 10.1056/NEJMoa1810171.
23. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol*. 2018;19(12):1654-1667. doi: 10.1016/S1470-2045(18)30649-1.
24. A Study Of Lorlatinib Versus Crizotinib In First Line Treatment Of Patients With ALK-Positive NSCLC. [clinicaltrials.gov/ct2/show/NCT03052608?cond=NCT03052608&draw=2&rank=1](https://clinicaltrials.gov/ct2/show/NCT03052608?cond=NCT03052608&draw=2&rank=1). Updated November 19, 2019. Accessed January 23, 2020.
25. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-1971. doi: 10.1056/NEJMoa1406766.
26. Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol*. 2019;20(12):1691-1701. doi: 10.1016/S1470-2045(19)30655-2.
27. Drilon A, Siena S, Ou SI, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). *Cancer Discov*. 2017;7(4):400-409. doi: 10.1158/2159-8290.CD-16-1237.
28. Ahn M, Cho BC, Siena S, et al. Entrectinib in patients with locally advanced or metastatic ROS1 fusion-positive non-small cell lung cancer (NSCLC). *J Thorac Onc*. 2017;12(11 suppl 2):S1783.
29. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. FDA website. [fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc). Published August 15, 2019. Updated August 16, 2019. Accessed January 23, 2020.
30. Drilon A, Ou SI, Cho BC, et al. Reprotrectinib (TPX-0005) is a next-generation ROS1/TRK/ALK inhibitor that potentially inhibits ROS1/TRK/ALK solvent-front mutations. *Cancer Discov*. 2018;8(10):1227-1236. doi: 10.1158/2159-8290.CD-18-0484.
31. A Study of Reprotrectinib (TPX-0005) in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1). [clinicaltrials.gov/ct2/show/NCT03093116?term=NCT03093116&draw=2&rank=1](https://clinicaltrials.gov/ct2/show/NCT03093116?term=NCT03093116&draw=2&rank=1). Updated January 27, 2020. Accessed January 23, 2020.
32. Marchetti A, Felicioni L, Malatesta S, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. *J Clin Oncol*. 2011;29(26):3574-3579. doi: 10.1200/JCO.2011.35.9638.
33. Subbiah V, Gervais R, Riey GJ, et al. Efficacy of vemurafenib in patients (pts) with non-small cell lung cancer (NSCLC) with BRAF<sup>V600</sup> mutation. *J Clin Oncol*. 2017;35(15 suppl, abstr 9074). doi: 10.1200/JCO.2017.35.15\_suppl.9074.
34. Mazieres J, Montane L, Barlesi F, et al. Vemurafenib in patients harboring V600 and non V600 BRAF mutations: final results of the NSCLC cohort from the AcSé trial. *J Thorac Oncol*. 2018;13(10):S348-S349. doi: 10.1016/j.jtho.2018.08.302.
35. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(5):642-650. doi: 10.1016/S1470-2045(16)00077-2.
36. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17(7):984-993. doi: 10.1016/S1470-2045(16)30146-2.
37. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF<sup>V600E</sup>-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18(10):1307-1316. doi: 10.1016/S1470-2045(17)30679-4.
38. Doebele R, Paz-Ares L, Farago AF, et al. Entrectinib in NTRK-fusion positive (NTRK-FP) non-small cell lung cancer (NSCLC): integrated analysis of patients enrolled in three trials (STARTRK-2, STARTRK-1 and ALKA-372-001). *Cancer Res*. 2019;79(13 suppl):CT131. doi: 10.1158/1538-7445.AM2019-CT131.
39. Hong DS, Bauer TM, Lee JJ, et al. Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study. *Ann Oncol*. 2019;30(2):325-331. doi: 10.1093/annonc/mdy539.
40. FDA approves larotrectinib for solid tumors with NTRK gene fusions. FDA website. [fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0](https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0). Published November 26, 2018. Updated December 14, 2018. Accessed January 23, 2020.
41. Aggarwal C, Thompson JC, Black TA, et al. Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non-small cell lung cancer. *JAMA Oncol*. 2019;5(2):173-180. doi: 10.1001/jamaoncol.2018.4305.
42. Leigh NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. *Clin Cancer Res*. 2019;25(15):4691-4700. doi: 10.1158/1078-0432.CCR-19-0624.
43. Freedman AN, Klabunde CN, Wiant K, et al. Use of next-generation sequencing tests to guide cancer treatment: results from a nationally representative survey of oncologists in the United States [published online November 13, 2018]. *JCO Precis Oncol*. doi: 10.1200/PO.18.00169 JCO.
44. Singh BP, Britton SL, Prins P, et al. Molecular profiling (MP) for malignancies: knowledge gaps and variable practice patterns among United States oncologists (onc). *J Clin Oncol*. 2019; 37(15 suppl, abstr 10510). doi: 10.1200/JCO.2019.37.15\_suppl.10510.





