Optimizing Sequencing in Patients with NSCLC and Actionable Mutations

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Overview
This activity is designed to inform physicians about optimizing sequencing in patients with non–small cell lung cancer (NSCLC) and actionable mutations.

Target Audience
This activity is directed towards medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with NSCLC. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Explain the key unmet needs in the treatment of advanced NSCLC for patients who have actionable mutations
- Describe the advantages and disadvantages of different types of molecular testing to identify patients with actionable mutations
- Discuss the most common genomic alterations that have been identified in NSCLC

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Introduction

Background

Lung cancer is the leading cause of cancer-related mortality in the United States.[1] In 2017 there will be an estimated 222,500 new cases of lung cancer (non–small cell lung cancer [NSCLC] and small cell lung cancer combined) and 155,870 related deaths.[1]

The initial treatment of NSCLC usually relies on surgical resection followed by systemic cytotoxic chemotherapy and/or radiation therapy. Advances in understanding NSCLC pathophysiology and immunology have led to the development of numerous targeted therapeutic approaches, improving patient outcomes.[2] Several targeted therapies are approved by the US FDA for use in various settings in NSCLC.

Epidermal growth factor receptor (EGFR)–targeted therapies affect activated tyrosine kinase receptors. FDA-approved drugs with an NSCLC indication include erlotinib, afatanib, gefitinib, necitumumab, and osimertinib. Erlotinib, afatanib, and gefitinib are small molecule tyrosine kinase inhibitors (TKIs) approved for treatment of *EGFR*-mutant lung tumors in the first-line setting. Osimertinib is indicated for those patients who have progressed on EGFR TKI therapy when the tumor has acquired resistance due to the T790M mutation. Necitumumab, an anti-EGFR monoclonal antibody, is used in combination with gemcitabine and cisplatin for first-line treatment of patients with metastatic squamous cell NSCLC. Anaplastic lymphoma kinase (ALK), a tyrosine kinase, is activated by translocation in approximately 5% of patients with NSCLC.[2] There are 3 FDA-approved ALK-targeted TKIs: crizotinib, ceritinib, and alectinib. Crizotinib is a first-generation ALK inhibitor. Ceritinib is indicated for patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Alectinib is a second-generation inhibitor used in the crizotinib-resistant population. Targeted therapy is a promising approach for patients with lung cancer.

Molecular Testing

The testing of patients with molecular technology has become increasingly more important to the treatment of patients with NSCLC, in part due to the recognized effectiveness of targeted therapies. The importance of molecular analysis continues to be highlighted by the large National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) trial, which plans on screening up to 6000 patients with various tumor types to examine for gene abnormalities for which a targeted therapy exists. This trial opened enrollment in August 2015, and will have 30 treatment arms. In an interim analysis of 645 patients screened for the NCI-MATCH trial, 48 patients with NSCLC (7.4%) were screened. As part of this analysis, 33 patients with various cancer types have been assigned therapy, of which 5 (15.2%) patients with NSCLC were assigned.[3] The primary endpoint for the NCI-MATCH trial is the objective response rate (ORR). This study highlights the importance of incorporating molecular testing into the determination of treatment approach.

Molecular testing should be ordered at the time of diagnosis for patients with advanced-stage NSCLC[4]; testing in patients with stage I-III NSCLC is controversial. When surgery or surgery followed by adjuvant chemotherapy is the initial plan for treatment, molecular testing for targeted therapy is not clearly indicated.[5] Testing early-stage NSCLC may identify targeted therapy, which could be useful for patients who experience recurrent NSCLC. It has been recommended to prioritize *EGFR, ALK,* and *ROS1* testing over other molecular predictive tests, due to the relative frequency and availability of effective therapies.[4] Molecular testing for *EGFR*, *ALK*, and *ROS1* is recommended to select patients for targeted therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.[4] Testing can also be performed to evaluate for genomic alterations such as *KRAS, BRAF, MET, RET,* neurotrophic tyrosine receptor kinase (*NTRK*), and human epidermal growth factor receptor 2 (*HER2*).

The primary tumor or metastatic lesions are suitable for molecular testing. However, in 2016, the FDA approved the first liquid biopsy test. Liquid biopsy makes it possible to determine a patient's suitability for EGFR-targeted therapy by analyzing circulating-free tumor DNA in peripheral blood samples. A liquid biopsy is minimally invasive, easily repeatable, and can be used for single-gene molecular testing. Both methods of testing have been shown to be effective, with a high rate of similarity.[6] Liquid biopsy has a high concordance of 88% to 90% with results from standard tests in the V600 mutation of *BRAF*.[7]

The cost of universal molecular testing of NSCLC is substantial, and it has been suggested that universal *EGFR* and *ALK* testing is not needed at the time of initial diagnosis.[8] At one facility, the estimated additional cost of *EGFR* and *ALK* testing for all newly diagnosed patients with NSCLC was $75,200 per year. The suggestion by these authors is to focus testing only on patients with locally advanced and advanced-stage disease.[8] In a retrospective analysis, it has been demonstrated that blood-based testing is significantly less costly than tissue-based biopsy methods, with a potential savings of $3000 to $7400 per patient with liquid biopsy compared with tissue-based biopsy.[9]

Actionable Mutations in NSCLC

Tumor molecular subtyping is paramount for advanced-stage NSCLC therapy guidance. Different types of genomic alterations have been identified involving multiple kinase genes, such as *EGFR, KRAS, ALK, ROS1, BRAF, MET, RET, NTRK,* and *HER2*.[10] These genomic alterations represent specific molecular subtypes of pulmonary adenocarcinomas, each with its own distinct biology, epidemiology, prognosis, and therapeutic susceptibility.

EGFR

The most common *EGFR*-activating mutations are the exon 19 deletion and exon 21 point L858R mutation, accounting for 85% to 90% of *EGFR* clinical mutations.[11] The effectiveness of EGFR TKIs in patients with *EGFR* variations has been demonstrated by several FDA-approved therapies (ie, erlotinib, afatanib, gefitinib, and osimertinib). The Iressa Pan-Asia Study (IPASS) trial examined gefitinib compared with platinum-based chemotherapy in patients with advanced pulmonary

adenocarcinoma. Progression-free survival (PFS) was significantly longer with gefitinib for patients whose tumors had both high *EGFR* gene copy number and *EGFR* mutation (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.34 to 0.67).[12] The IPASS trial supports recommendations that patients with advanced NSCLC who might be candidates for first-line EGFR TKIs erlotinib, afatinib, or gefitinib be tested for *EGFR* mutation status, and treated if positive.

A head-to-head comparison of a first-generation EGFR TKI and a second-generation EGFR TKI has been evaluated. The LUX-Lung 7 trial compared gefitinib with afatinib and found that afatinib significantly increased response rate (RR; 70% vs 56%, *P* = .0083), median PFS (11 vs 10.9 months; HR, 0.73; 95% CI, 0.57-0.95; *P* = .017), and median time to treatment failure (13.7 months vs 11.5 months; HR, 0.73; 95% CI, 0.58-0.92; *P* = .0073) over gefinitib.[13] Although the results of this trial might suggest that second-generation EGFR TKIs are more favorable compared with first-generation EGFR TKIs, there was no difference in overall survival (OS) between the 2 EGFR TKIs. Further studies are required to determine clinical outcomes of first-generation EGFR TKIs versus second-generation EGFR TKIs.

Treatment with EGFR TKIs improves outcomes for patients whose tumors harbor these *EGFR* mutations, but their efficacy is limited by the development of acquired resistance. The acquisition of a secondary mutation in exon 20 (T790M) is the most common *EGFR*-dependent acquired resistance mechanism. The T790M mutation is observed in up to 50% to 60% of resistant patients.[14] A third-generation EGFR TKI, osimertinib, is an *EGFR*-mutant–selective inhibitor with activity against the T790M mutant kinase and sensitizing *EGFR* mutations. Other novel third-generation TKIs are in early phases of development, including HM61713, ASP8273, EGF816, AZD3759, and HMPL-813.[15]

ALK

Chromosomal *ALK* rearrangements are found in approximately 3% to 7% of NSCLCs.[15] Crizotinib, a first-generation ALK inhibitor, targets ALK, ROS1, and MET tyrosine kinases, and is indicated for locally advanced or metastatic NSCLC that is *ALK*-positive as detected by an FDA-approved test. More recently, it has been indicated for metastatic NSCLC that is *ROS1*-rearrangement positive.[16]

The acquisition of a secondary *ALK* mutation is common with patients who develop ALK TKI resistance.[14] There have been many identified secondary *ALK* mutations, including but not limited to L1152R, L1196M, C1156Y, and F1174L.[14,17] Two drugs are FDA approved as second-generation ALK TKIs to overcome crizotinib resistance: ceritinib and alectinib. Ceritinib has demonstrated a significant improvement over chemotherapy in patients previously treated with crizotinib, with a reported RR of 39.1% compared with 6.9% with chemotherapy (ASCEND-5 trial). PFS was 5.4 months compared with 1.6 months with chemotherapy (HR, 0.49; *P* <.001). The most frequent grade 3/4 adverse eventts (AEs) with ceritinib were nausea (7.8%), vomiting (7.8%), and diarrhea (4.3%); with chemotherapy, they were neutropenia (15.5%), fatigue (4.4%), and nausea (1.8%).[18] However, treatment-related AEs were more frequent in the ceritinib arm than in the chemotherapy arm.

There are investigational drugs for those patients who acquire resistance to second-generation ALK inhibitors. It was recently shown that the use of lorlatinib may overcome resistance to ALK inhibitors, which remains a significant challenge for patients with *ALK*-positive NSCLC. In a dose-escalation phase I study of patients with *ALK*-positive or *ROS1*-positive NSCLC who were treatment-naïve or had disease progression after at least 1 prior TKI, the ORR and PFS with lorlatinib were 46% and 11.4 months, respectively, in patients treated with 1 prior TKI.[19] The most common treatment-related AEs were hypercholesterolemia (69%) and peripheral edema (37%).[19] Most patients had received 2 or more prior ALK TKIs. In these patients, the RR was 42% and PFS was 9.2 months.[15] The phase II ALTA trial (NCT02094573) of brigatinib in patients with crizotinib-refractory *ALK*-positive NSCLC reported interim analysis indicating 46% and 54% ORRs, respectively, in 2 groups: The first continuously took 90 mg of brigatinib per day in a 28-day cycle; the second took 90 mg of brigatinib per day for 7 days followed by 180 mg of brigatinib per day for the 28-day cycle. Reported AEs included increased elevated creatinine phosphokinase, hypertension, rash, pneumonia, and increased lipase.[20] Ensartinib has demonstrated clinical activity in the same crizotinib-refractory *ALK*-positive NSCLC patient population, with the most common AEs being rash (47%), nausea (28%), vomiting (25%), and fatigue (23%).[21] Lastly, an arm in the open-label, multicenter, global phase 2 basket study (STARTRK-2) is for patients with *ALK*- or *ROS1*-rearranged NSCLC previously treated with crizotinib. The STARTRK-2 trial is examining entrectinib in this patient population (NCT02568267).

The next generation of investigational ALK inhibitors in patients resistant to ALK TKIs are not ALK-selective inhibitors, and instead target other kinases such as ROS1 and MET.

ROS1

ROS1 gene rearrangements are found in 1% to 2% of NSCLCs.[15] ROS1 rearrangements in lung cancer share common carcinogenic properties to *ALK* rearrangements in terms of clinical characteristics, therapeutic susceptibilities, and acquired resistance mechanisms. Clinical development of next-generation dual ALK and ROS1 inhibitors (lorlatinib, ceritinib, brigatinib, and entrectinib) and other ROS1 inhibitors (cabozantinib and foretinib) is currently ongoing.[22] As previously mentioned, lorlatinib is being examined in *ROS1*-positive NSCLC and has demonstrated the ability to overcome crizotinib resistance. *ROS1*-positive NSCLC patients (n = 12) achieved ORRs of 33% and 66% in the crizotinib-pretreated and crizotinib-naïve subsets, respectively.[23]

KRAS

There are no FDA-approved therapies for *KRAS*-mutated tumors, and this represents an area of required research and development. *KRAS* has been referred to as clinically difficult to inhibit; therefore, strategies have focused on inhibition of downstream therapeutic approaches. The use of mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors has shown some promise in *KRAS*-positive NSCLC. A randomized, open-label phase II study in patients with advanced NSCLC, refractory to more than 1 prior therapy, and *KRAS*-positive examined 2 therapeutic

agents, MK-2206 and AZD6244. These agents demonstrated promise against *KRAS*-positive cancers. The disease control rate in *KRAS*-positive patients was 25% in those who took MK-2206, and 62% in those who took MK-2206 and AZD6244. The most common grade 3/4 AE seen in the combined MK-2206 plus AZD6244 arm was maculopapular rash.[24]

MET, BRAF, RET, HER2 and NTRK

There are several additional evolving targets in NSCLC including *MET, BRAF, RET, HER2,* and *NTRK*. *MET* oncogene dysregulation is found in approximately 10% of the NSCLC cases in which patients have acquired resistance.[15] Many *MET*-mutated cancers resulting in exon 14 skipping have been described; exon 14 skipping results in enhanced MET signaling.[25] Patients whose NSCLC harbors the exon 14 alteration can achieve clinical benefit from MET inhibitors. Several drug agents have been shown to have activity in patients with high *MET* expression or *MET* mutations, including crizotinib, cabozantinib, and capmatinib.[25-27] RET-targeting TKIs are being used clinically, including vandetanib, cabozantinib, lenvatinib, sunitinib, sorafenib, and alectinib.[15] The response rates to some of these drug agents have been reported to be 16% to 53% in previously treated patients with *RET* rearrangements in NSCLC.[28-30] *HER2* mutations have been identified as oncogenic drivers in lung cancers and are found in 1% to 2% of lung adenocarcinomas.[15] *HER2* mutations in NSCLC demonstrated some responsiveness to trastuzumab and chemotherapy in European cohorts, as well as to such monotherapies as afatinib, dacomitinib, and neratinib.[31,32] BRAF inhibition has shown antitumor activity in patients with *BRAF* V600E-mutant NSCLC. Recently, antitumor activity and safety of dabrafenib plus trametinib in patients with *BRAF* V600E-mutant NSCLC has been demonstrated (NCT01336634). An overall response was observed in 63.2% of patients, with the most common grade 3/4 AEs being neutropenia (9%), hyponatremia (7%), and anemia (5%).[33] Lastly, the frequency of *NTRK* mutations in lung adenocarcinomas is approximately 3.3%.[34] Entrectinib and larotrectinib are pan-tropomyosin receptor kinase inhibitors that are currently under investigation in phase I/II trials.[35,36]

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Moderator: What are some of the unmet needs in the treatment of advanced NSCLC for patients who have actionable mutations?

Dr Reckamp: There are 3 unmet needs that I would describe. First is resistance to targeted therapy. The actionable mutations or gene alterations that occur once a targeted therapy is given can invariably lead to resistance. This leads to progression, and most patients with advanced NSCLC still die of the disease. Compared with other cancer types, for lung cancer, our understanding of mechanisms of resistance for the most common markers of EGFR and ALK is growing. Our researchers are looking at resistance mechanisms and how to overcome and potentially prevent them. However, there remains a need for further research and advances can affect patient outcomes in a major way.

The second unmet need is understanding rare mutations or gene alterations, and how best to study targeted drugs in these patients. Targeted drug treatment options are needed for those patients who will benefit from these approaches. Examples of uncommon gene alterations would be *RET* and *MET*. Although drugs against the targets can be beneficial, drug development is challenging, from requiring large comparative clinical trials to obtaining FDA approval. We need to be forward-thinking about novel trial designs to evaluate these rare mutations. There are many basket trials out there that look at specific mutations in a tumor-agnostic manner, which help us to move the field forward. Trials like the NCI-MATCH trial look at mutations in rarer indications, with the purpose of examining response rates and meaningful efficacy endpoints to understand the benefit of these drugs for patients.

Third, evaluating investigational drugs in the neoadjuvant and adjuvant setting is important. These drugs could potentially lead to a cure when a patient has minimal residual or micrometastatic disease. Currently, we do not have data showing that these drugs prolong survival in the neoadjuvant and adjuvant setting; the primary use of such drugs are in patients with metastatic disease. There are ongoing trials looking at targeted agents, especially for ALK and EGFR, as adjuvant therapy, and those answers hopefully will come in the next decade.

Moderator: What do you feel could be done to further improve facilitation of molecular testing in community settings where patients with advanced NSCLC are managed?

Dr Reckamp: Numerous issues surround this important topic. I may miss some of the challenges a community practitioner encounters, as I do not practice in a community setting. It is likely that the single largest challenge is insurance coverage. Molecular testing is still an expensive endeavor. Molecular testing can arguably change a treatment approach, and potentially quality of life and overall survival for those patients who have alterations. These patients could be given targeted therapy. However, upfront testing when there is low probability of having a gene alteration remains a challenge that is faced, especially in community settings.

The lung cancer community is good about testing for *EGFR, ALK,* and *ROS1*, and now PD-L1, which is not a genetic alteration but also a marker that helps determine therapy. Most practices test for these mutations or markers. With the ability to test blood and tissue, we can do single-gene testing by PCR [polymerase chain reaction] and FISH [fluorescence in situ hybridization]. Next-generation sequencing provides more information on a smaller amount of material. These have differential costs based on insurance and location. The biggest challenge is understanding what the cost to the patient might be; this is often not known. This is further complicated by the fact that the best

test or platform to perform has not been compared or validated. For example, a person who is of Asian descent and a nonsmoker has a high pretest probability to have an *EGFR* mutation. In this scenario, doing single-gene testing may be best option for this patient and the most cost effective. However, if the *EGFR* test is negative for this patient case, then you would have to use more tissue in order to get answers about other genetic alterations. In our practice, we favor moving forward with next-generation sequencing (NGS). This provides the most information with the least amount of tissue, and eliminates the need to go back and do additional tests. In the community, NGS testing may not be standard and challenges remain, most of which are financial.

Blood testing provides multiple choices for patients and providers. These tests have different sensitivities, specificities, and prices. It is an enormous challenge to remain aware of all the various tests and determining which one will be best for your patient. None have been compared directly.

Moderator: What mutational subtypes inform therapeutic sequencing among patients with *EGFR*-mutated NSCLC? What if T790M is found prior to starting frontline therapy?

Dr Reckamp: Generally, when performing *EGFR* sequencing, about 90% are going to have the most common exon 19 deletions or exon 21, L858R. There are rarer mutations, some of which have a tendency toward resistance, some with sensitivity to approved EGFR TKIs, and for some mutations there is very little information available. Usually the exon 20 insertions tend to be resistant and some of the exon 18 mutations tend to be sensitive. It all depends on the mutation. We use fewer of the EGFR inhibitors in those patients who have exon 20 mutations. This is different than having a T790 mutation de novo, which is very rare but does occur, and is also an exon 20, but responds to osimertinib. The other exon 20 insertions are different.

Moderator: What are the advantages and disadvantages of a liquid biopsy in order to identify patients with metastatic NSCLC who are eligible for EGFR-targeted therapy?

Dr Reckamp: Liquid biopsy for *EGFR* mutations is FDA approved. An obvious advantage is that liquid biopsy does not require a tissue biopsy, which reduces cost and potential complications. It requires just a blood draw, and that is much easier for a patient and decreases potential risk. This is a clear advantage for patients. The cost of the biopsy is also less.

The main disadvantage is the false negative rate. In order to detect a mutation within the blood, there needs to be circulating cell-free DNA at sufficient levels to be able to detect the mutation. Even if the cancer is present, if there is not enough circulating cell-free DNA, then a liquid biopsy may provide a negative result, but it may be a false negative result. If the result is positive, it is likely to be a true positive and is a very good test for the patient to guide treatment choice.

Moderator: What strategies may soon enter the field of *ALK*-positive NSCLC management and how might that impact sequencing decisions for these patients? How may some of these strategies address the important problem of central nervous system metastases in advanced *ALK*-positive NSCLC?

Dr Reckamp: The strategies entering the field of *ALK*-positive have to do with 2 issues, the first being brain metastases. In general, crizotinib is less effective and less potent in the brain for patients with *ALK*-positive NSCLC. Therefore, patients who have initial brain metastases may respond more favorably with upfront therapy of ALK inhibitors that are more potent in the brain. Both of the approved second-generation inhibitors, ceritinib and alectinib, have excellent penetrance and responses in the brain. This may be reason to use these drugs in the first-line setting. There are data for ceritinib in first-line therapy versus chemotherapy that demonstrate a clinical benefit. However, alectinib has similar benefit in the brain. A provider will have to decide whether to use alectinib or ceritinib as a first-line therapy.

The second issue deals with *ALK*-positive NSCLC management in cases of resistance. Regarding other strategies for sequencing, our lung cancer community is moving toward a better understanding of the mutations that occur upon resistance. As more patients receive these second-generation inhibitors, we will understand more about these mechanisms of resistance, and if there are true patterns of some drugs being able to overcome resistant mutations better than others. There are several ALK inhibitors in development with differential response to various resistance mutations that occur in *ALK*-positive NSCLC. Although there may be a way to understand sequencing of ALK inhibitor therapy, we are not there yet for our patients.

Moderator: *ROS1* has recently been identified as an actionable marker. How can that marker be used to inform sequencing in advanced NSCLC?

Dr Reckamp: There are data indicating that the FDA-approved crizotinib is efficacious for *ROS1* gene alterations in NSCLC. We have new data on ceritinib that were presented in 2016 showing responses in patients with *ROS1* gene rearrangements. The evidence appears to indicate that ceritinib is not effective when patients develop resistance to crizotinib. These are both frontline therapies for patients with *ROS1* gene rearrangements. In my experience, crizotinib is an effective ROS1 inhibitor, and patients have prolonged progression-free survival.

Considering that patients with a *ROS1* gene alteration comprise a small subset of patients with lung cancer, it is going to be hard to develop a full understanding of how best to sequence these drugs. The fact that *ROS1* is a rare gene alteration, and patients do so well on crizotinib, will make it difficult to determine the best sequencing in advanced NSCLC.

Moderator: What role do MEK1/2 inhibitors have in the treatment of NSCLC?

Dr Reckamp: At this point, MEK inhibitors are still investigational, and it has not been determined how these drugs best fit into the treatment paradigm for *KRAS*-mutated NSCLC. There's still interest in drug combinations with MEK inhibitors. The use in *KRAS* patients remains a possibility. There is evidence of prolonged PFS and increased RR in

BRAF-positive patients when MEK inhibitors are used in combination with BRAF inhibitors. Currently, however, these drugs are still investigational, and further studies are required.

Moderator: How do you see the treatment of advanced NSCLC potentially evolving with regard to emerging actionable markers such as *HER2, KRAS, RET,* and *MET?*

Dr Reckamp: As previously mentioned, the less common actionable mutations are definitely an area of unmet need. It is challenging to develop drugs that target an actionable mutation, and enroll enough patients to provide efficacy data that would support an FDA approval. When considering emerging actionable markers, one has to examine them separately. The first question to consider about emerging actionable markers is if they are true actionable mutations or not. In the case of *HER2*, some may be actionable mutations and some may not. Response rates to HER2 TKIs in lung cancer and pan-HER TKIs in lung cancer are less than 20%. Usually when we have a true actionable oncogenic driver and give a targeted therapy, we get response rates at minimum of 50% into the 60% to 70% range. Therefore, *HER2* does not seem to be a straightforward actionable marker at this time. There is some heterogeneity in *HER2* mutations and *HER2* amplification that needs to be understood to help response rates get closer to 50%.

KRAS is another marker that has a lot of heterogeneity. Therefore, no single drug seems to cause large effects in *KRAS*. There are many trials and combination trials looking at various targeted therapies for KRAS, and we're still working to improve outcomes for those patients. Regarding *RET* as a marker, RET inhibitors have been multitargeted TKIs. More specific RET inhibitors may improve responses over the multitargeted RET inhibitors. This seems to be a true oncogenic target, and, again, there may be some heterogeneity in understanding the partner in the translocations that occur with *RET*. We are getting closer to understanding *RET* and moving forward with beneficial treatments for these patients.

MET is another marker that has been more recently studied, and there are multiple ways that we look at *MET*, from amplification, to overexpression, to mutations. Understanding which alteration responds best to the MET inhibitors in the therapeutic armamentarium is important. There are many trials ongoing that are looking at these drugs and various markers for *MET*. This is something that will evolve and provide information that will better help us treat our patients.

And then there are other less common alterations such as *NTRK*. *NTRK* is a marker for which new therapies are being developed. Some of the ALK and ROS1 inhibitors have some activity in these patients as well. Understanding how efficacious these targeted therapies are against these genes, understanding the heterogeneity within the biomarker itself, and understanding whether it is a true oncogenic driver versus a passenger effect, are all important to our field and to improving patient outcomes.

References

1. American Cancer Society (ACS). Cancer Facts and Figures 2017. ACS website. https://old.cancer.org/acs/groups/content/@editorial/documents/document/acspc-048738.pdf. Accessed March 13, 2017.
2. Le AD, Alzghari SK, Jean GW, La-Beck NM. Update on targeted therapies for advanced non-small cell lung cancer: nivolumab in context. *Ther Clin Risk Manag.* 2017;13:223-236. doi:10.2147/TCRM.S104343.
3. National Cancer Institute (NCI). Executive Summary: Interim Analysis of the NCI-MATCH Trial. NCI website. https://dctd.cancer.gov/majorinitiatives/NCI-MATCH_Interim_Analysis_Executive_Summary.pdf. Published May 6, 2016. Accessed March 15, 2017.
4. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol.* 2013;8(7):823-859. doi:10.1097/JTO.0b013e318290868f.
5. Lazarus DR, Ost DE. How and when to use genetic markers for non-small cell lung cancer. *Curr Opin Pulm Med.* 2013;19(4):331-339. doi:10.1097/MCP.0b013e328362075c.
6. Kwapisz D. The first liquid biopsy test approved. is it a new era of mutation testing for non-small cell lung cancer? *Ann Transl Med.* 2017;5(3):46. doi: 10.21037/atm.2017.01.32.
7. Janku F, Huang HJ, Claes B, et al. BRAF mutation testing in cell-free DNA from the plasma of patients with advanced cancers using a rapid, automated molecular diagnostics system. *Mol Cancer Ther.* 2016;15(6):1397-1404. doi: 10.1158/1535-7163.MCT-15-0712.
8. Sauter JL, Butnor KJ. Clinical and cost implications of universal versus locally advanced-stage and advanced-stage-only molecular testing for epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangements in non-small cell lung carcinoma: a tertiary academic institution experience. *Arch Pathol Lab Med.* 2016;140(4):358-361. doi: 10.5858/arpa.2015-0147-OA.
9. Magee M, Arnaud A, Bowling M. Costs and outcomes comparison of tissue and blood based biopsies for the purpose of biomarker testing for advanced non-small cell lung cancer. Poster presented at: 21st Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research; May 21 -25, 2016; Washington, DC. PCN57. https://www.ispor.org/research_pdfs/52/pdffiles/PCN57.pdf.
10. Swanton C, Govindan R. Clinical implications of genomic discoveries in lung cancer. *N Engl J Med.* 2016;374(19):1864-1873. doi: 10.1056/NEJMra1504688.
11. Piotrowska Z, Sequist LV. Epidermal growth factor receptor-mutant lung cancer: new drugs, new resistance mechanisms, and future treatment options. *Cancer J.* 2015;21(5): 371-377. doi: 10.1097/PPO.0000000000000147.
12. 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.
13. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol.* 2016;17(5): 577-589. doi: 10.1016/S1470-2045(16)30033-X.
14. Camidge DR, Pao W, Sequist LV. Acquired resistance to TKIs in solid tumours: learning from lung cancer. *Nat Rev Clin Oncol.* 2014;11(8):473-481. doi: 10.1038/nrclinonc.2014.104.
15. Zugazagoitia J, Molina-Pinelo S, Lopez-Rios F, Paz-Ares L. Biological therapies in nonsmall cell lung cancer. *Eur Respir J.* 2017;49(3). pii: 1601520. doi: 10.1183/13993003.01520-2016.
16. FDA approves crizotinib capsules [news release]. Silver Spring, MD: FDA; March 11, 2016. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm490391.htm. Accessed March 21, 2017.
17. Sasaki T, Koivunen J, Ogino A, et al. A novel ALK secondary mutation and EGFR signaling cause resistance to ALK kinase inhibitors. *Cancer Res.* 2011;71(18):6051-6060. doi:10.1158/0008-5472.CAN-11-1340.
18. Scagliotti G, Kim T, Crino L, et al. Ceritinib vs chemotherapy (CT) in patients (pts) with advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with CT and crizotinib (CRZ): results from the confirmatory phase 3 ASCEND-5 study. *Ann Oncol.* 2016;27(Suppl 6, LBA42_PR).
19. Pfizer presents promising data from next generation ALK/ROS1 inhibitor in advanced non-small cell lung cancer. New York, NY: Pfizer, Inc; June 6, 2016. http://www.pfizer.com/news/press-release/press-release-detail/pfizer_presents_promising_data_from_next_generation_alk_ros1_inhibitor_in_advanced_non_small_cell_lung_cancer. Accessed March 15, 2017.
20. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib (BRG) in patients (pts) with crizotinib (CRZ)-refractory ALK+ non-small cell lung cancer (NSCLC): first report of efficacy and safety from a pivotal randomized phase (ph) 2 trial (ALTA). *J Clin Oncol.* 2016;34(suppl; abstr 9007).
21. Reckamp KL, Infante JR, Blumenschein GR, et al. Phase I/II trial of X-396, a novel anaplastic lymphoma kinase (ALK) inhibitor, in patients with ALK+ non-small cell lung cancer (NSCLC). *J Thorac Oncol.* 2016;11(2):S36-S37. doi: 10.1016/j.jtho.2015.12.062.
22. Ye M, Zhang X, Li N, et al. ALK and ROS1 as targeted therapy paradigms and clinical implications to overcome crizotinib resistance. *Oncotarget.* 2016;7(11):12289-12304. doi: 10.18632/oncotarget.6935.
23. Solomon BJ, Bauer TM, Felip E, et al. Safety and efficacy of lorlatinib (PF-06463922) from the dose-escalation component of a study in patients with advanced ALK+ or ROS1+ non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2016;34(suppl, abstr 9009).
24. Papadimitrakopoulou V, Lee JJ, Wistuba II, et al. The BATTLE-2 study: a biomarker-integrated targeted therapy study in previously treated patients with advanced non–small-cell lung cancer. *J Clin Oncol.* 2016;30:3638-3647.
25. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov.* 2015;5(8):850-859. doi: 10.1158/2159-8290.CD-15-0285.
26. Camidge DR, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2014;32(5s suppl, abstr 8001).
27. Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. *Cancer Discov.* 2015;5(8):842-849. doi:10.1158/2159-8290.CD-14-1467.
28. Drilon AE, Sima CS, Somwar R, et al. Phase II study of cabozantinib for patients with advanced RET-rearranged lung cancers. *J Clin Oncol.* 2015;33(suppl, abstr 8007).
29. Seto T, Yoh K, Satouchi M, et al. A phase II open-label single-arm study of vandetanib in patients with advanced RET-rearranged non-small cell lung cancer (NSCLC): Luret study. *J Clin Oncol.* 2016;34(suppl, abstr 9012).
30. Velcheti V, Hida T, Reckamp KL, et al. Phase 2 study of lenvatinib (LN) in patients (Pts) with RET fusion-positive adenocarcinoma of the lung. *Ann Oncol.* 2016;27(suppl 6, 1204PD).
31. Mazières J, Barlesi F, Filleron T, et al. Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort. *Ann Oncol.* 2016;27(2):281-286. doi: 10.1093/annonc/mdv573.
32. Kris MG, Camidge DR, Giaccone G, et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. *Ann Oncol.* 2015;26(7): 1421-1427. doi:10.1093/annonc/mdv186.
33. Planchard D, Besse B, Groen HJ, 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.
34. Vaishnavi A, Capelletti M, Le AT, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. *Nat Med.* 2013;19(11):1469-1472. doi: 10.1038/nm.3352.
35. Patel MR, Bauer TM, Liu SV, et al. STARTRK-1: phase 1/2a study of entrectinib, an oral Pan-Trk, ROS1, and ALK inhibitor, in patients with advanced solid tumors with relevant molecular alterations. *J Clin Oncol.* 2015;33(suppl; abstr 2596).
36. Hong DS, Brose MS, Doebele RC, et al. Clinical safety and activity from a phase 1 study of LOXO-101, a selective TRKA/B/C inhibitor, in solid-tumor patients with NTRK gene fusions. Abstract presented at: American Association for Cancer Research – National Cancer Institute – European Organisation for Research and Treatment of Cancer International Conference on Molecular Targets and Cancer Therapeutics; November 8, 2015; Boston, MA.