Proposed Title

DEVELOPING AND OPTIMIZING STRATEGIES FOR EFFECTIVE MOLECULAR SCREENING, TREATMENT, AND MANAGEMENT OF NON-SMALL CELL LUNG CANCER

Goal

To maximize improvement of molecular screening and treatment methods for NSCLC; assess the latest disease state understandings and address existing unmet needs in new treatment options; improve personalized treatment for NSCLC patients; raise awareness of changes to clinical guideline criteria and policy; evaluate current physician practice patterns and attitudes.

Learning Objectives

On completion of the proposed educational activity, participants will be able to:

1. Perform more accurate, faster, and comprehensive molecular screening of NSCLC while improving awareness of biomarkers.
2. Develop strategies to improve patient outcomes by identifying the best current treatment available for each patient's unique molecular profile.
3. Develop an awareness and understanding of recent changes to guidelines for the diagnosis, management, and treatment of NSCLC.

Intended Audiences

The intended audiences for this educational activity include academic, medical, and community oncologists, nurse practitioners and physician assistants working in an oncology setting, specialty pharmacists, radiologists, oncology nurses, genetic counselors, geneticists, pathologists, and other specialists that may care for cancer patients.

Statement of Need

- There remains a general lack of clinical awareness regarding the complexity of NSCLC, biomarkers involved in the disease, and how these biomarkers can be utilized to personalize treatment.[1]
- Symptoms of the disease are hard to identify and many patients are not seek help and receive diagnosis until late stages of the disease.[2-3]
- Targeted treatments may be more effective, have fewer side effects, and be better suited to some patients with specific biomarkers than standard chemotherapy. However, these treatments remain underused and not as well understood by clinicians.[4-5]
- NSCLC is a difficult disease to treat despite the breadth of options available. Medical professionals remain unaware of the changing treatment landscape, particularly in the field of targeted therapies.

- Clinical trials are underway to evaluate new therapeutic interventions. Clinicians may not be aware of the latest findings and treatment options.
- Clinical guidelines and recommendations for the diagnosis, management, and treatment of NSCLC are changing rapidly.
    - Clinicians may not be up-to-date with new guidelines
    - Clinicians frequently recommended treatments not supported by the latest guidelines.[6]
    - Clinicians do not follow guidelines for the molecular screening for current and emerging biomarkers for NSCLC.[1]

IDENTIFIED GAPS AND BARRIERS

- *Physician-related:* lack of understanding of molecular biomarkers for the disease Lack of understanding of the changing treatment landscape, particularly regarding recent advances in targeting treatment. Unawareness of changing recommendations for NSCLC diagnosis, management, and treatment and a continued tendency to prescribe treatments not recommended in current guidelines.
- *Systems-related:* there is an unmet need to develop new therapies for NSCLC as no single therapy works for every patient.
- *Patient-related:* unawareness of symptoms and/or unwillingness to approach medical professionals to discuss symptoms until the disease is in a late stage.
- *Disease*-related: lack of knowledge of the molecular complexities of NSCLC and different biomarkers the disease.

EDUCATIONAL GAP ANALYSIS

Gap	Learning Objective	Expected Outcome	ABMS Core Competencies
Medical professionals have limited awareness of appropriate diagnostic and molecular screening techniques for NSCLC.	Review standard and emerging biomarkers for NSCLC along with the rationale and clinical implications for their use.	Clinicians will have increased understanding of the complexity of NSCLC and the breadth of biomarkers at their disposal in the selection of a treatment plan for patients. Clinicians will improve utilize	▪ Medical knowledge ▪ Patient care and procedural skills ▪ Practice-based learning and improvement

		molecular screening, allowing patients to receive personalized treatment specific to their unique molecular profile.	
Medical and health professionals are not fully aware of available of existing and new treatments for NSCLC patients, particularly in the changing field of targeted therapies.	Evaluate new and existing treatments for NSCLC, with an emphasis on the focus on targeted therapies.	Clinicians will have increased awareness of current and emerging treatments and their clinical trial data. Patients will receive relevant and clinically-tested treatment recommendations.	▪ Medical knowledge ▪ Patient care and procedural skills ▪ Practice-based learning and improvement ▪ Interpersonal and communication skills
There is a lack of understanding by medical professionals on the importance of keeping up-to-date with new guideline and recommendation releases. Patients benefit from the most current guideline-recommended diagnoses, management, and treatment protocols to which clinicians often do not adhere.	Review changing guidelines for the diagnosis, management, and treatment for NSCLC. Develop strategies to stay up-to-date with the latest recommendations and protocols.	Clinicians will be up-to-date with the latest diagnostic, management, and treatment guidelines for NSCLC. Patients will receive only guideline-recommended treatments, improving patient outcomes and well being.	▪ Medical knowledge ▪ Patient care and procedural skills ▪ Practice-based learning and improvement ▪ Interpersonal and communication skills

TENTATIVE CONTENT OUTLINE

Although content development for the activity has not yet begun, the following topics for are being considered for potential inclusion. This tentative content outline will be used to form the basis for discussion with activity faculty.

- Pre-test
- Introduction
- Confidence, practice, knowledge, and case-based questions
- Implications and importance of molecular screening in NSCLC
  - Standard biomarkers
    - EGFR mutations, ALK rearrangements, ROS1 rearrangements, the BRAF V600E mutation, PD-L1 expression
  - Emerging biomarkers
    - RET rearrangements, KRAS mutations, FGFR amplifications, MET amplifications
- Novel and current therapeutics for NSCLC, with a particular focus on the rapidly changing landscape of targeted therapeutics
  - Surgery, chemotherapy, and chemoradiation
  - Targeted therapeutics
    - Targeted therapeutics for patients with EGFR mutations, including examples of available (gefitinib, erlotinib, afatinib, and osimertinib) and emerging (savolitinib combination therapy with osimertinib or gefitinib) treatments.
    - Targeted therapeutics for patients with ROS1 and ALK rearrangements, including examples of current treatments (crizotinib, ceritinib, and alectinib)
    - New targeted therapeutics for the BRAF V600E mutation, including (dabrafenib/trametinib, dabrafenib, and vemurafenib)
    - Targeted therapeutics for PD-L1 expression, including examples of current and emerging treatments (Pembrolizumab, nivolumab, atezolizumab, atezolizumab, and durvalumab).
    - Targeted therapeutics for patients with RET gene rearrangements, including examples of current therapies (vandetanib, cabozantinib)
    - Targeted emerging therapeutics for patients with KRAS mutations (selumetinib, AZD4785, binimetinib) and FGFR1/3 amplifications (AZD4547 and BGJ398)
- Changing guidelines for the diagnosis, management, and treatment of NSCLC

        - Discuss rapidly changing guidelines for NSCLC, including
            - National Comprehensive Cancer Network (NCCN)
            - American Society for Clinical Oncology (ASCO)
            - American Cancer Society (ACS)
            - American College of Chest Physicians (ACCP)
            - Preventative Services Task Force (USPSTF)
        - Discuss importance of keeping up-to-date with guideline changes for patient care and well being.
        - Remind clinicians how to access updated guidelines and stay current with new guideline and recommendation releases.
- Conclusion: key points
- Post-test
    - Confidence, practice, knowledge, and case-based questions
- Evaluation

Literature Review

Lung cancer is the most prominent type of cancer worldwide and the cause of more than a quarter of cancer-related death in the United States.[2-3] The disease often remains undetected until more advanced stages. Around 50% of patients present with metastatic cancer at time of diagnosis and have a median survival of under a year.[2-3]

Lung cancer can be divided into two subcategories, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[2-3] Approximately 85-90% of all lung cancer patients have NSCLC.[2-3] The disease is commonly associated with smoking cigarettes, but around 15% of patients have a minimal history or even no history of smoking.[2] The most common symptom of the disease is coughing, which can also be caused by a number of common maladies. This may contribute to the late diagnosis of the disease.

NSCLC can be further subdivided into subtypes. The two most common subtypes are adenocarcinoma (40% of diagnoses) and squamous cell carcinoma (25% of diagnoses).[2] There are a wealth of biomarkers associated with these and other types of NSCLC. Patients that express these biomarkers may be candidates for treatments that are more effective and have fewer side effects than standard chemotherapy.

Overview of the Importance of Molecular Profiling in NSCLC Diagnosis

- Medical understanding of the complexities of NSCLC is quickly expanding. There are many well-studied key biomarkers in some patients that make

certain treatment options significantly more effective over standard chemotherapy.

- Several studies and surveys suggest that clinicians are unfamiliar with both biomarkers now considered standard in the care of NSCLC patients along with emerging biomarkers quickly becoming important in patient treatment.
    - Biomarkers like EGFR mutations, ALK rearrangements, ROS1 rearrangements, the BRAF V600E mutation, and PD-L1 expression are now considered standard biomarkers in guidelines that should be regularly assessed in patients by clinicans.[5] However, one recent study of 814 patients, a third of patients were not tested for *EGFR* or *ALK* and only 8% of patients underwent comprehensive genomic profiling.[4] When molecular testing was completed, it took a median time of 23 days from date of diagnosis for physicians to receive results.[4] This may be too slow for frailer patients that could still benefit from targeted therapy.
    - Another study found that 22% of surveyed clinicians lacked knowledge of the importance of molecular testing and its potential implications for the prognosis and treatment options for their patients.[1] Only a quarter of respondents intended to use genetic testing in over 90% of their patients.[1]
    - In a comprehensive survey of about 400,000 physicians, only 13% had recommended molecular testing in the past 6 months and only 25% expected to recommend it in the near future.[7-8]
- Even when clinicians follow guidelines for standard biomarkers, they may not be familiar with emerging biomarkers that could still benefit their patients during treatment selection.
    - Another study found that even when clinicians conduct molecular testing for biomarkers like EGFR and ALK, they often do not screen for additional mutations. Only half of respondents recommended next generation sequencing (NGS) to screen for other types of mutations.[4]
- Standard Biomarkers
    - Biomarkers commonly considered standard in NSCLC patients include EGFR mutations, ALK rearrangements, ROS1 rearrangements, the BRAF V600E mutation, and PD-L1 expression.[5]
    - Guidelines like the NCCN recommend regularly assessing NSCLC patients for these biomarkers based on the existence of targeted

treatments that can be more effective and have fewer side effects than standard chemotherapy.[5]

- **EGFR mutations**
  - The EGFR gene codes for the epidermal growth factor receptor protein. Most of the gene mutations result in a constitutively activated protein. Protein overexpression has been linked to the formation of many tumors, including tumors in the lung, prostate, kidney, colon, ovary, and bladder.[9-10]
  - EGFR mutations are the second most commonly identified type of mutation, impacting approximately 17% of patients with lung adenocarcinoma.[11]
  - The mutations are most common in Asian patients and non-smokers.[5, 9]
  - The majority of mutations occur in exons 18-21 which are responsible for encoding the tyrosine kinase domain. These mutations are associated with increased sensitivity to EGFR TKI therapy, discussed more below.[10]
  - The mutation T790M originates in exon 20 and is found in approximately 50% of patients with acquired resistance to EGFR TKI therapeutics. The amino acid is a "gatekeeper residue," and the bulkier methionine interferes with the binding of EGFR TKI therapeutics. The mutation is thought to occur during treatment, highlighting a potential benefit of periodically monitoring some patients for the development of new biomarkers.[10]
    - Understanding the significance of this mutation in patients can help clinicians select a therapy less prone to acquiring treatment resistance.
- **ALK rearrangements**
  - The ALK gene codes for anaplastic lymphoma kinase, a type of transmembrane tyrosine kinase.[12]
  - Common mutations fuse the gene with various partner genes. There are approximately 30 known ALK fusions, including a fusion with echinoderm microtubule associated protein-like 4 (EML4) that constitutively activates the protein.[5, 12]
  - ALK fusions are generally mutually exclusive to EGFR mutations.[5, 12]

- Patients with ALK fusions can be excellent candidates for ALK inhibitors, including those discussed more below.
- Non-smokers, women, and younger patients are more likely to have ALK fusions.[12]
- Since complete genetic profiling can be costly and require large tissue samples, early guidelines and recommendations suggested minimal screening. However, more recent guidelines are beginning to suggest more extensive screening, including look EML4-ALK fusions in patients with advanced lung adenocarcinoma.[12-13]
- Fluorescence in-situ hybridization (FISH) is the current standard for ALK fusion detection. Next generation sequencing can also be used.[5]

➢ **ROS1 rearrangements**

- ROS1 encodes tyrosine kinase receptor with high homology to ALK.
- Most patients with ROS1 rearrangements respond less well to treatments that solely work as ALK inhibitors. Treatments that specifically act on ROS1 are a better option.[5]
- The rearrangements are most common in young Asian women and non-smokers.[12]
- Similar to ALK rearrangements, FISH is also the standard method of detection for ROS1 rearrangements. Next generation sequencing can also be used.[5]

➢ **BRAF V600E mutation**

- This is the most common mutation in the BRAF (v-RAF murine sarcoma viral oncogene homolog B).
- Patients with this mutation are more likely to be current or former smokers.
- The BRAF V600E biomarker has recently been considered more of a standard than emerging biomarker based on the development of new treatments discussed below that could benefit patients with the mutation.
- To minimize testing and preserve tissue, guidelines recommend testing be done as part of a broader molecular profiling effort looking at standard biomarkers.[5]

➢ **PD-L1 Expression**

- Patient expression of PD-L1 is another biomarker to that can be used to identify patients likely to have a better response to immune checkpoint inhibitors.

        - Testing for PD-L1 is much more difficult than other biomarkers. However, the efficacy of new targeted therapies makes it an important biomarker and guidelines recommend that clinicians understand it and assess patients for it.[5]
        - Unique assays are in development for specific immune checkpoint inhibitors still in clinical trials.[5]

- Emerging Biomarkers
    - Guidelines also strongly advise additional molecular screening for emerging biomarkers in patients.[5]
    - Identifying emerging biomarkers like KRAS mutations, RET rearrangements, Met amplifications and mutations, or FGFR1/3 helps ensure patients receive the best possible treatment for their unique condition. It also could make some patients eligible for one of the many clinical trials currently examining emerging targeted therapies.[5]
    - **RET gene rearrangements**
        - The RET (rearranged during transfection) oncogene codes for a tyrosine kinase receptor. These gene rearrangements may be susceptible to targeted therapies.[14]
        - Some guidelines recommend testing for RET rearrangements because of new effective and approved therapies along with several emerging therapies.
    - **KRAS mutations**
        - The KRAS gene codes for the K-Ras signalling protein involved in regulating cell division. The majority of mutations in the gene result in a constitutively active protein that leads to unregulated cell division and tumour formation.[15]
        - KRAS mutations are the most common type of mutations in lung adenocarcinoma, impacting approximately 25% of patients.[11, 16]
        - The mutation is associated with resistance to EGFR TKI therapy.[5] Its discovery and impact on therapy selection has consequently nearly doubled the duration of survival for patients with EGFR mutations.[17]
        - The KRAS mutations are more common in smokers, non-Asian patients, and patients with mucinous adenomcarcinoma.[5]
        - Although there are no approved therapeutics that target KRAS, there are some agents in development.

- There are wide variety of methods that can facilitate easy screening and detection KRAS mutations.[18]

➢ **FGFR1/3**

- FGFR1/3 are commonly amplified genes throughout human cancers. FGFR1 amplifications in particular have previously been found in 13-22% of lung squamous cell carcinomas.
- There are still no approved therapies targeting these amplifications for NSCLC, but a number of promising therapeutics are currently in development.

➢ **MET amplifications and mutations**

- The MET gene codes for a kinase domain involved in the invasion, angiogenesis, and metastasis of tumors.[10]
- Amplifications are involved in EGFR TKI therapy resistance.[10] Screening for MET can therefore help clinicians select a the most effective therapy for their patient.
- Some available and emerging combination therapies discussed below combining targeted MET therapies with EGFR TKI therapies to improve treatment efficacy.

▪ *The proposed educational activity will provide a brief overview of appropriate molecular screening techniques for NSCLC. The activity will address common biomarkers now considered standard (e.g. EFGR mutations, ALK and ROS1 rearrangements, the BRAF V600E mutation, and PD-L1 expression) along with a selection of emerging biomarkers with clinical significance for patients (RET rearrangements, KRAS mutations, FGFR1/3, MET amplifications). The activity will address the implications of these biomarkers for patient prognosis and treatment.* ***[Learning Objective 1]***

Biomarker	Frequency	Examples of Targeted Agents
Standard Biomarkers		
EGFR mutations	40-50% in ADCs[a] 10-20% in ADCs[b]	gefitinib, erlotinib, afatinib, osimertinib
ALK Rearrangements	5% in ADCs	crizotinib, ceritinib, alectinib
ROS1 Rearrangements	1% in ADCs	crizotinib
BRAF V600E Mutation	1-4% in ADCs	dabrafenib-Trametinib, dabrafenib, vemurafenib.
PD-L1 Expression	Definition of positive varies	pembrolizumab, nivolumab, atezolizumab, durvalumab

Emerging Biomarkers		
RET Rearrangements	1% in ADCs	vandetanib, cabozantinib
KRAS Mutations	5-10% in ADCs[a] 20-30% in ADCs[b]	Several promising emerging therapies
FGFR1/3	1% in NSCLC	Several promising emerging therapies
MET Amplification	2-4% in ADCs	crizotinib

[a]Asian Populations, [b]Western Populations. ADC, adenocarcinoma; NSCLC, non-small cell lung cancer.

Table I. A selection of standard and emerging biomarkers, their frequency, and selected targeted agents.

Overview of Current and Emerging Therapeutics for NSCLC

- The landscape for the treatment of NSCLC is rapidly changing as scientists continue to uncover more information about the complexities of the disease. The discovery of new biomarkers and molecular targets quickly leads to the development and clinical testing of promising new therapies.
- Clinicians need to be kept up-to-date with this rapidly changing treatment landscape. Several studies, surveys, and questionnaires suggest that clinicians lack essential knowledge about current and emerging treatments.
    - "In addition to the high prevalence of NSCLC, contemporary management is becoming increasingly complex due to the identification of key biomarkers that influence optimal treatment selection and the development of targeted therapies," remarked Hirsch *et al* in a recent study examining the benefits of continuing medical education on clinician performance.[3]
    - There may even be knowledge gaps among clinicians in the treatment of NSCLC patients with standard biomarkers, like EGFR mutations.
        - In one Medscape survey, only 34% of clinicians correctly identified appropriate first-line treatments for a NSCLC patient with an EGFR mutation in a case study.[2]
        - In the same survey, only a quarter of clinicians correctly identified osimertinib as a possible subsequent treatment for patients with acquired resistance to EGFR TKI therapies.[2]

Surgical Resection, Chemotherapy, and Chemoradiation

- Surgery is the optimal treatment for early stage NSCLC. Unfortunately, patients are often diagnosed after the disease has progressed pass the point where surgical resection is possible.[5, 19]

- Chemotherapy is considered for approximately 80% of patients during the course of their illness.[5, 19]
    - Can be particularly effective for patients in earlier stages of the disease, particularly when surgical resection is not possible.
    - However, patients that are often prescribed chemotherapy in later stages of the disease could benefit from targeted treatments that are more effective and have fewer side effects.
- Radiation is also effective in earlier stages of NSCLC and can be used alone when surgical resection is not possible. It is less effective in later stages of the disease.[5, 19]

Targeted therapies for patients with EGFR mutations

- Current Therapies
    - **Gefitinib** and **Erlotinib** are effective first-line therapies for patients with sensitizing EGFR mutations.
        - Gefitinib and erlotinib are oral TKI therapies that are well tolerated by the majority of patients.
        - A phase 4 clinical study demonstrated that gefitinib is effective and safe for NSCLC patients with sensitizing EGFR mutations.[5]
        - A series of extensive clinical trails have demonstrated that patients with sensitizing EGFR mutations who receive a first-line TKI therapy like gefitinib and erlotinib generally have better responses and experience fewer side effects than those that receive standard chemotherapy.[5]
        - These studies have caused multiple guidelines and position statements to strongly recommend EGFR mutation testing in non-squamous NSCLC or NSCLC not otherwise specified. Some guidelines also recommend EGFR mutation testing for squamous cell NSCLC in some patient populations.[5]
    - **Afatinib** is an oral medication targeting the entire ErbB/HER receptor family, including EGFR and HER2.[20-21]
        - Afatinib is recommended as another first-line therapy for patients with sensitizing EGFR mutations.[5]
        - A phase 3 randomized trial showed that Afatinib had less adverse effects than standard chemotherapy [22] However, the medication was also possibly associated with 4 more treatment-related deaths than standard chemotherapy.[5]
        - Although more effective than standard chemotherapy as a first-line treatment for patients with EGFR mutations, patients may still develop the EGFR T790M mutation and drug resistance, leading to the need for a second-line therapy.[5]

- **Osimertinib** is a newer therapy with strong clinical evidence for the treatment of NSCLC patients with EGFR mutations.
    - The US NCCN Clinical Practice Guidelines were recently updated to include osimertinib as a first-line therapy for patients with locally advanced or metastatic NSCLC patients with documented EGFR mutations.[23]
    - The treatment selectively targets both EGFR mutations and the EGFR T790M mutation that sometimes develops during treatments and confers resistance to therapies like gefitinib, erlotinib, and afatinib.[24] In addition to being recommended as a first-line therapy, the medication is also recommended for subsequent treatment of patients with EGFR T790M mutations that have developed resistance for other first-line options.[5]
    - The randomized phase 3 FLAURA clinical trial found that osimertinib improved progression-free survival of patients by 54% compared to standard first-line therapies.[24]
    - The ongoing BLOOM study examining the effect of osimertinib on patients with leptomeningeal metastases from EGFR mutant NSCLC found that the drug penetrates the blood brain barrier, has good activity, and manageable adverse events.[25] The medication is consequently now recommended by the NCCN for patients with T730M who have progression with symptomatic brain metastases.[5]
- Emerging Therapies
    - **Savolitinib** alongside **osimertinib** or **gefitinib** are two promising combination regimens currently undergoing clinical trials for the treatment of EGFR mutation positive patients with NSCLC with MET-amplification.
        - Savolitinib is a c-MET receptor tyrosine kinase selective inhibitor. Two phase 1b/2 proof-of-concept studies showed that it can be effective when used in combination with either EGFR inhibitor in patients that have progressed after treatment with an EGFR inhibitor alone.[26-27]
        - Two phase 1b trails with the combination therapies in NSCLC patients with EGFR mutations and MET-amplification that had continued to progress after treatment with an EGFR inhibitor showed positive results.

Targeted therapies for patients with ALK and/or ROS1 rearrangements

- Current therapies
    - **Crizotinib** is an oral TKI and an effective first-line therapy for patients with ALK or ROS1 gene rearrangements. A phase 3 study found that the therapy had improved response rates and quality of

life in patients with ALK rearrangements compared to standard chemotherapy. Another study also found Crizotinib had a 70% response rate in patients with ROS1 rearrangements. It is the only first-line therapy currently recommended for the treatment of patients with ROS1 rearragnments.[5]

- **Ceritinib** is an oral TKI effective in patients with ALK rearrangements. Previous studies have shown patients have a good overall response to certinib after previous treatment with crizotinib. The therapy is therefore effective as a subsequent therapy for ALK-positive patients that have progressed after crizotinib. It can also make an effective first-line therapy. Results from a recent phase 3 study showing good efficacy and tolerability in ALK-positive metastatic NSCLC patient.[5]
- **Alectinib** is another oral TKI effective in patients with ALK rearrangements. Previous studies demonstrate its effectiveness as a subsequent therapy for patients that have progressed on or are intolerant to crizotinib. More recent studies also demonstrate that it can make an effective first-line therapy for ALK-positive metastatic NSCLC patients. One phase 3 trail found slower disease progression, fewer deaths, and fewer side effects in patients ALK-positive patients with advanced NSCLC on alectinib versus crizotinib.[5]

Targeted therapies for patients with the BRAF V600E mutation

- Current therapies
  - The combination regimen of **dabrafenib/trametinib** is the only approved targeted first-line therapy for patients with the BRAF V600E mutation. Dabrafenib is a TKI that inhibits BRAF V6000E mutations while trametinib can inhibit both BRAFV600E and MEK.[5]
    - The combination regimen had a high response rate of 63% with adverse events including pyrexia, hemoptysis, cutaneous squamous cell carcinoma, pyrexia, anemia, and a confused state.[5]
    - Despite the adverse events, the efficacy of the treatment has caused some guidelines to begin recommending that clinicians regularly screen for the BRAF V600E mutation to ensure patients receive the best possible care.[5]
  - When patients are unable to tolerate the combination therapy, single therapy with **dabrafenib** or **vemurafenib** can also be effective.

Targeted therapies for patients with PD-L1 expression

- Current therapies

- **Pembrolizumab** inhibits the PD-1 receptor and is the only targeted first-line therapy recommended for patients with PD-L1 expression. The FDA approved the therapy as a first-line treatment based on a phase 3 trial that found patients had a better response, an improved overall survival, and fewer treatment-related adverse events with pembrolizumab compared to standard chemotherapy.[5]
    - PD-L1 is not an ideal biomarker because it is still difficult to test for and its expression levels are continually changing. However, the efficacy of pembrolizumab makes it an important biomarker and guidelines recommend that clinicians routinely include it in their standard molecular assessments.[5]
- Recent studies also suggest that combination **pembrolizumab with chemotherapy** can be an effective first-line treatment in patients with advanced non-squamous NSCLC or NSCLC that is not otherwise specified. The combination therapy had a better response rate than patients on chemotherapy alone. However, patients on the combination regimen also experienced more treatment-related adverse events than those on chemotherapy alone.[5]
- **Nivolumab** inhibits PD-1 receptor and is recommended as subsequent therapy in patients with metastatic non-squamous and squamous NSCLC that have progressed after chemotherapy. It does not have a higher overall survival over chemotherapy in patients without PD-L1 expression but does have fewer treatment-related adverse events.[5]
- **Atezolizumab** inhibits PD-L1, and similar to pembrolizumab and nivolumab, it has fewer side effects than chemotherapy. Molecular screening for PD-L1 is not required but still could provide useful information about the patient's cancer.[5]

- Emerging therapies
    - **Durvalumab** is a human monoclonal antibody targeting PD-L1 currently used in earlier stages. It's still being studied as a first-line therapy for patients.
        - The FDA recently approved the medication for use as a maintenance therapy in NSCLC patients that are ineligible for surgery. Similarly, the European Medicines Agency recently accepted marketing authorization for this use.[28-29]

Targeted therapies for patients with RET gene rearrangements

- Current therapies
    - **Vandetanib** is recommended in patients with RET rearrangements. A smaller phase 2 study of 18 patients found that after treatment,

17% of patients had partial remission and 44% exhibited stable disease after treatment. However, 33% died shortly after enrollment from rapid tumor progression.[5]

- **Cabozantinib** is also recommended for patients with RET rearrangments based on a phase 2 study. Partial response to treatment was observed in 2 patients while a third had prolonged stable disease after treatment. [5]

Targeted therapies for patients with KRAS Mutations

- Emerging therapies
  - Although there are no approved therapeutics that target KRAS, likely because blocking its activity has so far proven very difficult.[30] However, there are some agents in development, including the following.
  - **Selumetinib** is a MEK-inhibitor that previously showed no significant improvement when combined with docetaxel as a second-line treatment for SCLC patients with KRAS mutations in a phase 3 trial. However, it is still being studied in other trails, including a phase 1b/2 study examining the therapy in combination with gefitinib in NSCLC patients that have developed resistance to EGFR TKI treatment[31] and a phase 1 study examining its effectiveness in combination with other chemotherapies.[32]
  - **AZD4785** is a promising emerging therapy for KRAS-dependent tumors. Preclinical studies showed that selectively targeted KRAS mRNA, lowering KRAS mRNA and protein levels. Studies in mice and monkeys verified the safety and efficacy the therapy.[30]
  - **Binimetinib** is a MEK-inhibitor currently being examined in a phase 1 study in NSCLC patients with KRAS mutations in combination with pemetrexed and cisplatin.

Targeted therapies for patients with FGFR1/3 amplifications

- Although there are no approved therapeutics that target FGFR1/3. However, there are some agents in development, including **AZD4547** and **BGJ398**. Both show good efficacy and tolerability in a variety of cancer types.[33]

- *The proposed educational activity will provide a brief review of the most up-to-date treatments for NSCLC along with upcoming therapies under investigation in patients with NSCLC, with a particular focus on the rapidly expanding field of targeted treatments. This will allow medical professionals to select appropriate and effective personalized treatments for their patients.* ***[Learning Objective 2]***

Improving Patient Outcomes by Informing Clinicians of Changes to Practice Guidelines and Recommendations

- Preferred methods for the diagnosis, management, and treatment of NSCLC patients are changing rapidly as new research is uncovered. It is imperative that clinicians remain up-to-date with current guidelines.
  - One recently reported study in a primary care clinic found that adherence to lung cancer screening guidelines improved from 60% to 82.2% after a clinical reminder about guideline importance.[34]
  - Another study found that clinicians ignored guidelines recommending screening for common biomarkers. In a study of 814 patients, less than 60% met the guideline recommendations for EGF and ALK testing.[4]
  - Another study reviewing 592 eligible NSCLC patient cases found that found that early stage NSCLC patients that received a guideline recommended therapy had an improved survival rate. Unfortunately, the same study also found that one third of the reviewed cases did not receive a guideline recommended therapy, highlighting the importance of guideline medical education.[6]
- There are a variety of guidelines recommendations, and position statements for the treatment of NSCLC, including[19, 35]
  - National Comprehensive Cancer Network (NCCN)
  - American Society for Clinical Oncology (ASCO)
  - American Cancer Society (ACS)
  - American College of Chest Physicians (ACCP)
  - Preventative Services Task Force (USPSTF)
- Recent changes have been made in these and other guidelines over the course of the last year to reflect new diagnostic measure and FDA approvals. In particular, there have been new updates concerning approved targeted therapies and biomarkers for metastatic NSCLC patients.

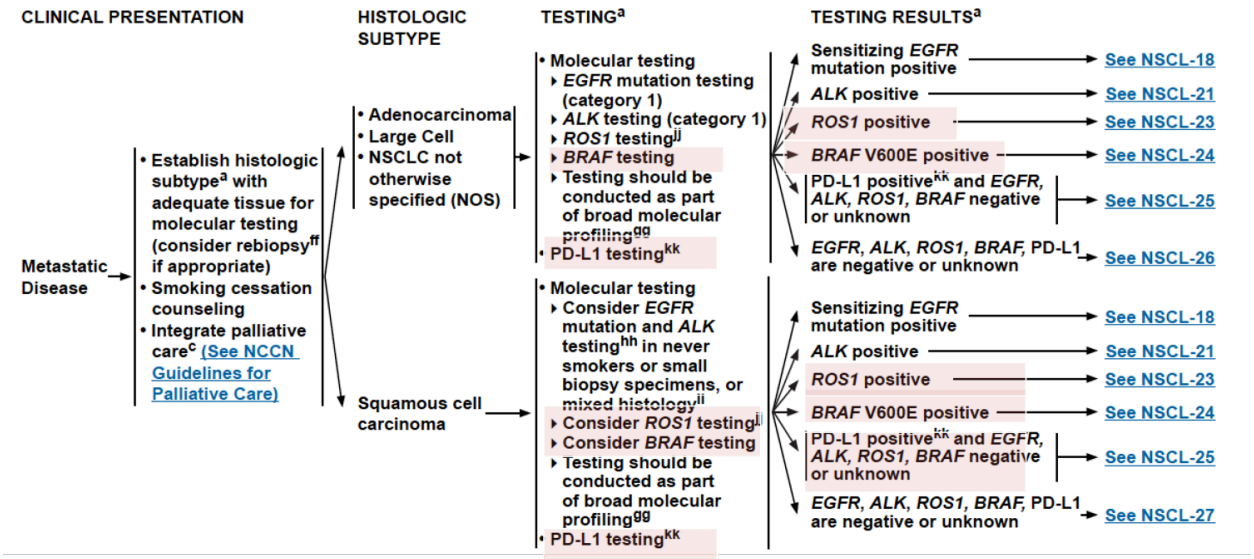

Figure 1. A representative example of guideline changes for molecular testing and treatment of metastatic NSCLC patients. Highlighted sections represent just a sample of recent changes to one guideline.[5]

- *The proposed educational activity will identify strategies to improve patient outcomes by familiarizing clinicians with the most current guidelines for the diagnosis, management, and treatment of patients with NSCLC. The educational activity will emphasize the rapidly changing nature of guidelines and highlight how clinicians can stay up-to-date with future changes.* ***[Learning Objective 3]***

Expert Opinion

"Significant knowledge gaps exist about molecular testing in NSCLC among specialists that diagnose the disease. Specialist education significantly improves knowledge and awareness about molecular testing and its importance in NSCLC."[36]

"In addition to the high prevalence of NSCLC, contemporary management is becoming increasingly complex due to the identification of key biomarkers that influence optimal treatment selection and the development of targeted therapies."[3]

Public Health Data

- Lung cancer is the leading cause of cancer-related deaths.[3]
  - A total of 215,951 people in 2014 were diagnosed with lung cancer, including 102,625 women and 113,326 men.

    - A total of 155,526 deaths in the United States in 2014 were attributed to lung cancer, including 70,667 women and 84,859 men.[37]
- The disease often remains undetected until more advanced stages. Around 50% of patients present with metastatic cancer at time of diagnosis.[2-3]
- The disease is commonly associated with smoking cigarettes, but around 15% of patients have a minimal history or even no history of smoking.[2]
- Costs of healthcare for NSCLC patients are significantly lower if diagnosed early. One study of 1,210 patients found that per-patient-per-month costs for the care of patients diagnosed at Stage IV ($21,441) was more than double than those diagnosed at Stage I ($7,239)[38]

Observed Need

NSCLC is a highlight prevalent disease requiring further study to increase medical knowledge and provide patients with treat patients with effective targeted therapies. A search of the National Institute of Health clinical trials database at www.clinicaltrials.gov found a total of 263 phase 3 and 4 ongoing and recently completed clinical studies with NSCLC patients, of which 105 studies are currently recruiting and 22 studies are completed with results. These clinical trials will evaluate the safety and efficacy of a range of general and targeted treatments for NSCLC, and the results of will be invaluable for accuracy in the diagnosis and treatment of patients. Advanced knowledge and improved patient care will result from addressing educational needs of health professionals in NSCLC.

References

1. Gray SW, Hicks-Courant K, Cronin A, et al. Physicians' attitudes about multiplex tumor genomic testing. J Clin Oncol. 2014;32(13):1317–1323.
2. Eaby-Sandy B, Shih HW. EGFR Targeted Therapies for Advanced Non-Small Cell Lung Cancer (NSCLC). https://www.medscape.org/viewarticle/871996. November 30, 2016. Accessed October 14, 2017.
3. Hirsch FR, Jotte RM, Berry CA, Mencia WA, Stowell SA, Gardner AJ. Quality of care of patients with non-small-cell lung cancer: a report of a performance improvement initiative. Cancer Control. 2014;21(1):90-7.
4. Gutierrez ME, Choi K, Lanman RB, et al. Genomic Profiling of Advanced Non-Small Cell Lung Cancer in Community Settings: Gaps and Opportunities. Clin Lung Cancer. 2017 [Epub ahead of Print].
5. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 9.2017, NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. September 28, 2017. Accessed October 15, 2017.

6. Duggan KJ, Descallar J, Vinod SK. Application of Guideline Recommended Treatment in Routine Clinical Practice: A Population-based Study of Stage I-IIIB Non-small Cell Lung Cancer. Clin Oncol (R Coll Radiol). 2016;(10):639-47.
7. Herrmann T, Peters P, Williamson C, Rhodes E. Educational outcomes in the era of the Affordable Care Act: impact of personalized education about non-small cell lung cancer. J Contin Educ Health Prof. 2015;35 Suppl 1:S5-12.
8. Stanek EJ, Sanders CL, Taber KA, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. Clin Pharmacol Ther. 2012;91(3):450–458.
9. U.S. National Library of Medicine. KRAS gene. https://ghr.nlm.nih.gov/gene/EGFR. October 17, 2017. Accessed October 18, 2017.
10. Singh M, Jadhav HR. Targeting non-small cell lung cancer with small-molecule EGFR tyrosine kinase inhibitors. Drug Discov Today. 2017. pii: S1359-6446(17)30371-9.
11. Chia PL, Mitchell P, Dobrovic A, John T. Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors. Clin Epidemiol. 2014;6:423-32.
12. Chalela R, Curull V, Enríquez C, Pijuan L, Bellosillo B, Gea J. Lung adenocarcinoma: from molecular basis to genome-guided therapy and immunotherapy. J Thorac Dis. 2017;9(7):2142-2158.
13. Villar Álvarez F, Muguruza Trueba I, Belda Sanchis J, et al. Executive summary of the SEPAR recommendations for the diagnosis and treatment of non-small cell lung cancer. Arch Bronconeumol. 2016;52(7):378-88.
14. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(4):504-535.
15. U.S. National Library of Medicine. KRAS gene. https://ghr.nlm.nih.gov/gene/KRAS. October 17, 2017. Accessed October 18, 2017.
16. Brose MS, Volpe P, Feldman M, et al. BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res. 2002;62(23):6997-7000.
17. Suda K, Tomizawa K, Mitsudomi T. Biological and clinical significance of KRAS mutations in lung cancer: an oncogenic driver that contrasts with EGFR mutation. Cancer Metastasis Rev. 2010;29(1):49-60.
18. Johnson M. AstraZeneca Publishes Head-to-Head Study of 13 KRAS Mutation Detection Technologies. https://www.genomeweb.com/pcr/astrazeneca-publishes-head-head-study-13-kras-mutation-detection-technologies. October 17, 2017. Accessed October 20, 2017.
19. Tan WW. Non-small cell lung cancer. https://emedicine.medscape.com/article/279960-overview. August 17, 2017. Accessed October 15, 2017.
20. Nelson V, Ziehr J, Agulnik M, Johnson M. Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC. Onco Targets Ther. 2013;6:135-43.

21. De Grève J, Teugels E, Geers C, et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer. 2012;76(1):123-7.
22. Yang JC, Hirsh V, Schuler M, Yet al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3342-50.
23. AstraZeneca. TAGRISSO® (osimertinib) granted Breakthrough Therapy Designation by US FDA for the 1st-line treatment of patients with EGFR-mutation positive non-small cell lung cancer. https://www.astrazeneca-us.com/media/press-releases/2017/tagrisso-osimertinib-granted-breakthrough-therapy-designation-by-us-fda-for-the-1st-line-treatment-of-patients-with-egfr-mutation-positive-non-small-cell-lung-cancer-10092017.html. October 9, 2017. October 15, 2017.
24. ESMO 2017 Press Release. Osimertinib Improves Progression-free Survival in Patients with EGFR Mutated Lung Cancer. http://www.esmo.org/Conferences/ESMO-2017-Congress/Press-Media/Press-Releases/Osimertinib-Improves-Progression-free-Survival-in-Patients-with-EGFR-Mutated-Lung-Cancer. September 9, 2017. Accesssed October 17, 2017.
25. Yang J C-H, et al. Osimertinib for Patients with Leptomeningeal Metastases from EGFR-Mutant Non-Small Cell Lung Cancer: Updated Results from the BLOOM Study Abstract 2020 [Poster 262]. Presented at the annual meeting of the American Society of Clinical Oncology, 2-6 June 2017, Chicago, USA.
26. Ahn M-J, et al. TATTON Phase Ib Expansion Cohort: Osimertinib Plus Savolitinib for Patients with EGFR-mutant MET-amplified NSCLC After Progression on Prior EGFR-TKI. Abstract #8985. Presented at the World Lung Cancer Congress (WCLC) 2017, Yokohama, Japan.
27. Yang J-J, et al. A Phase Ib Trial of Savolitinib Plus Gefitinib for Patients with EGFR-mutant MET-amplified Advanced NSCLC. Abstract #8995. Presented at the World Lung Cancer Congress (WCLC) 2017, Yokohama, Japan.
28. AstraZeneca. The European Medicines Agency accepts marketing authorisation application for Imfinzi in locally-advanced unresectable non-small cell lung cancer. https://www.astrazeneca.com/media-centre/press-releases/2017/the-european-medicines-agency-accepts-marketing-authorisation-application-for-imfinzi-in-locally-advanced-unresectable-non-small-cell-lung-cancer-09102017.html. October 9, 2017. Accessed October 15, 2017.
29. AstraZeneca. Imfinzi granted Breakthrough Therapy Designation by US FDA for patients with locally-advanced unresectable non-small cell lung cancer. https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2017/imfinzi-granted-breakthrough-therapy-designation-by-us-fda-for-patients-with-locally-advanced-unresectable-non-small-cell-lung-cancer-31072017.html. July 31, 2017. Accessed October 20, 2017.
30. Ross SJ, Revenko AS, Hanson LL, et al. Targeting KRAS-dependent tumors with AZD4785, a high-affinity therapeutic antisense oligonucleotide inhibitor of KRAS. Sci Transl Med. 2017;9(394).

31. Yang C-H and Lin S-H. Selumetinib in Combination With Gefitinib in NSCLC Patients. ClinicalTrials.gov Identifier: NCT02025114.
32. Nicholas G and Goffin J. Study of Selumetinib in Patients With Previously Treated or Untreated Advanced/Metastatic NSCLC. ClinicalTrials.gov Identifier: NCT01783197.
33. Misra K. Reinvestigation of FGFR Inhibitors in Lung Cancer Under Way. http://www.targetedonc.com/news/reinvestigation-fgfr-inhibitors-in-lung-cancer-underway. January 11, 2016. Accessed October 20, 2017.
34. Johnson K, Hughes N, Williams B, Beyth R, Lo M, Olson A. A Clinical Reminder Improves Adherence to Lung Cancer Screening Guidelines. Presented at the American Thoracic Society International Conference, 2017. Washington, DC.
35. Tan WW. Non-Small Cell Lung Cancer Guidelines. https://emedicine.medscape.com/article/2241676-overview. October 20, 2015. Accessed October 14, 2017.
36. Zer A, Cutz JC, Sekhon HS, et al. A targeted intervention to improve awareness to molecular testing in NSCLC. Presented at: American Society of Clinical Oncology Annual Meeting, 2014. Chicago, IL.
37. CDC. Lung Cancer Statistics. https://www.cdc.gov/cancer/lung/statistics/index.htm. May 23, 2017. Accessed Octoer 20, 2017.
38. Gildea TR, DaCosta Byfield S, Hogarth DK, Wilson DS, Quinn CC. A retrospective analysis of delays in the diagnosis of lung cancer and associated costs. Clinicoecon Outcomes Res. 2017;9:261-269.