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Learning Objectives

1. Review the molecular pathology of lung cancer and examine its relevance for clinical practice.

2. Outline the safety and efficacy of first-line therapies for advanced NSCLC, including first generation EGFR and ALK inhibitors.

3. Evaluate treatment approaches used to overcome EGFR and ALK resistance in advanced NSCLC, including the safety and efficacy of second- and third-line therapies and recommended molecular testing.

4. Appraise emerging concepts with EGFR TKIs and ALK inhibitors, including their role in adjuvant therapy, combination therapies, and other evolving data.
Molecular Pathology of Lung Cancer

Overview and Relevance for Clinical Practice
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Program Director
Lowe Center for Thoracic Oncology
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts
Disclosures

• Consultant for: AstraZeneca, Boehringer Ingelheim, Pfizer, Genentech, Roche, ARIAD, Chugai Pharmaceuticals, ACEA Biosciences, Merrimack Pharmaceuticals

• Research Funding: AstraZeneca, Astellas

• Stockholder in: Gatekeeper Pharmaceuticals

• Other: LabCorp – post-marketing royalties from DFCI owned intellectual property on EGFR mutations
Lung Adenocarcinoma

Progress in Identifying Genomic Alterations

- **1984 - 2003**
  - No known genotype
  - KRAS

- **2004**
  - No known genotype
  - KRAS

- **2009**
  - No known genotype
  - KRAS
  - EGFR
  - PIK3CA
  - ALK
  - BRAF
  - HER2

- **2016**
  - No known genotype
  - KRAS
  - EGFR
  - PIK3CA
  - ALK
  - BRAF
  - HER2
  - NTRK1
  - MET
  - ROS1
Lung Squamous Carcinoma
Genomic Alterations

- FGFR1 amplification
- FGFR mutation
- FGFR fusion
- PIK3CA mutation/amplification
- DDR2 mutation
- PDGFRA amplification
- BRAF mutation
- EGFR amplification
- ERBB2 amplification
- None

Metastatic NSCLC

**SYSTEMIC THERAPY FOR METASTATIC DISEASE**

- Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy if appropriate)
- Smoking cessation counseling
- Integrate palliative care (See NCCN Guidelines for Palliative Care)

**HISTOLOGIC SUBTYPE**

- Adenocarcinoma
- Large Cell
- NSCLC not otherwise specified (NOS)

**TESTING**

- EGFR mutation testing (category 1)
- ALK testing (category 1)
- EGFR and ALK testing should be conducted as part of broad molecular profiling

**TESTING RESULTS**

- Sensitizing EGFR mutation positive
- ALK positive
- Both sensitizing EGFR mutation and ALK are negative or unknown

- Consider EGFR mutation and ALK testing especially in never smokers or small biopsy specimens, or mixed histology
- EGFR and ALK testing should be conducted as part of broad molecular profiling

- Sensitizing EGFR mutation positive
- ALK positive
- Both sensitizing EGFR mutation and ALK are negative or unknown

See First-Line Therapy (NSCL-17)
See First-Line Therapy (NSCL-18)
See First-Line Therapy (NSCL-19)
See First-Line Therapy (NSCL-20)
Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

“The major recommendations are to use testing for EGFR mutations and ALK fusions to guide patient selection for therapy with an epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) inhibitor, respectively, in all patients with advanced-stage adenocarcinoma, regardless of sex, race, smoking history, or other clinical risk factors, and to prioritize EGFR and ALK testing over other molecular predictive tests.”

Genomic Tests

Factors Affecting Choice

• Availability of test?

• How quickly can you get a result?

• Do you need to test for more than one genomic alteration?

• Cost?

• Will the result help in choosing a therapy and/or enrolling a patient into a clinical trial?
## Genomic Alterations

### Testing Methods

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Method</th>
<th>Lab</th>
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<tbody>
<tr>
<td>EGFR</td>
<td>Mutation</td>
<td>Sequencing</td>
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<td>Amplification</td>
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</tr>
</tbody>
</table>

- Genotyping can be multiplexed
- FISH is difficult to multiplex
- Need separate assays for ALK, ROS, RET, MET, ERBB2, FGFR1
  - $6 \times $800 = $4800
- Most NSCLC biopsies not amenable to 6 FISH tests & sequencing
Next-Generation Sequencing
Types of Alterations Detected

Reference sequence
Chr 1

Non-human sequence
Chr 5

Point mutation
Indel

Copy number alterations

Homozygous deletion
Hemizygous deletion
Gain
Translocation breakpoint
Pathogen

<table>
<thead>
<tr>
<th>Gene Symbol</th>
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</tr>
</tbody>
</table>

Neal Lindeman – Center for Advanced Molecular Diagnostics at Brigham and Woman’s Department of Pathology.
Molecular Testing of NSCLC

**DFCI Algorithm**

- Advanced NSCLC Receiving therapy
  - Clinical Targeted NGS
    - 300 genes
    - Rearrangements in 30 genes
  - Turn Around Time: 2-3 weeks

- Advanced NSCLC Treatment naive
  - Clinical Targeted NGS
    - 300 genes
    - Rearrangements in 30 genes
  - Turn Around Time: 2-3 weeks

- Rapid EGFR ALK & ROS1 IHC
  - Turn Around Time: 48-72 hours

Neal Lindeman & Lynette Sholl – Center for Advanced Molecular Diagnostics at Brigham and Woman’s Department of Pathology.
Molecular Testing of NSCLC
NGS in The Clinic

• Targeted NGS has been adopted as our standard genotyping assay.
  – Results appear in medical record

• Initial experience (ASCO 2014)
  – Ordered on 188 pts from 7/13 – 12/13
  – 51 (27%) insufficient
  – Median turnaround time was 24 days

Oxnard GR, et al. ASCO. 2014.
### NSCLC

**Spectrum of Genomic Alterations**

<table>
<thead>
<tr>
<th>Alteration type</th>
<th>Non-squamous (N=117)</th>
<th>Squamous (N=17)</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
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<tr>
<td><strong>Point mutations</strong></td>
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<tr>
<td><strong>EGFR</strong></td>
<td>13</td>
<td>11%</td>
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<tr>
<td><strong>BRAF</strong></td>
<td>6</td>
<td>5%</td>
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<tr>
<td><strong>PIK3CA</strong></td>
<td>6</td>
<td>5%</td>
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<tr>
<td><strong>KRAS</strong></td>
<td>41</td>
<td>35%</td>
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<td><strong>Insertions/deletions</strong></td>
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<td><strong>EGFR</strong></td>
<td>7</td>
<td>6%</td>
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<td><strong>HER2</strong></td>
<td>2</td>
<td>2%</td>
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<tr>
<td><strong>Rearrangements</strong></td>
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<td><strong>ALK</strong></td>
<td>4</td>
<td>3%</td>
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<tr>
<td><strong>ROS1</strong></td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>RET</strong></td>
<td>1</td>
<td>1%</td>
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<tr>
<td><strong>High amplification</strong></td>
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<tr>
<td><strong>EGFR</strong></td>
<td>3</td>
<td>3%</td>
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<tr>
<td><strong>HER2</strong></td>
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<td><strong>MET</strong></td>
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<td>3%</td>
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<tr>
<td><strong>PIK3CA</strong></td>
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<td>1%</td>
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<tr>
<td><strong>FGFR1</strong></td>
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<td>1%</td>
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</tbody>
</table>

Oxnard GR, et al. ASCO. 2014.
NGS in The Clinic

It Can Help Guide Clinical Management

61 yo never smoker; s/p 1st line chemotherapy; tumor pan “wild type” by conventional genomic assays

Oxnard GR, et al. ASCO. 2014.
NGS in The Clinic

It Can Help Guide Clinical Management

61 yo never smoker; s/p 1st line chemotherapy; tumor pan “wild type” by conventional genomic assays

- Patient initiated second-line erlotinib at 150 mg daily and had a response in lung mass
- Developed progression in brain after 5 months, but systemic response has been sustained now 9 months on erlotinib

Oxnard GR, et al. ASCO. 2014.
Lung Adenocarcinoma

Progress in Identifying Genomic Alterations

1984 - 2003

No known genotype

2004

No known genotype

2009

No known genotype

EGFR, KRAS

1984 - 2003

EGFR, KRAS

2004

No known genotype

2009

No known genotype

EGFR, KRAS

2016

No known genotype

EGFR, KRAS, ALK, BRAF, HER2, PIK3CA, MET, NTRK1, RET, ROS1
Crizotinib in ROS1-rearranged NSCLC

Efficacy

RR: 72%; PFS: 19.2 months

RR: 80%; PFS: 9.1 months

# NSCLC

## Summary of BRAF Mutations

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Histology</th>
<th>Stage</th>
<th>Testing</th>
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<tbody>
<tr>
<td>Paik</td>
<td>697</td>
<td>ADC</td>
<td>I-IV</td>
<td>V600, D594, G469</td>
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<tr>
<td>Marchetti</td>
<td>1046</td>
<td>ADC &amp; SCC</td>
<td>I-IV</td>
<td>Exons 11 &amp; 15</td>
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<tr>
<td>Cardarella</td>
<td>883</td>
<td>ADC</td>
<td>I-IV</td>
<td>Exons 11 &amp; 15</td>
</tr>
</tbody>
</table>

### Exon 11
- V600E
- V600L, K601 E/N, T599_V600InsT, V600E_K601delInsE
- W604R, G606 A/V
- L597 R/V/Q

### Exon 12
- G464 E/V
- G469A

### Exon 13
- G469del
- G466 V/R

### Exon 14
- D594 G/N

---

Frequency of BRAF Mutations
Melanoma vs Lung Adenocarcinoma

Melanoma

Lung Adenocarcinoma
Inhibiting MAPK/ERK Pathway

**Dabrafenib and Trametinib**

**Dabrafenib mode of action**
- Reversible, small molecule
- BRAF inhibitor
- ATP competitive
- BRAF V600E: IC$_{50}$ 0.65 nM

**Trametinib mode of action**
- Reversible, small molecule
- MEK1 and MEK2 allosteric inhibitor
- MEK1 and MEK2: IC$_{50}$ 0.7 and 0.9 nM

---

BRAF V600E NSCLC
Dabrafenib Monotherapy

Best Confirmed Response
- PR
- SD
- PD
- NE

RR: 33%
PFS: 5.5 months

**BRAF V600E Metastatic NSCLC**

**Dabrafenib + Trametinib**

Maximum Percent Reduction at Time of Best Disease Assessment

- RR: 63%
- PFS: Not Reached

One patient discontinued at day 23 and did not have any post-baseline scans for efficacy.

Lung Adenocarcinoma
**ALK and RET Gene Fusions**

Several drugs (sunitinib, sorafenib, vandetanib, cabozantinib) inhibit RET but none are specific RET inhibitors

**RET-Rearranged Lung Adenocarcinoma Response to Cabozantinib**

<table>
<thead>
<tr>
<th>Best Response</th>
<th>% (N)</th>
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<td>PR</td>
<td>44% (7/16)</td>
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<tr>
<td>Confirmed</td>
<td>38% (6/16)</td>
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<tr>
<td>Unconfirmed</td>
<td>6% (1/16)</td>
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<tr>
<td>SD</td>
<td>56% (9/16)</td>
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</table>

**ORR 38% (95% CI 15%-65%)**

**ORR$_{12wks}$ 36% (95% CI 13%-65%)**

(5 PRs of 14 evaluable at 12 wks)

**NSCLC**

**MET Exon 14 Skip Mutations**

*MET* exon 14 cancers can have *MET* amplification and/or high level of *MET* expression.

Prevalence of *MET* exon 14 skip mutations:

- KRAS (34%)
- EGFR (19%)
- No oncogenic mutation identified (30%)
- MET ex14 (3%)
- ALK (3.9%)
- BRAF (3.8%)
- PIK3CA (2.9%)
- NRAS (1%)
- ROS1 (1%)
- HRAS (<1%)
- map2K1 (<1%)
- RET (1%)
- AKT (<1%)
- ERBB2 (1%)
- ERBB2 (1%)
- MAP2K1 (<1%)

MET Exon 14 Skip Tumors Sensitive to MET Inhibitors

Pre-Treatment

On Crizotinib (at 2 months)

## NSCLC With Genetic Alterations

### Emerging Targeted Agents

<table>
<thead>
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<th>Genetic Alteration (eg, driver event)</th>
<th>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</th>
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</thead>
<tbody>
<tr>
<td><strong>BRAF</strong> V600E mutation*</td>
<td>vemurafenib</td>
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<tr>
<td></td>
<td>dabrafenib</td>
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<tr>
<td></td>
<td>dabrafenib + trametinib</td>
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<tr>
<td>High level MET amplification or MET exon 14 skipping mutation</td>
<td>crizotinib</td>
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<tr>
<td><strong>RET</strong> rearrangements</td>
<td>cabozantinib</td>
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<td><strong>ROS1</strong> rearrangements</td>
<td>crizotinib</td>
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<tr>
<td><strong>HER2</strong> mutations</td>
<td>trastuzumab (category 2B)</td>
</tr>
<tr>
<td></td>
<td>afatinib (category 2B)</td>
</tr>
</tbody>
</table>

*Non-V600E mutations have variable kinase activity and response to these agents
Do Genomic Changes Predict for Sensitivity to Immunotherapy?
Mutation Load Across Cancer Types

*High Mutational Burden in Lung Cancer*

## Anti-PD-1/PD-L1 mAbs in NSCLC
### Impact of Smoking Status

<table>
<thead>
<tr>
<th>Agent</th>
<th>ORR, % (n/N)</th>
<th>Current/former smoker</th>
<th>Never smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>26% (NR/129)</td>
<td>8% (NR/60)</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>26% (11/43)</td>
<td>10% (1/10)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agent</th>
<th>ORR, % (n/N)</th>
<th>&gt;5 pack-years</th>
<th>≤5 pack-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>37% (19/52)</td>
<td></td>
<td>0% (0/10)</td>
</tr>
</tbody>
</table>

NR=not reported

---

Clinical Benefit of Anti-PD-1 Therapy

Effect of Nonsynonymous Mutation Burden

Clinical Benefit of Anti-PD-1 Therapy

Effect of Molecular Smoking Signature


(n=18) (HR 0.15, 95% 0.06-0.39, log-rank P=0.001)
## Anti-PD-1/PD-L1 mAbs in NSCLC
### Impact of EGFR, KRAS Status

### EGFR Status

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mutant</th>
<th>Wild-type</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab¹</td>
<td>17% (2/12)</td>
<td>20% (11/56)</td>
<td>15% (9/61)</td>
</tr>
<tr>
<td>Atezolizumab²,³</td>
<td>17% (1/6)</td>
<td>23% (9/40)</td>
<td>NR</td>
</tr>
</tbody>
</table>

### KRAS Status

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mutant</th>
<th>Wild-type</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab¹</td>
<td>14% (3/21)</td>
<td>25% (9/36)</td>
<td>14% (10/72)</td>
</tr>
<tr>
<td>Atezolizumab²</td>
<td>10% (1/10)</td>
<td>30% (8/27)</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR=not reported

Clinical Benefit of Anti-PD-1 Therapy

OS in Predefined Subgroups


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Unstratified Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>582</td>
<td>0.75 (0.62-0.91)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>339</td>
<td>0.81 (0.62-1.04)</td>
</tr>
<tr>
<td>≥65 to &lt;75 yr</td>
<td>200</td>
<td>0.63 (0.45-0.89)</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>43</td>
<td>0.9 (0.43-1.87)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>319</td>
<td>0.73 (0.56-0.96)</td>
</tr>
<tr>
<td>Female</td>
<td>263</td>
<td>0.78 (0.58-1.04)</td>
</tr>
<tr>
<td>ECOG performance-status score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>179</td>
<td>0.64 (0.44-0.93)</td>
</tr>
<tr>
<td>1</td>
<td>402</td>
<td>0.8 (0.63-1)</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>458</td>
<td>0.7 (0.56-0.86)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>118</td>
<td>1.02 (0.64-1.61)</td>
</tr>
<tr>
<td>EGFR mutation status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>82</td>
<td>1.18 (0.69-2)</td>
</tr>
<tr>
<td>Not detected</td>
<td>340</td>
<td>0.66 (0.51-0.86)</td>
</tr>
<tr>
<td>Not reported</td>
<td>160</td>
<td>0.74 (0.51-1.06)</td>
</tr>
</tbody>
</table>
Noninvasive Detection of Response and Resistance
Liquid Biopsy
Circulating Tumor-Derived Cells or DNA

Plasma ddPCR
Detection of Mutations in ctDNA

Plasma ddPCR
Non-Invasive Disease Monitoring

Stage IV NSCLC
EGFR mutant
Treatment naive

Erlotinib
150 mg

Biopsy at resistance
Circulating tumor cells
Plasma for ctDNA

Serial monitoring for EGFR activating and EGFR T790M resistance mutation in erlotinib treated EGFR mutant patients

Prospective Validation
**DFCI# 14-147 Schema**

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Diagnostic analysis</th>
<th>Follow-up analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1:</strong> First-line patients</td>
<td>Collect 2 paired blood specimens</td>
<td>Compare plasma &amp; tumor genotype</td>
</tr>
<tr>
<td><strong>Cohort 2:</strong> Acquired resistance patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cohort 3:</strong> Genotyped patients starting new treatment</td>
<td></td>
<td>2 blood specimens on therapy</td>
</tr>
</tbody>
</table>

Same day registration and initial blood draw

Adrian Sacher, Geoff Oxnard, Cloud Paweletz
Detection of EGFR and KRAS Mutations
Validation of Plasma Genotyping

Plasma ddPCR

Advantages

Day 0:
 Plasma ddPCR ordered

Day 0:
 Repeat biopsy ordered

Day 1:
 EGFR T790M plasma positive

Day 25:
 EGFR T790M tissue positive

Day 31:
 osimertinib initiated

24 day delay in initiating therapy while awaiting tissue genotyping

Symptomatic disease progression on erlotinib

Clinical and radiographic response to AZD9291

- Plasma ddPCR detected *EGFR* and *KRAS* mutations rapidly with the high specificity needed to select therapy and avoid repeat biopsies.

- Plasma ddPCR may also detect *EGFR* T790M missed by tissue genotyping due to tumor heterogeneity in resistant disease.

Plasma NGS
Detects Actionable Genomic Alterations

RET Rearrangement

MET amplification

EGFR TKI resistance

Novel EGFR mutation

Molecular Pathology of Lung Cancer

Summary

• Genomic testing can identify targetable drug sensitive alteration.

• Multiplex genomic testing should be standard of care.
  – Identify both common and rare but targetable alterations
  – May help select patients more likely to benefit from immunotherapy

• Blood testing is rapidly evolving and will complement and/or augment tissue based testing.
Thank you!

Please visit us at: www.ceconcepts.com