Current Status of Molecular Testing in Defining Optimal Treatment Strategies in Non-Small Cell Lung Cancer

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Professor of Medicine
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…… molecular testing has been a game changer in the treatment of non small cell lung cancer...

…it has enabled more rational therapeutic decision making, often reducing toxicity and enhancing treatment efficacy…

… molecular testing is a mandatory element of treatment planning in several settings….

… testing technology is rapidly evolving requiring continuous oversight….
Overview

• Background
• Chemotherapy status
• Moving beyond chemotherapy
  – Molecularly targeted therapies
  – Immunologic therapies
• Molecular testing principles
• Summary
Non Small Cell Lung Cancer Facts

• 200,000 new cases in US in 2019
• Leading cause of cancer deaths in men and women
• Potentially curable when diagnosed at an early stage
• Patients with advanced stage disease not currently curable
• Most patients will require systemic therapy
  – Chemotherapy
  – Targeted therapy
  – Immunotherapy
Current Treatment Approaches for Non Small Cell Lung Cancer

• **Stage I, II** – goal is cure
  – Surgical resection or stereotactically focused radiotherapy (SBRT)
  – Chemotherapy added in some cases

• **Stage III** – goal is cure
  – Radiotherapy combined with chemotherapy followed by consolidation with durvalumab

• **Stage IV** – goal is symptom relief and prolonging survival; cure not feasible; prolonged survival in a minority
  – Chemotherapy
  – Molecularly targeted agents
  – Immunologic agents
  – Chemotherapy + immunologic agents
NSCLC: Status of Chemotherapy

- Stage I/II – modestly improves cure rate post resection
- Stage III – modestly improves cure rate in combination with radiotherapy
- Stage IV - modestly prolongs survival compared with best supportive care
  - Improved quality of life with treatment
  - Maintenance chemotherapy can extend survival
  - Histology important factor in deciding treatment regimens
NSCLC: Limitations of Chemotherapy

- Have reached a therapeutic plateau with available conventional agents
- Last effective conventional cytotoxic agent (protein bound - paclitaxel) approved for lung cancer treatment in 2012
- Recent progress has been realized through fundamentally different treatment approaches
  - Molecularly targeting “driver” mutations
  - Immune based approaches
- **Optimal use of new approaches requires reliable molecular analysis**
Concept of Molecularly Targeting “Driver” Genomic Alterations

- Progress in molecular oncology has improved the understanding of mechanisms involved in transformation and growth of malignant cells.
- Aberrant growth factor receptor systems, signal transduction, angiogenic and apoptotic pathways have all become prime foci for selective targeting.
- Since 2004, a number of “driver” genomic alterations (point mutations, deletions, translocations, gene amplifications) have been identified in non squamous NSCLC providing promising targets for new agents.
- New agents targeting these genomic changes have demonstrated enhanced efficacy and reduced toxicity.
Genomic Alterations in NSCLC: Adenocarcinomas - 2019

Biomarker Profile of Adenocarcinoma

<table>
<thead>
<tr>
<th>Frequency of driver mutations in NSCLC</th>
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<tbody>
<tr>
<td>ALK</td>
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<td>BRAF</td>
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<td>EGFR</td>
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<td>MET</td>
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<td>RET</td>
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<td>ROS1</td>
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Genomic Alterations in NSCLC: Adenocarcinomas - 2019

Biomarker Profile of Adenocarcinoma

Frequency of driver mutations in NSCLC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>ALK</td>
<td>3–7%</td>
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<tr>
<td>BRAF</td>
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<tr>
<td>EGFR</td>
<td>10–35%</td>
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<tr>
<td>HER2</td>
<td>2–4%</td>
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<tr>
<td>KRAS</td>
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<tr>
<td>MEK1</td>
<td>1%</td>
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<tr>
<td>MET</td>
<td>4%</td>
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<tr>
<td>NRAS</td>
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<td>RET</td>
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Gefitinib: First EGFR Targeted Agent Approved for NSCLC

• July 2002  Gefitinib approved in Japan for inoperable or recurrent NSCLC

• May 5, 2003  “Accelerated approval” by FDA for third-line treatment in advanced NSCLC previously treated with cisplatin-based chemotherapy and docetaxel
  – 15/142 (10.6%) patients with objective response; responses more common in females and never smokers

• June 2005  Following three unsuccessful phase confirmatory III trials, use restricted to patients already on treatment

• April 2012  Astra Zeneca withdrew the NDA
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.
Clustering Mutations in ATP Cleft of Tyrosine Kinase Domain of EGFR Gene

Functional Effect of Mutational Alteration of EGFR-TKI Domain

• Growth advantage
  – Ligand independent receptor activation (constitutive activity)
  – Increased receptor activation after ligand binding

• “Achilles Heel”
  – Enhanced inhibition by EGFR tyrosine kinase inhibitors (afatanib, erlotinib, gefitinib)
Genomic Alterations in NSCLC: Adenocarcinomas - 2019

Biomarker Profile of Adenocarcinoma

Frequency of driver mutations in NSCLC:

- ALK: 3-7%
- BRAF: 1-3%
- EGFR: 10-35%
- HER2: 2-4%
- KRAS: 15-25%
- MEK1: 1%
- MET: 4%
- NRAS: 1%
- NTRK1: 1-3%
- PIK3CA: 1-3%
- RET: 1-2%
- ROS1: 1-2%

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Stage IV NSCLC Patients With Targetable Genomic Changes: General Principles

- Relevant genomic changes with FDA approved agents: EGFR mutations (exons 19,21); ALK, ROS-1 translocations; BRAF^{V600E} mutation
- Frequency
  - 15 - 20% in patients with significant smoking history
  - > 50% of never smokers
- A targeted agent is the superior (EGFR, ALK) or reasonable (ROS-1, BRAF^{V600E}) initial treatment of choice
- Greater efficacy and reduced toxicity compared to chemotherapy and immunotherapy
- Prolonged survival (years) possible
FDA - Approved Molecularly Targeted Agents in NSCLC

- **EGFR mutations** – exon 19 del; exon 21 point mutations
  - First generation: gefitinib; erlotinib
  - Second generation: afatanib, dacomitinib
  - Third generation: osimertinib

- **ALK translocations**
  - First generation: crizotinib
  - Second generation: ceritinib; alectinib; brigatinib
  - Third generation: lorlatinib

- **ROS -1 translocations**
  - First generation: crizotinib
  - Second generation: entrectinib

- **BRAF^{V600E} mutation**
  - First generation: dabrafenib + trametinib
Genomic Alterations in Squamous NSCLC

A. Lung Adenocarcinoma
   - Other?
   - KRAS
   - EGFR
   - ALK
   - RET
   - ROS
   - MEK1
   - MET
   - BRAF
   - NRAS
   - ERBB2
   - PIK3CA

B. Lung Squamous Cancer
   - Other?
   - EGFR
   - FGFR
   - PI3K
   - MAPK
   - PTEN

S1400 LUNG MASTER PROTOCOL
S1400 Lung Master Protocol Design

- Second-line advanced squamous cell cancer
- All patients undergo next generation sequencing
- Multiple arms open simultaneously
  - “matched” arms – require presence of a specific genomic abnormality
  - “non-match” arms for patients without a matched target – immunotherapy approach
- Opened June 6, 2014; Closed January 28, 2019
- 1864 patients enrolled
- 6 matched and 2 non-matched studies completed
- S1400 replaced by LUNG-MAP
  - added non squamous patients; 518 clinical sites
*LUNGMAP screening protocol (activated 1/28/19) allows all histologic types of NSCLC. S1400, the original screening/umbrella protocol included only squamous lung cancer. S1400 accrued patients between 6/16/2014 and 1/28/2019. While S1400 is closed to accrual, patients enrolled to S1400 may participate in sub-studies they are eligible for.
Molecular Testing for Targeted Agents
Basic Principles - Tissue

- Testing mandatory in all stage IV patients with non squamous histology
- Testing also recommended with any non–small-cell histology when clinical features indicate a higher probability of an oncogenic driver
- Testing may be required in stage IV squamous and stage I – III patients for entry into investigational protocols
- Mandatory minimum gene panel
  - EGFR, ALK, ROS-1, BRAF
- Multiplexed genetic sequencing panels preferred to identify other genomic changes (HER2, KRAS, MET, RET, NTRK123) with potential treatment options
- Patients with an EGFR mutation progressing on first/second generation EGFR TKI treatment should be tested for the T790M mutation
Molecular Tissue Testing for Targeted Agents
What Test to Use?

• Real-time PCR (EGFR, BRAF))
  – Single-gene testing; tissue requirements less; quick; can be done in-house
• FISH, IHC (ALK, ROS-1)
  – Single-gene testing; tissue requirements less, quick; can be done in-house
• Targeted DNA-based Next Generation Sequencing (NGS)
  – Multiplex-gene testing (50 – 600 genes); slower; requires more tissue than single RT-PCR but more efficient for multi-gene testing; typically performed as a send-out; also allows assessment of TMB
• Targeted RNA-based Sequencing (RNAseq)
  – Useful for detection of fusions and METex14 alterations in DNA-based NGS driver-negative samples
Potential Value of RNA Sequencing in NSCLC

- Study at MSKCC profiled 2,522 adenocarcinomas using MSK-IMPACT
- Among 275 driver negative cases, 254 had sufficient tissue for RNAseq
- Previously unidentified alteration identified in 14% (36/254)
- 33 cases with actionable (27 in-frame fusions; 6 METex 14 mutations)
- 10 patients then received matched targeted therapy, with clinical benefit in 8 patients
  - ALK (1)
  - ROS1 (4)
  - NTRK (2)
  - NRG1 (2)
  - METex 14 skip alteration (1)

Molecular Testing For Targeted Agents
Basic Principles - Plasma

- A variety of plasma-based components (cfDNA, ctDNA, CTC’s) can be used for genomic analysis
- Cannot use plasma-based techniques to diagnose a primary lung adenocarcinoma
- Can use cfDNA when tissue is limited/insufficient to identify targetable alterations (NGS)
- Can use cfDNA to identify resistance mutations (T790M)
- Excellent specificity (90-95%) but sensitivity ~ 70%
- If plasma testing is negative for a given mutation, tissue testing then becomes mandatory
Immunotherapy in NSCLC

• Historically immunotherapy not successful in NSCLC
• To date vaccines have been a major disappointment
• Check-point inhibitors
  – Preliminary evidence of some activity with CTLA-4 inhibitor (ipilimumab) added to chemotherapy
  – Promising activity with agents targeting the Programmed Death-1 Pathway (PD1)
    • Anti PD1 antibodies
    • Anti PD-L1 antibodies
Role of PD-1 in Suppressing Antitumor Immunity

Activation (cytokines, lysis, prolif., migration)

Inhibition (anergy, exhaustion, death)

Predictive Testing for PD – 1 Directed Agents

- Unlike gene mutation testing, predictive tests for PD-1 directed agents are imprecise
- Consistent trend for greater benefit with positive PD-L1 expression
- Current PD-L1 testing is tissue-based; blood-based assays in development
- Each approved PD-1 directed agent has a different companion/complementary IHC assay
- Interchanging assays can lead to 5–15% loss in predictive performance
- Use an approved companion assay for the PD-1 directed agent
  - Pembrolizumab : Dako 22C3
  - Nivolumab : Agilent/Dako 28-8
  - Atezolizumab : Ventana SP142
  - Durvalumab : Ventana SP263
- Other predictive tests being evaluated : TMB, MSI-H/dMMR
FDA Approved Programmed Death (PD) – 1 Directed Agents in NSCLC

Second – Line (Stage 4)

• March 4, 2015  Nivolumab (OPDIVO®)
  – post platinum chemotherapy independent of PD-L1 status
• October 2, 2015  Pembrolizumab (KEYTRUDA®)
  – post platinum chemotherapy, PD-L1 ≥ 1 %
• October 18, 2016  Atezolizumab (TECENTRIQ®)
  – post platinum chemotherapy, independent of PD-L1 status

Consolidation (Stage 3)

• February 16, 2018  Durvalumab (IMFINZI®)
  – Unresectable, non progressing stage III NSCLC post chemotherapy/radiation independent of PD-L1 status
FDA Approved PD–1 Directed Agents in NSCLC

FIRST – LINE (Stage 4)

- October 24, 2016 (mono) Pembrolizumab
  - first-line stage 4 non small cell lung cancer, PD-L1 > 50%
- May 10, 2017; August 20, 2018 (combo) Pembrolizumab
  - first-line stage 4 non squamous non small lung cancer in combination with carboplatin and pemetrexed independent of PD-L1 status
- October 30, 2018 (combo) Pembrolizumab
  - first-line stage 4 squamous non small cell carcinoma in combination with carboplatin + paclitaxel or nab-paclitaxel independent of PD-L1 status
- December 6, 2018 (combo) Atezolizumab
  - first-line stage 4 non squamous non small cell carcinoma in combination with carboplatin, paclitaxel and bevacizumab independent of PD-L1 status
- April 11, 2019 (mono) Pembrolizumab
  - First-line stage III (not candidate for definitive RX) or stage 4 (PD-L1 > 1%)
FDA Approved Programmed Death (PD) – 1 Directed Agents in SCLC

THIRD– LINE Extensive Stage Small Cell

- August 16, 2018 (accelerated) Nivolumab
  - Metastatic SCLC following platinum-based chemotherapy and at least one other therapy independent of PD-L1 status
- June 17, 2019 (accelerated) Pembrolizumab
  - Metastatic SCLC following platinum-based chemotherapy and at least one other therapy independent of PD-L1 status

FIRST – LINE Extensive Stage Small Cell

- March 18, 2019 Atezolizumab
  - First-line extensive stage small cell lung cancer in combination with carboplatin and etoposide independent of PD-L1 status
Stage IV NSCLC
Basic Principles: First-line therapy

- No targetable mutations, PD-L1 expression ≥ 50%
  - Pembrolizumab alone or in combination with chemotherapy
- No targetable mutations, PD-L1 expression < 50%
  - Immunotherapy eligible
    - Platinum – based combination chemotherapy + pembrolizumab or atezolizumab
  - Immunotherapy ineligible
    - Platinum – based combination chemotherapy
- Sensitizing EGFR mutation: osimertinib
- ALK gene rearrangement: alectinib
- ROS 1 gene rearrangement: crizotinib or entrectinib
- BRAF$^{V600E}$: dabrafenib + trametinib or platinum –based combination
Molecular Testing in NSCLC: Summary

• Molecular testing is now an essential element of the diagnostic evaluation of all patients with advanced NSCLC
• Plasma based testing (cfDNA) can complement but not replace tissue-based testing (excellent PPV; 70-80% sensitivity)
• All advanced stage NSCLC patients require PD-L1 testing
• Advanced non-squamous and select other histology NSCLC patients require testing for targetable genomic alterations with FDA approved agents (EGFR, ALK, ROS-1, BRAF\textsuperscript{V600E})
• Molecular testing results will define first-line and later treatment options
• Molecular testing for stage IV squamous and stage I – III non-squamous and squamous patients should be performed in the context of clinical trials