Progress in Non-small Cell Lung Cancer
Implications for APPs

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Disclosures - Helen J. Ross, MD

• Employee of Mayo Clinic
• Grant funding from NCI
• Mayo Clinic receives funding for trials led by me sponsored by
  • BMS
  • Genentech
  • Merck
  • Lilly
  • Incyte
  • NCI
Objectives

• Explain the current state of NSCLC treatment
• Discuss molecular testing and targeted therapy
• Review most important side effects of treatment
• Note upcoming treatment strategies and clinical trials
Smooth Character

SURGEON GENERAL’S WARNING: Cigarette Smoke Contains Carbon Monoxide.

16 mg. “tar”, 1.0 mg. nicotine avg. per cigarette by FTC method.
The Evolution of Cigarette Advertising

**Warning**

The toxic chemicals in tobacco smoke damage your blood vessels, damage your body's cells, and attack your immune system.

Brand Variant

**Don’t Let Children Breathe Your Smoke**

For good smoking taste, it makes good sense to smoke Kent

All over America... more scientists and educators smoke Kent with the Micronite Filter than any other cigarette!
Australia’s Plain Packaging Law
Case Study
Anyone Can Have Lung Cancer

- Joan is a 30 year old never smoking physician with aches and pains
- Visited PCP for over six months without imaging
Anyone Can Have Lung Cancer

- Joan is a 30 year old never smoking physician with aches and pains
- Visited PCP for over six months without imaging
- PET/CT lights up
- VATS biopsy shows pulmonary adenocarcinoma
Why is Lung Cancer Important?

• Leading cause of cancer deaths in US men and women
  - A new diagnosis is made every 3 minutes
• >200,000 cases annually US and >1M worldwide
• Most patients are diagnosed late when cancer considered incurable BUT
• Treatment prolongs survival and improves QoL for all stages and lung cancer types
Major Causes of Lung Cancer

• Tobacco - 80%
• Radiation Exposure
• Environmental/Occupational Exposure
  • Asbestos
  • Radon
  • Pollution
• Gene mutations
• ????
Lung Cancer Types

- **Non Small Cell Lung Cancer (NSCLC)**
  - 85% of cases
  - In the US, mostly adenocarcinoma
  - Others squamous, large cell, mixed

- **Small Cell Lung Cancer (SCLC)**
  - 15% of cases
  - Medical emergency
Factors that Determine Lung Cancer Treatments & Outcome

• Stage at diagnosis
  • Surgical vs chemoradiotherapy vs systemic therapy

• Overall health of the patient
  • Lung function, cardiac issues, immune system, other illnesses

• Lung cancer type

• Molecular diagnostic tests

• Immunologic characteristics
Women and Lung Cancer

- Women are probably more susceptible to tobacco carcinogenesis
- Women are diagnosed at later stage
  - Especially younger women
- Women have better overall outcome (especially older women), but more side effects from treatment
Male-Female Differences in Lung Cancer Presentation

- Most nonsmokers diagnosed with lung cancer are females with adenocarcinoma
- Adenocarcinoma more likely in females than males (25% of male lung cancer, 38% of female lung cancer)
- Small cell lung cancer more common in females (12% of male lung cancer, 18% of female lung cancer)
- Younger patients more likely to be female (60% of patients under 50 are female)
Lung Cancer in Never Smokers

• ~15% of all new lung cancer cases - risk is increasing

• 22,100 new cases per year in never-smokers
  - About equal to pancreatic cancer
  - More common than ovarian cancer

• 80% of lung cancers in never-smokers are in women
  - 17,600 annually

• Outcomes overall better than average

• Higher incidence of targetable mutations
  - EGFR targeted treatments (erlotinib, afatinib)
  - ALK/ROS-1 targeted treatments (crizotinib, ceritinib)

• Non-mutated patients should receive chemotherapy
  - It is vital not to guess
New Therapies

- Standard targeted therapies
  - EGFR-TKIs
  - EGFR antibodies
  - ALK inhibitors

- Immunotherapy

- Clinical trials
  - Immunotherapy
  - Novel targets
    - Antibodies
    - Small molecules
Chemotherapy Extends Life

- Quality and length of life improved
- Most modern lung cancer chemotherapy is well tolerated
- Most patients continue to work and live fairly normally
- Some patients are eligible for targeted therapy
- Many patients can now live years
Implications for Your Referral Base

• Screening in at risk patients
• Diagnostics
  • Core Bx
  • Accurate Staging
• Referral patterns
  • Treatment differs between specialists/generalists
  • Surgery expertise crucial
• Clinical trials are the way forward
  • Chronic disease for some patients
Treatment for NSCLC

• Stage I/II curable with surgery
  • Usually with adjuvant chemotherapy

• Stage III curable with chemoRT
  • Often can relapse, *sometimes in the brain only*
  • Length and type of chemotherapy not certain
  • Role of immunotherapy uncertain

• Stage IV disease palliated with chemo with increased QoL and OS
  • Targeted vs “standard” treatments
  • Newer drugs better tolerated
  • Many patients now live years
  • Clinical trials participation vital for continued progress
Early Stage Lung Cancer

- Often diagnosed incidentally
- Screening in high risk populations
  - Smoking history
  - Age 50-75
  - Prior history of lung cancer
- Minimally invasive resection optimal
- Adjuvant chemotherapy for most patients
NLST

- Asymptomatic, fit, current or former cigarette smokers within the past 15 years, 55 to 74 years of age with at least 30 pack years.
- 53,454 current and former smokers were randomly assigned to be screened once a year for 3 years with low-dose CT or chest X-ray.
- Data after average 6.5 year follow up:

| Benefit: How did CT scans help compared to chest X-ray, an ineffective screening test? |
|-------------------------------------------------|-----------------|-----------------|
| 3 in 1,000 fewer died from lung cancer          | 18 in 1,000     | versus          |
| 5 in 1,000 fewer died from all causes          | 70 in 1,000     | versus          |

| Harm: What problems did CT scans cause compared to chest X-ray? |
|---------------------------------------------------------------|-----------------|-----------------|
| 223 in 1,000 more had at least one false alarm               | 365 in 1,000    | versus          |
| 18 in 1,000 more had a false alarm leading to an invasive procedure, such as bronchoscopy, biopsy, or surgery | 25 in 1,000     | versus          |
| 2 in 1,000 more had a major complication from invasive procedures | 3 in 1,000     | versus          |
Case Study
 Locally Advanced NSCLC

- Hazel is a 75 year old woman who stopped smoking in 1990 but has coughed for 6 months without improvement with antibiotics
- CT shows large LUL cancer with enlarged mediastinal nodes
- Biopsy adenocarcinoma
- Concurrent chemoRT was tolerated well with usual side effects of fatigue and esophagitis
Treatment Results

• Radiation pneumonitis four months out with shortness of breath, cough and fever.

• Extensive scarring seen on CT with acute inflammation

• Consolidated scar with no evidence of tumor twelve months out from treatment
Solitary brain metastasis 5 years after primary therapy
ASTRO Clinical Questions

(1) What is the ideal external-beam dose-fractionation for the curative-intent treatment of LA-NSCLC with radiation therapy alone?

(2) What is the ideal external-beam dose-fractionation for the curative-intent treatment of LA-NSCLC with chemoradiotherapy?

(3) What is the ideal timing of external-beam radiation therapy in relation to systemic chemotherapy for the curative-intent treatment of LA-NSCLC?

(4) What are the indications for adjuvant post-operative radiotherapy for the curative-intent treatment of LA-NSCLC?

(5) When is neoadjuvant radiotherapy prior to surgery indicated for the curative-intent treatment of LA-NSCLC?
Target Population and Audience

• Patients with stage II to III NSCLC who cannot undergo a definitive resection (either because of surgical resectability and/or medical operability factors [see Definition of Terms in Data Supplement]) and patients with stage II to III NSCLC who can undergo a definitive resection after assessment

• Oncology clinicians and patients
Summary of Recommendations

The Role and Timing of Radiotherapy With or Without Chemotherapy for Patients With Unresectable LA-NSCLC (ASTRO)

• There is phase III evidence demonstrating improved overall survival, local control, and response rate associated with concurrent chemoradiation when compared against sequential chemotherapy followed by radiation (high-quality evidence [HQE], “Strong”).

• For patients that cannot tolerate concurrent chemoradiotherapy, sequential chemotherapy followed by radical radiation has been shown to be associated with an overall survival benefit when compared to radiotherapy alone (HQE, “Strong”).

• Radiotherapy alone may be used as definitive radical treatment for patients with LA-NSCLC who are ineligible for combined modality therapy (i.e. due to poor performance status, medical comorbidity, extensive weight loss, and/or patient preferences) but with a tradeoff of survival for improved treatment tolerability (HQE, “Strong”).
Summary of Recommendations

The Role and Timing of Radiotherapy With or Without Chemotherapy for Patients With Unresectable LA-NSCLC (ASTRO)

• There is no proven role for the routine use of induction chemotherapy prior to chemoradiotherapy; although, this treatment paradigm can be considered for the management of bulky tumors to allow for radical planning after chemotherapy response (moderate quality evidence [MQE], “Strong”).

• There are no phase III data specifically supporting the role for consolidation chemotherapy after chemoradiotherapy for the improvement of overall survival; however, this treatment is still routinely given to manage potential micrometastatic disease particularly if full systemic chemotherapy doses were not delivered during radiotherapy (low quality evidence [LQE], “Strong”).

• The ideal concurrent chemotherapy regimen has not been determined; however, the two most common regimens (cisplatin/etoposide and carboplatin/paclitaxel) are the subject of a completed phase III clinical trial, (NCT01494558). (No evidence rating, “Strong”).
Summary of Recommendations

Appropriate Dose of Radiotherapy for Patients With Unresectable LA-NSCLC (ASTRO)

• In the context of conventionally fractionated radiotherapy, a minimum dose of 60 Gy is recommended to optimize important clinical outcomes such as local control (HQE, “Strong”).

• The standard thoracic radiotherapy dose-fractionation for patients treated with concurrent chemotherapy is 60 Gy given in 2 Gy once daily fractions over 6 weeks (MQE, “Strong”).

• Dose escalation beyond 60 Gy with conventional fractionation has not been demonstrated to be associated with any clinical benefits including overall survival (MQE, “Strong”).
Summary of Recommendations

Relevant ASTRO Statements Concerning the Role of Postoperative Radiotherapy in Resected LA-NSCLC

ASCO agrees and has summarized these statements as follows:

*Postoperative radiotherapy may be recommended for patients with complete resection of N2 disease to improve local control, but should be delivered sequentially after adjuvant chemotherapy.*

Other ASTRO recommendations addressing the postoperative setting had LQE, which the ASTRO panel rated as “Strong” recommendations. ASCO endorses and summarizes them as follows:

*Postoperative radiotherapy is recommended for patients with incomplete resection (microscopic or gross positive margin, or gross residual disease), to be given either concurrently or sequentially with chemotherapy.*
Summary of Recommendations

Role of Radiotherapy in the Context of Trimodality Treatment of LA-NSCLC (ASTRO)

• There is no level I evidence recommending the use of induction radiotherapy (or chemoradiotherapy) followed by surgery for patients with resectable stage III NSCLC (HQE, “Strong”).

• In those patients who are selected for trimodality approach, preoperatively planned lobectomy (as opposed to pneumonectomy), based on best surgical judgment, is preferable, since it was associated with survival benefit in the exploratory post-hoc North American Intergroup study INT 0139 analysis (MQE, “Strong”).

• No definitive statement can be made about best patient selection criteria for the trimodality therapy, although no weight loss, female gender, and one (vs. more) involved nodal stations were associated with improved outcome in INT 0139 (MQE, “Strong”).
Discussion Summary Points

Limitations
• Controversy regarding which dose of radiotherapy to consider standard. The ASTRO guideline has two statements:
  – “a minimum dose of 60 Gy is recommended... “ (that refers to radiotherapy alone, without concurrent chemotherapy)

  and

  – “the standard... dose-fractionation is 60 Gy given in 2 Gy once daily fractions over 6 weeks (which refers to concurrent chemoradiotherapy).

• Some studies suggest that higher doses provide better local control, but phase III studies have not demonstrated the superiority of any doses higher than 60 Gy over 30 fractions.
  – The ASCO panel believed that it could state that 60 Gy is optimal, but could state that 60 Gy is standard.

Role of consolidation chemotherapy after concurrent chemotherapy
• Supported by early trials that has become standard in many centers, but which current interpretation of data does not support. Notably, the ASTRO guideline on this issue reflected low-quality evidence, and the ASCO panel emphasized lack of phase III evidence of the benefit.
Endorsement Recommendation

ASCO endorses "Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small Cell Lung Cancer: An American Society for Radiation Oncology (ASTRO) Evidence-Based Clinical Practice Guideline," summarized by Rodrigues et al\textsuperscript{1,2} in 2015 in \textit{Practical Radiation Oncology}, with minor qualifying statements. The full ASTRO guideline can be accessed in the supplementary materials of the executive summaries by Rodrigues et al.


www.asco.org/endorsements/NSCLCradiotherapy
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Additional Resources

More information, including a Data Supplement with a reprint of all ASTRO recommendations, a Methodology Supplement, slide sets, and clinical tools and resources, is available at:

www.asco.org/endorsements/NSCLCradiotherapy

All original ASTRO recommendations can be found at:
www.practicalradonc.org

Patient information is available at www.cancer.net
Metastatic Lung Cancer
Patient Characteristics Matter

• Cancer Type
  • Squamous vs non-squamous
    • determines chemotherapy and molecular testing needs

• Sex and age
  • Females do better stage for stage
  • Younger men do better than older
  • Older women do better than younger

• Smoking status
  • Never-smokers do better than former smokers who do better than current smokers

• Comorbidities
Cis/Gem vs Cis/Pem in Advanced NSCLC: OS by Histology

Nonsquamous

- Median Survival
  - C/P: 11.8 mos
  - C/G: 10.4 mos
  - C/P vs C/G
  - Adjusted HR: 0.81
  - (95% CI: 0.70-0.94)

Squamous

- Median Survival
  - C/P: 9.4 mos
  - C/G: 10.8 mos
  - C/P vs C/G
  - Adjusted HR: 1.23
  - (95% CI: 1.00-1.51)

Carbo/Nab-Paclitaxel vs Carbo/Paclitaxel in Advanced NSCLC: Responses*

<table>
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<tr>
<th></th>
<th>Intent to Treat</th>
<th>Squamous†</th>
<th>Nonsquamous†</th>
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<tr>
<td>Response Rate (%)</td>
<td>33% 25%</td>
<td>41% 24%</td>
<td>26% 25%</td>
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<tr>
<td>n</td>
<td>521 531</td>
<td>229 221</td>
<td>292 310</td>
</tr>
</tbody>
</table>

*Independent radiological review. †Not a prespecified endpoint. Interaction $P$ value for histology = .036

IFCT-0501: Doublet vs Single-Agent Chemotherapy in Elderly Advanced NSCLC

- Stage III/IV NSCLC
- 70-89 yrs,
- PS 0-2
(N = 451)

Vinorelbine 30 mg/m² or Gemcitabine 1150 mg/m² on Days 1, 8 q3w x 5 cycles
Paclitaxel 90 mg/m² on Days 1, 8, 15 + Carboplatin AUC 6 on Day 1 q4w x 4 cycles

HR: 0.64 (95% CI: 0.52-0.78; P < .0001)

Pemetrexed vs Carbo+Pem for PS 2 PFS

- Multicenter randomized trial
- Advanced NSCLC
- ECOG PS = 2
- Any histology at beginning of trial, non-squamous after Scagliotti data
- No prior chemotherapy
- Adequate organ function
- 4 cycles P vs CP (AUC of 5 and 500 mg/m2)
- Primary end point: OS

Median PFS:
P = 2.8 mo CP = 5.8 mo
HR = 0.46; (95% CI, 0.35 to 0.63; \( P = .001 \))

## Bevacizumab in Advanced Non-squamous NSCLC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E4599(^1) (N = 878)</th>
<th>AVAiL(^2,3) (N = 1043; (P) values vs placebo)</th>
<th>JO19907(^4) (N = 180)</th>
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<tbody>
<tr>
<td></td>
<td>PCB</td>
<td>PC</td>
<td>CGB (7.5 mg/kg)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>35</td>
<td>15</td>
<td>37.8</td>
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<tr>
<td></td>
<td>(P &lt; .001)</td>
<td>(P &lt; .0001)</td>
<td>(P = .0002)</td>
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<tr>
<td>HR for PFS</td>
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<td>0.85</td>
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<tr>
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<td>(P &lt; .001)</td>
<td>(P = .0003)</td>
<td>(P = .046)</td>
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<td>Median PFS, mos</td>
<td>6.2</td>
<td>4.5</td>
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<tr>
<td>HR for OS</td>
<td>0.79</td>
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<tr>
<td></td>
<td>(P = .003)</td>
<td>(P = NS)</td>
<td>(P = NS)</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>12.3</td>
<td>10.3</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Maintenance Therapy for Patients With Nonprogressive Disease*

Patients with at least stable disease after 4 cycles of CT, PS 0-1

- **Continuation Maintenance**
  - Observation

- **Switch Maintenance**
  - Observation

- **Early 2nd-line Therapy**
  - Observation

**Options:**
- Bevacizumab, cetuximab, or pemetrexed (cat 1)
- Bev + Pem
- Gemcitabine (2B)

**Category 2B:**
- Docetaxel,
- Pemetrexed,
- Erlotinib,
- Gefitinib

*After initial platinum-based chemotherapy.

NCCN. Clinical Practice Guidelines in Oncology: non-small-cell lung cancer. v.5.2015.
NSCLC Maintenance Therapy: Advantages and Disadvantages

Advantages
- Maintains disease control
- Improves PFS
- Improves OS
- Maintains quality of life
- Opportunity to treat more patients
- Patients support maintenance therapy

Disadvantages
- Induction regimens of 4 vs 6 cycles may achieve the same improvement in PFS
- Careful follow-up reveals more patients available for second-line therapy than initially estimated by early reports
- Cumulative toxicity with Grade 3/4 AEs in 30% to 40% of patients
- Cost prohibitive
- Lack of reliable biomarkers
Second-line & Beyond for Non-target-driven Advanced NSCLC

- Commonly used options
  - Docetaxel +/- Ramucirumab
  - Pemetrexed
  - Erlotinib
  - Gemcitabine
  - Nivolumab (SCC approved)

- CONSIDER CLINICAL TRIALS

Adapted from NCCN. Clinical Practice Guidelines in Oncology: non-small-cell lung cancer. v.5.2015.
Case Study
• 65 yo never smoking M hospitalized w acute dyspnea, hemoptysis, PS=3
• Baseline PS=1
• Comorbidities: diverticulitis
• CTA: RUL mass, mediastinal nodes, liver metastases, multiple PEs
- Rx enoxaparin, supportive care
- Imaging w resolution of PEs on anticoagulation
- Brain MRI negative for metastases
- Biopsy NSCLC TTF1+
  - No actionable mutation
- PS improved to 2
- Treatment?
What treatment would you select

1. Cb+Pac+Bev
2. Cb+Nab-Pac
3. Cis+Pem
4. Cb+Pem
5. Erlotinib
6. Supportive care only
• Rx CbPem x 4 cycles w complications of flare of diverticulitis & hospitalization after cycle 3

• Imaging showed excellent PR

• Pem maintenance x 3 cycles stopped after recurrence of diverticulitis flare
  • Diverticular abscess w CVF
  • Surgery not felt feasible
• Antibiotics for chronic UTI from CVF
• Rapid progression in liver, bones, lungs off therapy
• Brain MRI diffuse metastases
  • WBRT recommended
  • Memantine during WBRT
• Ongoing decline
  • PS = 3
• Options?
Treatment Options

1. Begin second line docetaxel
2. Begin second line docetaxel + ramucirumab
3. Begin second line erlotinib
4. Repeat biopsy
5. Obtain additional testing
6. Refer for hospice evaluation
• Veristrat Good
• Erlotinib 150 mg daily started
• Colovesical fistula ongoing
• Requiring chronic antibiotics
• Nausea, fatigue
• PET/CT after 6 weeks

Re-evaluation for EGFRm >> L858R
Surgery persuaded to repair CVF
Ongoing response
Targeted Therapy in Lung Cancer
What is Targeted Therapy?

- Specifically block cancer cell growth and/or metastatic potential by impairing the function of cancer-causing or cancer associated genes or proteins

- Strategies that otherwise encourage the “host” response against “foreign” cancer cells
Principles of Targeted Therapy

• Focus on cancer specific abnormalities
• In theory, toxicity should be less, specific anticancer effects should be greater
  • Resistance can develop
  • Effects on normal tissues can occur
• Ideally an oral agent with few troublesome side effects allowing long-term use
Incidence of Single Driver Mutations

Mutation found in 54% (280/516) of tumors completely tested (CI 50-59%)
Molecular Subsets of Lung Cancer Defined by Driver Mutations

Frequency of Driver Mutations in NSCLC, %

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>AKT1</td>
<td>1</td>
</tr>
<tr>
<td>ALK</td>
<td>3-7</td>
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<tr>
<td>BRAF</td>
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<tr>
<td>EGFR</td>
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<td>HER2</td>
<td>2-4</td>
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<tr>
<td>KRAS</td>
<td>15-25</td>
</tr>
<tr>
<td>MEK1</td>
<td>1</td>
</tr>
<tr>
<td>NRAS</td>
<td>1</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>1-3</td>
</tr>
<tr>
<td>RET</td>
<td>1-2</td>
</tr>
<tr>
<td>ROS1</td>
<td>1</td>
</tr>
</tbody>
</table>
Who Should Get Targeted Lung Cancer Therapy?

- Patients with sensitizing EGFR mutations
- Patients who have had first and second line chemotherapy without EGFR mutations
  - Can consider Veristrat for second line decisions
- Patients with ALK rearrangements
- Patients with ROS1 rearrangements
- Smattering of others occasionally feasible
- Patients participating in clinical trials
Molecular Testing for Selection of Patients with Lung Cancer for EGFR and ALK Tyrosine Kinase Inhibitors

ASCO Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association of Molecular Pathologists Guideline

www.asco.org/endorsements/lungmarkers © 2014 American Society of Clinical Oncology®. All rights reserved.
Recommendation Overview

• The major recommendation from the CAP/IASLC/AMP:
  – use testing for *EGFR* mutations and *ALK* rearrangements to guide patient selection for therapy with *EGFR* or *ALK* inhibitors, respectively, in all patients with advanced-stage lung adenocarcinoma or tumors with an adenocarcinoma component, irrespective of clinical characteristics (smoking history, sex, race, or other clinical factors).

• Also recommended:
  – small tumor samples of other histologies, for which an adenocarcinoma component cannot be excluded because of sampling, can be considered for testing, particularly if clinical criteria are suggestive (eg, younger age, lack of smoking history).
  – Both primary tumors and metastatic lesions are suitable for testing.

• Additional guidance is provided regarding laboratory methods, specimen processing, testing validation, quality assurance, and result reporting in the full guideline: http://www.archivesofpathology.org/doi/full/10.5858/arpa.2012-0720-OA
Recommendations Highlights:
When should molecular testing of lung cancers be performed?

• 2.1a: *EGFR* mutation testing should be ordered at the time of diagnosis for patients who present with advanced-stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested.

• 2.1b: (Suggestion) *ALK* rearrangement testing should be ordered at the time of diagnosis for patients who present with advanced-stage disease (stage IV according to the 7th edition TNM staging system) and are suitable for therapy, or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested.
Recommendations:
When should molecular testing of lung cancers be performed?

- 2.2a: Expert consensus opinion: *EGFR* testing of tumors at diagnosis from patients who present with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

- 2.2b: Expert consensus opinion: *ALK* testing of tumors at diagnosis from patients who present with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

- 2.3: Recommendation: Tissue should be prioritized for *EGFR* and *ALK* testing.
Other Recommendations:
How should EGFR testing be performed?

What is the role of KRAS analysis in selecting patients for targeted therapy with EGFR TKIs?

• 7.1: KRAS mutation testing is not recommended as a sole determinant of EGFR TKI therapy.

Are other molecular markers suitable for testing in lung cancer?

• 10.1a: Testing for EGFR should be prioritized over other molecular markers in lung adenocarcinoma.

• 10.1b: (Suggestion) After EGFR testing, testing for ALK should be prioritized over other proposed molecular markers in lung adenocarcinoma, for which published evidence is insufficient to support testing guideline development at the present time.
Molecular Testing Guideline: EGFR and ALK

- Obtain as much tissue as possible at each biopsy
- DO NOT treat with 1st line EGFR/ALK inhibitors based on clinical characteristics alone
  - Doing so would give EGFR inhibitors inappropriately to 40% to 60% of pts
- DO NOT offer or deny molecular testing based on clinical characteristics alone
- Avoid bone biopsy for molecular testing due to decalcifying solutions, which denature DNA
Pathologic Assessment of Histology Helps Determine Optimal Treatment

- Histology still guides the therapeutic choice for the vast majority of patients
  - Squamous or non-squamous

- Adenocarcinomas are TTF1 positive (70% to 90%) and generally negative for p63 (70%) and p40 (97%)[^1-4]

- Squamous cells are typically p63 (or p40) positive and TTF1 negative[^1-4]

- All pts who do not have bona fide squamous NSCLC should be considered non-squamous

Tissue Issues

- Biopsy material matters
- Re-biopsy at progression whenever possible
- Involve pathologist prior to and at time of biopsy
  - Adequate samples crucial
  - Do not biopsy bone for molecular diagnostics
- Screen in logical order to conserve samples
- Refer for clinical trials whenever possible
Meta-analysis of Randomized First-line EGFR TKI Studies: Improved PFS

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
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<tr>
<td>EURTAC</td>
<td>0.37 (0.25-0.54)</td>
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<tr>
<td>First-SIGNAL</td>
<td>0.54 (0.27-1.10)</td>
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<tr>
<td>GTOWG</td>
<td>1.08 (0.24-4.90)</td>
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<td>INTACT1-2</td>
<td>0.55 (0.19-1.60)</td>
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<td>IPASS</td>
<td>0.48 (0.36-0.64)</td>
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<td>0.58 (0.43-0.78)</td>
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<td></td>
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<tr>
<td>Subtotal</td>
<td>0.43 (0.38-0.49)</td>
<td></td>
</tr>
</tbody>
</table>

## LUX-Lung 3+6: OS by Mutation Status

<table>
<thead>
<tr>
<th>Mutation Status</th>
<th>Afatinib (n = 236)</th>
<th>Chemo (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del(19)</td>
<td>Median, mo 31.7</td>
<td>20.7</td>
</tr>
<tr>
<td></td>
<td>HR (95%CI), 0.59 (0.45-0.77)</td>
<td><em>P</em> = .0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mutation Status</th>
<th>Afatinib (n = 183)</th>
<th>Chemo (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L858R</td>
<td>Median, mo 22.1</td>
<td>26.9</td>
</tr>
<tr>
<td></td>
<td>HR (95%CI), 1.25 (0.92-1.71)</td>
<td><em>P</em> = .1600</td>
</tr>
</tbody>
</table>

Options for EGFR TKI Resistance

- Chemotherapy
- Radiation
  - Continue erlotinib
- Afatinib
- Cetuximab – not FDA approved for this
- Clinical trials
  - Rocelitinib approval hoped for soon
  - AZ compound not far behind
  - EAP available

- 49% T790M
- 5-10% SCLC
- Met amplification
- Her2 amplification
- Others
Retrospective Analysis: Local Ablative Therapy in NSCLC w/Acquired Resistance

- 65 pts (38 ALK+, 27 EGFR mut+) of whom 51 (28 ALK, 23 EGFR) progressed
- 25 (49%) with CNS (no LMC) or ≤ 4 extracranial sites of progression

IMPRESS: Cis/Pem ± Gefitinib in Stage IIIb/IV NSCLC w/ EGFR Mutations: PFS

- Gefitinib (n = 133)
- Placebo (n = 132)

**Probability of PFS**

- Median PFS, mo: Gefitinib 5.4 vs Placebo 5.4
- No. of events, n (%): Gefitinib 98 (73.7) vs Placebo 107 (81.1)
- HR (95% CI): 0.86 (0.65-1.13); $P = .273$
- HR <1 implies lower risk of progression with gefitinib

**Patients at risk:**
- Gefitinib: 133, 110, 88, 40, 25, 12, 6, 0
- Placebo: 132, 100, 85, 39, 17, 5, 4, 0

**Med OS:** 14.8 mo (G) vs 17.2 mo (P)
- HR: 1.62 ($P = .029$) but 33% of events

Mok T, et al. ESMO 2014. Abstract LBA2_PR.
## 3rd Generation EGFR TKIs

<table>
<thead>
<tr>
<th>EGFR TKI</th>
<th>ORR: T790M+, %</th>
<th>ORR: T790M-, %</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib/Cetuximab</td>
<td>32</td>
<td>28</td>
<td>4.66 mo</td>
</tr>
<tr>
<td>Rociletinib (CO-1686)</td>
<td>58</td>
<td>Inc.</td>
<td>↑</td>
</tr>
<tr>
<td>AZD 9291</td>
<td>65</td>
<td>22</td>
<td>↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE (any grade), %</th>
<th>Diarrhea</th>
<th>Rash</th>
<th>ILD/SOB</th>
<th>Inc BS</th>
<th>QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib/Cetuximab</td>
<td>71</td>
<td>97</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rociletinib (CO-1686)</td>
<td>23</td>
<td>4</td>
<td>NR</td>
<td>55</td>
<td>15 (7% Gr 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD 9291</td>
<td>20</td>
<td>27</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HM 61713</td>
<td>21</td>
<td>24</td>
<td>10</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Lynch TJ. ASCO 2014 discussion on abstracts 8009 (Janne, et al) and 8010 (Sequist, et al).
### EGFR Inhibitor–Associated Skin Rash: Management

<table>
<thead>
<tr>
<th>Preventive</th>
<th>Recommended</th>
<th>Not Recommended</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Topical    | Hydrocortisone 1% cream with moisturizer, sunscreen twice daily | Pimecrolimus 1% cream  
Tazarotene 0.05% cream  
Sunscreen as single agent | |
| Systemic   | ▪ Minocycline 100 mg/day  
▪ Doxycycline 100 mg BID | ▪ Tetracycline 500 mg BID | Doxycycline is preferred in patients with renal impairment; minocycline is less photosensitizing |
| Treatment |             |                 |          |
| Topical    | ▪ Alclometasone 0.05% cream  
▪ Fluocinonide 0.05% cream BID  
▪ Clindamycin 1% | ▪ Vitamin K1 cream | |
| Systemic   | ▪ Doxycycline 100 mg BID  
▪ Minocycline 100 mg/day  
▪ Isotretinoin at low doses (20-30 mg/day) | ▪ Acitretin | Photosensitizing agents |

ALK Rearrangement in NSCLC

- Present in ~4% of NSCLC cases
- Enriched in younger never or light smokers with adeno-carcinoma histology
- Rarely overlaps with EGFR and KRAS mutations
- Potent oncogenic driver in cell line and animal models
Clinical Implications

• Pts with ALK rearrangements compared to general population
  • Younger, little or no tobacco exposure
  • Adenocarcinoma – often a characteristic microscopic picture

• Most patients respond to crizotinib
  • Response rates lower than seen with EGFR targets
  • Response durations likely shorter
  • Second line ceritinib FDA approved

• Strategies to overcome resistance under active study
  • Newer molecules in development

• Studies ongoing for ROS1 rearrangements
Tumor Responses to Crizotinib for Patients with ALK-positive NSCLC

- Progressive disease
- Stable disease
- Confirmed partial response
- Confirmed complete response

Maximum change in tumor size (%)

US FDA accelerated approval Aug 26, 2011
Full approval Nov 21, 2013

*Partial response patients with 100% change have non-target disease present
Phase I ASCEND-1: Ceritinib in ALK-Positive NSCLC

- Treatment (N = 246): 750 mg/day (MTD from dose-escalation phase)
- Antitumor activity independent of prior ALK inhibitor treatment
- Most common grade 3/4 AEs: increased ALT (29.8%) and AST (9.8%)
- Most common AEs (all grades): diarrhea (86.7%), nausea (82.7%), vomiting (61.6%)

Felipe E, et al. ESMO 2014. Abstract 1295P.
Ceritinib in ALK+ NSCLC: Best % Change From Baseline in Target Lesions

**ORR (CR + PR): 58%**
- Prior crizotinib: 56%
- Crizotinib naïve: 62%

Other second-generation ALK inhibitors in development:
- CH5424802 (alectinib)
- AP26113
- X-396
- ASP3026
- GSK 1838705
- CEP-28122

Response of an ROS1-positive patient with advanced non–small-cell lung cancer to crizotinib.

Bergethon K et al. JCO 2012;30:863-870
Activity of Crizotinib in Patients With ROS1 Fusions: Best Response

- ORR: 72%

Immunotherapy
Tumors arise when cancer cell-mediated immune suppression allows developing cancers to evade immune surveillance.

Immunotherapy goals include:

- Restoration of immunologic recognition of host-derived cancer as foreign
- Boost cancer-specific immune responses
- Abrogate tumor-mediated immunosuppression and immune tolerance of host-derived cancer cells
Targeted therapy

a Pro-apoptotic signal

Dying tumour cells

Adoptive cell transfer

b Increased antigen presentation

Recruitment and activation of adoptively transferred T cells

Recruitment and activation of endogenous T cells

Tumour antigen

APC

Tumour-derived peptide

MHC class I

TCR

Treatment with cytokines, chemokines, anti-angiogenic factors

c Decreased immunosuppression

Tumour cells

T<sub>Reg</sub> cell

MDSC

Killing

Proliferation

T cells
Cancer and the Immune System

- Cancer cell immune recognition
  - Tumor antigens presented on APC by MHC class I molecule

- T cell activation results from immune recognition requiring
  - T cell receptor
  - Co stimulatory B7-CD28 complex

- Activated T cells kill tumor cells if not inhibited by tumor or host factors

- Activated T cell inhibition can be overcome therapeutically

Adapted from Brahmer, AACR 2013
Immune Recognition Requirements

- Initiation of recognition by APCs
  - Internalize tumor antigens and process on MHC
  - Present MHC bound tumor antigens on surface of APC

- Presented antigens + costimulatory complex B7.1/B7.2 direct APCs to nodes

- APCs present antigens to resting T-cells through specific TCR

- Activated T cells recognize tumor antigens leading to immune recruitment and creation of memory T cells
Immune Checkpoints

• Dampen the immune response to protect against autoimmunity and inflammation

• But this process can allow immune tolerance to tumor cells via competition for B7.1/B7.2 binding thus blocking co-stimulation and T cell activation (CTLA-4).

• PD1 up-regulation on activated T-cells can engage PD-L1 produced by tumor cells in response to tumor related inflammation (IFN-γ mediated) and inactivate T-cells
PD-1 Blockade: Binding to PD-L1 (B7-H1) and PD-L2 (B7-DC) Revives T Cells

- PD-L1 expression on tumor cells induced by interferon-γ
- Activated T cells that could kill tumors are specifically disabled

CheckMate 017: Nivolumab vs Docetaxel in Advanced Squamous NSCLC

Advanced squamous NSCLC Progression on or after 1 previous platinum-based doublet CT regimen (N = 272)

- **Nivolumab** (n = 135)
  - MedOS (95% CI), mos: 9.2 (7.3 - 13.3)
  - 1 yr OS (%): 42
  - HR (95% CI): .59 (.44-.79)
  - P value: .00025

- **Docetaxel** (n = 137)
  - MedOS (95% CI), mos: 6.0 (5.1 – 7.3)
  - 1 yr OS (%): 22

Pembrolizumab Activity in NSCLC Correlates with PD-L1 Expression

- 282 treatment-naïve or previously treated patients with advanced NSCLC
- ORR by RECIST ~21%
  - 26% in 42 treatment-naïve patients
  - 20% in 194 previously treated patients
  - 23% for pts staining + for PD-L1
  - 9% for pts w/o PD-L1 staining
- Median PFS
  - 27 weeks treatment-naïve
  - 10 weeks previously treated
- Grade 3-5 AEs 9%, most commonly pneumonitis

Response Rate by Level of PD-L1 Expression (RECIST 1.1, Central Review)

- Weak Positive (n=46): 17 ORR
- Total (N=129): 22 ORR
- Negative (n=42): 10 ORR

Strong PD-L1 expression: defined as ≥50% membranous staining

 Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per imaging assessment criteria. Analysis cut-off date: March 3, 2014.

Slide courtesy of E Garon
KEYNOTE-001 Study: Survival

**PFS (RECIST v1.1, Central Review)**

- Treatment naive
  - Median PFS: 27 weeks (95% CI, 14-45)
  - 24-week PFS: 51%
- Previously treated
  - Median PFS: 10 weeks (9.1-15.3)
  - 24-week PFS: 26%

**OS**

- Treatment naive
  - Median OS: NR (95% CI, NE-NE)
  - 6-month OS: 86%
- Previously treated
  - Median OS: 8.2 months (7.3-NR)
  - 6-month OS: 59%

Phase 3 Study of Nivolumab* Compared with Docetaxel in 2nd/3rd-Line Advanced/Metastatic Non-Squamous NSCLC (CA209-057/NCT01673867)

Primary Endpoint: OS
Secondary Endpoints: PFS, ORR, QoL, PD-LI protein expression

Key Eligibility Criteria
- ≥18 years of age, ECOG PS 0-1
- Stage IIIB/IV non-squamous NSCLC
- Prior Pt-containing chemotherapy required
- Additional TKI therapy allowed
- Maintenance after 1st line chemo allowed
- No prior checkpoint or T-cell targeted immunoRx

ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Pt = platinum; QoL = quality of life; TKI = tyrosine kinase inhibitor.

*Nivolumab is not FDA-indicated for non-squamous NSCLC.

https://clinicaltrials.gov/ct2/show/NCT01673867?term=NCT01673867&rank=1
Overall Survival

Nivolumab (n = 292)  Docetaxel (n = 290)

mOS, mo
12.2  9.4

HR = 0.73 (96% CI: 0.59, 0.89); P = 0.0015

1-yr OS rate = 51%
1-yr OS rate = 39%

Symbols represent censored observations.
## Treatment Effect on OS in Predefined Subgroups

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>582</td>
<td>0.75 (0.62, 0.91)</td>
</tr>
<tr>
<td><strong>Age Categorization (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>339</td>
<td>0.81 (0.62, 1.04)</td>
</tr>
<tr>
<td>≥65 and &lt;75</td>
<td>200</td>
<td>0.63 (0.45, 0.89)</td>
</tr>
<tr>
<td>≥75</td>
<td>43</td>
<td>0.90 (0.43, 1.87)</td>
</tr>
<tr>
<td><strong>Gender</strong></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><strong>Baseline ECOG PS</strong></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>0.80 (0.63, 1.00)</td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/Former Smoker</td>
<td>458</td>
<td>0.70 (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><strong>EGFR Mutation Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>82</td>
<td>1.18 (0.69, 2.00)</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>

All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

---

Presented By Luis Paz-Ares at 2015 ASCO Annual Meeting
## Objective Response Rate

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 292)</th>
<th>Docetaxel (n = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (95% CI)</strong></td>
<td>19% (15, 24)</td>
<td>12% (9, 17)</td>
</tr>
<tr>
<td><strong>Odds Ratio (95% CI)</strong></td>
<td>1.72 (1.1, 2.6)</td>
<td></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td></td>
<td>0.0246</td>
</tr>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Partial response</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Stable disease</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>44</td>
<td>29</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td><strong>Median time to response, mo</strong> (range)</td>
<td>2.1 (1.2, 8.6)</td>
<td>2.6 (1.4, 6.3)</td>
</tr>
<tr>
<td><strong>Median DOR, mo</strong> (range)</td>
<td>17.2 (1.8, 22.6+)</td>
<td>5.6 (1.2+, 15.2+)</td>
</tr>
<tr>
<td><strong>Ongoing response, %</strong></td>
<td>52</td>
<td>14</td>
</tr>
</tbody>
</table>

- 71 (24%) patients on nivolumab were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16 patients (not included in best overall response)

---

*a* Based on two-sided stratified Cochran Mantel Haenszel test; *b* Values are for all responders (nivolumab, n = 56; docetaxel, n = 36); *c* Ongoing response at last tumor assessment before censoring. Symbol + indicates a censored value.

---

Presented By Luis Paz-Ares at 2015 ASCO Annual Meeting
OS by PD-L1 Expression

≥1% PD-L1 expression level

- Nivo: 17.2 months
- Doc: 9.0 months

HR (95% CI) = 0.59 (0.43, 0.82)

≥5% PD-L1 expression level

- Nivo: 18.2 months
- Doc: 8.1 months

HR (95% CI) = 0.43 (0.30, 0.63)

≥10% PD-L1 expression level

- Nivo: 19.4 months
- Doc: 8.0 months

HR (95% CI) = 0.40 (0.26, 0.59)

<1% PD-L1 expression level

- Nivo: 10.4 months
- Doc: 10.1 months

HR (95% CI) = 0.90 (0.66, 1.24)

<5% PD-L1 expression level

- Nivo: 9.7 months
- Doc: 10.1 months

HR (95% CI) = 1.01 (0.77, 1.34)

<10% PD-L1 expression level

- Nivo: 9.9 months
- Doc: 10.3 months

HR (95% CI) = 1.00 (0.76, 1.31)

Symbols represent censored observations.
Immune Related Toxicity of T-cell Activating Agents

• Primarily affects GI tract, liver, skin, lung, endocrine system, nervous system
• Mandates cessation of immunotherapy if progressing or severe
• Steroids should be given early and until resolution
Immune Related Adverse Events

• Begin subtly and may not seem serious at first
  • While usually mild, can be fatal if not recognized and treated promptly

• Significant toxicities:
  • Pneumonitis
  • Rash
  • GI tract
  • Neuropathy
  • Endocrinopathy
Take Home Messages

• Treatment benefits patients with all stages of NSCLC
• Standard targeted therapies are a reality now for ~ 15% of NSCLC patients
  • In US, up to half of never-smokers
• Response and survival are improved when the right target is treated with the right agent at the right time
• Guessing can result in poor outcomes
• Clinical trials of resistance modulators and novel target/Rx combinations are key
• New trials methodology needed
Take Home Messages: Immunotherapy

- While immunotherapy for NSCLC is not yet fully approved in the US, there is clearly a subgroup of patients that derives substantial benefit
  - Compendia listed so most patient can receive if appropriate

- The optimal timing, combination, duration, selection biomarkers and agents are under active study in dozens of preclinical, clinical and translational trials

- Patients should be referred for clinical trials whenever possible
Questions?