Collaborative Practice in the Management of Patients With Cancer

Non-Small Cell Lung Cancer: Management of Patients on Cytotoxic Chemotherapy
Program Chair

Beth Eaby-Sandy, MSN, CRNP, OCN®
Abramson Cancer Center
University of Pennsylvania
Philadelphia, PA
Disclosures

Faculty

Ms. Eaby-Sandy has acted as a consultant for AstraZeneca and Clovis; she has served on speakers bureaus for Amgen, Celgene, Eisai, and Merck.

Planning Committee

Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has nothing to disclose. Alana Brody, Terry Logan, Lynn Rubin, and Wendy Smith (MEI) have nothing to disclose. Sandra Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose. Claudine Kiffer and Annie Yueh (Harborside Press) have nothing to disclose.
Learning Objectives

• Demonstrate a foundational understanding of how to interpret imaging studies that are used in the management of NSCLC
• Choose relevant molecular/biomarker tests to identify the most appropriate therapy for the patient with NSCLC (e.g., targeted or immunotherapy)
• Use appropriate management strategies for toxicities associated with targeted therapies
• Differentiate between the various treatment options available for NSCLC: Comparing mechanisms of action, toxicity profiles, and monitoring
• Manage toxicities associated with different agents used to treat NSCLC
• Demonstrate an understanding of the science behind immune checkpoint inhibition and how this drug category differs from other available and evolving options for NSCLC, including cytotoxic chemotherapy
Objectives

• Lung cancer demographics and overview
• Chemotherapy options
  – First line
  – Maintenance
  – Second line and beyond
• Toxicity management of chemotherapy
  – Chemotherapy-induced nausea and vomiting
Case Study #2 (continued)

• JO is a 58-year-old man who works per diem jobs for the carpenter’s union. He does not have insurance and rarely goes to the doctor.

• He smokes a pack of cigarettes a day and in January 2016 developed a cold and a wheeze that wouldn’t go away with OTC medication.

• He presented to the ER, due to lack of insurance. He was on no medications and PMH only significant for non-Hodgkin’s Lymphoma in 1988, treated with radiation only, and femur fracture with rod placed in 1965.

• CXR performed in ER followed up by a CT chest
Case Study #2 (continued)

- CT chest confirms large RLL mass with lymphadenopathy.
- PET/CT confirms several lymph nodes positive in mediastinum, hilum, supraclavicular region, and subpectoral area. + Left and right adrenal lesion.
- MRI brain also shows 2 small brain mets with edema.
- Bronchoscopy performed 2/19/2016 + for adenocarcinoma consistent with lung primary. TTF-1 +, CK7 and Napsin +.
NSCLC: Scope of the Problem

Estimated Number of New Cases in US by Sex: 2016

- **Prostate:** 180,890 (21%)
- **Lung/Bronchus:** 117,920 (14%)
- **Colon/Rectum:** 47,710/23,110 (8%)

- **Breast:** 246,660 (29%)
- **Lung/Bronchus:** 106,470 (13%)
- **Colon/Rectum:** 47,560/16,110 (8%)

NSCLC: Scope of the Problem

Estimated Deaths: 2016

PERSPECTIVE (Deaths)
Lung/Bronchus = 158,040 (27%)
Breast + Prostate + Colon/Rectum = 116,200 (20%)

1. Prostate: 180,890 (21%)
2. Lung/Bronchus: 117,920 (14%)
3. Colon/Rectum: 47,710/23,110 (8%)

1. Breast: 246,660 (29%)
2. Lung/Bronchus: 106,470 (13%)
3. Colon/Rectum: 47,560/16,110 (8%)
Lung Cancer Stages and Survival

Understanding the Histology of Lung Cancer

• Non-small cell lung cancer
  – 83% of lung cancers
  – About 10-15% of cases are never-smokers

• Small cell lung cancer
  – 13% of lung cancers
  – Very aggressive type
  – 99% of cases associated with smoking

NSCLC: Histology Matters

- **Adenocarcinoma**
  - Most likely to harbor a genetic mutation
  - Most common type in non-smokers

- **Squamous cell**
  - Generally more centrally located

- **Mixed subtypes or other**
  - NOS, mixed histologies, mixed NSCLC/SCLC, other rare types

- **Large Cell**
  - Often associated with neuroendocrine features, but not a small cell

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• Discussed various chemotherapy options with Mr. JO and decided to go forward with pemetrexed and carboplatin chemotherapy.

• Unlikely to have a molecular abnormality given he was a smoker; however, testing should be performed because there is a chance.

• Incidence of EGFR mutation:
  – 4.9% in current smokers\textsuperscript{1}
  – 43% in never smokers\textsuperscript{1}
  – 51% in Asians\textsuperscript{2}
  – 79% female never-smoker Asians\textsuperscript{3}

Which Agents to Use

• Several chemotherapy agents approved or show activity in NSCLC
• Platinum-based doublet chemotherapy standard of care 1st line
• Decision-making depends on patient characteristics and patient’s expectations of treatment
• Several drugs approved depending on histologic subtype of NSCLC
• Some targeted agents approved with chemotherapy or alone in all lines of therapy
First-Line Treatment of Non-Squamous NSCLC

• Cisplatin or carboplatin + any of drugs below
• Bevacizumab added in eligible patients
• Pemetrexed added to platinum is superior to gemcitabine
• Other drugs can combine with platinum in PS 0-1
  – Docetaxel  – Nab-paclitaxel
  – Gemcitabine  – Paclitaxel
  – Etoposide  – Vinorelbine
ECOG 1594:
All Platinum Doublets Essentially Equal

1,207 patients, stage IIIB/IV (15/85%), PS 0-2
Median age 63; male/female: 64/36%

\( AUC = \text{area under the curve.} \)

- Cisplatin + Paclitaxel
  - 75 mg/m\(^2\) D2
  - 135 mg/m\(^2\)/24h q3wk
- Cisplatin + Gemcitabine
  - 100 mg/m\(^2\) D1
  - 1 g/m\(^2\) D1,8,15 q4wk
- Cisplatin + Docetaxel
  - 75 mg/m\(^2\) D1
  - 75 mg/m\(^2\) D1 q3wk
- Carboplatin + Paclitaxel
  - AUC = 6 mg/mL/min D1
  - 225 mg/m\(^2\)/3h D1 q3wk

Similar efficacy for all doublets
NON-SQUAMOUS NSCLC
Importance of Histology

Pemetrexed/Cisplatin vs. Gemcitabine/Cisplatin

Study design
- Multicenter, randomized, open label
- Noninferiority

Primary endpoint
- OS

Secondary
- PFS
- Time to progression
- Objective response rate
- Duration of response
- Toxicity

Pemetrexed/Cisplatin (n = 862)
- Pemetrexed 500 mg/m² IV
- Cisplatin 75 mg/m² IV
- Every 21 days, max 6 cycles, vitamin and dexamethasone prophylaxis

Gemcitabine/Cisplatin (n = 863)
- Gemcitabine 1,250 mg/m² IV days 1 and 8
- Cisplatin 75 mg/m² day 1
- Every 21 days, max 6 cycles, vitamin and dexamethasone prophylaxis

Importance of Histology (continued)

Overall Survival Improved With Pemetrexed/Cisplatin vs. Gemcitabine/Cisplatin in First-Line Adenocarcinoma Patients

CI = confidence interval.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (months) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed/Cisplatin (n=436)</td>
<td>12.6 (10.7-13.6)</td>
</tr>
<tr>
<td>Gemcitabine/Cisplatin (n=411)</td>
<td>10.9 (10.2-11.9)</td>
</tr>
</tbody>
</table>

**Graph:***
- **Survival Probability** against **Survival Time (Months)**
- Orange line represents Pemetrexed/Cisplatin with a median OS of 12.6 months (95% CI: 10.7-13.6)
- Green line represents Gemcitabine/Cisplatin with a median OS of 10.9 months (95% CI: 10.2-11.9)
What About Bevacizumab?

• Targeted therapy that can be added to chemotherapy in metastatic NSCLC

• Eligibility criteria and warnings:
  – Nonsquamous histology only
  – No history hemoptysis (postprocedure ok?)
  – No recent history of arterial thrombotic event
  – No uncontrolled hypertension
  – Nephrotic syndrome (proteinuria $\geq 3.5$ g)
  – No surgery within 28 days
  – Gastrointestinal perforation
  – Non-gastrointestinal fistula formation
  – Reversible posterior leukoencephalopathy syndrome
  – Infusion reactions
  – Ovarian failure

Bevacizumab Prescribing Information. 2013.
ECOG 4599 Trial
Bevacizumab + PC vs. PC Alone in First-Line Nonsquamous NSCLC

Stratified by:
• Disease stage
• Degree of weight loss
• Prior radiotherapy
• Measurable disease

First-line treatment of patients with stage IIIB and malignant pleural effusion, stage IV, or recurrent NSCLC (N = 878)

Paclitaxel 200 mg/m² + carboplatin AUC = 6 q3wk x 6 (no crossover permitted) (n = 444)

Bev 15 mg/kg Solution for IV infusion q3wk + PC x 6 (n = 434)

Bev 15 mg/kg q3wk until disease progression or unacceptable toxicity

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary endpoints</td>
<td>Response rate, PFS, toxicity</td>
</tr>
</tbody>
</table>

PC = paclitaxel/carboplatin.
ECOG 4599 Trial

Bevacizumab + PC vs. PC Alone in First-Line Nonsquamous NSCLC (cont)

Median OS
12.3 mo Bevacizumab + PC vs. 10.3 mo for PC alone ($P = .013$)

1-yr survival: 51% vs. 44%
2-yr survival: 23% vs. 15%

SQUAMOUS HISTOLOGY
NCCN Guidelines: First-Line Treatment of Squamous NSCLC

- Carboplatin/nab-paclitaxel
- Carboplatin/docetaxel
- Carboplatin/etoposide
- Carboplatin/gemcitabine
- Carboplatin/paclitaxel
- Carboplatin/vinorelbine
- Cisplatin/docetaxel
- Cisplatin/etoposide
- Cisplatin/gemcitabine
- Cisplatin/gemcitabine/necitumumab
- Cisplatin/paclitaxel
- Cisplatin/vinorelbine
- Gemcitabine/docetaxel
- Gemcitabine/vinorelbine
EGFRI MABs in First-Line NSCLC

• EGFR protein overexpression in squamous NSCLC approximately 58%¹

• Cetuximab FLEX trial data, does not have an indication in NSCLC

• Necitumumab approved in late 2015 for squamous NSCLC in addition to chemotherapy

• Modest improvements in OS, is it worth the toxicity for little benefit? Cost?

EGFRI = epidermal growth factor receptor inhibitor; MAB = monoclonal antibody
SQUIRE: Necitumumab in Squamous NSCLC

First-line stage IV Squamous NSCLC ECOG PS 0-2

Gem-Cis + NECI q3wk (n = 545)
NECI 800 mg day 1, 8
Gem 1250 mg/m² day 1, 8
Cisplatin 75 mg/m² day 1

NECI q3wk 800 mg D1, D8

Maximum of 6 cycles

Gem-Cis q3wk (n = 548)
Gem 1250 mg/m² day 1, 8
Cisplatin 75 mg/m² day 1

PR CR SD PD

• Patient selection not based on EGFR protein expression
• Tissue collection was eligibility criterion

FLEX: Cetuximab in Squamous NSCLC

Chemotherapy-naive patients with EGFR-expressing stage wet IIIB or IV NSCLC ECOG PS 0-2

Cis-Vin + Cetux (n=557)
- Cisplatin 80 mg/m² IV day 1 q3wk
- Vinorelbine 25-30 mg/m² IV days 1, 8 q3wk
- Cetuximab 400 mg/m² IV day 1, then 250 mg/m² from day 8 weekly

Cis-Vin (n=568)
- Cisplatin 80 mg/m² IV day 1
- Vinorelbine 25-30 mg/m² IV days 1, 8 q3wk

Primary endpoint: Median OS
Cetuximab does not have FDA indication for NSCLC but does have Medicare compendia listing

CR PR SD PD

OS = overall survival; PFS = progression-free survival
# Results of Necitumumab (SQUIRE) and Cetuximab (FLEX) Trials in NSCLC

<table>
<thead>
<tr>
<th>Primary Endpoint and Serious Adverse Events</th>
<th>SQUIRE Necitumumab (n = 545)</th>
<th>P Value</th>
<th>FLEX Cetuximab* (n = 557)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem/Cis/Neci Gem/Cis</td>
<td>Cis/Vin/Cetux</td>
<td>Cis/Vin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>11.5 mo</td>
<td>9.9 mo</td>
<td>11.3 mo</td>
<td>10.1 mo</td>
</tr>
<tr>
<td><strong>Grade 3/4 hypomagnesemia</strong></td>
<td>9%</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3 rash</strong></td>
<td>4%</td>
<td>&lt;1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3 acne-like skin rash</strong></td>
<td></td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td><strong>Grade 3/4 diarrhea</strong></td>
<td></td>
<td></td>
<td></td>
<td>4%</td>
</tr>
</tbody>
</table>

*Cetuximab does not have an FDA indication for NSCLC, but does have a Medicare compendia listing and data to support its use in NSCLC

SPECIAL POPULATIONS: ELDERLY
Average Age at NSCLC Diagnosis

Median age at diagnosis: 70

**nab-Paclitaxel in Elderly Patients**

- In elderly patients, a non-significant trend toward improved PFS (8.0 vs. 6.8 months; HR = 0.687; 95% CI: 0.420-1.123; \( P = .134 \))

- A significant improvement in OS was observed with nab-PC vs. sb-PC

- In patients <70 years old, there was no difference in PFS or OS

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sb = solvent-based.
Populations That Benefited Most

- North America
- Elderly (age ≥ 70)
- Squamous histology

Case Study #2 (continued)

• JO received 1st cycle of pemetrexed and carboplatin chemotherapy and returns to your office to receive C2.
• He experienced chemotherapy-induced nausea and vomiting (CINV) for 4 days after chemotherapy. With C1, he was premedicated with ondansetron 16 mg and dexamethasone 12 mg prior to receiving infusion of chemotherapy.
Risk Factors for CINV for Our Patient JO

• Pemetrexed/carboplatin, what is NCCN risk level for these drugs?
  HIGH MODERATE LOW

• Patient-associated risk factors for CINV
  – Age younger than 50
  – Female
  – Low alcohol intake
  – Anxiety
  – Motion sickness, pregnancy sickness, h/o CINV
<table>
<thead>
<tr>
<th>Option A</th>
<th>Option B</th>
<th>Option C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serotonin (5-HT₃) antagonist:</strong></td>
<td><strong>Netupitant-containing regimen:</strong></td>
<td><strong>Olanzapine-containing regimen:</strong></td>
</tr>
<tr>
<td>• Dolasetron 100 mg PO once</td>
<td>• Netupitant 300 mg/palonosetron 0.5 mg PO once</td>
<td>• Olanzapine 10 mg PO</td>
</tr>
<tr>
<td>• Granisetron 2 mg PO once, or 0.01 mg/kg IV once, or 3.1 mg/24 h transdermal patch</td>
<td>• Dexamethasone 12 mg PO/IV once</td>
<td>• Palonosetron 0.25 mg IV once</td>
</tr>
<tr>
<td>• Ondansetron 16-24 mg PO once or 8-16 mg IV once</td>
<td></td>
<td>• Dexamethasone 20 mg IV once</td>
</tr>
<tr>
<td>• Palonosetron 0.25 mg IV once</td>
<td><strong>AND</strong></td>
<td><strong>WITH/WITHOUT</strong></td>
</tr>
<tr>
<td><strong>Steroid:</strong></td>
<td><strong>NK1 antagonist:</strong></td>
<td><strong>NK1 antagonist:</strong></td>
</tr>
<tr>
<td>• Dexamethasone 12 mg PO/IV once</td>
<td>• Aprepitant 125 mg PO once</td>
<td>• Aprepitant 125 mg PO once</td>
</tr>
<tr>
<td></td>
<td>• Fosaprepitant 150 mg IV once</td>
<td>• Fosaprepitant 150 mg IV once</td>
</tr>
<tr>
<td></td>
<td>• Rolapitant 180 mg PO once</td>
<td>• Rolapitant 180 mg PO once</td>
</tr>
</tbody>
</table>
### NCCN Guidelines: Moderately Emetogenic Chemotherapy: Days 2 & 3

<table>
<thead>
<tr>
<th>Option A (see previous slide)</th>
<th>Option B (see previous slide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>If no NK1 antagonist given on day 1:</td>
<td>± Dexamethasone 8 mg PO/IV daily on days 2, 3</td>
</tr>
<tr>
<td>Serotonin (5-HT₃) antagonist monotherapy (dolasetron, granisetron, ondansetron) OR Steroid monotherapy</td>
<td></td>
</tr>
<tr>
<td>• Dexamethasone 8 mg PO/IV daily on days 2, 3</td>
<td></td>
</tr>
</tbody>
</table>

If NK1 antagonist given on day 1:
- If aprepitant given day 1, then aprepitant 80 mg PO daily on days 2, 3 ± dexamethasone 8 mg PO/IV daily on days 2, 3
- If fosaprepitant given day 1, then no further NK1 antagonist needed on days 2, 3 ± dexamethasone on days 2, 3
- If rolapitant given day 1, then no further NK1 antagonist needed on days 2, 3 ± dexamethasone on days 2, 3

<table>
<thead>
<tr>
<th>Option C (see previous slide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine 10 mg PO daily on days 2, 3</td>
</tr>
</tbody>
</table>
**Netupitant/Palonosetron (1 tablet)**
- First combined tablet of an NK-1 RA netupitant (300 mg) with oral 5HT-3 RA palonosetron (0.5 mg)
- One capsule taken 1 hour prior to chemotherapy (with or without food)
- Superior in highly and moderately emetogenic chemotherapy regimens to just oral palonosetron (both arms with dexamethasone)

**Rolapitant**
- NK-1 RA, oral
- 180-hr half-life (7.5 days)
- No CYP3A4 pathway inhibition

**Olanzapine (old drug)**
- Recently added to the NCCN Guidelines as a prevention
- Targets multiple receptors: dopaminergic, serotinergic, adrenergic, histaminergic, muscarinic
- Some side effects of somnolence, hypotension, constipation, dizziness, fatigue, dyspepsia, and restlessness
  - None were grade 3 or 4 toxicities
Newer CINV Agents (continued)

**Long-acting granisetron**
- August 2016: FDA approves a new formulation of long-acting granisetron
- Subcutaneous injection, 10 mg, given 30 minutes prior to chemotherapy
- For the prevention of acute and delayed CINV in moderately emetogenic regimens or anthracycline plus cyclophosphamide regimens
# Continuation Maintenance Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Continuation Agent</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belani et al. (64% had an ECOG PS of 2)</td>
<td>Gemcitabine Best supportive care</td>
<td>7.4 7.7</td>
<td>8.0* 9.3</td>
</tr>
<tr>
<td>IFCT</td>
<td>Gemcitabine Erlotinib Best supportive care</td>
<td>3.8 2.9 1.9</td>
<td>12.1 11.4 10.8</td>
</tr>
<tr>
<td>PARAMOUNT</td>
<td>Pemetrexed Placebo</td>
<td>4.1 2.8</td>
<td>13.9† 16.0‡</td>
</tr>
</tbody>
</table>

*Large proportion of patients had poor performance status.
†From randomization.
‡From initiation of treatment.
## Switch Maintenance Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Switch Agent</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias, et al</td>
<td>Immediate docetaxel Delayed docetaxel</td>
<td>5.7</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.7</td>
<td>9.7</td>
</tr>
<tr>
<td>JMEN*</td>
<td>Pemetrexed Placebo</td>
<td>4.3</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6</td>
<td>10.6</td>
</tr>
<tr>
<td>SATURN*</td>
<td>Erlotinib Placebo</td>
<td>2.8</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6</td>
<td>11.0</td>
</tr>
<tr>
<td>ATLAS</td>
<td>Erlotinib + bevacizumab Placebo + bevacizumab</td>
<td>4.8</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.8</td>
<td>13.9</td>
</tr>
<tr>
<td>INFORM</td>
<td>Gefitinib Placebo</td>
<td>4.8</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6</td>
<td>16.9</td>
</tr>
</tbody>
</table>

*Statistically significant results.*

PointBreak Trial: Data Did Not Favor Either Maintenance Regimen

- Randomized, open-label, phase III superiority study conducted in US
- Pemetrexed 500 mg/m²; carboplatin AUC 6; bevacizumab 15 mg/kg
- Paclitaxel 200 mg/m²; carboplatin AUC 6; bevacizumab 15 mg/kg
- Primary endpoint OS; secondary endpoint PFS

**Inclusion**
- No prior systemic therapy for lung cancer
- PS 0/1
- Stage IIIB-IV nonsquamous NSCLC
- Stable treated brain metastasized

**Exclusion**
- Peripheral neuropathy ≥ grade 1
- Uncontrolled pleural effusions

**Induction phase**
- q21d, 4 cycles
- Pemetrexed + carboplatin + bevacizumab
- Paclitaxel + carboplatin + bevacizumab

**Maintenance phase**
- q21d until PD
- Pemetrexed + bevacizumab
- Bevacizumab + placebo

450 patients each

SATURN Trial: Erlotinib Maintenance

- Chemotherapy-naive, advanced NSCLC
- Included patients with squamous and nonsquamous cell carcinoma
- Mandatory tumor sampling
- Enrolled patients (N=1,949) treated with 1 of 7 standard chemotherapy regimens containing cisplatin or carboplatin + second agent

Co-primary endpoints
- PFS in all patients
- PFS in patients with EGFR IHC-positive tumors

Secondary endpoints
- OS in all patients and those with EGFR IHC-positive tumors
- OS and PFS in EGFR IHC-negative tumors
- Safety

IHC = immunohistochemistry.
SATURN Trial: Erlotinib Maintenance

19% reduction in risk of death

OS in a broad ITT population
OS rates in the SATURN ITT population at milestone

HR = 0.81
95% CI: 0.70-0.95; P = .0088

Median 12.0 mo with erlotinib vs 11.0 mo with placebo

ITT = intent-to-treat.
Maintenance Treatment Conclusions

• Again, there are options, as in first-line chemotherapy
• Do patients want a break or wish to continue?
• Toxicity profile
  – Pemetrexed is chemotherapy: potential for lowering of blood counts, fatigue, requires vitamin supplementation
  – Bevacizumab and erlotinib are targeted agents, with the potential for hypertension/cardiac toxicity, rash
• Cost? Should this be an issue?
• Insurance coverage/denials?
Second-Line (Subsequent) Therapy

• NCCN-recommended second-line treatment for NSCLC:
  – Docetaxel +/- ramucirumab
  – Erlotinib (regardless of EGFR mutation status)
  – Pemetrexed (non-squamous histology only, if not used 1st line)
  – Nivolumab or pembrolizumab
  – Gemcitabine

• NCCN Guidelines also list:
  – Afatinib, gefitinib if EGFR mutation +
  – Crizotinib if ALK +
  – Best supportive care
REVEL Trial: Ramucirumab

Primary endpoint: OS
Secondary endpoints: PFS, ORR, safety, patient-reported outcomes

Stratification factors:
- ECOG PS 0 vs 1
- Gender
- Prior maintenance
- East Asia vs rest of the world

• Stage IV NSCLC after 1 platinum-based CT +/- maintenance
• Prior bev allowed
• All histology
• PS 0 or 1
N = 1,253

Ramucirumab 10 mg/kg + Docetaxel 75 mg/m² q3wk (n = 628)

Placebo + Docetaxel 75 mg/m² q3wk (n = 625)

CT, chemotherapy; Bev, bevacizumab, OS, overall survival; PFS, progression-free survival, Ram, ramucirumab.
REVEL: Progression-Free Survival, ITT Population, Investigator Assessment

## REVEL: Adverse Effects of Ramucirumab

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ramucirumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Stomatitis/mucosal inflammation</td>
<td>37%</td>
<td>19%</td>
</tr>
<tr>
<td>Neutropenia (grade 3/4)</td>
<td>49%</td>
<td>40%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous</td>
<td>7% (1% grade 3)</td>
<td>6% (1% grade 3)</td>
</tr>
<tr>
<td>Squamous</td>
<td>10% (2% grade 3)</td>
<td>12% (2% grade 3)</td>
</tr>
</tbody>
</table>

Summary and Conclusions

• Chemotherapy in NSCLC: many options and combinations
• Discussion with patients of potential side effects of various chemotherapy +/- targeted agents in very important
• Knowledge of patient comorbidities important in choosing regimens