Lung Cancer

Jennifer Howder, Pharm.D., BCOP
Clinical Oncology Pharmacist
Amber Pharmacy

Disclaimer

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Faculty Biography

Dr. Jennifer Howder graduated from Creighton University with her Doctorate of Pharmacy degree in 2006. She then completed a pharmacy practice residency at the University of Michigan, followed by an oncology specialty residency at Nebraska Medicine. Dr. Howder practiced as a Clinical Oncology Pharmacist at Nebraska Medicine for almost 10 years. She also provided lectures for the Therapeutics course at the University of Nebraska Medical Center’s College of Pharmacy. She recently joined Amber Specialty Pharmacy and serves as a Clinical Oncology Pharmacist. Dr. Howder is an active member of the Hematology/Oncology Pharmacy Association (HOPA) and her interests include solid tumor disease states.

Jennifer Howder, Pharm.D., BCOP
Clinical Oncology Pharmacist
Amber Pharmacy
Omaha, Nebraska

Faculty Disclosures

- I am a clinical oncology pharmacist for Amber Pharmacy, a leading specialty pharmacy provider, located in Omaha, NE.
- I have no commercial disclosures.
- I intend to discuss FDA approved drugs and pipeline products relative to the treatment of lung cancer.
Objectives

- Describe the epidemiology, risk factors, pathology, and etiology of lung cancer.
- Discuss the screening, diagnosis, and staging of both SCLC and NSCLC.
- Differentiate the treatment options between SCLC and NSCLC.
- Apply treatment guidelines in patient case-study situations.

Lung Cancer
Epidemiology

Incidence
- Second most common malignancy in the U.S.
- 2014: estimated 224,210 lung cancer diagnoses
- Incidence in men has declined since 1985; plateau in women

Mortality
- Most common cause of cancer-related deaths in men and women in the U.S.
- Estimated about 159,260 died from the disease in 2014
- Only 15% of all lung cancer patients are alive 5 years after diagnosis.

Epidemiology

Age
- Peak: 50-75 years
- Rare before age 45

Geography
- Incidence and mortality parallel tobacco smoking prevalence worldwide

Gender and Race
- Males have a higher mortality rate than females (1 in 13 vs. 1 in 16)
- African-Americans: higher incidence and mortality rates than Caucasian
### Etiology/ Pathogenesis

<table>
<thead>
<tr>
<th>K-ras</th>
<th>EGFR</th>
<th>EML4-ALK</th>
<th>ROS1- Rearrangement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations in adenocarcinoma exclusive to smokers</td>
<td>Mutations activate the pathway, leading to increased cell proliferation, motility, and invasion</td>
<td>Inversion in chromosome 2 that links the 5’ end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3’ end of the anaplastic lymphoma kinase</td>
<td>Encodes a tyrosine kinase related to ALK</td>
</tr>
<tr>
<td>Overall frequency in NSCLC=10-30%</td>
<td>Overall frequency in NSCLC=10-15%</td>
<td>Overall frequency in NSCLC=4-8%</td>
<td>Leads to fusion of the portion of ROS 1 that includes the TK domain with 1 of 12 different partner proteins</td>
</tr>
<tr>
<td>Predicts primary resistance to EGFR-TKI therapy</td>
<td>Predicts treatment benefit from EGFR-TKI therapy</td>
<td>Clinical features: adenocarcinoma histology, no/light smoking hx, younger age</td>
<td>Overall frequency in NSCLC = 1%</td>
</tr>
<tr>
<td>Prognostic; associated with smoking and poor survival</td>
<td></td>
<td></td>
<td>Adenocarcinoma histology, no/light smoking history</td>
</tr>
</tbody>
</table>

NCCN guidelines: Non-Small Cell Lung Cancer 2015

### Risk Factors

- Tobacco
- Radon, Ionizing radiation
- Asbestos
- Diet
- Blue collar workers (occupational exposure)
- Coexisting Lung Disease
- Genetic Predisposition

Pathophysiology

- Small cell lung cancer (13-17% of all lung cancers)
  - Most aggressive
  - Clear relationship to smoking
  - Paraneoplastic syndromes common
  - Initially highly sensitive to radiation and chemotherapy
  - Surgery has nearly no role


Pathophysiology

- Non-small cell lung cancer (80-87% of all lung cancer)
  - Overall:
    - Often slower growing
    - Usually moderately sensitive to radiation
    - Low sensitivity to chemotherapy
  - Types:
    - Adenocarcinoma (37-47% of all lung cancers)
      - Bronchioloalveolar carcinoma (BAC)-EGFR mutations
    - Squamous cell (epidermoid) carcinoma (25-32%)
    - Large cell carcinoma (10-18%)

**Patient Case**

- **64 y/o WF**, hospitalized for persistent URIs/PNA
- Weight 130lbs, Height 5’9”, BSA 1.72 m²
- HPI: Presented to ER 2 days prior to admission with worsening cough, blood-tinged sputum, dyspnea, hoarseness, and progressive weight loss. Recently treated with clarithromycin for presumed bronchitis. Some tingling and weakness in left arm.

**Patient Case**

- **PMH**: COPD x 4 years
- **FH/SH**: Widowed, retired. Smoked 2 packs/day for last 30 years. Occasional alcohol use.
- **Meds**: Tiotropium 18mcg inhaled QAM, Albuterol 2 puffs Q4H PRN dyspnea; NKMA
- **Physical Exam**:
  - BP 130/75, P 75, T 99.2
  - Lung: decreased breath sounds, bilateral wheezes
  - Extremities: clubbing of fingers bilaterally, decreased left arm strength
Prevention/Screening

- No known effective method of chemoprevention at this time
- Smoking cessation

National Lung Screening Trial (NLST)
- Screening with annual low-dose, spiral CT scans can improve lung cancer-specific mortality and all-cause mortality in asymptomatic high-risk individuals
- Can detect early stage NSCLC
- Does not appear useful for detecting SCLC

NCCN guidelines: Non-Small Cell Lung Cancer 2015
NCCN guidelines: Small Cell Lung Cancer 2015

Diagnosis

- Signs and Symptoms
  - Cough= most common
  - Weight loss
  - Dyspnea
  - Chest pain
  - Hemoptysis
  - Others: wheezing, pneumonia, hoarseness, dysphagia, fatigue, clubbing, bone pain, sputum production

**Diagnosis: Paraneoplastic Syndromes**

<table>
<thead>
<tr>
<th>SCLC</th>
<th>NSCLC</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SIADH</td>
<td>• Hypercalcemia</td>
<td>• Hypercoagulability</td>
</tr>
<tr>
<td>• Cushing’s Syndrome</td>
<td>• Clubbing</td>
<td>• Dermatomyositis</td>
</tr>
<tr>
<td>• Eaton-Lambert (myasthenia-gravis like syndrome)</td>
<td></td>
<td>• Cancer-related cachexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anemia, leukocytosis</td>
</tr>
</tbody>
</table>

NCCN guidelines: Non-Small Cell Lung Cancer 2015
NCCN guidelines: Small Cell Lung Cancer 2015

**Diagnosis**

- **Location**
  - Central = squamous, small cell
  - Peripheral masses or pleural involvement = adenocarcinoma, large cell

- **Diagnostic/Staging**
  - CXR, chest CT, PET scan for surgical candidates
  - MRI (if concern for chest wall invasion, brain mets)
  - PFTs
  - H&P, CBC, BMP
  - Tissue sampling
  - Molecular studies and biomarker analysis

Patient Case

- CXR: L peripheral mass, enlarged hilar lymph nodes
- CT scan: 4 x 6 cm mass on the upper lobe
- CT guided fine needle aspirate pathology positive for SCLC
- Bone scan positive for disease in T3-5 vertebral bodies
- MRI of head: Four <2cm lesions in cerebral cortex, asymptomatic

Metastasis

<table>
<thead>
<tr>
<th>Sites</th>
<th>Bone, bone marrow, brain, liver, lymph nodes, adrenal glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Cell Lung Cancer</td>
<td>Rapid proliferation, systemic disease at diagnosis, 60-70% of patients present with metastases</td>
</tr>
<tr>
<td>Non-Small Cell Lung Cancer</td>
<td>Slower growing, 50% of patients present with metastases</td>
</tr>
</tbody>
</table>

Staging

- Small cell lung cancer
  - Limited stage (30-40%): one hemithorax and regional lymph nodes can be contained in a tolerable radiation port
  - Extensive stage (60-70%): dx does not fit criteria for limited stage

- Non-small cell lung cancer
  - TNM


Staging

<table>
<thead>
<tr>
<th>7th Edition T/ M</th>
<th>7th Edition T/ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIA</td>
<td>T1a-b N1 M0</td>
</tr>
<tr>
<td></td>
<td>T2a N1 M0</td>
</tr>
<tr>
<td></td>
<td>T2b N0 M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2b N1 M0</td>
</tr>
<tr>
<td></td>
<td>T3 N0 M0</td>
</tr>
<tr>
<td></td>
<td>T4 (same lobe nodules) N0 M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1a N0 M0</td>
</tr>
<tr>
<td></td>
<td>T1b N0 M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2a N0 M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1a-b N1 M0</td>
</tr>
<tr>
<td></td>
<td>T2a N1 M0</td>
</tr>
<tr>
<td></td>
<td>T2b N0 M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2b N1 M0</td>
</tr>
<tr>
<td></td>
<td>T3 N0 M0</td>
</tr>
<tr>
<td></td>
<td>T4 (same lobe nodules) N0 M0</td>
</tr>
</tbody>
</table>

Staging

Table. AJCC TNM Staging System for Lung Cancer (7th edition, 2010)

<table>
<thead>
<tr>
<th>T1</th>
<th>Primary Tumor (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Tumor ≤ 5 cm in greatest dimension, surrounded by lung or visceral pleura, without invasion more proximal than other bronchus</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt; 5 cm but ≤ 7 cm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt; 7 cm or any size with the following:</td>
</tr>
<tr>
<td></td>
<td>Invasion of mediastinum</td>
</tr>
<tr>
<td></td>
<td>Invasion of heart or great vessels</td>
</tr>
<tr>
<td></td>
<td>Invasion of trachea or esophagus</td>
</tr>
<tr>
<td></td>
<td>Recurrent brachial plexus</td>
</tr>
<tr>
<td></td>
<td>Invasion of vertebral body or carina</td>
</tr>
<tr>
<td></td>
<td>Presence of malignant pleural or pericardial effusion</td>
</tr>
<tr>
<td></td>
<td>Satellites tumor nodule(s) within same lobe as primary tumor</td>
</tr>
</tbody>
</table>

| T2 | Tumor > 3 cm but ≤ 5 cm in greatest dimension |
| T2a | Tumor > 3 cm but ≤ 5 cm in greatest dimension |
| T2b | Tumor > 5 cm but ≤ 7 cm in greatest dimension |
| T2c | Tumor > 7 cm or any size with the following: |
|     | Invasion of mediastinum |
|     | Invasion of heart or great vessels |
|     | Invasion of trachea or esophagus |
|     | Recurrent brachial plexus |
|     | Invasion of vertebral body or carina |
|     | Presence of malignant pleural or pericardial effusion |
|     | Satellites tumor nodule(s) within same lobe as primary tumor |

| T3 | Tumor > 7 cm or any size with the following: |
|     | Invasion of mediastinum |
|     | Invasion of heart or great vessels |
|     | Invasion of trachea or esophagus |
|     | Recurrent brachial plexus |
|     | Invasion of vertebral body or carina |
|     | Presence of malignant pleural or pericardial effusion |
|     | Satellites tumor nodule(s) within same lobe as primary tumor |

| N0 | No regional lymph node metastasis |
| N1 | Metastasis to ipsilateral hilar and/or ipsilateral peribronchial nodes, including involvement by direct extension |
| N2 | Metastasis to ipsilateral mediastinal and/or subcarinal nodes |
| N3 | Metastasis to contralateral mediastinal or hilar nodes OR ipsilateral or contralateral scalene or supraclavicular nodes |

| M0 | Distant metastases absent |
| M1 | Distant metastases |
| M1a | Separate tumor node(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural or pericardial effusion |
| M1b | Distant metastases |

Treatment Overview - SCLC

- **General Points:**
  - Very sensitive to radiation and chemotherapy effects
  - Systemic chemotherapy is the backbone of treatment at all stages in eligible patients
  - Surgery has no established role
  - Participation in clinical trials is encouraged
  - Overall 5 year survival = <5%
## Treatment Overview- SCLC

**Limited stage**
- W/out treatment = 11 week survival
- Curative intent; 40% alive at 2 years; median survival = 16-22 months
- Cure rate = 20%
- Response rates = 65-95% ORR, 45-75% CR

**Treatment**
- Concurrent chemoradiotherapy
- Cisplatin-etoposide w/ concurrent radiation has the best supporting clinical data
- 4-6 cycles of chemotherapy are given; maintenance therapy is of no value
- Prophylactic cranial irradiation

NCCN guidelines: Small Cell Lung Cancer 2015

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**Extensive stage**
- W/out treatment = 5 week survival
- Rarely curable; <5% alive at 2 years; prolongs survival to 9-11 months
- Response rates = 60-80% ORR, 15-20% CR

**Treatment**
- Cisplatin or carboplatin-based combination chemotherapy for 4-6 cycles
  - Combined with either etoposide or irinotecan
- Chest radiation
- Cranial radiation
- Prolonged or maintenance therapy has not been associated with improved results

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Commonly Used Regimens

- **Limited Stage**
  - Cisplatin 60mg/m² IV D1, etoposide 120mg/m² IV D1-3 x 4 cycles WITH radiation

- **Extensive Stage**
  - Cisplatin 75mg/m² IV D1, etoposide 100mg/m² IV D1-3 x 4-6 cycles
  - Carboplatin AUC 5-6 IV D1, etoposide 100mg/m² IV D1-3 x 4-6 cycles
  - Cisplatin 60mg/m² IV D1, irinotecan 60mg/m² IV D1, 8, and 15
    - Japanese study
  - Carboplatin AUC 5 IV D1, irinotecan 50mg/m² IV D1, 8, 15
  - Three drug regimens are NOT superior to two


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**Table: Selected Chemotherapy Regimens for the Treatment of Small Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Agents and Duration</th>
<th>Reference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE (GP)</td>
<td>Cisplatin 75 mg/m² IV D1, etoposide 100 mg/m² IV D1-3, 5 4-6 cycles (2 cycles post best response to max of 6)</td>
<td>Polsk K, et al. N Engl J Med 2002;346:55-91</td>
<td>Reference regimen for treatment of extensive stage: sensitive, 3 cycles, 2 cycles post best response to max of 6</td>
</tr>
<tr>
<td></td>
<td>Cisplatin 80 mg/m² IV D1, etoposide 80 mg/m² IV D1-3, 5-6 cycles</td>
<td>Fukuda M, et al. J Natl Cancer Inst 1991;83:555-61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin 75 mg/m² IV D1, etoposide 100 mg/m² IV D1-3, 5-6 cycles</td>
<td>Sundstrom S, et al. J Clin Oncol 2002;20:4655-65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carboplatin AUC 5-6 IV D1, etoposide 100 mg/m² IV D1-3, 5-6 cycles</td>
<td>Bock B, et al. J Clin Oncol 1992;10:282-91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carboplatin AUC 5-6 IV D1, etoposide 100 mg/m² IV D1, 8, 15</td>
<td>Bode DC, et al. J Clin Oncol 1999;14:1202-9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carboplatin AUC 5-6 IV D1, etoposide 100 mg/m² IV D1-3, 5-6 cycles</td>
<td>Evans WK, et al. J Clin Oncol 1995;13:1471-7</td>
<td></td>
</tr>
<tr>
<td>Carboplatin + Etoposide</td>
<td>Carboplatin AUC 5-6 IV D1, etoposide 100 mg/m² IV D1-3, 5-6 cycles</td>
<td>Skarlos DV, et al. Ann Oncol 2001;12:1231-7</td>
<td>Japanese study showed superiority to PE, but later study in the US found no difference versus PE</td>
</tr>
<tr>
<td>Carboplatin + Imitocan</td>
<td>Carboplatin AUC 5-6 IV D1, etoposide 100 mg/m² IV D1-3, 5-6 cycles</td>
<td>Schlattel A, et al. Ann Oncol 2008;19:613-7</td>
<td></td>
</tr>
<tr>
<td>Cisplatin + Imitocan</td>
<td>Cisplatin 60 mg/m² IV D1, etoposide 100 mg/m² IV D1-3, 5-6 cycles</td>
<td>Polsk K, et al. N Engl J Med 2002;346:85-91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin 60 mg/m² IV D1, etoposide 100 mg/m² IV D1-3, 5-6 cycles</td>
<td>Hanna N, et al. J Clin Oncol 2006;24:2030-4</td>
<td></td>
</tr>
</tbody>
</table>

NCCN guidelines: Small Cell Lung Cancer 2015
Patient Case

- Extensive stage SCLC admitted to receive cisplatin 75mg/m² IV day 1 and etoposide 100mg/m² IV days 1-3. Plan for 4 cycles, then reassess.

- Pre and post cisplatin: 1 L NS over 6 hours

- Hyperfractionated radiation to begin on day 2

Second-Line Treatment

- Second-line therapy
  - Chemotherapy-sensitive relapse (>3 months): 20-30% ORR
  - Chemotherapy-resistant relapse(<3 months): <10%

- Clinical trial is preferred

- Time to relapse <2-3 months, PS 0-2: ifosfamide, taxane, topotecan, gemcitabine, irinotecan

- Time to relapse >2-3 months, PS 0-2: topotecan, irinotecan, CAV, taxane, vinorelbine, gemcitabine, irinotecan

- Time to relapse >6 months, PS 0-2, repeat initial regimen

Second-Line Treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topoisomerase I Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topotecan</td>
<td>1.5mg/m2 IV Days 1-5 or 2.3mg/m2 PO Days 1-5 every 21 days</td>
<td>17-23%</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>100mg/m2 IV weekly</td>
<td>16-24%</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000mg/m2 IV Days 1,8,15 every 28 days</td>
<td>14%</td>
</tr>
<tr>
<td>Taxanes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>175mg/m2 IV every 21 days of 80mg/m2 IV weekly x 6 every 8 weeks</td>
<td>23.8-29%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>100mg/m2 IV every 21 days</td>
<td>25%</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>25-30mg/m2 IV weekly</td>
<td>12.5-16%</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>75mg/m2 PO daily x 21 days every 28 days</td>
<td>16%</td>
</tr>
</tbody>
</table>

Patient Case

- Treatment with chemotherapy induces a partial remission. Whole brain radiotherapy completed.

- She returns 6 weeks after completing radiation with complaints of increasing cough, dyspnea, and chest pain. Upon work-up, relapsed disease in the L hilum is discovered.

- Plan to give salvage therapy with topotecan 1.5mg/m2/day for IV 5 days.
Take Home Points

- SCLC
  - Limited stage: concurrent chemoradiotherapy (cisplatin/etoposide)
  - Extensive stage: chemotherapy (platinum-based), possible radiation (palliation)

- Second line therapy
  - Topotecan

Patient Case #2

- JM 55 y/o WF with complaints of cough, dyspnea, hoarseness, and chest pain

- Weight 130lbs, Height 5’9”

- HPI: presented to FPP 2 weeks prior to admission with same complaints, treated for bronchitis.
Patient Case #2

- PMH: HTN, controlled with enalapril
- Meds: Enalapril; NKMA
- Physical Exam:
  - BP 125/81, P 70, T 98.2
  - Lung: decreased breath sounds on right
- Workup:
  - CXR: R peripheral mass and pleural effusion
  - CT scan: 4 x 7 cm mass and pleural effusion
  - CT scan of abdomen showed mass on R adrenal gland
  - Cytology from the pleural fluid (drained) revealed adenocarcinoma

NSCLC-Overview

- Resectable (Stages I, II, IIIA)
  - Surgery is the treatment of choice
  - Radiation
  - Chemotherapy
- Unresectable (Stage IIIIB, IV)
  - Histology-based treatment

Surgery and Radiation Therapy

- **Surgery**
  - Resectable: Stage I, II, and some IIIA
  - Treatment of choice; best chance for cure

- **Radiation therapy**
  - In place of surgery in stage I and II (pts unable to tolerate surgery), but is inferior
  - Can reduce size of lesions, making surgery possible
  - Avoid post-op adjuvant XRT with stage I or II, unless they have positive margins, or stage II with negative margins and specific characteristics

Adjuvant Chemotherapy

- No role in SCLC; only NSCLC
- Now considered SOC
- Can improve overall 5-year survival
- Most benefit: cisplatin/vinorelbine or carboplatin/paclitaxel (no head to head trials)
- Carbo/pac for patients not able to tolerate cisplatin, or patients with comorbidities

### Chemotherapy Regimens for Neoadjuvant & Adjuvant Therapy

**Adjuvant Chemotherapy**

<table>
<thead>
<tr>
<th>Regimen Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin 50mg/m² days 1 &amp; 8; vinorelbine 25mg/m² days 1, 8, 15, 22, Q28 days x 4 cycles</strong></td>
</tr>
<tr>
<td><strong>Cisplatin 100mg/m² day 1; vinorelbine 30mg/m² days 1, 8, 15, 22, Q28 days x 4 cycles</strong></td>
</tr>
<tr>
<td><strong>Cisplatin 75-80mg/m² day 1; vinorelbine 25-30mg/m² days 1 &amp; 8, Q21 days x 4 cycles</strong></td>
</tr>
<tr>
<td><strong>Cisplatin 100mg/m² day 1; etoposide 100mg/m² days 1-3, Q28 days for 4 cycles</strong></td>
</tr>
</tbody>
</table>


**Adjuvant Chemotherapy**

<table>
<thead>
<tr>
<th>Regimen Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin 80mg/m² days 1, 22, 43, 64; vinblastine 4mg/m² days 1, 8, 15, 22, 29, then every 2 weeks after day 43, Q21 days x 4 cycles</strong></td>
</tr>
<tr>
<td><strong>Cisplatin 75mg/m² day 1; gemcitabine 1250mg/m² days 1 &amp; 8, Q21 days x 4 cycles</strong></td>
</tr>
<tr>
<td><strong>Cisplatin 75mg/m² day 1; docetaxel 75mg/m² day 1, Q21 days x 4 cycles</strong></td>
</tr>
<tr>
<td><strong>Cisplatin 75mg/m² day 1; pemetrexed 500mg/m² day 1 for adenocarcinoma and large cell carcinoma and NSCLC NOS, Q21 days x 4 cycles</strong></td>
</tr>
</tbody>
</table>

Treatment-Stage IIIA

- Surgical resection, chemotherapy, radiation
- Management is controversial
- Minimal N2 disease may be resectable
- Chemotherapy usually precedes surgery (neoadjuvant/induction chemotherapy) and/or followed by chemotherapy with or without radiation


Take Home Points

- NSCLC: Stages I, II, IIIA
  - Combinations of surgery, radiation, and chemotherapy
  - Platinum-based regimens (i.e. cisplatin + vinorelbine, carboplatin + paclitaxel)
Treatment-Stage III B and Unresectable III A (bulky N2)

- Platinum-based chemotherapy + XRT
  - Combined modality therapy superior to radiation alone
  - Goal is to downstage for resection

- Concurrent therapy appears to be superior to sequential therapy (but is more toxic)

- Best chemotherapy regimen and duration of therapy is unclear
  - Duration should not exceed 8 cycles


### Preferred Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Preferred Chemotherapy Regimens</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin 50mg/m² IV D1,8,29,36 Etoposide 50mg/m² IV D1-5, 29-33 RT-total of 61Gy</td>
<td>Albain KS, et al. <em>J Clin Oncol</em> 2002; 20:3454-60</td>
</tr>
<tr>
<td>Cisplatin 100mg/m² IV D1, 29 Vinblastine 5mg/m² IV weekly x 5 RT - 63Gy</td>
<td>Curran WJ, et al. <em>J Natl Cancer Inst</em> 2011;103:1452-60</td>
</tr>
</tbody>
</table>

Note: Pemetrexed/platinum regimens also an option; however not preferred over the two regimens above due to strength of data

References in table
Take Home Points

- NSCLC: Stages III B and unresectable III A
  - Concurrent (occasionally sequential) chemotherapy and radiation
  - Platinum-based regimen (i.e. cisplatin + etoposide or vinblastine. Alternatives: carboplatin + paclitaxel, pemetrexed + platinum)

Treatment-Stage IV

- Principles of Care
  - Early supportive care
  - Chemo compared to best supportive care
  - Cost effective
  - PS 3-4: no benefit from therapy (exception: erlotinib)
  - Optimal platinum-based regimen unclear (optimal duration = 4-6 cycles)
  - FDA approved nab-paclitaxel for NSCLC

**Treatment - Stage IV**

- **Histology based treatment**
  - Non-squamous (adenocarcinoma, large cell or NSCLC not otherwise known)
  - **Molecular testing algorithm**
    - EGFR mutation positive - erlotinib 150mg PO daily
      - PS 0-4 (only therapy to consider in PS 3-4 patients)
      - Afatinib 40mg PO daily is an alternative option
    - EGFR mutation negative - send tissues for presence of ALK gene rearrangement
    - EML4-ALK rearrangement positive - crizotinib 250mg PO twice daily
      - Ceritinib 750mg PO daily for patients who progressed on or are intolerant to crizotinib


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**Treatment - Stage IV**

- **Erlotinib**
  - 150mg PO daily
  - Predictors of response = female, never smoker, adenocarcinoma histology, Asian ethnicity
  - Acneiform rash
    - Occurred in 49% of patients in lung cancer clinical trials
    - Regular use of moisturizer, sunscreen, topical clindamycin
    - Common on face and chest; can occur anywhere

- **Afatinib**
  - FDA approved (2013) for the treatment of metastatic NSCLC in patients with EGFR exon 19 deletions or exon 21 substitution mutations.
  - 40mg PO daily
  - Side effects similar to erlotinib

www.tarceva.com: Package Insert
www.gilotrif.com: Package Insert
Treatment - Stage IV

**Crizotinib**
- FDA approved (2011) for patients with locally advanced or metastatic NSCLC that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test
- 250mg PO BID
- Continue as long as clinical benefit exists

- **Toxicities**
  - Visual disorders
  - Increased LFTs
  - Pneumonitis

[www.xalkori.com](http://www.xalkori.com); Package Insert.

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**Treatment - Stage IV**

**Ceritinib**
- FDA approved (2014) for the treatment of ALK-positive metastatic NSCLC in patients who have progressed on or are intolerant to crizotinib
- 750mg PO daily

- **Toxicities**
  - Gastrointestinal toxicities
  - Increased LFTs
  - Pneumonitis
  - QT prolongation

[www.zykadia.com](http://www.zykadia.com); Package Insert.
Treatment - Stage IV

- Squamous
  - Molecular testing not recommended UNLESS:
    - Non-smoker
    - Small biopsy sample
  - Platinum-based doublet

- Platinum-based regimens recommended for all patients eligible for treatment
  - Cisplatin/carboplatin-based combinations (“doublet chemotherapy”)
  - Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed
  - New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine)
### Treatment-Stage IV

#### Examples of Commonly Used Platinum-Based Doublets

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin/Paclitaxel</td>
<td>17-25%</td>
</tr>
<tr>
<td>Cisplatin/Docetaxel</td>
<td>17%</td>
</tr>
<tr>
<td>Cisplatin/Paclitaxel</td>
<td>21%</td>
</tr>
<tr>
<td>Cisplatin/Gemcitabine</td>
<td>22%</td>
</tr>
<tr>
<td>Cisplatin/Vinorelbine</td>
<td>28%</td>
</tr>
<tr>
<td>Cisplatin/Irinotecan</td>
<td>31%</td>
</tr>
<tr>
<td>Carboplatin/nano-albumin-bound (nab) paclitaxel</td>
<td>33% (41% in squamous subset)</td>
</tr>
<tr>
<td>Carboplatin/Paclitaxel</td>
<td>27%</td>
</tr>
</tbody>
</table>

**Source:**

#### First-Line Therapy

- **PS 0-1**
  - Doublet chemotherapy
  - Bevacizumab + chemotherapy (nonsquamous histology)
    - Give bevacizumab until disease progression
    - Cisplatin + pemetrexed (nonsquamous histology)
  - Erlotinib is indicated as a first-line therapy in patients with EGFR mutations
  - Crizotinib is indicated as a first-line therapy in patients that are ALK positive
  - Two-drug regimens are preferred; a third cytotoxic drug increases response rate but not survival

**NCCN guidelines: Non-Small Cell Lung Cancer 2015.**
Treatment-Stage IV

First-Line Therapy
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  - Doublet chemotherapy
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Treatment-Stage IV

- Cisplatin + gemcitabine vs. cisplatin + pemetrexed
  - Noninferiority trial assessing 1745 patients with advanced NSCLC
  - Patients with nonsquamous cell histology had improved survival with cisplatin + pemetrexed (12.6 vs. 10.9 months)
  - Patient with squamous cell histology had improved survival and reduced toxicity with cisplatin + gemcitabine (10.8 vs. 9.4 months)
- Pemetrexed has an FDA-approved indication for first-line treatment in combination with cisplatin

Treatment - Stage IV

- PS 2
  - Chemotherapy alone (single agent or doublet)

- PS 3-4
  - Do not benefit from therapy, except erlotinib in EGFR mutated patients


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Treatment - Stage IV

- Maintenance Therapy
  - Continuation vs Switch

- Continuation Maintenance
  - Continuation of bevacizumab after 4-6 cycles of platinum-doublet chemo and bevacizumab
  - Continuation of pemetrexed after 4-6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell
  - Continuation of bevacizumab + pemetrexed after 4-6 cycles of bevacizumab, pemetrexed, cisplatin/carboplatin, for patients with histologies other than squamous cell carcinoma.

Treatment - Stage IV

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>359</td>
<td>4.1 months (3.2-4.6)</td>
<td>13.9 months</td>
</tr>
<tr>
<td>Placebo</td>
<td>180</td>
<td>2.8 months (2.6-3.1)</td>
<td>11 months</td>
</tr>
</tbody>
</table>

Hazard Ratio

- 0.62 (0.49-0.79)  
  p<0.0001
- 0.78 (0.64-0.96)  
  p = 0.02


Treatment - Stage IV

- Erlotinib maintenance
  - FDA approved April 16, 2010
  - 150mg/day following 4 cycles of chemotherapy in non-progressive disease
  - N=889, randomized 1:1 to placebo or erlotinib
  - Primary outcome - PFS
  - 70% EFGR positive by IHC

Treatment-Stage IV

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>OS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>526</td>
<td>10.6 months</td>
</tr>
<tr>
<td>Supportive Care</td>
<td>533</td>
<td>10.5 months</td>
</tr>
</tbody>
</table>

*P = 0.95


Treatment-Stage IV

- Maintenance Therapy
  - Switch Maintenance
    - Two recent studies have shown a benefit in progression-free survival and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy, in patients without disease progression after 4-6 cycles of therapy
    - Initiation of pemetrexed after 4-6 cycles of first-line platinum-doublet chemotherapy, for patients with histologies other than squamous cell
    - Initiation of erlotinib after 4-6 cycles of first-line platinum-doublet chemotherapy
    - Initiation of docetaxel after 4-6 cycles of first-line platinum-doublet chemotherapy in patients with squamous cell histology
    - Close follow up of patients without therapy is a reasonable alternative to switch maintenance

Treatment-Stage IV

Results of Switch Maintenance Therapy Trials

<table>
<thead>
<tr>
<th>Total Population</th>
<th>N</th>
<th>PFS*</th>
<th>OS*</th>
<th>Subsequent Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>441</td>
<td>4.2 months</td>
<td>13.4 months</td>
<td>51%</td>
</tr>
<tr>
<td>Supportive Care</td>
<td>222</td>
<td>2.6 months</td>
<td>10.6 months</td>
<td>67%</td>
</tr>
</tbody>
</table>

*P<0.05 for hazard ratio between groups

Results of Switch Maintenance Therapy Trials in Non-Squamous Patients

<table>
<thead>
<tr>
<th>Total Population</th>
<th>N</th>
<th>PFS*</th>
<th>OS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>326</td>
<td>4.5 months</td>
<td>15.5 months</td>
</tr>
<tr>
<td>Supportive Care</td>
<td>156</td>
<td>2.6 months</td>
<td>10.3 months</td>
</tr>
</tbody>
</table>

*P<0.05 for hazard ratio between groups


Treatment-Stage IV

- **Second-Line Therapy/Subsequent Therapy**
  - In patients who have experienced disease progression either during or after first-line therapy:
    - Erlotinib
    - Docetaxel
    - Pemetrexed - **B12/ folate**
    - Ramucirumab + docetaxel
    - Afatinib
    - Ceritinib

- **Third-Line Therapy**
  - Erlotinib

- **Continuation After Disease Progression**

Treatment-Stage IV

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Pemetrexed (N=265)</th>
<th>Docetaxel (N=276)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia</td>
<td>1.9</td>
<td>12.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5.3</td>
<td>40.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infection with Grade 3 or 4 Neutropenia</td>
<td>0</td>
<td>5.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diarrhea (Grade 3 or 4)</td>
<td>0.4</td>
<td>2.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Alopecia (all grades)</td>
<td>6.4</td>
<td>37.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALT elevation (any grade)</td>
<td>7.9</td>
<td>1.4</td>
<td>0.034</td>
</tr>
</tbody>
</table>


Commonly Used Regimens

- **Regimens**
  - **Cisplatin/vinorelbine**: cisplatin 100-120mg/m2 IV D1, vinorelbine 20-30mg/m2 IV D1,15,22, q4weeks
  - **Cisplatin/paclitaxel**: cisplatin 75mg/m2 IV D1, paclitaxel 135-175mg/m2 IV over 3-24 hours, q3weeks
  - **Carboplatin/paclitaxel**: carboplatin AUC 5-7, paclitaxel 175-225mg/m2 IV over 3 hours, q3weeks
  - **Cisplatin/gemcitabine**: cisplatin 75-100mg/m2 IV D1, gemcitabine 1250mg/m2 IV D1,8 (or 1000mg/m2 IV D1,D8, D15), q3weeks
  - **Cisplatin/ pemetrexed**: cisplatin 75mg/m2 IV D1, pemetrexed 500mg/m2 IV D1, q3weeks. **Non-squamous histology**
  - **Cisplatin/ docetaxel**: cisplatin 75mg/m2 IV D1, docetaxel 75mg/m2 IV D1, q3weeks

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**Commonly Used Regimens**

- **Regimens**
  - **Cisplatin/irinotecan**: cisplatin 80mg/m2 IV D1, irinotecan 60mg/m2 IV D1,8,15, q4weeks
  - **Carboplatin/paclitaxel/bevacizumab**: carboplatin AUC 6, paclitaxel 200mg/m2, bevacizumab 15mg/kg all on D1; q3weeks. **Bevacizumab continued q3weeks after 6 cycles of combination.** Non-squamous histology only

NCCN guidelines: Non-Small Cell Lung Cancer 2015

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**Patient Case**

- **Stage IV NSCLC**
  - Scheduled to receive carboplatin AUC 6, paclitaxel 200mg/m2, bevacizumab 15mg/kg on D1; repeat every 3 weeks for 6 cycles (if responding)
  - Reassess after 4 cycles
Prevention

- Risk of second primary cancers
  - SCLC: 2-14%/year
  - NSCLC: 1-2%/year

- No known effective method of chemoprevention at this time

- Smoking cessation decreases risk


Prognosis

<table>
<thead>
<tr>
<th>Resectable</th>
<th>5 Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>IB</td>
<td>60%</td>
</tr>
<tr>
<td>IIA</td>
<td>50%</td>
</tr>
<tr>
<td>IIB</td>
<td>30-40%</td>
</tr>
<tr>
<td>IIIA</td>
<td>10-30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unresectable</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIB</td>
<td>10-14 months</td>
</tr>
<tr>
<td>IV</td>
<td>4-12 Months</td>
</tr>
</tbody>
</table>

NCCN guidelines: Non-Small Cell Lung Cancer 2015
Pipeline

- Continued tailoring of NSCLC therapy based on tumor genetics will evolve

- Novel Agents
  - Nivolumab (PD-1 inhibitor) → approved 2015 in metastatic squamous cell NSCLC
  - Buparlisib (pan-PI3K inhibitor)
  - Veliparib (PARP inhibitor, ADP inhibitor)
  - Dacomitinib (pan-HER kinase inhibitor)
  - Lambrolizumab (PD-1 inhibitor)
  - Motesanib (VEGF, PDGFR, c-kit inhibitor)
  - PF-06463922 (ALK, ROS1 inhibitor)
  - Several others

Important Points....

- Smoking, smoking, smoking

- Paraneoplastic syndromes

- Metastases

- SCLC
  - Surgery = nearly no role
  - Chemo+radiation for limited
  - Chemo for extensive
  - EP
  - 2nd line = topotecan
**Important Points….**

- **NSCLC**
  - Resectable: adjuvant chemo SOC (carbo/paclitaxel, cisplatin/vinorelbine)
  - Unresectable
    - Histology- and molecularly-defined driven treatment
    - PS 0-1, Non-squamous
      - Platinum-based doublets (+ bevacizumab)
      - Cisplatin + pemetrexed
    - PS 0-1, Squamous
      - Platinum-based doublet chemotherapy
    - PS 2
      - Consider single agent treatment or platinum-based doublet regardless of histology

**Important Points….**

- **Maintenance**
  - Bevacizumab
  - Pemetrexed (non-squamous)
  - Bevacizumab + pemetrexed (non-squamous)
  - Erlotinib
  - Docetaxel (squamous)
Important Points....

- Second-Line
  - Docetaxel +/- ramucirumab
  - Pemetrexed *(folate and vitamin B12 to reduce toxicity)*
  - Erlotinib, afatinib, ceritinib

- Erlotinib, Afatinib
  - EGFR mutation positive: PS 0-4
  - Rash

- Crizotinib, Ceritinib
  - ALK-rearrangements

Thank you!