Updates in Lung Cancer

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Learning Objectives

• Describe screening recommendations for lung cancer
• Interpret the impact of mutations on selection of drug therapy
• Assess the role of bevacizumab in the treatment of lung cancer
• Determine the place in therapy for targeted agents for the treatment of lung cancer

Leading New Cancer Cases and Deaths – 2012 Estimation

<table>
<thead>
<tr>
<th>Male</th>
<th>Estimated New Cases</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Leading New Cancer Cases and Deaths – 2012 Estimation

<table>
<thead>
<tr>
<th>Female</th>
<th>Estimated New Cases</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Excludes breast and prostate cancer in situ and leukemias except myelodysplasia.
Pathology: Non-small Cell Lung Cancer

- Adenocarcinoma, inc bronchoalveolar — 40%
- Squamous cell carcinoma — 20%
- Large cell carcinoma — 15%
- Others (carcinoid, etc.)

Lung Cancer Risk Factors

- Tobacco, tobacco, tobacco (85% lung ca.)
  - Including passive smoking
  - Prior aerodigestive malignancy
  - COPD
- Other exposures
  - Asbestos, radon, polycyclic aromatic hydrocarbons, chromium, nickel, inorganic arsenic – mining, ship building, oil refining
- Genetic predisposition
  - Familial lung cancer – 6q23-25 (Am J Hum Gen, 9/04)

Primary Prevention

- Smoking cessation
  - Decline in California lung cancer rates 1988-1997 declined 14%, compared with 2.7% in non-California SEER sites, coincident with declining smoking rates probably due to California tobacco control initiatives
  - Cowling DW et al., MMWR 49:1066-9, 2000
Effect of Smoking Cessation on Lung Cancer Deaths
Lung Health Study, 14.5 yr F/U

Phase III Lung Chemoprevention Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATBC 1994</td>
<td>29,133 smokers</td>
<td>β-carotene +/- vit E</td>
<td>18% risk lung ca.</td>
</tr>
<tr>
<td>CARET 1996</td>
<td>18,314 Smokers or asbestos</td>
<td>β-carotene + retinol</td>
<td>Inc risk lung ca RR=1.36</td>
</tr>
<tr>
<td>EUROSCAN 2000</td>
<td>2592 lung, H&amp;N ca</td>
<td>Retinyl palm +/- NAC</td>
<td>No benefit</td>
</tr>
<tr>
<td>Intergroup 2001</td>
<td>1265 lung ca</td>
<td>13-cRA</td>
<td>No benefit</td>
</tr>
<tr>
<td>SELECT 2011 Meta analysis</td>
<td>Selenium</td>
<td>No benefit</td>
<td></td>
</tr>
</tbody>
</table>

Recently Completed NCI-Sponsored Lung Cancer Screening Studies

- PLCO
  - 74,000 men/women
  - Age 55-74
  - CXR vs. none (prevalence, then x3)

- NLST
  - 50,000 smokers (current and former)
  - Age 55-74
  - Spiral CT vs. chest X-ray (prevalence, then x2)
Figure 1. Flow of Participants Through the Trial

PLCO Trial
Ages: 55-74
Multiple Screenings
15 years of follow-up
Smoking history not required


Figure 2. Lung Cancer Incidence by Year


Figure 3. Lung Cancer Mortality by Year

National Lung Cancer Screening Trial (NLST)

- Enrolled 53,544 subjects at high risk of lung cancer
  - 55-74 years old
  - 30+ pack year smoking history
  - Current smoker or quit 15 years ago or less
- Randomly assigned to annual screening with low dose (spiral) CT or chest X-ray
- Primary endpoint is lung cancer mortality

Aberle et al. NEJM 2011:395-405
Spiral CT recommended for screening for high risk individuals by NCCN

320 subjects need to be screened to save one death from lung cancer

However CMS and insurance are not paying for screening

### Cost of Screening

- Patients who want the screening must pay out of pocket ($300-$500) for the screening. Seven million individuals in the US are eligible for screening, annual costs of screening are estimated $2.1 billion
- If an abnormality is detected on screening, insurance will cover the subsequent work-up, the estimated cost of a negative work-up is $1000.
- The annual cost of working up the false positive associated with screening in the US is estimated at 1.6 billion dollars

### Current Treatment of NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>5 yr SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Surgery</td>
<td>&gt; 60-70%</td>
</tr>
<tr>
<td>IB</td>
<td>Induction chemotherapy or surgery</td>
<td>&gt; 40-50%</td>
</tr>
<tr>
<td>IIA (resectable)</td>
<td>Induction chemotherapy or surgery</td>
<td>&gt; 15-30%</td>
</tr>
<tr>
<td>IIA (unresectable)</td>
<td>Induction chemotherapy or surgery</td>
<td>None</td>
</tr>
<tr>
<td>IIB</td>
<td>Induction chemotherapy or surgery</td>
<td>Median survival: 8-10 Mo</td>
</tr>
<tr>
<td>IIIA (N3)</td>
<td>chemotherapy</td>
<td>1 yr SR, 30-35%</td>
</tr>
<tr>
<td>IIIA (pleural effusion)</td>
<td>chemotherapy</td>
<td>None</td>
</tr>
<tr>
<td>IIIB (N3)</td>
<td>chemotherapy or Erlotinib in EGFR mutation positive Crizotinib in ALK mutation positive</td>
<td>None</td>
</tr>
<tr>
<td>IIIB (pleural effusion)</td>
<td>chemotherapy or Erlotinib in EGFR mutation positive Crizotinib in ALK mutation positive</td>
<td>None</td>
</tr>
<tr>
<td>IV</td>
<td>None</td>
<td>1 yr SR, 10-15%</td>
</tr>
</tbody>
</table>

Aberle et al. NEJM 2011;395:405
Driver Mutations in Non Small Cell Lung Cancer


Metastatic Lung Cancer

<table>
<thead>
<tr>
<th>Performance Status</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Chemotherapy* or Bevacizumab + Chemotherapy* or Cisplatin + pemetrexed or Cetuximab + vinorelbine + cisplatin or Erlotinib in EGFR mutation positive patients Crizotinib in ALK positive patients</td>
</tr>
<tr>
<td>2</td>
<td>Chemotherapy* or Cetuximab + vinorelbine + cisplatin or Erlotinib in EGFR mutation positive patients Crizotinib in ALK positive patients</td>
</tr>
<tr>
<td>3-4</td>
<td>Erlotinib in EGFR mutation positive patients Crizotinib in ALK positive patients Best supportive care</td>
</tr>
</tbody>
</table>

*Chemotherapy= cisplatin + docetaxel, cisplatin + paclitaxel, carboplatin + paclitaxel, or Cisplatin + gemcitabine

Metastatic Lung Cancer

Treatment considerations
- EGFR mutation status
  - Erlotinib
- ALK mutation status
  - Crizotinib
- Bevacizumab criteria
  - Nonsquamous histology
  - No hemoptysis
  - No CNS metastasis
- Pemetrexed
  - Cisplatin + pemetrexed more active and less toxic than cisplatin + gemcitabine for adenocarcinoma
  - Has not been compared to cisplatin + docetaxel, cisplatin + paclitaxel or carboplatin + paclitaxel
Metastatic Lung Cancer Standard of Care – 1st Line

2-drug platinum-based regimens

Results

Median survival
8 mo.

Response rate
19%

Median time to tumor progression (TTP) 3.7 mo.

Phase III Trial of Bevacizumab in Non-Squamous NSCLC: ECOG 4599
N=855 (eligible)

Eligibility:
- Non-squamous NSCLC
- No Hx of hemoptysis
- No CNS metastases

Stratification Variables:
- RT vs no RT
- Stage IB or IV vs recurrent
- WT loss <5% vs ≥5%
- Measurable vs non-measurable

(PC)
Paclitaxel 200 mg/m² Carboplatin AUC = 6 (q 3 weeks) x 6 cycles

(PCB)
Paclitaxel 200 mg/m² Carboplatin AUC = 6 (q 3 weeks) x 6 cycles + Bevacizumab (15mg/kg q 3 wks) to PD

Sandler, et al. NEJM, Dec 2006
E4599: Overall Survival

HR: 0.80, \( P = 0.003 \)

PCB 51.0% 22.0%
PC 44.4% 15.4%

Medians: 10.3, 12.3

Grade 3 – 5 Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th></th>
<th>PC (N = 441)</th>
<th>PCB (N = 427)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>1.1</td>
<td>4.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>0.5%</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>0.2%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>0.5%</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Other†</td>
<td>0.2%</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.7%</td>
<td>7.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>---</td>
<td>3.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>3.2%</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>1.6%</td>
<td>2.8%</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Related Deaths

<table>
<thead>
<tr>
<th></th>
<th>PC 427</th>
<th>PCB 420</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>GI bleed</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary Embolus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>

* Two deaths due to cardiac ischemia not felt to be treatment related
Angiogenesis Inhibitor-Bevacizumab

• Indications
  – Bevacizumab, in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.
    • Dose is 5 or 10 mg/kg every 2 weeks
  – Bevacizumab, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.
    • Dose is 15mg/kg every 3 weeks
• Glioblastoma
  – 10mg/kg every 2 weeks
• Metastatic renal cell cancer in combination with interferon
  – 10mg/kg every 2 weeks

Bevacizumab Toxicity

• Gastrointestinal perforation, fistula and/or intra-abdominal abscess
  – Overall incidence in clinical studies was 1%, 30% of these are fatal
  – Clinical presentation
    • Abdominal pain, nausea and fever
    • Most events in first 50 days
• Wound Healing Complications
  – Avoid bevacizumab within 30 days of surgery
• Severe or fatal hemorrhages, including hemoptysis, gastrointestinal bleeding, hematoma, CNS hemorrhage, epistaxis, and vaginal bleeding
  – Five-fold more frequently in bevacizumab treated patients compared to patients treated with chemotherapy alone.
  – NCI-CTC Grade 3-5 hemorrhagic events occurred in 4.7% of NSCLC patients and 5.2% of mCRC patients receiving AVASTIN compared to 1.1% and 0.7% for the control groups respectively.

Bevacizumab Toxicity

• Arterial thrombotic events
  – 3% in bevacizumab arms compared to 1% in chemotherapy alone arms
• Venous thrombotic events
  – Increased by about 50% in bezacizumab arms
• Hypertension
• Ovarian failure
• Increased myelosuppression
**Bevacizumab Toxicity**

- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
  - Incidence of <0.1%
  - Neurological disorder
    - Headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances.
    - Mild to severe hypertension
  - Magnetic Resonance Imaging (MRI) is necessary to confirm the diagnosis of RPLS.
  - Onset of symptoms from 16 hours to 1 year after initiation of bevacizumab

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**Crizotinib: Rationale for Development of a c-MET inhibitor**

- c-MET is potentially one of the most frequently genetically altered receptor tyrosine kinases in human cancers
  - Activating mutations
    - Hereditary papillary RCC: 100%, sporadic papillary RCC (13%)
    - HNSCC: 10%
    - NSCLC (8%) and SCLC (13%)
  - Gene amplification
    - Gastric carcinoma: 5-10%
    - Colorectal carcinoma: 4% primary tumors, 20% liver metastases
    - Esophageal adenocarcinoma: 5-10%
- Anaplastic lymphoma Kinase (ALK) (2* target for crizotinib)
  - Anaplastic lymphoma is very sensitive to chemotherapy
  - ALK point mutations and gene amplification are implicated in neuroblastoma ... a rare tumor
  - ALK translocations in inflammatory myofibroblastic tumors ... a very rare tumor

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**Most Common Treatment-related Adverse Events**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>50 mg QD (n=3)</th>
<th>100 mg QD (n=4)</th>
<th>200 mg QD (n=8)</th>
<th>200 mg QD BID (n=7)</th>
<th>300 mg BID (n=6)</th>
<th>250 mg BID (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>1–2</td>
<td>1–2</td>
<td>1–2</td>
<td>1–2</td>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

3 objective responses observed in this part of the Phase I trial
First Description of EML4-ALK Translocation in NSCLC

- Inflammatory myofibroblastic sarcoma: NPM-ALK translocation
- NSCLC (2): EML4-ALK translocation

Kwak EL, et al. ESMO/ECCO 2009 (Abstract #6 and oral presentation)

• Of the 3 objective responders, all had ALK translocations:
  - Inflammatory myofibroblastic sarcoma: NPM-ALK translocation
  - NSCLC (2): EML4-ALK translocation

Crizotinib in EML4-ALK Positive NSCLC
Grade 3/4 Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event (AE)</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT elevation</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>AST elevation</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>


Crizotinib

- Indicated for ALK mutation positive advanced, metastatic NSCLC
- 250mg po bid with or without food
- Extensive hepatic metabolism via CYP3A4/5, consider dose reductions (qd dosing) in hepatic impairment
- Drug interactions with CYP3A4/5 inducers, inhibitors and substrates

Crizotinib Label Recommendations

- Approved for EML-ALK4 mutation positive patients with advanced or metastatic NSCLC
- Mutation testing recommend for all patients with NSCLC
Erlotinib and Gefitinib

- Orally bioavailable
- Selective inhibitor of epidermal growth factor receptor tyrosine kinase (EGFR-TK)
- Competitive inhibitor of ATP binding

**EGFR Inhibitors: Erlotinib, gefitinib, panitumumab, cetuximab**

### Erlotinib- BR-21

- **Design:** Randomized, placebo-controlled, double-blind trial to determine whether the epidermal growth factor receptor inhibitor erlotinib prolongs survival in non-small-cell lung cancer after the failure of first-line or second-line chemotherapy
- **Population:** Stage IIIB or IV non-small-cell lung cancer who had received one or two prior chemotherapy regimens


#### BR21: overall survival

<table>
<thead>
<tr>
<th>Erlotinib (n=488)</th>
<th>Placebo (n=243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>6.7</td>
</tr>
<tr>
<td>1-year survival, %</td>
<td>31</td>
</tr>
</tbody>
</table>

*HR for median survival, 0.73; p<0.001
*Adjusted for stratification factors (except centre) and EGFR status; HR, hazard ratio

Responses to Erlotinib in Patients with EGFR and KRAS Mutations

<table>
<thead>
<tr>
<th>% of Patients with</th>
<th>Response Rates (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutation = 17%</td>
<td>Wild type = 7%</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Mutant = 27%</td>
<td></td>
</tr>
<tr>
<td>KRAS mutation = 15%</td>
<td>Wild type = 10%</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>Mutant = 5%</td>
<td></td>
</tr>
<tr>
<td>↑EGFR copy number by FISH = 38%</td>
<td>Negative = 5%</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Positive = 21%</td>
<td></td>
</tr>
</tbody>
</table>

**EURTAC study design**

- **Primary endpoint**
  - Progression-free survival (PFS)
    - Interim analysis planned at 88 events

- **Secondary endpoints**
  - Objective response rate
  - Overall survival (OS)
  - Location of progression
  - Safety
  - EGFR mutation analysis in serum
  - Quality of life

**Stratification**
- Mutation type
- ECOG PS (0 vs 1 vs 2)
- Platinum-based doublet chemotherapy x 4 cycles

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**EUROTAC: First-line treatment in EGFR mutation positive NSCLC**

- Erlotinib (n=86)
- Chemotherapy (n=87)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>PFS probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>9</td>
<td>0.4</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>15</td>
<td>0.0</td>
</tr>
</tbody>
</table>

HR=0.37 (0.25–0.54)

Log-rank p<0.0001

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**Erlotinib**

- **Usual Dose:** 150mg po daily until disease progression or unacceptable toxicity
- **Genetic testing:** EGFR mutant with better response, erlotinib is first line therapy in EGFR mutant
- **Drug Interactions:** CYP3A4 substrate, avoid concurrent CYP3A4 inducers and inhibitors
  - Inducers: St. Johns wort, rifampin, phenytoin, etc
  - Inhibitors: Ketoconazole, verapamil, isoniazid, erythromycin

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**EUROTAC** First line treatment in EGFR mutation positive NSCLC

Erlotinib: Food effect

- Food effect, food increased bioavailability up to 100%, but variable
- Package insert recommends empty stomach, 40% availability

Erlotinib: Toxicity and Management

- Common
  - Edema: Diuretics as needed
  - Rash: Topical products
  - Diarrhea: Dose reduce
  - Elevated liver function tests: Monitor and dose reduce
- Rare but serious
  - Bleeding: Counsel and advise patient to monitor
  - Interstitial lung disease: Counsel and advise patient to monitor

Testing Guidelines 2011

- 2011 NCCN, ESMO, and ASCO
  - “On the basis of the results of five phase III randomized controlled trials, patients with NSCLC who are being considered for first-line therapy with an EGFR TKI should have their tumor tested for EGFR mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.”
  - 40% of EGFR mutations are found in active and former smokers
  - From ASCO: “…recommendation applies mainly, but not exclusively, to patients with adenocarcinoma.”

Keedy VL, et al. JCO 2011;29:2121-7
D’Angelo SP, et al. JCO 2011;29:2066-70
Label Recommendations Gefitinib and Erlotinib

- Genetic testing: EGFR mutant and Kras wild-types with better response, consider testing, no FDA label change yet, but has been incorporated into clinical practice guidelines for Erlotinib
- Gefitinib not currently on the market in the US

Maintenance Therapy

- Advanced NSCLC typically treated with 4-6 cycles of chemotherapy and re-treated at recurrence
- Recurrence is nearly universal and second line treatments not as effective
- Maintenance therapy investigated as a way to prolong benefit

Erlotinib Maintenance

A: All patients  
B: EGFR positive by IHC  
C: EGFR activating mutations  
D: EGFR wild-type

Pemetrexed Maintenance


Pemetrexed Maintenance

Pemetrexed Dosing

- Combination use in Non-Small Cell Lung Cancer and Mesothelioma: Recommended dose of pemetrexed is 500 mg/m² i.v. on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m² i.v. beginning 30 minutes after ALIMTA administration.

- Single-Agent use in Non-Small Cell Lung Cancer (adenocarcinoma or large cell): Recommended dose of pemetrexed is 500 mg/m² i.v. on Day 1 of each 21-day cycle.

- Indicated for maintenance therapy in patients who have not progressed after 4 cycles of platinum based chemotherapy

- Premedication regimen: Instruct patients to take folic acid and vitamin B12. Pretreatment with dexamethasone or equivalent reduces cutaneous reaction.

Adverse Effects and Management

- Common
  - Hypertension
    - Monitor and use antihypertensives
  - Nausea and vomiting
    - Antiemetics
  - Myelosuppression
    - Monitor and dose reduce

- Rare but serious
  - Renal failure
    - Monitor and discontinue

Renal, Hepatic and Drug Interactions

- Do not administer to patients whose creatinine clearance is <45 mL/min

- There was no effect of elevated AST, ALT, or total bilirubin on the pharmacokinetics of pemetrexed

- Caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Other NSAIDs and nephrotoxins should also be used with caution
### Summary

- **Screening:** Spiral CT decreases mortality but is too expensive to implement
- **Personalized Therapy:** One new drug and one old drug new used in a new way
- **Maintenance:** Small improvement for advanced NSCLC