Treatment of Metastatic Non-Small Cell Lung Cancer

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April 2, 2011

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MD ANDERSON
CANCER CENTER

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Outline: Metastatic NSCLC

- **Background**
- **Epidemiology**
- **Histology**

- **Front-line Metastatic**
  - Squamous Cell Adenocarcinoma – EGFR mutants
  - EML4 ALK fusion, EGFR WT

- **Maintenance Therapy**
  - Terminology
    - Maintenance trials: JMEN, SATURN
    - ASCO 2010 abstracts: gemcitabine

- **Salvage**
  - Standard Practice
    - ASCO 2010 novel agents: ARQ197
    - nab-paclitaxel
Lung Cancer Epidemiology

- Lung cancer is the #1 cause of cancer-related death world-wide
- 2009 USA estimates 219,440 new cases with 159,390 deaths per year
- 5-year survival all patients ~15%
Survival by Stage

5-year survival rates
Stage IA 67%
Stage IB 57%
Stage IIA 55%
Stage IIB 38-39%
Stage IIIA 23-25%
Stage IIIB 3-7%
Stage IV 1%

Stages I to II: Surgery as the primary modality then adjuvant chemotherapy for stage II
Stage III: multimodality therapy
Stage IV: Palliative chemotherapy
Lung Cancer - Histology

87% NSCLC

13% SCLC

NSCLC NOS 1–15%

SCLC 13%

Large Cell 10-15%

Adenocarcinoma 40%
(Includes BAC)

Squamous Cell (SCC) 25-30%

87% NSCLC
13% SCLC
## 2004 WHO Classification of Lung Tumors

<table>
<thead>
<tr>
<th>NSCLC (87%)</th>
<th>SCLC (13%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenocarcinoma (45%)</strong></td>
<td></td>
</tr>
<tr>
<td>Mixed subtype</td>
<td></td>
</tr>
<tr>
<td>Acinar</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td></td>
</tr>
<tr>
<td>BAC Nonmucinous Mucinous Mixed</td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td></td>
</tr>
<tr>
<td>SCC (33%)</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td></td>
</tr>
<tr>
<td>Small cell</td>
<td></td>
</tr>
<tr>
<td>Basaloid</td>
<td></td>
</tr>
<tr>
<td>LCC (9%)</td>
<td></td>
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<tr>
<td>LCNEC Combined LCNEC</td>
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<tr>
<td>Clear cell</td>
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<td>Basaloid</td>
<td></td>
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<tr>
<td>Lymphoepithelioma-like</td>
<td></td>
</tr>
<tr>
<td>LCC with rhabdoid phenotype</td>
<td></td>
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<tr>
<td>Combined SCLC</td>
<td></td>
</tr>
</tbody>
</table>

Emerging data indicate that specific regimens show greater benefit depending on tumor histology.

BAC=bronchioloalveolar carcinoma; LCC=large cell carcinoma; LCNEC=large cell neuroendocrine carcinoma; SCC=squamous cell carcinoma; SCLC=small cell lung cancer; WHO=World Health Organization.

Outline: Metastatic NSCLC

- **Background**
- **Front-line Metastatic**
- **Maintenance Therapy**
- **Salvage**

**Epidemiology**

**Histology**

**Squamous Cell Adenocarcinoma** – EGFR mutants, EML4 ALK fusion, EGFR WT

**Terminology**

Maintenance trials: JMEN, SATURN

ASCO 2010 abstracts: gemcitabine

**Standard Practice**

ASCO 2010 novel agents: ARQ197, nab-paclitaxel
Survival by Treatment Group
All Randomized Cases

E1594: Chemo and Metastatic NSCLC

- Cis/Paclitaxel
- Cis/Gemcitabine
- Cis/Docetaxel
- Carbo/Paclitaxel

All Eligible Patients (N=1155)

RR 19%
Median Survival 7.9 mos
Evolution of FDA approved agents for front-line NSCLC

*Label does not include NSCLC-specific indication

Options for First-Line NSCLC Regimens

- Cisplatin + paclitaxel (24 hr)
- Cisplatin + vinorelbine
- Cisplatin + gemcitabine
- Cisplatin + docetaxel
- Non-platinum based doublets
- Cisplatin + pemetrexed in non-SCC
- Bevacizumab + carboplatin + paclitaxel (3 hr) in non-SCC
- Gefitinib/Erlotinib monotherapy in EGFR mutants
- Cetuximab + platinum doublet (not EMEA nor FDA approved)
Histology and Molecular Profiling

NSCLC PATIENT

Non-SCC

Neuroendocrine

Platinum-etoposide

EGFR TKI
1st or 2nd line Maintenance (IPASS, BR.21, SATURN)

Adenocarcinoma

EGFR mutation

EML 4 ALK

crizotinib

EML 4 ALK

Consider 2nd line EGFR TKI or maintenance erlotinib (BR.21, SATURN)

EGFR wild-type

Platinum-doublet-bevacizumab
Platinum-pemetrexed ± bevacizumab
Non-platinum or platinum based doublet
Switch Maintenance: pemetrexed, erlotinib (E4599, AVAiL, Pointbreak, SATURN, JMEN)

SCC

Avoid pemetrexed or bevacizumab

Histology and Molecular Profiling
Histology and Molecular Profiling

NSCLC PATIENT

Non-SCC
- Neuroendocrine
  - Platinum-etoposide
    - EGFR TKI
      - 1st or 2nd line
        - Maintenance (IPASS, BR.21, SATURN)
- Adenocarcinoma
  - EGFR mutation
- EGFR wild-type
  - EML 4 ALK
    - crizotinib
  - Consider 2nd line EGFR TKI or maintenance erlotinib (BR.21, SATURN)

SCC
- Avoid pemetrexed or bevacizumab

Platinum-doublet-bevacizumab
- Platinum-pemetrexed + bevacizumab
- Non-platinum or platinum based doublet
- Switch Maintenance: pemetrexed, erlotinib (E4599, AVAiL, Pointbreak, SATURN, JMEN)
Angiogenesis Inhibition and Safety in SCC

• Antiangiogenic agents seem to produce either cavitation and/or bleeding
  – Clearly a class effect
  – Likely more associated with histology than location
  – Seems limited to primary lung cancer
  – More studies are needed to better assess risks and potential therapeutic interventions

• SCC appears to be a consistent contraindication and safety concern for angiogenesis inhibitors as a class

Bevacizumab in NSCLC: Bleeding in a Randomized Phase II Trial

- 6 life-threatening cases of pulmonary hemoptysis; 4 fatal
  - Overall incidence: 9% (6/66)
  - 5 occurred with bevacizumab 7.5 mg/kg
- Apparent risk factors
  - Baseline hemoptysis
  - Histology
    - Squamous histology: 31% (4/13)
    - Nonsquamous histology: 4% (2/53)

Chemotherapy-naïve stage IIIB (wet) or IV NSCLC N=99

PD=progressive disease; PH=pulmonary hemorrhage.

Phase III Trial of Pemetrexed vs. Docetaxel

- This is a retrospective analysis by histology. Histologic types considered: adenocarcinoma, large cell lung cancer, squamous cell carcinoma. Other types grouped as “other/indeterminate” category.
- Within histologic groups, Kaplan-Meier plots and Cox cofactor-adjusted treatment hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained for OS and PFS.

Phase III Pemetrexed vs. Docetaxel
Retrospective Analysis of Histology and OS

Non-SCC (n=399)
HR=0.778, p=0.048
(95% CI: 0.607–0.997)
Pemetrexed
Median OS: 9.3 mos

Docetaxel
Median OS: 8.0 mos

SCC (n=172)
HR=1.563, p=0.018
(95% CI: 1.079–2.264)
Pemetrexed
Median OS: 6.2 mos

Docetaxel
Median OS: 7.4 mos

Pemetrexed improves overall survival in patients with non-SCC NSCLC but does not benefit patients with SCC histology.

TS mRNA Levels are Higher in Resected Squamous NSCLC

- FFPE tissue
  - Adeno (n = 30)
  - Squamous (n = 21)
- TS by RT-PCR
- Other pre-clinical data correlates high TS expression with reduced pemetrexed sensitivity

Histology and Molecular Profiling

**NSCLC PATIENT**

**SCC**

**Front-line chemotherapy**
- Platinum-taxane
- Platinum-gemcitabine
- Platinum-vinorelbine

Not EMEA/FDA approved:
- Platinum-doublet + cetuximab (FLEX, BMS-099)

New agents: *nab*-paclitaxel

**Maintenance therapy**
- Erlotinib (SATURN)

Avoid pemetrexed or bevacizumab
Histology and Molecular Profiling

NSCLC PATIENT

Non-SCC

Neuroendocrine

Platinum-etoposide

EGFR TKI 1\textsuperscript{st} or 2\textsuperscript{nd} line Maintenance (IPASS, BR.21, SATURN)

Adenocarcinoma

EGFR mutation

EML 4 ALK

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EGFR wild-type

Consider 2\textsuperscript{nd} line EGFR TKI or maintenance erlotinib (BR.21, SATURN)

SCC

Avoid pemetrexed or bevacizumab

Non-platinum or platinum based doublet

Switch Maintenance: pemetrexed, erlotinib (E4599, AVAiL, Pointbreak, SATURN, JMEN)

Platinum-doublet-bevacizumab

Platinum-pemetrexed ± bevacizumab
EGFR and Lung Cancer

- HER1/EGFR signaling pathway plays a pivotal role in tumorigenesis and disease progression
- Aberrant in NSCLC
- Overexpression linked to poor prognosis
  - EGFR overexpression predicts a shortened survival time (Selvaggi 2004)
- Targeting EGFR in preclinical models demonstrates anticancer effect
EGFR mutations

- Found in 10% - 15% of all lung cancer patients and 85% who clinically respond to EGFR TKIs
- Found more commonly in never-smokers, adenocarcinomas, BAC, women, Asians
- Predominantly located in EGFR exons 19 - 21
- EGFR mutations are not the same. There are sensitive mutations and acquired resistance mutations (T790M).
- 85% of EGFR mutations are either deletion exon 19 or L858 mutation.

Patient with EGFR mutation deletion exon 19
Patient with L858 EGFR mutation

Newly diagnosed
3-16-07

3 months of erlotinib
6-18-07
**EGFR T790M: Frequently Found in Tumor Cells From Patients With Acquired Resistance to EGFR TKIs**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Smoking</th>
<th>Drug</th>
<th>Duration</th>
<th>Prior chemo</th>
<th>Prior RT</th>
<th>Sites Examined for Acquired Resistance</th>
<th>Primary Mutation</th>
<th>Secondary Mutation</th>
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<tr>
<td>1a,b</td>
<td>F</td>
<td>Never</td>
<td>E</td>
<td>19</td>
<td>Y</td>
<td>N</td>
<td>Lung, spine</td>
<td>del L747-E749;A750P</td>
<td>T790M</td>
<td>5.7</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Never</td>
<td>G</td>
<td>13</td>
<td>Y</td>
<td>Y</td>
<td>Lung</td>
<td>del L747-S752</td>
<td>T790M</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Oligo</td>
<td>G</td>
<td>11</td>
<td>Y</td>
<td>Y</td>
<td>Omentum</td>
<td>del E746-A750</td>
<td>T790M</td>
<td>5.1 → 6.3</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
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<td>G</td>
<td>15</td>
<td>Y</td>
<td>N</td>
<td>Lung, pericardial fluid</td>
<td>del L747-P753insS</td>
<td>T790M</td>
<td>9.6 → 11</td>
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<tr>
<td>5</td>
<td>F</td>
<td>Never</td>
<td>E</td>
<td>10</td>
<td>N</td>
<td>N</td>
<td>Pleural fluid</td>
<td>del E746-T751insA</td>
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<td>nd</td>
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<tr>
<td>6</td>
<td>F</td>
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<td>G→Eα</td>
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<td>N</td>
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<td>del E746-A750</td>
<td>T790M</td>
<td>nd</td>
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<tr>
<td>7a</td>
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<td>Never</td>
<td>G</td>
<td>10</td>
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<td>N</td>
<td>Pleural fluid</td>
<td>L858R</td>
<td>T790M</td>
<td>nd</td>
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<td>8</td>
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<td>Never</td>
<td>G</td>
<td>15</td>
<td>N</td>
<td>N</td>
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<td>L858R</td>
<td>T790M</td>
<td>nd</td>
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<tr>
<td>9</td>
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<td>Never</td>
<td>G</td>
<td>13</td>
<td>N</td>
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<td>Lung</td>
<td>L858R</td>
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<td>nd</td>
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<tr>
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<td>Never</td>
<td>G</td>
<td>13</td>
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<td>Y</td>
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<td>E</td>
<td>16</td>
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<td>N</td>
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<td>nd</td>
</tr>
<tr>
<td>13a</td>
<td>M</td>
<td>Never</td>
<td>G</td>
<td>11</td>
<td>N</td>
<td>N</td>
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<td>2.9 → 6.1</td>
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<tr>
<td>14</td>
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<td>G</td>
<td>19</td>
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<td>N</td>
<td>Ascites</td>
<td>del E746-A750</td>
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<td>nd</td>
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<tr>
<td>15</td>
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<td>G</td>
<td>8</td>
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<td>N</td>
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<td>8.4</td>
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<td>16</td>
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<td>E</td>
<td>10</td>
<td>Y</td>
<td>N</td>
<td>Lung</td>
<td>del E746-A750</td>
<td>None</td>
<td>5.7</td>
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<td>E</td>
<td>9</td>
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<td>N</td>
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<td>7.2</td>
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<td>N</td>
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<td>del^α</td>
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<td>M</td>
<td>Former</td>
<td>G</td>
<td>12</td>
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<td>Y</td>
<td>Inguinal lymph node</td>
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<td>Y</td>
<td>Pleural fluid</td>
<td>L858R</td>
<td>None</td>
<td>nd</td>
</tr>
</tbody>
</table>

T790M blocks erlotinib binding and leads to a resistant phenotype.
IPASS: Phase III Trial of Gefitinib vs Carboplatin/Paclitaxel in Selected Patients With Advanced NSCLC

Never or light ex-smoker* with adenocarcinoma histology
PS 0-2
Stage IIIB or IV chemotherapy-naïve NSCLC
N=1217

Gefitinib (250 mg/day)
Offered carboplatin/paclitaxel on progression

Carboplatin (AUC 5 or 6) + Paclitaxel (200 mg/m²)
3 times weekly up to 6 cycles

Primary endpoint: PFS (noninferiority)
Secondary endpoints: ORR, OS, QOL, disease-related symptoms, safety, and tolerability
Exploratory: biomarkers – EGFR mutation, gene copy number, and protein expression

*Never smoker=smoked <100 cigarettes in lifetime; light ex-smoker=stopped ≥15 years ago and smoked ≤10 pack-years.
IPASS: Results in ITT Population

PFS

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>C/P</th>
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<tbody>
<tr>
<td>No. of Pts</td>
<td>609</td>
<td>608</td>
</tr>
<tr>
<td>Events</td>
<td>453 (74.4%)</td>
<td>497 (81.7%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.7 mos</td>
<td>5.8 mos</td>
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<tr>
<td>12-Mo PFS</td>
<td>25%</td>
<td>7%</td>
</tr>
</tbody>
</table>

HR=0.74; \( P<0.001 \)

OS*

<table>
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<th>Gefitinib</th>
<th>C/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>223 (36.6%)</td>
<td>227 (37.3%)</td>
</tr>
<tr>
<td>ORR</td>
<td>43.0%</td>
<td>32.2%</td>
</tr>
<tr>
<td>Median OS</td>
<td>18.6 mos</td>
<td>17.3 mos</td>
</tr>
<tr>
<td>12-Mo OS</td>
<td>68%</td>
<td>64%</td>
</tr>
</tbody>
</table>

HR=0.91; \( P=NR \)

*Follow-up ongoing.

C/P=carboplatin/paclitaxel; ITT=intent to treat.

IPASS: PFS by EGFR Mutation Status Within Treatment Arms

Gefitinib EGFR M+ (N=132)
Gefitinib EGFR M– (N=91)
Carboplatin/paclitaxel EGFR M+ (N=129)
Carboplatin/paclitaxel EGFR M– (N=85)

Gefitinib, HR=0.19; P<0.0001
Carboplatin/paclitaxel, HR=0.78; P=0.1103

HR <1 implies a lower risk of progression in the M+ group compared with the M– group.

M=mutation.

IPASS: Response Rates

**ORR (RECIST) in ITT Population**

- **Gefitinib** (N=609): 43.0%
- **Carboplatin/paclitaxel** (N=608): 32.2%

**ORR in Patients With an EGFR Mutation**

- **Gefitinib** (M+ N=91): 71.2%
- **Carboplatin/paclitaxel** (M+ N=85): 23.5%

- **Gefitinib** (M– N=132): 47.3%
- **Carboplatin/paclitaxel** (M– N=129): 1.1%

**HR**

- Gefitinib vs Carboplatin/paclitaxel:
  - ORR: HR=1.59; P=0.0001
  - Mutation Positive: M+ HR=2.75; P=0.0001
  - Mutation Negative: M– HR=0.04; P=0.0013

**Note:**

- RECIST=Response Evaluation Criteria in Solid Tumors.
IPASS: OS by EGFR Mutation Status

EGFR Mutation Positive
- Gefitinib (N=132)
- Carboplatin/paclitaxel (N=129)

EGFR Mutation Negative
- Gefitinib (N=91)
- Carboplatin/paclitaxel (N=85)

HR (95% CI)=0.78 (0.50-1.20)
No. events gefitinib, 38 (28.8%)
No. events C/P, 43 (33.3%)

HR (95% CI)=1.38 (0.92-2.09)
No. events gefitinib, 52 (57.1%)
No. events C/P, 42 (49.4%)

- Cox analysis with covariates
- HR<1 implies a lower risk of death on gefitinib
- ITT population
- Post hoc analysis of OS by EGFR mutation status

# IPASS: Safety Profile

<table>
<thead>
<tr>
<th>CTC Grade 3-5 AEs</th>
<th>Gefitinib (N=607)</th>
<th>Carboplatin/Paclitaxel (N=589)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>192 (31.6%)</td>
<td>368 (62.5%)</td>
</tr>
<tr>
<td>Rash/acne</td>
<td>19 (3.1%)</td>
<td>5 (0.8%)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>2 (0.3%)</td>
<td>29 (4.9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (3.8%)</td>
<td>8 (1.4%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9 (1.5%)</td>
<td>16 (2.7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (0.3%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Asthenic conditions</td>
<td>2 (0.3%)</td>
<td>11 (1.9%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.2%)</td>
<td>16 (2.7%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (0.5%)</td>
<td>10 (1.7%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 (3.7%)</td>
<td>387 (67.1%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9 (1.5%)</td>
<td>202 (35%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (2.2%)</td>
<td>61 (10.6%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (1.0%)</td>
<td>32 (5.5%)</td>
</tr>
</tbody>
</table>

CTC=Common Terminology Criteria.
Front-line EGFR TKI

- EGFR TKI monotherapy in NSCLC patients with sensitive EGFR mutations improves PFS over chemotherapy.
- However, EGFR TKI monotherapy should not be given to patients without EGFR mutations, i.e. EGFR wild-type (WT). EGFR WT patients need front-line chemotherapy.

- It is unclear whether EGFR TKI + chemo or chemo then maintenance erlotinib would improve survival for EGFR mutation patients.
  - CALGB 30406 frontline study (ASCO 2010)
  - FAST - ACT (intercalating EGFR TKI with chemo) – await results. There are concerns over combining erlotinib-chemo as erlotinib arrests the cancer cells in the G1 checkpoint and chemo usually works best in the mitotic phase.
  - SATURN – showed that EGFR mutation patients had significant survival improvement with maintenance erlotinib after 4 cycles of chemo.
Histology and Molecular Profiling

NSCLC PATIENT

Non-SCC

Adenocarcinoma

EGFR mutation

EGFR TKI
1st or 2nd line Maintenance (IPASS, BR.21, SATURN)

EGFR wild-type

EML 4 ALK

crizotinib
EML4-ALK Fusion Gene

ALK – anaplastic lymphoma kinase
EML 4 – echinoderm microtubule associated protein like 4

- Found Primarily in Adenocarcinoma patients who are never- or light former smokers, **EGFR and KRAS WT**, and younger age

  Caucasian never-smoker and adenocarcinoma
  EGFR mutation: 35%
  Caucasian never-smoker, adenocarcinoma, EGFR WT
  EML4-ALK: ~10-20%

- EML4-ALK-positive tumors may be a distinct entity among lung adenocarcinomas (EGFR and KRAS WT)

- Encouraging results from phase 1 study with an ALK inhibitor (crizotinib) in NSCLC patients harboring EML4-ALK translocations

EML4-ALK Fusion Gene

FISH assay for ALK rearrangement

ALK break-apart FISH assay
[Courtesy John lafrate, Massachusetts General Hospital]

*Assay is positive if rearrangements can be detected in ≥15% of cells
FISH = fluorescence in situ hybridization

Examples of EML4-ALK Positive NSCLC

FISH images courtesy of Lee C; IHC images courtesy of Rodig S; both Brigham & Womens Hospital from Janne lecture IASLC 2009
Patients with EML4-ALK fusion do not appear to respond to EGFR TKIs.

Platinum-based chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>ALK (N=12)</th>
<th>EGFR (N=8)</th>
<th>WT/WT* (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, %</td>
<td>25</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>TTP, months</td>
<td>9</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

EGFR TKI

<table>
<thead>
<tr>
<th></th>
<th>ALK (N=10)</th>
<th>EGFR (N=23)</th>
<th>WT/WT* (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, %</td>
<td>0</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>TTP, months</td>
<td>5</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>

TTP for chemotherapy\(^1\)

TTP for EGFR TKI\(^1\)

\(^*WT/WT = wild type: no ALK fusion or EGFR mutation\)

\(^1Shaw AT et al. J Clin Oncol 2009;27:4247–4253\)
### Crizotinib selectivity profile

**Upstate 102 kinase**

**13 kinase “hits” <100X selective for c-MET**

**Cellular selectivity on 10 of 13 relevant hits**

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC$_{50}$ (nM) mean*</th>
<th>Selectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-MET</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>ALK</td>
<td>20</td>
<td>2X</td>
</tr>
<tr>
<td>RON</td>
<td>298</td>
<td>34X</td>
</tr>
<tr>
<td>Axl</td>
<td>189</td>
<td>22X</td>
</tr>
<tr>
<td>Tie-2</td>
<td>294</td>
<td>34X</td>
</tr>
<tr>
<td>Trk A</td>
<td>448</td>
<td>37X</td>
</tr>
<tr>
<td>Trk B</td>
<td>580</td>
<td>67X</td>
</tr>
<tr>
<td>Abl</td>
<td>399</td>
<td>46X</td>
</tr>
<tr>
<td>IRK</td>
<td>1,159</td>
<td>166X</td>
</tr>
<tr>
<td>Lck</td>
<td>2,887</td>
<td>334X</td>
</tr>
<tr>
<td>Sky</td>
<td>&gt;10,000</td>
<td>&gt;1,000X</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>&gt;10,000</td>
<td>&gt;1,000X</td>
</tr>
<tr>
<td>PDGFRβ</td>
<td>&gt;10,000</td>
<td>&gt;1,000X</td>
</tr>
</tbody>
</table>

*The cellular kinase activities were measured using ELISA capture method*

**Selectivity findings**

- **Crizotinib – ALK and c-MET inhibition at clinically relevant dose levels**
- **Crizotinib – low probability of pharmacologically relevant inhibition of any other kinase at clinically relevant dose levels**

*Crizotinib (PF-02341066)*

Pfizer Inc. Data on file
ASCO 2010 Critzotinib: first in human trial

Part 1: Dose escalation
- Cohort 1 (n=3): 50 mg QD
- Cohort 2 (n=4): 100 mg QD
- Cohort 3 (n=8): 200 mg QD
- Cohort 4 (n=7): 200 mg BID
- Cohort 5 (n=6): 300 mg BID

2 DLTs: grade 3 fatigue
- Cohort 6 (n=9): 250 mg BID MTD/RP2D

Part 2: Molecularly enriched cohorts (ALK and c-MET)
- Enrolling patients with ALK-positive NSCLC after preliminary observation of impressive activity in a few patients
  - Data from database April 7, 2010
  - Data presented for 82 patients, study ongoing

ALT = alanine aminotransferase
Tumor responses to Crizotinib

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

*Partial response patients with 100% change have non-target disease present
77% of ALK (+) patients remain on crizotinib

- Duration of treatment (median: 5.7 months)
  - 0–3 mo: 13 pts
  - >3–6 mo: 29 pts
  - >6–9 mo: 24 pts
  - >9–12 mo: 9 pts
  - >12–18 mo: 4 pts
  - >18 mo: 3 pts

- Reasons for discontinuation
  - Related AEs: 1
  - Non-related AEs: 1
  - Unrelated death: 2
  - Other: 2
  - Progression: 13

N=82; red bars represent discontinued patients
ALK Inhibitor Efficacy in EML4-ALK NSCLC

Baseline

2 months of crizotinib

Kwak EL. J Clin Oncol 2009;27(suppl):Abstract 3509
PFS: median PFS has not been reached

PFS probability at 6 months: 72% (95% CI: 61, 83%)

70% of patients in f/u for PFS

Median follow-up for PFS: 6.4 months (25–75% percentile: 3.5–10 months)

95% Hall–Wellner confidence bands
### Treatment-related Grade 3/4 AE

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>10 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>ALT elevation*</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>5 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Based on laboratory data (n=71), ALT increase to grade 1, 52%; to grade 2, 4% (In preclinical toxicology studies, no histologic changes in the liver were observed) 1 patient discontinued for ALT elevation
Crizotinib – ASCO 2010 Plenary

• Treatment with crizotinib resulted in impressive clinical activity in patients with $ALK$-positive advanced NSCLC
  • ORR: 57%
  • DCR at 8 weeks: 87%
  • PFS probability at 6 months: 72%
• Crizotinib was well tolerated
  Most frequent AEs: mild/moderate GI events and mild visual disturbances
• For patients with $ALK$-positive NSCLC, crizotinib may offer a potential new standard of care.
Ongoing Crizotinib Trials

PROFILE 1007

Key entry criteria
- Positive for ALK by central laboratory
- 1 prior chemotherapy (platinum-based)

RANDOMIZE

Crizotinib 250 mg BID (n=159) administered on a continuous dosing schedule

Pemetrexed 500 mg/m² or docetaxel 75 mg/m² (n=159) infused on day 1 of a 21-day cycle

N=318

PROFILE 1005

Key entry criteria
- Positive for ALK by central laboratory
- Progressive disease in Arm B of study A8081007
- >1 prior chemotherapy

N=250

Crizotinib 250 mg BID (N=250) administered on a continuous dosing schedule

PROFILE 1007: NCT00932893; PROFILE 1005: NCT00932451
**Histology and Molecular Profiling**

**NSCLC PATIENT**

**Non-SCC**

**Adenocarcinoma**

**EGFR mutation**

**EGFR TKI**

1\textsuperscript{st} or 2\textsuperscript{nd} line Maintenance (IPASS, BR.21, SATURN)

**EML 4 ALK**

**crizotinib**

**EGFR wild-type**

**Platinum-doublet-bevacizumab**

**Platinum-pemetrexed ± bevacizumab**

**Non-platinum or platinum based doublet**

Switch Maintenance: pemetrexed, erlotinib (E4599, AVAiL, Pointbreak, SATURN, JMEN)
Adenocarcinoma EGFR WT Patient

Bevacizumab-eligible
Bevacizumab + Platinum Doublet

Bevacizumab-ineligible
Platinum-taxane
Platinum-gemcitabine
Platinum-pemetrexed (JMDB)
Platinum-vinorelbine

Not-FDA or EMEA approved:
Platinum-doublet-cetuximab (FLEX, BMS099)
JMDB: Phase III Trial of Cisplatin/Pemetrexed vs Cisplatin/Gemcitabine in Advanced NSCLC

Primary endpoint: OS

Chemotherapy-naïve stage IIIB/IV NSCLC N=1725

Cisplatin 75 mg/m² d1
Pemetrexed 500 mg/m² d1
N=862
Every 3 weeks up to 6 cycles

Cisplatin 75 mg/m² d1
Gemcitabine 1250 mg/m² d1, 8
N=863

Survival Probability

Median Survival
CP 10.3 mos
CG 10.3 mos

Adjusted HR (95% CI)
0.94 (0.84-1.05)

CP=cisplatin/pemetrexed.
Cisplatin/Pemetrexed vs Cisplatin/Gemcitabine in Advanced NSCLC: Results

### Nonsquamous

- **CP**: Median Survival 11.8 mos
- **CG**: Median Survival 10.4 mos
- **CP vs CG**: Adjusted HR (95% CI) 0.81 (0.7-0.94) \( P=0.005 \)

### Squamous

- **CP**: Median Survival 9.4 mos
- **CG**: Median Survival 10.8 mos
- **CP vs CG**: Adjusted HR (95% CI) 1.23 (1.00-1.51) \( P=0.05 \)

## Cisplatin/Pemetrexed vs Cisplatin/Gemcitabine in Advanced NSCLC: Safety

<table>
<thead>
<tr>
<th>Grade 3/4 AEs</th>
<th>Cisplatin/Pemetrexed (N=839)</th>
<th>Cisplatin/Gemcitabine (N=830)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>15.1%</td>
<td>26.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>5.6%</td>
<td>9.9%</td>
<td>0.001</td>
</tr>
<tr>
<td>Thromobocytopenia</td>
<td>4.1%</td>
<td>12.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4.8%</td>
<td>7.6%</td>
<td>0.019</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.3%</td>
<td>3.7%</td>
<td>0.002</td>
</tr>
<tr>
<td>Alopecia, any grade</td>
<td>11.9%</td>
<td>21.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.2%</td>
<td>3.9%</td>
<td>0.004</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.1%</td>
<td>6.1%</td>
<td>1.000</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.7%</td>
<td>4.9%</td>
<td>0.143</td>
</tr>
</tbody>
</table>

Frontline pemetrexed-platinum for Non-SCC NSCLC

• JMDB trial led to FDA approval of platinum-pemetrexed for non-SCC NSCLC.
• Pemetrexed is well tolerated and requires less time for infusion.
• Pemetrexed appears to work especially well in adenocarcinoma.

• Premedication with Vitamin B12 (1000 mcq IM Q9 wks), folic acid (400 mg daily) for 1 week prior to pemetrexed administration is recommended.
Cetuximab

IgG1 chimerized antibody to EGFR
Blocks ligand binding of EGF/TGFα to EGFR

- Potentiates apoptosis
- Inhibits cell cycle progression
- Decreases production of angiogenic factors
- Inhibits invasion and metastasis
FLEX: Phase III Trial of Cisplatin/Vinorelbine Cetuximab in EGFR IHC–Positive Advanced NSCLC

Stage IIIB or IV EGFR-expressing (IHC) chemotherapy-naïve NSCLC N=1125

Cisplatin 80 mg/m² d1
Vinorelbine 25 mg/m² d1,8
Cetuximab 400 mg/m² d1, then 250 mg/m² weekly N=557
21-day cycle, up to 6 cycles

Cisplatin 80 mg/m² d1
Vinorelbine 25 mg/m² d1,8 N=568

Primary endpoint: OS
Secondary endpoints: 1- and 2-year survival rates, 6-month and 12-month PFS rates, RR, safety, and QOL

QOL=quality of life.

FLEX: Results

CV + Cetuximab

<table>
<thead>
<tr>
<th></th>
<th>CV + Cetuximab</th>
<th>CV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>36%</td>
<td>29%</td>
<td>0.010</td>
</tr>
<tr>
<td>PFS</td>
<td>4.8 mos</td>
<td>4.8 mos</td>
<td>0.39</td>
</tr>
<tr>
<td>TTF</td>
<td>4.2 mos</td>
<td>3.7 mos</td>
<td>0.015</td>
</tr>
</tbody>
</table>

CV = cisplatin/vinorelbine; TTF = time to treatment failure.

BMS-099: Phase III Trial of a Taxane/Carboplatin Cetuximab in Advanced NSCLC

Stage IIIB or IV chemotherapy-naïve NSCLC N=676

Primary endpoint: PFS by IRRC
Secondary endpoints: PFS by investigators, response rate by IRRC and investigators, OS, QOL, and safety

*Investigator’s choice of taxane.

AUC=area under the curve; IRRC=Independent Radiologic Review Committee.
## BMS-099: PFS per IRRC

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Taxane/Carboplatin + Cetuximab (N=338)</th>
<th>Taxane/Carboplatin (N=338)</th>
<th>HR and P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS per IRRC</td>
<td>4.40 mos</td>
<td>4.24 mos</td>
<td>HR=0.902; P=0.2358</td>
</tr>
<tr>
<td>Median PFS per investigators</td>
<td>4.30 mos</td>
<td>3.78 mos</td>
<td>HR=0.766; P=0.0015</td>
</tr>
<tr>
<td>ORR per IRRC</td>
<td>25.7%</td>
<td>17.2%</td>
<td>P=0.0066</td>
</tr>
<tr>
<td>ORR per investigators</td>
<td>27.5%</td>
<td>22.5%</td>
<td>P=0.132</td>
</tr>
</tbody>
</table>

ORR=overall response rate.

BMS-099: OS

**Time (Months)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=338</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxane/carboplatin + cetuximab</td>
<td>338</td>
<td>277</td>
</tr>
<tr>
<td>Taxane/carboplatin</td>
<td>338</td>
<td>287</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.890 (0.754-1.051)
Stratified log-rank P value = 0.17

8.38 months (95% CI: 7.33-9.92)
9.69 months (95% CI: 8.28-11.50)

### Comparison of Results From FLEX, BMS-099

<table>
<thead>
<tr>
<th></th>
<th><strong>FLEX</strong></th>
<th></th>
<th><strong>BMS-099</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CV + C225 (N=557)</td>
<td>CV (N=568)</td>
<td>HR, P-value</td>
<td>Taxane/ Cb + C225 (N=338)</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>11.3 mos</td>
<td>10.1 mos</td>
<td>HR 0.871, p=0.044</td>
<td>9.7 mos</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>4.8 mos</td>
<td>4.8 mos</td>
<td>P=NS</td>
<td>4.4 mos</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td>36%</td>
<td>29%</td>
<td>P=0.01</td>
<td>25.7%</td>
</tr>
</tbody>
</table>

Despite a 1.2 month median OS improvement, cetuximab is not FDA/EMEA approved for use in metastatic NSCLC.

I would not recommend giving cetuximab in place of bevacizumab to a bevacizumab eligible patient. Only consider cetuximab with platinum-doublet in SCC or non-bevacizumab eligible patients.

Adenocarcinoma EGFR WT Patient

**Bevacizumab-eligible**
- Bevacizumab
- + Platinum Doublet

**Phase III trials:**
- E4599
- AVail
- AVail - anticoagulation
- PASSPORT – brain mets

**Bevacizumab-ineligible**
- Platinum-taxane
- Platinum-gemcitabine
- Platinum-pemetrexed (JMDB)
- Platinum-vinorelbine

Not-FDA approved:
- Platinum-doublet-cetuximab (FLEX)

**Ongoing phase III trials:**
- Pointbreak – Carbo-pem-bev
- AverPerl – pem/bev maintenance
ECOG 4599: Phase III Trial of Paclitaxel/Carboplatin Bevacizumab

- Key eligibility criteria
  - Chemotherapy-naïve, stage IIIB/IV, nonsquamous NSCLC
  - No CNS metastases
  - No uncontrolled hypertension
  - No history of thrombotic or hemorrhagic disorders
  - No history of current gross hemoptysis (≥½ tsp bright red blood)
  - NSCLC NOS permitted (20% of patients enrolled as NSCLC NOS)

CNS=central nervous system; NOS=not otherwise specified; PC=paclitaxel/carboplatin; PCB=paclitaxel/carboplatin + bevacizumab.

ECOG 4599: Key Outcomes

- RR: 15% for PC vs 35% for PCB ($P<0.001$)
- PFS: 4.5 mos for PC vs 6.2 mos for PCB ($P<0.001$)

### Toxicity

<table>
<thead>
<tr>
<th></th>
<th>PC (N=440)</th>
<th>PCB (N=427)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>0.7%</td>
<td>4.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.7%</td>
<td>7.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>3.0%</td>
<td>3.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>1.0%</td>
<td>1.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Deaths</td>
<td>2</td>
<td>15</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>0</td>
<td>5</td>
<td>ND</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>1</td>
<td>2</td>
<td>ND</td>
</tr>
</tbody>
</table>

No hemoptysis in NSCLC NOS

GI=gastrointestinal; HR=hazard ratio; ND=not done; NS=not significant; OS=overall survival; PFS=progression-free survival.

AVAiL: Phase III Trial of Cisplatin/Gemcitabine Bevacizumab in Advanced NSCLC

Chemotherapy-naïve stage IIIb/IV or recurrent nonsquamous NSCLC N=1043

Exclusion criteria: grade ≥2 hemoptysis; brain metastases; uncontrolled hypertension; history of thrombotic or hemorrhagic disorder; therapeutic anticoagulation at enrollment

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CG + Placebo</th>
<th>CG + Bevacizumab 7.5 mg/kg</th>
<th>CG + Bevacizumab 15 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, HR (95% CI)</td>
<td>NA</td>
<td>0.75 (0.62-0.91); P=0.003</td>
<td>0.82 (0.68-0.98); P=0.03</td>
</tr>
<tr>
<td>Median PFS</td>
<td>6.1 mos</td>
<td>6.7 mos</td>
<td>6.5 mos</td>
</tr>
<tr>
<td>RR</td>
<td>20%</td>
<td>34% (P&lt;0.0001)</td>
<td>30% (P=0.0023)</td>
</tr>
<tr>
<td>Median OS</td>
<td>13.1 mos</td>
<td>13.6 mos</td>
<td>13.4 mos</td>
</tr>
</tbody>
</table>

CG=cisplatin/gemcitabine; CI=confidence interval; NA=not applicable. 
## AVAiL: Severe AEs (Grade ≥3)

<table>
<thead>
<tr>
<th>Severe AEs (Grade ≥3)</th>
<th>CG + Placebo (N=327)</th>
<th>CG + Bevacizumab 7.5 mg/kg (N=330)</th>
<th>CG + Bevacizumab 15 mg/kg (N=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>2%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2%</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>–</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>GI perforation</td>
<td>&lt;1%</td>
<td>–</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ischemic events* (ATEs)</td>
<td>5%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Venous TEEs</td>
<td>6%</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*Includes myocardial infarction or ischemia, cerebral infarction, cerebrovascular accident, cerebral ischemia, ischemic stroke, and peripheral ATEs.

AE=adverse events; ATE=arterial thrombotic events; TEE=thromboembolic events.

### AVAiL: Pulmonary Hemorrhage Events

<table>
<thead>
<tr>
<th></th>
<th>CG + Placebo N=327</th>
<th>CG + Bevacizumab 7.5 mg/kg N=330</th>
<th>CG + Bevacizumab 15 mg/kg N=329</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH (All Grades)</td>
<td>17 (5.2%)</td>
<td>23 (7.0%)</td>
<td>32 (9.7%)</td>
</tr>
<tr>
<td>PH (Grade ≥3)</td>
<td>2 (0.6%)</td>
<td>5 (1.5%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Fatal PH</td>
<td>1 (0.3%)</td>
<td>4 (1.2%)</td>
<td>3 (0.9%)</td>
</tr>
</tbody>
</table>

- 38% of patients had **central lesions**
  - 4/10 patients with severe PH had central lesions

- 9% of patients had **therapeutic anticoagulation**
  - None of these patients had a severe PH

PASSPORT: Phase II Trial of Safety of Bevacizumab in Patients With Brain Metastases

Nonsquamous advanced NSCLC and previously treated brain metastases N=115

Frontline: Bevacizumab 15 mg/kg + platinum doublet chemotherapy or Erlotinib, q21d until PD N=76

Second line: Bevacizumab 15 mg/kg + Erlotinib or single-agent chemotherapy, q21d until PD N=39

• Systemic treatment was not initiated until at least 4 weeks posttreatment for brain metastases
• No grade ≥2 CNS hemorrhage events were reported
• 6 weeks after data cutoff, 1 additional death occurred due to grade 5 PH
• 9% of patients were discontinued due to death from an AE

<table>
<thead>
<tr>
<th>AE</th>
<th>N=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS hemorrhage (grade ≥2)</td>
<td>0</td>
</tr>
<tr>
<td>PH (any grade)</td>
<td>3 (2.8%)</td>
</tr>
<tr>
<td>Non-CNS/non-PH (grade ≥3)</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Arterial TEEs (any grade)</td>
<td>0</td>
</tr>
<tr>
<td>New or exacerbated hypertension (grade ≥3)</td>
<td>3 (2.8%)</td>
</tr>
</tbody>
</table>

Avastin-based therapy: improved PFS/TTP compared with other first-line regimens in non-squamous NSCLC

Median PFS or TTP (months)

Avastin-based therapy: improved OS compared with other first-line regimens in non-squamous NSCLC

Median OS (months)

- **JMDB**: 11.0 (HR=0.84)
- **FLEX**: 11.3 (HR=0.87)
- **E4599**: 12.3
- **AVAiL (15mg/kg)**: 13.4 (HR=0.79)
- **AVAiL (7.5mg/kg)**: 13.6 (HR=0.93)
- **SAiL**: 14.6

Consistent OS in Avastin-treated patients

Guidelines for Avastin Eligibility

Eligible for Avastin*

- First-line, locally advanced, metastatic, or recurrent NSCLC
- Non-squamous predominant histologies
  - Adenocarcinoma
  - Large cell
  - Bronchioloalveolar carcinoma
  - Undifferentiated, not otherwise specified (NOS)
- Centrally located tumors
- ECOG PS 0-1

Ineligible for Avastin*

- Squamous-predominant histology
- Gross hemoptysis (≥0.5 tsp red blood)
- Unstable angina
- Prior history of ATE (<6m)
- Symptomatic CHF
- Untreated CNS metastases

Special Populations
Consistent with Approved Indication, but not studied in E4599

- Treated CNS metastases
- Therapeutic anticoagulation (INR >1.5)
- ECOG PS 2

Phase II carboplatin-pemetrexed-bevacizumab

Untreated stage IIIB/IV non-squamous NSCLC (n=43)

Avastin 15mg/kg
Pemetrexed 500mg/m²
Carboplatin AUC 6 q3w x 6

Avastin 15mg/kg q3w
Pemetrexed 500mg/m²

PD

Untreated stage IIIB/IV non-squamous NSCLC (n=43)

Avastin 15mg/kg
Pemetrexed 500mg/m²
Carboplatin AUC 6 q3w x 6

Avastin 15mg/kg q3w
Pemetrexed 500mg/m²

Median PFS
7.8
14.1*

Median OS or PFS (months)

*94% of patients had adenocarcinoma histology

Patel, et al. JCO 2009
Ongoing phase III trials of Avastin with pemetrexed in advanced non-squamous NSCLC

- AVAPERL1
  - first-line Avastin in combination with cisplatin and pemetrexed then avastin ± pemetrexed maintenance

- PointBreak
  - first-line Avastin in combination with carboplatin and pemetrexed or paclitaxel

PointBreak trial design

Tsao Summary Front-line NSCLC

- Treatment Goal: Palliative Therapy

- For patients with a sensitive EGFR mutation, frontline treatment with an EGFR TKI is recommended.

- Platinum-doublets, non-platinum doublets, platinum-doublet-bevacizumab are all appropriate frontline regimens. Platinum-pemetrexed and platinum-taxane-bevacizumab is only used for frontline non-SCC NSCLC. Platinum-pemetrexed-bevacizumab is in a phase III trial.

- Cetuximab added to chemo (FLEX, BMS-099) yield 1.2 month improvement in median OS. However, survival was modest and may not be worth the toxicity, except in SCC patients.
Outline: Metastatic NSCLC

Background

Epidemiology
Histology

Front-line Metastatic

Squamous Cell
Adenocarcinoma – EGFR mutants
EML4 ALK fusion, EGFR WT

Terminology
Maintenance trials: JMEN, SATURN
ASCO 2010 abstracts: gemcitabine

Maintenance Therapy

Standard Practice
ASCO 2010 novel agents: ARQ197
nab-paclitaxel

Salvage

ASCO 2010 novel agents:  ARQ197
Maintenance Therapy

• Are these terms equivalent?
  – Early second line
  – Consolidation/sequential
  – Maintenance

• Continuation maintenance: use of an agent that was given in first-line therapy (i.e. bevacizumab)

• Switch maintenance: initiation of a different agent that was not given in first-line therapy

National Comprehensive Cancer Network website.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>PFS benefit</th>
<th>Overall OS benefit</th>
<th>Subgroup greater OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciuleanu et al.</td>
<td>Pemetrexed</td>
<td>Yes</td>
<td>Yes</td>
<td>Non-SCC</td>
</tr>
<tr>
<td>WJTOG</td>
<td>Gefitinib</td>
<td>Yes</td>
<td>No</td>
<td>AdenoCA</td>
</tr>
<tr>
<td>Fidias et al.</td>
<td>Docetaxel</td>
<td>Yes</td>
<td>No – but trend seen</td>
<td>NR</td>
</tr>
<tr>
<td>ATLAS</td>
<td>Bevacizumab + Erlotinib</td>
<td>Yes</td>
<td>Not between 2 arms</td>
<td>?</td>
</tr>
<tr>
<td>SATURN</td>
<td>Erlotinib</td>
<td>Yes</td>
<td>Yes</td>
<td>EGFR mutants</td>
</tr>
<tr>
<td>Belani et al.</td>
<td>Gemcitabine</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>IFCT – GFPC 0502</td>
<td>Gemcitabine + Erlotinib</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes - ESMO</td>
</tr>
</tbody>
</table>
JMEN: Phase III Trial of Maintenance Pemetrexed in Advanced NSCLC

Primary endpoint: PFS

Stage IIIB/IV NSCLC
- PS 0/1
- 4 prior cycles of gemcitabine, docetaxel, or paclitaxel plus cisplatin, or carboplatin with CR, PR, or SD

Randomize 2:1

Pemetrexed 500 mg/m² q3 weeks
Best supportive care
N=441

Placebo q3 weeks
Best supportive care
N=222

B₁₂, folate, and dexamethasone given in both arms.

CR=complete response; PR=partial response; SD=stable disease.

JMEN: Efficacy of Maintenance Pemetrexed vs Placebo in Nonprogressing Patients With Advanced NSCLC

PFS*

- **Pemetrexed**: Median PFS: 4.0 mos
- **Placebo**: Median PFS: 2.0 mos

**HR=0.60**
(95% CI: 0.49-0.73)
*P < 0.0001*

*By independent review.*

OS

- **Pemetrexed**: Median OS: 13.4 mos
- **Placebo**: Median OS: 10.6 mos

**HR=0.79**
(95% CI: 0.65-0.95)
*P = 0.012*

**JMEN: Efficacy of Maintenance Pemetrexed by Histologic Groups**

<table>
<thead>
<tr>
<th>Histologic Group</th>
<th>Median PFS* (Months)</th>
<th>CR+PR+SD†</th>
<th>Median OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pem</td>
<td>Plac</td>
<td>P Value</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>4.4</td>
<td>1.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adeno</td>
<td>4.6</td>
<td>2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Large cell</td>
<td>4.5</td>
<td>1.5</td>
<td>0.125</td>
</tr>
<tr>
<td>Other</td>
<td>4.1</td>
<td>1.6</td>
<td>0.0003</td>
</tr>
<tr>
<td>Squamous</td>
<td>2.4</td>
<td>2.5</td>
<td>0.896</td>
</tr>
</tbody>
</table>

Statistically significant treatment-by-histology interaction with both PFS ($P=0.036$) and OS ($P=0.033$).

*Independent review.

†Disease control rate (CR+PR+SD) was significantly improved with pemetrexed vs placebo in the ITT population (49% vs 29%, $P<0.0001$) by independent review.

Adeno=adenocarcinoma; Pem=pemetrexed; Plac=placebo.

## JMEN: Safety Profile

<table>
<thead>
<tr>
<th>Grade 3/4 AEs</th>
<th>Pemetrexed</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6%</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6%</td>
<td>2%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>15%</td>
<td>3%</td>
<td>5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ALT</td>
<td>10%</td>
<td>&lt;1%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>19%</td>
<td>2%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24%</td>
<td>5%</td>
<td>10%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Infection</td>
<td>5%</td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5%</td>
<td>&lt;1%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>19%</td>
<td>&lt;1%</td>
<td>5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>7%</td>
<td>&lt;1%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>9%</td>
<td>&lt;1%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

SATURN: Treatment Schema

Chemotherapy-naïve advanced NSCLC N=1949

4 cycles of first-line platinum doublet chemotherapy*

No PD N=889

1:1

Erlotinib 150 mg/day

PD

Placebo

PD

Stratification factors:
- EGFR IHC (positive vs negative vs indeterminate)
- Stage (IIIB vs IV)
- ECOG PS (0 vs 1)
- Chemotherapy regimen (cisplatin/gemcitabine vs carboplatin/docetaxel vs others)
- Smoking history (current vs former vs never)
- Region

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

Secondary endpoints:
- OS in all patients and those with EGFR IHC+ tumors, OS and PFS in EGFR IHC–tumors, biomarker analyses, safety, time to symptom progression, and QOL

*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel; cisplatin/vinorelbine; carboplatin/gemcitabine; carboplatin/docetaxel; carboplatin/paclitaxel.

Cappuzzo. ASCO. 2009 (abstr 8001).
SATURN: PFS by ITT

PFS Probability

<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Erlotinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, wks</td>
<td>12.3</td>
<td>11.1</td>
</tr>
<tr>
<td>PFS at 12 wks</td>
<td>53%</td>
<td>40%</td>
</tr>
<tr>
<td>PFS at 24 wks</td>
<td>31%</td>
<td>17%</td>
</tr>
</tbody>
</table>

HR=0.71 (0.62-0.82)
Log-rank P<0.0001

*PFS is measured from time of randomization into the maintenance phase; assessments were every 6 weeks.

Cappuzzo. ASCO. 2009 (abstr 8001).
SATURN: PFS by Histology

**Adenocarcinoma**
- HR = 0.60 (0.48–0.75)
- Log-rank $P < 0.0001$

<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Erlotinib (N=204)</th>
<th>Placebo (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>16</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>24</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>32</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>40</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>48</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>56</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>64</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>72</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>80</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>88</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**SCC**
- HR = 0.76 (0.60–0.95)
- Log-rank $P = 0.0148$

<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Erlotinib (N=166)</th>
<th>Placebo (N=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>16</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>24</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>32</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>40</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>48</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>56</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>64</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>72</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>80</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>88</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Cappuzzo. ASCO. 2009 (abstr 8001).
About 50% of all tumors were able to be sequenced for EGFR mutation.

Cappuzzo. ASCO. 2009 (abstr 8001).
SATURN: Safety Profile

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib (N=433)</th>
<th>Placebo (N=445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal Due to Any AE</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Dose Modification/Interruption Due to Any AE</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>AEs Occurring in ≥10% of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>60%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- No unexpected safety signals were observed in this study
- No deterioration in QOL was observed in the erlotinib or placebo arms (FACT-L questionnaire)

Cappuzzo. ASCO. 2009 (abstr 8001).
SATURN: OS

OS*: Intent to Treat

OS: EGFR Wild Type

*OS is measured from time of randomization into the maintenance phase.

Cappuzzo. IASLC. 2009.
Chemo-naïve IIIB/IV

Stratified by: PS, stage, best tumor response

PS 0-2

CR, PR, SD

Carbo AUC 5 Q3wk
Gemcitabine 1000 mg/m² d1, 8 x 4 cycles

RANDOMIZED

Gemcitabine 1000 mg/m² s d1, 8 Q3wk + BSC

BSC

Off-study

Primary endpoint: OS
Secondary endpoint: RR, PFS, safety/toxicity

Maintenance radiographic evaluation = every 9 wks or 3 cycles

Belani et al. ASCO 2010
Both PFS and OS were negative for any benefit to maintenance gemcitabine. The BSC arm had better numerical survival data.

Trials had 2/3 of patients with PS2, unclear if this affected the survival results.
Abstract 7507 Phase III maintenance gem vs erlotinib vs obs

- Stratification: gender, histology, smoking status, response to cis-gem
- Cisplatin-gemcitabine (cis 80 mg/m² d1, gem 1250 mg/m² d1, d8)
- Maintenance: gem 1250 mg/m² d1, d8 Q3wk, erlotinib 150 mg daily

Abstract 7507, ASCO 2010
Exploratory subgroup analyses showed all pts. had PFS benefit with either maintenance gemcitabine or erlotinib.
Preliminary Overall Survival

- **Observation**
- **Gemcitabine**
- **Erlotinib**

**Gemcitabine vs observation**
HR = 0.86 (0.66–1.12)

**Erlotinib vs observation**
HR = 0.91 (0.80–1.04)
# Grade 3/4 Adverse Events

<table>
<thead>
<tr>
<th>Grade 3/4 AE</th>
<th>Gemcitabine N=154</th>
<th>Erlotinib N=155</th>
<th>Observation N=155</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2.6</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20.8</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.6</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0.6</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.3</td>
<td>2.6</td>
<td>0</td>
</tr>
<tr>
<td>Drug related deaths</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abstract 7507, ASCO 2010
Two continuation maintenance gemcitabine trials. One showing no PFS or OS difference and the other suggesting a PFS improvement.

Belani et al. trial had limitations: high rate PS 2 (64%), low post-study treatment rate (16-17%), lack of histologic subclassification. Full toxicity profile not reported. It’s unclear whether high PS2 rate impacted the survival results.

Given the gemcitabine maintenance regimen toxicity (15% neutropenic rate), inconvenience of the weekly schedule, and also that pemetrexed and erlotinib are both FDA approved for maintenance NSCLC (JMEN, SATURN), I would not routinely recommend gemcitabine for maintenance therapy.
Summary Maintenance Treatment

- At this time, there are 2 FDA approved agents for use in switch maintenance therapy after frontline chemo: pemetrexed (non-SCC only) and erlotinib (SCC and non-SCC).
- Certain subgroups of patients may derive significant benefit: Japanese adenoCA (gefitinib), non-SCC (pemetrexed), EGFR mutation (erlotinib).
- Due to QOL, toxicity, and convenience issues, I do not favor gemcitabine or docetaxel maintenance, despite some trials having suggested PFS positive benefit.
- Many targeted agents have the maintenance portion built into the regimen – i.e. bevacizumab. Future studies to validate molecular biomarkers will ultimately select patients that will benefit from maintenance targeted therapy.
Outline: Metastatic NSCLC

- Background
- Front-line Metastatic
- Maintenance Therapy
- Salvage

Epidemiology
Histology

Squamous Cell Adenocarcinoma – EGFR mutants EML4 ALK fusion, EGFR WT

Terminology
Maintenance trials: JMEN, SATURN
ASCO 2010 abstracts: gemcitabine

Standard Practice
ASCO 2010 novel agents: ARQ197 nab-paclitaxel
Treatment of Relapsed/Refractory NSCLC

Current NCCN Treatment Paradigm for Advanced or Metastatic NSCLC

Stage III (locally advanced)

Stage IV (metastatic)

Unresectable

First-Line therapy

Recurrent Cancer

Second-Line¹
Docetaxel
Erlotinib
Pemetrexed

Third-Line¹
Erlotinib

NCCN=National Comprehensive Cancer Network.

Phase III Trials of Docetaxel for Second-Line Treatment of NSCLC

**TAX 317 (International)**
NSCLC refractory to 1-2 prior platinum-containing regimens

- docetaxel
- BSC

**TAX 320 (US)**
NSCLC refractory to 1-2 prior platinum-containing regimens

- docetaxel 100mg/m²
- docetaxel 75 mg/m²
- ifosfamide or vinorelbine

*Shepherd et al. JCO 18 (10): 2095-2103, 2000*  
*Fossella et al. JCO 18 (12): 2354-2362, 2000*

*Slide courtesy of Dr. Frank Fossella*
Pemetrexed vs. Docetaxel in 2nd-line NSCLC

Stratified by:

- PS 0/1 vs. 2
- Stage III vs. IV
- # of prior chemo
- Best response to prior chemo
- Time since last chemo
- Prior platinum
- Prior taxane
- Homocysteine level
- Center

Pemetrexed

- 500 mg/m² IV q3wks
- (folic acid + vitamin B₁₂
dexamethasone)

Docetaxel

- 75 mg/m² IV q3wks
- (dexamethasone)

Hanna et al. JCO 22:1589-1597, 2004
Phase III Overall Survival (ITT)

Pemetrexed (n=283)

Docetaxel (n=288)

Survival Distribution Function

Months

0.00 0.25 0.50 0.75 1.00

0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5

MST 8.3 months
1-yr OS: 29.7%

MST 7.9 months
1-yr OS: 29.7%

HR 0.99
95% CI of HR (0.82, 1.20)

ITT = intent to treat
HR = hazard ratio
CI = confidence interval
MST = median survival time

Hanna et al. JCO 22:1589-1597, 2004
BR.21: Erlotinib Overall Survival

Survival distribution function

- Erlotinib (n=488)
  - Median survival (months): 6.7
  - 1-year survival (%): 31%

- Placebo (n=243)
  - Median survival (months): 4.7
  - 1-year survival (%): 21%

HR=0.70; p-value < 0.001

42.5% improvement in median survival

Shepherd et al. NEJM 2005;353:123-132
INTEREST Study

Patients
- Age ≥18 years
- Life expectancy ≥ 8 weeks
- Progressive or recurrent disease following CT
- Considered candidates for further CT with docetaxel
- 1 or 2 CT regimens (≥1 platinum)
- PS 0-2

Endpoints
Primary
- Overall survival (co-primary analyses\(^a\) of non-inferiority in all patients and superiority in patients with high EGFR gene copy number)

Secondary
- Progression-free survival
- Objective response rate
- Quality of life
- Disease related symptoms
- Safety and tolerability

Exploratory
- Biomarkers

Gefitinib 250 mg/day

Docetaxel 75 mg/m\(^2\) every 3 weeks

1:1 randomization

\(^a\)modified Hochberg procedure applied to control for multiple testing

CT, chemotherapy; PS, performance status; EGFR, epidermal growth factor receptor

JY Douillard et al. WCLC 2007
96% of historical docetaxel advantage over BSC from TAX-317 retained by gefitinib (96% CI: 52%, 129%)

Indirect comparison of gefitinib to BSC: HR (96% CI) = 0.63 (0.42, 0.92), p=0.0137

PP, per-protocol; NI, non-inferiority; HR, hazard ratio; OS, overall survival; BSC, best supportive care

Pre-specified NI limit in HR terms (translates to ≥ 50% effect retention [Rothmann 2003]) = 1.154

96% of historical docetaxel advantage over BSC from TAX-317 retained by gefitinib (96% CI: 52%, 129%)

Indirect comparison of gefitinib to BSC: HR (96% CI) = 0.63 (0.42, 0.92), p=0.0137

PP, per-protocol; NI, non-inferiority; HR, hazard ratio; OS, overall survival; BSC, best supportive care

JY Douillard et al. WCLC 2007
Quality of life and symptom improvement rates (EFQ population)

% patients with sustained clinically relevant improvement

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib (n=490)</th>
<th>Docetaxel (n=476)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total FACT-L</strong></td>
<td>25.1</td>
<td>14.7</td>
</tr>
<tr>
<td><strong>TOI</strong></td>
<td>17.3</td>
<td>10.3</td>
</tr>
<tr>
<td><strong>LCS</strong></td>
<td>20.4</td>
<td>16.8</td>
</tr>
</tbody>
</table>

*p*-values from logistic regression with covariates. Clinically relevant improvement pre-defined as 6 point improvement for FACT-L and TOI; 2 point improvement for LCS, maintained for at least 21 days.

EFQ, evaluable for quality of life, FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale

JY Douillard et al. WCLC 2007
Choosing 2\textsuperscript{nd} line therapy

Patient Clinical Characteristics
Patient Performance Status
Patient Preference
Co-morbidities: diabetes, GI problems

Patient’s Cancer
Histology
Molecular Profiles (future)

- Pemetrexed does not work in SCC due to elevated thymidylate synthase in SCC.
- Erlotinib has higher response rates in certain subgroups:
  Never-smokers
  Women
  Asians
  Adenocarcinoma (BAC)
ASCO 2010 Abstract 7502: c-Met inhibition

- C-Met receptor tyrosine kinase inhibitor is involved in tumor cell migration, invasion, proliferation, and angiogenesis.

- C-Met amplification is associated with a poor prognosis in NSCLC and resistance to EGFR TKI.

- **ARQ197** is a non-ATP competitive inhibitor of c-Met, works by stabilizing the inactive conformation of c-Met.

- ARQ197 + EGFR TKI has heightened anti-tumor effect in vivo compared to either single agent alone.
ARQ 197-209 Phase II Randomized double-blind placebo controlled trial

**NSCLC**
- Inoperable locally adv/ metastatic dz.
- ≥1 prior chemo (no prior EGFR TKI)

**Endpoints**
- 1º PFS
- 2º ORR, OS
- Subset analyses
- Crossover: ORR

- 33 sites in 6 countries
- Study accrual over 11 months (10/08-9/09)
- Randomization stratified by prognostic factors incl. sex, age, smoking, histology, performance status, prior therapy and best response, and geography (U.S. vs. ex-U.S.)

**Treatments**
- Erlotinib 150 mg PO QD + ARQ 197 360 mg PO BID 28-day cycle
- Erlotinib 150 mg PO QD + Placebo 28-day cycle
After adjusting for prognostic factors, the PFS was improved with the combination ARQ197 + erlotinib ($p<0.005$)
Both PFS and OS benefit were seen (after adjusting for prognostic factors) in the non-SCC NSCLC subgroup with the combination ARQ197 + erlotinib (p<0.005)
**PFS in histologic and molecular subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Median PFS (95% CI, weeks)</th>
<th>Unadjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARQ197/erlotinib</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous Cell</td>
<td>26 / 24</td>
<td>13.7 (8.0–18.1)</td>
<td>8.4 (7.9–21.0)</td>
</tr>
<tr>
<td>Non-Squamous Cell</td>
<td>58 / 59</td>
<td>18.9 (15.0–31.1)</td>
<td>9.7 (8.0–16.0)</td>
</tr>
<tr>
<td>c-MET FISH &gt;4</td>
<td>19 / 18</td>
<td>15.4 (8.1–24.4)</td>
<td>15.3 (7.1–16.3)</td>
</tr>
<tr>
<td>c-MET FISH &gt;5</td>
<td>8 / 11</td>
<td>24.1 (16.3–NE)</td>
<td>15.6 (7.9–31.4)</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>6 / 11</td>
<td>24.1 (8.0–32.1)</td>
<td>21.0 (8.1–36.0)</td>
</tr>
<tr>
<td>EGFR wt</td>
<td>51 / 48</td>
<td>13.7 (8.1–18.1)</td>
<td>8.1 (7.9–9.9)</td>
</tr>
<tr>
<td><strong>KRAS mutant</strong></td>
<td>10 / 5</td>
<td>9.7 (7.9–NE)</td>
<td>4.3 (1.1–8.0)</td>
</tr>
<tr>
<td><strong>KRAS wt</strong></td>
<td>49 / 45</td>
<td>15.4 (8.1–18.1)</td>
<td>9.9 (8.0–16.0)</td>
</tr>
</tbody>
</table>

KRAS mutant patients appear to have PFS benefit with the combination of ARQ197 and erlotinib. HR = 0.18
Abstract 7511: Nab-paclitaxel

- Cremophor (polyoxyethylated castor oil) may decrease efficacy and lead to hypersensitivity and neuropathy.

- Nanoparticle bound (nab) paclitaxel may be more efficacious than solvent-based paclitaxel in metastatic breast cancer.

- nab-paclitaxel leverages the gp60/caveolin-1/SPARC transcytosis pathway to increase intratumoral drug concentrations.

Gradishar et al. 2005, Desai et al. 2008
Abstract 7511 Phase III Trial *nab*-paclitaxel-carbo vs carbo-paclitaxel

**Chemo-naïve NSCLC**
- Stage IIIb/IV
- ECOG PS 0-1
- Baseline peripheral neuropathy ≥ grade 2
- N=1050

**Randomized**

- Nab-paclitaxel 100 mg/m² d1,8,15
  - Carbo AUC 6 d1
  - No premeds

- Paclitaxel 200 mg/m² d1
  - Carbo AUC 6 d1
  - Premeds: dex, antihistamines

Stratification factors: stage IIIb vs IV, age <70 or ≥ 70, gender, histology (SCC vs non-SCC), geography

Primary endpoint: ORR
Secondary endpoint: PFS, OS, DCR, safety (NCI CTCAE v3)
Nab-paclitaxel with carboplatin had higher response rates than carbo-paclitaxel for all histologic subtypes.
This improvement in RR from *nab*-paclitaxel with carboplatin was especially seen in SCC patients (41% vs. 24%, p<0.001)
Nab-paclitaxel-carboplatin had a higher response rate than carbo-paclitaxel (33% vs 25%, p<0.001); especially in the SCC population (41% vs 24%, p<0.001)

Nab-paclitaxel –carboplatin had more anemia and thrombocytopenia, but less sensory neuropathy, myalgia and neutropenia when compared to carbo-paclitaxel.
Tsao Conclusions: Histology and Molecular Profiling

NSCLC PATIENT

Non-SCC

- Neuroendocrine
  - Platinum-etoposide
    - EGFR TKI 1st or 2nd line Maintenance (IPASS, BR.21, SATURN)

Non-SCC

- Adenocarcinoma
  - EGFR mutation
    - EML 4 ALK
      - crizotinib
  - EGFR wild-type

SCC

- Avoid pemetrexed or bevacizumab
- Consider 2nd line EGFR TKI or maintenance erlotinib (BR.21, SATURN)

Platinum-doublet-bevacizumab
Platinum-pemetrexed ± bevacizumab
Non-platinum or platinum based doublet
Switch Maintenance: pemetrexed, erlotinib (E4599, AVAiL, Pointbreak, SATURN, JMEN)