Tailoring Treatment Plans to Improve Outcomes in the Management of NSCLC

Martin J. Edelman, MD
Educational Objectives

- Review efficacy and safety data for current and emerging targeted agents and chemotherapy regimens in the treatment of advanced NSCLC
- Analyze the emerging use of histological subtypes and molecular biomarkers for guiding appropriate treatment selection in patients with advanced NSCLC
- Discuss ASCO and NCCN's latest guidelines on the treatment of advanced NSCLC
- Describe the importance of molecular testing and sampling in all patients with advanced NSCLC
- Identify methods to ensure adequate tissue sampling and accurate pathology assessment in patients who are suspected to have advanced NSCLC

Lung Cancer: Incidence and Mortality

- New cases in 2013: 228,190
  - 40% with stage IV disease at presentation (~90,000)
- ~160,000 deaths in 2012, comparable to prostate, pancreas, breast, and colon cancer combined
- 5-yr relative survival rate: 3.7% for patients with distant-stage disease
Lung Cancer: Clinical Presentation

- **Common presentations:** cough, fatigue, dyspnea, and weight loss (> 10 lbs)
- **Often metastasizes to** adrenal glands, liver, brain, bones
  - Site of involvement can determine other symptoms
- **Metastatic disease indicators may be found on exam**
  - Lymphadenopathy (> 1 cm)
  - Bone tenderness
  - Hoarseness
  - Facial and arm swelling
  - Hepatomegaly
  - Neurologic symptoms
Lung Cancer Screening

- NLST demonstrated 20% reduction in risk of lung cancer mortality with low dose CT.
- NNT = 300 (superior to mammography)
- Recommended by ASCO, ACCP
- Cautions:
  - Experienced institutions
  - Results appropriate for population screened
  - Very high false positive rate

Lung Cancer: Evaluation

- Suspected disease evaluated using chest radiography, CT, or PET imaging to evaluate a lesion
- Diagnosis confirmed through pathologic evaluation
- Pathologic assessment after resection provides information on **tumor histology and molecular abnormalities** that may be useful in selecting therapy
- Advanced NSCLC
  - Metastatic disease
  - Patients with stage IIIB often considered to have advanced NSCLC and not surgical candidates, but tumor has not yet metastasized (ie, M0)
Lung Cancer Staging

Stage at Diagnosis

Stage Directed NSCLC Management: The Basics

- Stage I,II
  - surgery in operable patients
  - Radiotherapy (SBRT, standard fx): inoperable or borderline patients
  - Adjuvant chemotherapy (all N1, N2, T>4 cm)
- Stage III
  - Combined modality therapy
- Stage IV
  - Systemic therapy (chemotherapy, “targeted” etc)
  - Palliative XRT, surgical procedures as appropriate
Adjuvant (Post-operative) Chemotherapy

- Absolute improvement in 5 yr OS = 15% (69% vs 54%)
  Winton et al. NEJM 2005

- Absolute improvement in 5 yr OS = 11% (67% vs 56%); benefit persists at 9+ yrs
  Vincent, Butts et al, 2009

- HR 0.69
- 5 yr: 69% vs 54%
- MST 94 m vs 73 m

Stage III Disease

- Superior outcome (cure rate) for chemotherapy + radiotherapy vs. radiotherapy alone in locally advanced disease. (Dillman, NEJM, JNCI)
- Concurrent chemo/XRT improves outcome.
- Ongoing controversy regarding optimal chemotherapy, role of surgery
ADVANCED DISEASE: OVERVIEW

“Unfortunately, there’s no cure—there’s not even a race for a cure.”
NSCLC: Prognostic Factors

- Factors correlated with adverse prognosis
  - Presence of pulmonary symptoms
  - Large tumor size (>3 cm)
  - Nonsquamous histology
  - Metastases to multiple lymph nodes within a TNM-defined nodal station
  - Vascular invasion
- For patients with inoperable disease, prognosis is adversely affected by poor performance score, weight loss of more than 10%
- Advanced age alone has not been shown to influence response or survival with therapy

Why Treat?

- Meta-analysis of 8 trials (778 patients) using cisplatin-based chemotherapy\(^1\)
  - Absolute improvement in survival of 10% at 1 yr\(^1\)
  - Median survival, BSC vs chemo: 4 vs 8+ mos, respectively
- QOL uniformly superior with chemotherapy.

Curable Stage IV NSCLC

- Some patients with metastatic NSCLC are curable.
- Solitary metastatic disease
  - Brain
  - Adrenal
  - Bone
- Local therapy (surgery, SABR, conventional XRT) +/- chemotherapy.
- Needs extensive metastatic w/u before therapy

Considerations for First-line Therapy

- Performance score
- Age
- Organ function, nutritional status
- Histology
- Molecular variables
- Other
  - CNS metastases: who goes first?
  - Critical local issues
### First-line Therapy: 2005

<table>
<thead>
<tr>
<th>Platinum agent (select one)</th>
<th>“1990s agent” (select one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cisplatin</td>
<td>• Vinorelbine</td>
</tr>
<tr>
<td>• Carboplatin</td>
<td>• Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>• Docetaxel</td>
</tr>
<tr>
<td></td>
<td>• Gemcitabine</td>
</tr>
</tbody>
</table>

### First-line Therapy: 2013

<table>
<thead>
<tr>
<th>Column A</th>
<th>Column B</th>
<th>Column C</th>
<th>Column D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Vinorelbine</td>
<td>Bevacizumab</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Gemcitabine</td>
<td>Cetuximab?</td>
<td>Crizotinib</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pemetrexed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nab-paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Early Palliative Therapy in Advanced NSCLC: Randomized Study**

- Early palliative care + standard oncologic care vs standard oncologic care alone (N = 151)
- Early palliative care arm
  - Improved median survival
  - Better QoL ($P = 0.03$)
  - Fewer depressive symptoms (16% vs 38%; $P = .01$)


**Chemotherapy and Early Palliative Care**

Chemotherapy And Hospice Within 60 Days of Death


2013: First-line Treatment of Advanced/Metastatic NSCLC

<table>
<thead>
<tr>
<th>Mutational analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutation</td>
</tr>
<tr>
<td>KRAS or no “actionable” mutation: 80%</td>
</tr>
<tr>
<td>EGFR-TKI (Erlotinib, Afatinib)</td>
</tr>
<tr>
<td>10%</td>
</tr>
<tr>
<td>90%</td>
</tr>
<tr>
<td>Other mutations 5% to 10%</td>
</tr>
<tr>
<td>EML4/ALK, ROS1, RET</td>
</tr>
<tr>
<td>Crizotinib, Vandetanib, Cabozantinib</td>
</tr>
<tr>
<td>Platinum + paclitaxel, docetaxel, gemcitabine or vinorelbine nab-paclitaxel (?) cetuximab</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Nonsquamous</td>
</tr>
<tr>
<td>Squamous</td>
</tr>
<tr>
<td>No hemoptysis</td>
</tr>
<tr>
<td>Carboplatin + paclitaxel + bevacizumab or platinum + pemetrexed</td>
</tr>
<tr>
<td>Any hemoptysis</td>
</tr>
<tr>
<td>Platinum + pemetrexed</td>
</tr>
</tbody>
</table>

Table 3: Chemotherapy Use and Hospice Services at End of Life in 128

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chemotherapy Use</th>
<th>Early Radiation Use</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any within 60 days of death</td>
<td>47 of 67 (70.1)</td>
<td>32 of 61 (52.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Any within 14 days of death</td>
<td>15 of 67 (23.9)</td>
<td>9 of 66 (13.8)</td>
<td>.16</td>
</tr>
</tbody>
</table>

Intensive:

- Median: 17.0
- Range: 3.0-54.0
- Mean: 40.0

- Median: 8.0
- Range: 0.0-50.0
- Mean: 45.0

Non-Intensive:

- Median: 2.5
- Range: 0.0-30.0
- Mean: 4.0

- Median: 0.0
- Range: 0.0-15.0
- Mean: 0.0

NOTE: Not all denominators sum to 128 because of incomplete or missing data for certain participants. Bold font indicates statistical significance. Abbreviation: SD, standard deviation.
NCCN Guidelines

HISTOLOGY

- Adenocarcinoma
- Large Cell
- NSCLC NOS

Establish histology: subtype?

Squamous non-carcinoma

EGFR mutation and ALK testing are not routinely recommended.

EGFR mutation: positive

EGFR mutation: negative, ALK-negative, or unknown

- EGFR mutation: positive
  - ALK-positive
    - CIOZOND
    - Progression
    - See Second-line Therapy (page 1244)
  - ALK-negative
    - MAY add experimental cytotoxic chemotherapy (Category 2c)
    - Progression
    - See Second-line Therapy (page 1244)
  - EGFR mutation: unknown or rare
    - See First-Line Therapy (page 1242)

- EGFR mutation: negative, ALK-negative, or unknown
  - See First-Line Therapy (page 1242)
Complexities of Lung Cancer Pathogenesis Result in Diverse Histologic Subtypes

- SCC (~ 25%)
- SCLC (~ 15%)
- LPA (formerly BAC) (~ 5% to 10%)
- Adenocarcinoma (~ 45%)
- Large Cell (~ 5% to 10%)
- NOS (~ 10% to 30%)


Pathologist Agreement for Squamous vs Nonsquamous Histology

- Kappa (all pathologists) = 0.55 (95% CI: 0.53-0.58; P < .001)
- Kappa (expert pathologists) = 0.64
- Kappa (community pathologists) = 0.41

W/U of Lung Cancer Bx Specimens

TTF-1 can be neg in adeno

‘Molecular Biopsy’

• Biopsy/procedure for the specific purpose of molecular testing
• Multiple interdisciplinary communication issues
• Requires establishing:
  – Ordering procedure
  – Tissue acquisition guidelines (2 cores + FNA)
  – Tissue routing
  – Processing and handling procedure
  – Identification of molecular priority for pathologist
  – Routing to molecular studies
Special Tissue Handling for Maximizing Molecular Testing

- Typical Process
  - 1 Block
  - Biopsies
  - Top view
  - Side view

- 1. Aggressive Facing
- 2. Extensive IHC Workup
- 3. Potential Re-facing
- 4. Tissue Wastage

- Minimal to No Tissue for Molecular Testing

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Special Tissue Handling for Maximizing Molecular Testing

- Molecular
- Only Process
  - Each biopsy is put into its own block
  - Top view

- 1. Shallow Facing
- 2. Initial Pre-cut Slides
- 3. No to minimal IHC

- FISH
- Mutation Analysis

- A & B
  - A
  - B

- Longer cores cut in half to further increase the number of potentially usable blocks
- FNA made into a cell block and handled similarly
ECOG E4599: Bev + Carbo and Paclitaxel in Metastatic Nonsquamous NSCLC

- Median OS, BPC vs PC: 12.3 vs 10.3, respectively (HR: 0.79; P = .003)
- Median PFS: 6.2 vs 4.5 mos (HR: 0.66; P < .001)
- Response rates: 35% vs 15% (P < .001)


AVAiL: NO Difference in Overall Survival

- Reck et al. Ann Oncol 21: 1804, 2010 published 3 years after the initial presentation of PFS results
VEGFR Inhibitors

- Common adverse effects
  - Hypertension; renal vascular injury, manifested by proteinuria and thrombotic microangiopathy; congestive heart failure
- Management strategies
  - Risk assessment and monitoring
  - Symptom treatment
  - Dose reductions and treatment cessation


Efficacy of Pemetrexed

Overall Population

Non-Squamous
**Pemetrexed maintenance: Overall Survival by Histology**

**Non-squamous (n=481)**
- HR=0.70 (95% CI: 0.56-0.88)
- \( P = 0.002 \)
- Pemetrexed 15.5 mos
- Placebo 10.3 mos

**Squamous (n=182)**
- HR=1.07 (95% CI: 0.49-1.73)
- \( P = 0.678 \)
- Pemetrexed 9.9 mos
- Placebo 10.8 mos

**Survival Probability**

**Time (months)**

**Belani, ASCO 2009**

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**CA031 Trial: Carboplatin + Nab-Paclitaxel vs Sb-Paclitaxel in Advanced NSCLC**

- Randomized, safety and efficacy phase III trial

**Patients randomly assigned 1:1 (N = 1052)**

- nab-Paclitaxel + Carboplatin (n = 521; 100%)
- sb-Paclitaxel + Carboplatin (n = 531; 100%)

**Treated population**
- nab-Paclitaxel + Carboplatin (n = 514; 99%)
- sb-Paclitaxel + Carboplatin (n = 524; 99%)

**Excluded**
- (n = 7; 1%)
### CA031 Trial: Results

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>Squamous Subset</th>
<th>Nonsquamous Subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab-PC</td>
<td>33 (n = 521)</td>
<td>41 (n = 229)</td>
<td>26 (n = 292)</td>
</tr>
<tr>
<td>sb-PC</td>
<td>25 (n = 531)</td>
<td>24 (n = 221)</td>
<td>25 (n = 310)</td>
</tr>
<tr>
<td>P value</td>
<td>.005</td>
<td>&lt;.001</td>
<td>.808</td>
</tr>
</tbody>
</table>

- nab-PC associated with less neuropathy vs sb-PC
- No statistically significant differences in PFS (median: 6.3 vs 5.8 mos; \( P = .214 \)) or OS (median: 12.1 vs 11.2 mos; \( P = .271 \))

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**THE ELDERLY**
Did these results apply to the elderly (>70) and is that important?

- Median age on trials is about 62
- The majority of patients with advanced NSCLC are >70 years of age.
- Physiological differences in drug metabolism, coexisting morbidities render results of trials in younger patients of unclear applicability.

Treatment and Outcomes of Advanced NSCLC in the Elderly: SEER/Medicare Data base

## Treatment of the Elderly and PS = 2

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>RR</th>
<th>PFS</th>
<th>MST</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB Paclitaxel CBDCA/Pac</td>
<td>78</td>
<td>21</td>
<td>nr</td>
<td>5.8</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>36</td>
<td>nr</td>
<td>8.0</td>
<td>35</td>
</tr>
<tr>
<td>IFCT Vin or Gem CBDCA/Pac</td>
<td>226</td>
<td>11</td>
<td>3.0</td>
<td>6.2</td>
<td>26.9</td>
</tr>
<tr>
<td></td>
<td>225</td>
<td>29*</td>
<td>6.1*</td>
<td>10.3*</td>
<td>43.1*</td>
</tr>
</tbody>
</table>

### PS = 2

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>RR</th>
<th>PFS</th>
<th>MST</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB Paclitaxel CBDCA/Pac</td>
<td>50</td>
<td>10</td>
<td>nr</td>
<td>2.4</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>24</td>
<td>nr</td>
<td>4.7</td>
<td>18</td>
</tr>
<tr>
<td>Brazil Pemetrexed CBDCA/Pem</td>
<td>102</td>
<td>10</td>
<td>3.0</td>
<td>5.6</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>103</td>
<td>24*</td>
<td>5.9*</td>
<td>9.1*</td>
<td>39*</td>
</tr>
</tbody>
</table>

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

- Doublet chemotherapy superior to single-agent chemotherapy in elderly patients with advanced NSCLC

![Graph showing OS (%) vs Duration (Mos) for doublet and monotherapy with statistical significance.](image)

- Patients aged 70-89 yrs, w/ stage III-IV NSCLC and PS 0-2 (N = 451)

- Quoix, Proc ASCO 2010
- Lilenbaum, Proc ASCO 2012

DRIVER MUTATIONS

Lung Cancer is Genetically Very Complex

- Carcinogen associated epithelial cancers (colon, lung, melanoma) are exceedingly complex.
First-line Treatment With EGFR TKIs vs Chemotherapy in EGFR-Mutated Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Median PFS (mos)</th>
<th>Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maemondo[2]</td>
<td>Gefitinib vs carboplatin/ paclitaxel</td>
<td>230</td>
<td>10.8 vs 5.4</td>
<td>30.5 vs 23.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>($P &lt; .001$)</td>
<td>($P = .31$)</td>
</tr>
<tr>
<td>Mitsudomi[2,3]</td>
<td>Gefitinib vs cisplatin/ docetaxel</td>
<td>177</td>
<td>9.2 vs 6.3</td>
<td>36 vs 39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>($P &lt; .0001$)</td>
<td>(HR: 1.19)</td>
</tr>
<tr>
<td>OPTIMAL[4,5]</td>
<td>Erlotinib vs carboplatin/ gemcitabine</td>
<td>165</td>
<td>13.1 vs 4.6</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>($P &lt; .0001$)</td>
<td></td>
</tr>
<tr>
<td>EURTAC[6]</td>
<td>Erlotinib vs platinum-based chemotherapy</td>
<td>174</td>
<td>9.7 vs 5.2</td>
<td>19.3 vs 19.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>($P &lt; .0001$)</td>
<td>($P = .87$)</td>
</tr>
<tr>
<td>LUX-Lung 3[7]</td>
<td>Afatanib vs CDDP/pemetrexed</td>
<td>345</td>
<td>11.1 vs 6.9</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>($P &lt; .0004$)</td>
<td></td>
</tr>
</tbody>
</table>


TAILOR Study Design

- Advanced/recurrent
- Previous platinum based doublet
- EGFR wild-type
- KRAS determined
- ECOG PS 0-2

- STRATIFICATION
  - minimization approach
  - centre
  - recurrent/progressed
  - type of prior chemotherapy regimen (pem vs gem vs vnb)
  - ECOG-PS (0-1 vs 2)
  - adequacy of tissue sample (optimal vs suboptimal)

- CROSS OVER NOT ALLOWED

ERLOTINIB
- 150 mg po, daily

DOCETAXEL
- 75 mg/m² iv day 1,21 OR 35 mg/m² iv day 1,8,15,28

- LBA 7501, Proc ASCO 2012
**PFS [ITT]**

- HR 0.69 (95%CI 0.52-0.93)  p=0.014

<table>
<thead>
<tr>
<th></th>
<th>Median mos.</th>
<th>6-mos PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>3.4</td>
<td>28.9%</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2.4</td>
<td>16.9%</td>
</tr>
</tbody>
</table>

**Patients at risk**

| Docetaxel | 110 | 95 | 74 | 43 | 37 | 30 | 22 | 19 |
| Erlotinib | 109 | 90 | 67 | 33 | 24 | 18 | 16 | 11 |

**Months**

-/docetaxel/ vs. /erlotinib/

**Crizotinib: Molecular Success Story**

- Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer
- Rapid timeline from compound identification, target discovery, and clinical results
- First clinical responses observed in ALK+ tumors
- FDA approval
- Phase 3 lung cancer trial initiated
- 2005-2012 timeline

**References**

PROFILE 1007: Crizotinib vs Chemotherapy as Second-Line Therapy in ALK+ NSCLC

Key entry criteria:
- ALK+ by central FISH testing
- Stage III/IV NSCLC
- 1 prior chemotherapy (platinum-based)
- ECOG PS 0-2
- Measurable disease
- Treated brain metastases allowed

Endpoints
- Primary
  - PFS (RECIST 1.1, independent radiology review)
- Secondary
  - ORR, DCR, DR
  - OS
  - Safety
  - Patient-reported outcomes (EORTC QLQ-C30, LC13)

Study Design
N = 318

PROFILE 1007: Primary Endpoint—PFS by Independent Radiologic Review (ITT Population)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Crizotinib  (n = 173)</th>
<th>Chemotherapy (n = 174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>127 (73)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>7.7</td>
<td>3.0</td>
</tr>
<tr>
<td>HR (95%) CI</td>
<td>0.49 (0.37-0.64)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FISH = fluorescense in situ hybridization; ORR = overall response rate; DCR = disease control rate; DR = duration of response. ALK status determined using standard ALK break-apart FISH assay. Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no). Shaw AT et al. ESMO 2012 Annual Meeting. Abstract LBA-1.
**ROS1 Rearrangements in NSCLC: Clinical Implications**

- **ROS1 rearrangements**
  - Similar phenotype to other mutations: scant or never smokers, adenocarcinoma histology, etc
  - Responsive to crizotinib

Response of a ROS1-positive patient with advanced NSCLC to crizotinib. CT scans of the chest were obtained (A and C) at baseline and (B and D) after 12 wks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.

__K-Ras and Lung Cancer__

- **RAS mutations** occur in 15-20% NSCLC, with >90% involving **KRAS**
- Associated with smoking and adenocarcinoma
- In 1990, KRAS mutation was first reported as a prognostic marker in lung adenocarcinoma

![K-Ras and Lung Cancer Diagram](image-url)
Predictive Effect for Cetuximab & Panitumumab by KRAS Allele in CRC


Prognostic Effect of KRAS Codon 12 &13 Mutations on OS
(Obs. Arm)

- Multivariable analysis
- Variable
- Deaths/Pts
- HR [95% CI]

- KRAS WT
308 / 611
1

- Codon 12 mut
62 / 130
1.04 [0.77-1.40]

- Codon 13 mut
7 / 15
1.01 [0.47-2.17]

p=0.96

logrank : p = 0.83
Treatment Effect in Patients With KRAS mutations: Codon 12 & 13

- Codon 12 mutation
- Codon 13 mutation

![Graphs showing treatment effect](Image)

- Global Interaction Specific KRAS Mutation x Treatment p=0.002

Targeting K-ras Mutant Disease

- K-ras mutations are a difficult target as the mutation does not directly alter the ATP binding site, but rather the stability of the ras-GTP complex.
- Targeting downstream is a therapeutic strategy.
- Selumetinib (AZD6244, ARRY-142866) inhibits MEK 1,2, downstream of Ras.
- 422 patients screened.
- Toxicity
  - 15.9% febrile neutropenia (vs. 0%)

<table>
<thead>
<tr>
<th>Arm</th>
<th>n</th>
<th>RR(%)</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doc</td>
<td>43</td>
<td>0</td>
<td>2.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Doc+ S</td>
<td>44</td>
<td>37</td>
<td>5.3 (p=.014)</td>
<td>9.4 (p=.21)</td>
</tr>
</tbody>
</table>

[Janne, Proc ASCO 2012 #7503]
Further Developments in other mutation subsets Adenocarcinoma

- ALK
  - Resistance mechanisms
  - New alk inhibitors with activity
- ROS (PASCO 2012#7508)
  - Similar to alk
  - Responds to crizotinib
  - N=14, RR = 54%, median duration of response 13 wks
- Ret (PASCO 2012 #7510)
  - In vitro response to vandetanib, ? Other anti-vegfr tki’s


SWOG 0023

- Definitive TX
  - Reg #1
    - Projected 840 pts
  - CDDP 50 mg/2
    - d 1,8,29,36
  - VP-16 50 mg/m2
    - d1-5, 29-33
  - XRT 1.8- 2 GY/d
    - 61 Gy
  - Eligible: 571 pts

- Consolidation
  - Reg #2
    - DOCETAXEL
      - 75 mg/m2
      - x 3 cycles
    - PLACEBO
  - 642 pts (80%)

- Maintenance
  - Reg #3
    - GEFTINIB
      - 500 mg/day
    - 250 mg/day
      - (5-1-03)
    - PLACEBO
  - 243 pts (43%)
S0023: Overall Survival

- 100% Survival
- 20% Survival
- 40% Survival
- 60% Survival
- 80% Survival
- 100% Survival

- Gefitinib
- Placebo

- Median Events in Months
- Median FU time:
  - 27 months

- Median in Months
- Months After RANDOMIZATION

- N: 118
- N: 125
- Events: 71
- Events: 54
- P = .01

- 1 YR OS: 73%
- 2 YR OS: 46%
- 3 YR OS: 59%
- 5 YR OS: 81%

- Squamous Carcinoma

- 178 tumor pairs evaluated.
  - Genetically complex – nearly 100%
  - P53 abnormalities are nearly universal.

- Govindan, Proc ASCO 2012 abstract #7006
Therapeutic implications

- Many of the genetic abnormalities identified are associated with therapeutics currently in development
- However, none are “actionable”, i.e. you can’t write a prescription.

New and Interesting Side Effects

- Rash
- Hypertension, proteinuria, RPLS
- Esophageal perforation (with XRT)
- As well as plenty of good, old fashioned stomatitis, myelosuppression etc.
## Duration and Maintenance

### Duration of First-line Therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>OS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP x 4 vs CP</td>
<td>230</td>
<td>6.6 mos</td>
<td>Increased neuropathy</td>
</tr>
<tr>
<td>indefinite¹</td>
<td></td>
<td>8.5 mos</td>
<td>(19% vs 48%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P = .63)</td>
<td></td>
</tr>
<tr>
<td>CV x 3 vs CV x 6²</td>
<td>300</td>
<td>28 wks</td>
<td>Increased anemia, transfusions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32 wks</td>
<td>(P = .58)</td>
</tr>
</tbody>
</table>

Switch vs Continuation Maintenance Therapy

**Switch**
- 4 courses of platinum + Drug A
- PS 0-1 → Randomize
- Drug B
- Observation
- PD

**Continuation**
- 4 courses of platinum + Drug A
- SD, or R PS 0-1 → Randomize
- Drug A
- Observation
- PD
- Off study

Switch Maintenance Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Switch Agent</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias et al[1]</td>
<td>Immediate docetaxel</td>
<td>5.7</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>Delayed docetaxel</td>
<td>2.7</td>
<td>9.7</td>
</tr>
<tr>
<td>JMEN[2]</td>
<td>Pemetrexed</td>
<td>4.3</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2.6</td>
<td>10.6</td>
</tr>
<tr>
<td>SATURN[3]</td>
<td>Erlotinib</td>
<td>2.8</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2.6</td>
<td>11.0</td>
</tr>
<tr>
<td>ATLAS[4,5]</td>
<td>Erlotinib + bevacinumbab</td>
<td>4.8</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td>Placebo + bevacinumbab</td>
<td>3.8</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2.6</td>
<td>16.9</td>
</tr>
</tbody>
</table>

Continuation Maintenance Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Continuation Agent</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belani et al[^1]</td>
<td>Gemcitabine</td>
<td>7.4</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Best supportive care</td>
<td>7.7</td>
<td>9.3</td>
</tr>
<tr>
<td>IFCT[^2]</td>
<td>Gemcitabine</td>
<td>3.8</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>2.9</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>Best supportive care</td>
<td>1.9</td>
<td>10.8</td>
</tr>
<tr>
<td>PARAMOUNT[^3]</td>
<td>Pemetrexed</td>
<td>4.1</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>

Positives and Negatives of Maintenance Trials

- **Positives**
  - OS positive in sequential and continuation studies
  - Erlotinib and pemetrexed approved for this indication

- **Negatives**
  - Only 4 (not 6) cycles of platinum-based therapy
  - Treatment of control arm not mandated
    - Substantial numbers of patients not crossed over or treated with appropriate agents
  - Unclear who is likely to benefit
    - Responding vs nonresponding patients
  - Considerable cost

[^1]: Belani CP, et al. 2010 ASCO. Abstract 7506.
Second-line Treatment

Considerations for Second-line Therapy

- Previous therapy
  - Agents
  - Time elapsed
  - Indication
    - Metastatic disease
    - Adjuvant
    - Multimodality

- ECOG performance score, age
- Organ function
- Histology
- Molecular variables
Second-line Therapy

- ECOG performance score 0-2
  - Docetaxel
  - Pemetrexed
  - Erlotinib (also for third line)
  - Platinum doublet ± bevacizumab (if erlotinib or crizotinib given as first-line therapy AND nonsquamous subtype)

- ECOG performance score 3-4
  - Erlotinib
  - Best supportive care only

### Second-Line Therapy Trials

<table>
<thead>
<tr>
<th>Agent(s) Studied</th>
<th>Endpoints</th>
<th>Main Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel vs BSC (N = 104)(^1)</td>
<td>• Primary: OS</td>
<td>• OS: 7.0 vs 4.6 mos ((P = .047))</td>
</tr>
<tr>
<td></td>
<td>• Secondary: TTP, OTR, DOR, QoL</td>
<td>• TTP: 10.6 vs 6.7 wks ((P = .001))</td>
</tr>
<tr>
<td>Docetaxel (D75/D100) vs vinorelbine/ifosfamide (N = 373)(^2)</td>
<td>• Primary: survival (OS, 1-yr survival, PFS at 26 wks)</td>
<td>• OS: 5.5 (D100) vs 5.6 ((P = NS))</td>
</tr>
<tr>
<td></td>
<td>• Secondary: ORR, DOR, TTP, toxicity, QoL</td>
<td>• 1-yr survival: 32% (D75) vs 19% ((P = .025))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PFS at 26 wks: 19% (D100) vs 8% ((P = .005))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ORR: 10.8% (D100) vs 0.8% ((P = .001))</td>
</tr>
</tbody>
</table>

### Summary of Second-line Therapy Trials

<table>
<thead>
<tr>
<th>Agent(s) Studied</th>
<th>Endpoints</th>
<th>Main Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed vs docetaxel (N = 571)</td>
<td>• Primary: survival (MPFS, MST, 1-yr survival)</td>
<td>• MPFS: 2.9 mos</td>
</tr>
<tr>
<td></td>
<td>• Secondary: toxicity, ORR, PFS, TPD, TTF, TTR, DOR, QoL</td>
<td>• MST: 8.3 vs 7.9 mos (P = NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 1-yr survival: 29.7%</td>
</tr>
<tr>
<td>Erlotinib vs placebo (N = 731)</td>
<td>• Primary: OS</td>
<td>• PFS: 2.2 vs 1.8 mos (P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td>• Secondary: PFS, ORR, DOR, toxicity, QoL</td>
<td>• OS: 6.7 vs 4.7 mos (P &lt; .001); ORR: 8.9% vs &lt; 1.0% (P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MDOR: 7.9 vs 3.7 mos</td>
</tr>
</tbody>
</table>

#### No combination therapy has proven benefit over single agents

#### Numerous factors involved in choice of treatment
- Previous therapy
- Histology
- Performance status
- Organ function

#### EGFR TKIs are an option comparable to chemotherapy
- Less toxic; better QoL
- Survival similar across all subgroups
- Considerable cross-over on all studies

#### In many cases, the question is not whether a patient will receive a drug, but when and in what sequence
IMMUNOTHERAPY: PD-1 AND CTLA4

What is PD-1?

- Involved in T cell regulation
- Expressed by activated memory and regulatory T cell
- Down regulates T cell by binding to PD-L1/L2
Clinical Activity of BMS-936558 in NSCLC Patients

- ORR was assessed using modified RECIST v1.0
- 3 NSCLC patients had a persistent reduction in baseline target lesions in the presence of new lesions but were not classified as responders for the ORR

### Activity in NSCLC: 10 mg/kg

- History: 60 y/o diagnosed with Large cell NSCLC in 2002
- Multiple prior chemotherapy regimens
- Prior radiation

**Screening - 12/17/09**

**Cycle 2 - 4/26/10**

**J Brahmer, NEJM 2012**

<table>
<thead>
<tr>
<th>Pop</th>
<th>Dose (mg/kg)</th>
<th>Pts n</th>
<th>ORR n (%)</th>
<th>Duration of Response (mo)</th>
<th>SD ≥24 wk n (%)</th>
<th>PFSR at 24 wk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL NSCLC</td>
<td>1-10</td>
<td>76</td>
<td>14 (18)</td>
<td>1.9+ to 30.8+</td>
<td>5 (7)</td>
<td>26</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1</td>
<td>18</td>
<td>1 (6)</td>
<td>9.2+</td>
<td>1 (6)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>19</td>
<td>6 (32)</td>
<td>1.9+ to 30.8+</td>
<td>2 (11)</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>39</td>
<td>7 (18)</td>
<td>3.7 to 14.8+</td>
<td>2 (5)</td>
<td>24</td>
</tr>
</tbody>
</table>
Comments

• Anti-PD-1 and anti PD-L1 are unique and likely to become validated targets.
• Significant questions
  - What will be the precise role? (refractory, in combination with chemotherapy, adjuvant etc).
  - Can this modality be combined with radiotherapy? (pneumonitis).

Conclusions

• Advanced NSCLC: A prevalent and deadly cancer
• First-line therapy: Several chemotherapy and targeted agents approved in recent years; choices driven by histology and/or mutational status (ie, EGFR and possibly others)
• Second-line therapy: Choices depend on ECOG scores, prior treatment, current organ function, tumor histology and molecular variables
• Special considerations: Important to consider patient age, initiating early palliative care, management of treatment-related side effects (eg, CINV, rash/cutaneous, cardiac)
• Future directions/ongoing needs: Many patients do not respond to or relapse on existing therapies; promising agents under investigation include monoclonal antibodies and small molecule inhibitors of EGFR and VEGFR pathways
for more information on lung cancer, keep smoking.

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