Maintenance Therapy in NSCLC

Ramaswamy Govindan M.D.
Director, Thoracic Medical Oncology
Alvin J Siteman Center at Washington University
School of Medicine, St Louis

Advanced NCLC

c 2008

- Four cycles of platinum based doublet therapy
- All platinum based doublets are equal
- No monotherapy with molecularly targeted agents
- No maintenance therapy

Semantics

- Maintenance therapy
- Continuation of therapy
- Consolidation therapy
- Early second line therapy
Duration of Chemotherapy for Advanced NSCLC

**PFS**

Soon, et al. JCO published on line, 2009

<table>
<thead>
<tr>
<th>Study Year Published</th>
<th>Extended duration</th>
<th>Standard duration</th>
<th>Hazard ratio (HR)</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cremes et al. (2002)</td>
<td>95</td>
<td>94</td>
<td>0.75</td>
<td>0.69-0.81</td>
<td>0.00001</td>
</tr>
<tr>
<td>Park et al. (2004)</td>
<td>94</td>
<td>93</td>
<td>0.75</td>
<td>0.69-0.81</td>
<td>0.00001</td>
</tr>
<tr>
<td>Brock et al. (2005)</td>
<td>93</td>
<td>92</td>
<td>0.75</td>
<td>0.69-0.81</td>
<td>0.00001</td>
</tr>
<tr>
<td>Fidias et al. (2009)</td>
<td>92</td>
<td>91</td>
<td>0.75</td>
<td>0.69-0.81</td>
<td>0.00001</td>
</tr>
<tr>
<td>Brown et al. (2000)</td>
<td>91</td>
<td>90</td>
<td>0.75</td>
<td>0.69-0.81</td>
<td>0.00001</td>
</tr>
<tr>
<td>Walker et al. (2002)</td>
<td>90</td>
<td>89</td>
<td>0.75</td>
<td>0.69-0.81</td>
<td>0.00001</td>
</tr>
<tr>
<td>Packer et al. (2005)</td>
<td>89</td>
<td>88</td>
<td>0.75</td>
<td>0.69-0.81</td>
<td>0.00001</td>
</tr>
<tr>
<td>Smith et al. (2009)</td>
<td>88</td>
<td>87</td>
<td>0.75</td>
<td>0.69-0.81</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

Total (95% CI): 1420/1,141

Test for univariate: z = 1.71; p = 0.09; CI = 0.69-0.81

**Phase III Trial: Immediate vs. Delayed Second-Line Docetaxel in Advanced NSCLC**

**Chemotherapy-naive stage IIIB/IV NSCLC**

Immediate Docetaxel
- 75 mg/m² day 1, every 21 days until PD or maximum 6 cycles
- N=153 (99%)

Delayed Docetaxel
- Best supportive care until PD, then 75 mg/m² day 1, every 21 days until PD or maximum 6 cycles
- N=154 (99%

Primary endpoint: OS measured from date of randomization until death
Secondary endpoints: tumor response rate, PFS, toxicity, quality of life

Fidias et al. JCO 2009

**Immediate vs. Delayed Second-Line Docetaxel in Advanced NSCLC: Results**

<table>
<thead>
<tr>
<th>Results</th>
<th>Immediate Docetaxel</th>
<th>Delayed Docetaxel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>12.3</td>
<td>9.7</td>
<td>0.083</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>5.7</td>
<td>2.7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Fidias et al. JCO 2009
Survival for Patients Actually Receiving Docetaxel on Immediate and Delayed Arms (Fidias)

- Immediate: MST 12.5 months
- Delayed: MST 12.5 months

N: 145 Immediate, 98 Delayed

Maintenance Pemetrexed Study Design

- Double-blind, Placebo-controlled, Multicenter, Phase III Trial
- Randomization: 2:1
- Primary Endpoint: PFS
- Secondary: OS, RR, DCR, Tox
- Treatment:
  - Pemetrexed 500 mg/m² (d1,q21d) + BSC (N=441)*
  - Placebo (d1, q21d) + BSC (N=222)*

- Randomization factors:
  - Stage IIIA/IV NSCLC
  - ECOG PS 0-1
  - 4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD
  - Best tumor response
  - Non-platinum drug
  - Brain mets

Progression-free Survival

- HR=0.60 (95% CI: 0.49–0.73)
- P <0.00001

- Progression-free Survival:
  - Pemetrexed 4.0 mos
  - Placebo 2.0 mos
Overall Survival (Intent-to-treat Population)

HR = 0.79 (95% CI: 0.65–0.95)  
\( P = 0.012 \)

Pemetrexed 13.4 mos
Placebo 10.6 mos

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

Systemic Post-study Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Pemetrexed (N=441)</th>
<th>Placebo (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with post-study therapy</td>
<td>52%</td>
<td>67%</td>
</tr>
<tr>
<td>Most common post-study therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>22%</td>
<td>29%</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>1%</td>
<td>19%</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>13%</td>
<td>17%</td>
</tr>
</tbody>
</table>

* Higher rate of follow-up treatment on the placebo arm
* Balanced selection of therapies between arms and low rate of crossover
SATURN—Phase III double-blind, placebo-controlled trial of Maintenance Erlotinib in Non-progressors following 1st Line Platinum-based Chemotherapy

Cappuzzo F et al. ASCO 2009, abstr #8001

1:1 Chemonaïve advanced NSCLC n=1,949 Non-PD n=889
4 cycles of first-line platinum doublet chemotherapy*

Placebo

PFS*: all patients (ITT)

Erlotinib Placebo
PFS at 12 wks (%) 53 40
PFS at 24 wks (%) 31 17
HR=0.71 (0.62–0.82)
Log-rank p<0.0001

OS*: all patients (ITT)

Erlotinib Placebo
HR=0.81 (0.70–0.95)
Log-rank p=0.0088

*PFS is measured from time of randomisation into the maintenance phase; assessments were every 6 weeks; ITT = intent-to-treat population

*OS is measured from time of randomisation into the maintenance phase; ITT = intent-to-treat population

Stratification factors:
- EGFR IHC (positive vs negative vs indeterminate)
- Stage (IIIB vs IV)
- ECOG PS (0 vs 1)
- CT regimen (cis/gem vs carb/doci vs others)
- Smoking history (current vs former vs never)
- Region

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

Secondary endpoints:
- OS in all patients and those with EGFR IHC+ tumours, OS and PFS in EGFR IHC+ tumours, biomarker analyses; safety; time to symptom progression; QoL

*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel carboplatin/paclitaxel; carboplatin/gemcitabine; docetaxel/gemcitabine; docetaxel/carboplatin; docetaxel/cisplatin;
### ATLAS – Phase III Randomized, Double-Blind, Placebo-controlled Trial of Maintenance Erlotinib in Non-Progressors Following 1st Line Platinum-based Chemotherapy

Miller V et al. ASCO 2009, abstr # 8002

**Study population**

- Chemo-naïve advanced NSCLC
- N=1,160

**Eligibility**

- Stage III**B/IV NSCLC
- ECOG performance status 0-1
- Stratification factors
  - Gender
  - Smoking history (never vs former/current)
- ECOG performance status (0 vs ≥1)
- Chemotherapy regimen

**Randomization**

- 1:1
- Non-PD (n=768 [80%])
- Bevacizumab (15mg/kg) + erlotinib (150mg) to PD

**Post progression therapy**

- Bevacizumab + erlotinib (n=370)
- Bevacizumab + placebo (n=373)

**Primary endpoint**

- PFS in all randomized pts

**Secondary endpoints**

- Overall survival
- Safety
- Exploratory endpoints
- Biomarker analyses (IHC, FISH, EGFR & K-Ras mutation)

**Eligibility**

- Former/current

**Chemotherapy regimen**

- 4 cycles of 1st-line chemotherapy + bevacizumab

**Outcomes**

- HR=0.722 (0.592-0.881)
- Log-rank P=0.0012

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### ATLAS: Progression-Free Survival

(ITT population, investigator assessment)

<table>
<thead>
<tr>
<th>Progression-Free Survival (months)</th>
<th>Bev + Placebo (n=373)</th>
<th>Bev + Erlotinib (n=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>178</td>
<td>178</td>
</tr>
<tr>
<td>2</td>
<td>142</td>
<td>142</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No. of patients at risk:

- Bev + Placebo 373
- Bev + Erlotinib 370

HR=0.722 (0.592-0.881)
Log-rank P=0.0012

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### Post-study treatment

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib (n=438)</th>
<th>Placebo (n=451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with at least one treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All classes</td>
<td>71</td>
<td>72</td>
</tr>
<tr>
<td>taxanes (including docetaxel)</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>antimetabolites (including pemetrexed)</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>antineoplastic agents</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>tyrosine-kinase inhibitors</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>platinum compounds</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>
Summary of maintenance

<table>
<thead>
<tr>
<th>First Author</th>
<th>Comparison</th>
<th>PFS (months)</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias</td>
<td>Doc. vs. Observation</td>
<td>5.7 vs. 2.7 mons</td>
<td>12.3 vs. 9.7 mons</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.0001</td>
<td>p=0.083</td>
</tr>
<tr>
<td>Ciuleanu</td>
<td>Pem. vs. Placebo</td>
<td>4.0 vs. 2.0 mons*</td>
<td>13.4 vs. 10.6 mons*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR=0.86, p=0.0001</td>
<td>HR=0.79 (95% CI: 0.65-0.95) p=0.212</td>
</tr>
<tr>
<td>Cappuzzo</td>
<td>Erlotinib vs. Placebo</td>
<td>12.3 vs. 11.1 weeks</td>
<td>12 vs. 11 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR=0.71, p=0.0001</td>
<td>HR=0.81 (95% CI: 0.70 to 0.95) p=0.0088</td>
</tr>
<tr>
<td>Miller</td>
<td>Erlotinib/Bev vs. Bev alone</td>
<td>3.75 vs. 4.76 mons</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR=0.722, p=0.0012</td>
<td></td>
</tr>
</tbody>
</table>

* Intent to treat patient population

CALGB 30607: Sunitinib as Maintenance Therapy in Non-progressing Advanced NSCLC Patients Following Chemotherapy

- Phase III, randomized, placebo-controlled trial
- Planned randomization: 156 patients (amended to 256)

- Patients with untreated stage IIIB/IV NSCLC and ECOG PS 0–1
- Randomization of responding patients or patients with stable disease stratified by prior treatment with or without bevacizumab
- 4 cycles of platinum-based chemotherapy*
- Sunilinb 37.5 mg/day
- Placebo
- Continue until disease progression
- Planned follow-up: 1 year
- 1ˢᵗ Endpoint - PFS

*Platinum-based regimen may include carboplatin/cisplatin plus paclitaxel, docetaxel, vinorelbine or gemcitabine with or without bevacizumab (bevacizumab discontinued after four cycles)

At progression, patients receiving placebo may cross over to the sunitinib arm

Maintenance therapy - the other side

- Trial designs- unequal comparison
- Improving progression free survival alone
- Lack of information on quality of life
- Cumulative side effects of chemotherapy
Maintenance therapy - where to from here

- Individualized approach
- Involving patient in the decision making process
- Molecular profiling and appropriate treatment assignment

HR=0.10 (0.04–0.25)
Log-rank p<0.0001

SATURN: PFS in EGFR mutation+ tumors

PFS probability

*60% censored

Cappuzzo, F et al. Abstract #8001

Molecular targeting of cancer: