Lung Cancer Update From ASCO

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Disclosure

- No financial disclosures
- Investigator on ATLAS and ZODIAC trials
Structure of Talk

• Adjuvant Therapy (2)
• Chemoradiotherapy (2)
• Vandetanib in Metastatic Disease (3)
• Biomarkers in Metastatic Disease (2)
• Maintenance Therapy (3)
• Catch 10:30 Flight Back to World Lung Conference in San Francisco
Adjuvant Therapy Abstracts


Neo-adj vs. Adj vs. Surg Alone

- Approx 600 pts 1:1:1
- Essentially Stage 1 and 2 disease
- 88% Men, 50% Squamous Cell
- 3 Cycles Carbo (AUC6) Paclitaxel (200mg/m²)
- No difference in OS or DFS
JBR.10- Cis/Vin Adj vs Surg

• More than 9 years median survival
• Almost 500 stage I & II pts, more than half died (of lung cancer in about 75%)
• HR 0.78, p= 0.04 (N1- 0.68, N0- 1.03)
• For N1 disease- OS survival favors adj rx (6.8 yrs vs. 3.6 yrs, p = 0.01)
Update for Adj/Neoadj Rx

• Still no randomized trial showing survival difference of adjuvant vs. neoadjuvant rx
• Still no randomized trial showing survival benefit to non-cisplatin based therapy
• Still no randomized trial showing survival benefit in node negative patients
• Continued benefit for cisplatin based rx
Chemoradiotherapy Abstracts


Trial Adding Thalidomide

• About 550 patients with unresectable IIIA or dry IIIB disease
• Weekly carbo AUC2, paclitaxel 45mg/m² +/- thalidomide
• Closed early due to futility
Carbo/Pemetrexed/Cetuximab

- 99 Stage III Patients
- Carbo AUC5, pemetrexed 500mg/m², 70 Gy +/- weekly cetuximab
- Insufficient Statistical Power
- Regimens were considered tolerable
- No benefit seen with addition of cetuximab
  FFS 12-13 mos, OS 22 mos
Vandetanib in Metastatic Disease Abstracts


ZODIAC: Docetaxel +/- Vandetanib

- Vandetanib is oral inhibitor of EGFR, VEGFR and RET
- Nearly 1400 patients were randomized
- 30% F, 25% Squam, 10% Brain Mets
- Study arm showed improved RR, PFS (4 vs. 3.2 mos), deterioration of symptoms
- For OS (10.6 mos vs. 10 mos), p= 0.196
ZEST: Vandetanib vs Erlotinib

- 1240 patients with 1 or 2 prior therapies
- Randomized 1:1
- 38% F, 22% Squam
- Vandetanib was not superior
- Pre-planned non-inferiority analysis showed non-inferiority
- Slightly greater grade III toxicity with vandetanib (largely hypertension)
ZEAL- Pemetrexed +/- Vandetanib

- Over 500 patients randomized
- 38% F, 21% squam, 8% brain mets
- Study arm had predictable additional toxicity, but also had some decreases in toxicity (anemia, nausea, fatigue)
- Trends towards PFS ($p= .108$) and OS ($p= 0.219$)
Conclusions for Vandetanib Abstracts

• Drug appears to have activity
• Not superior to erlotinib
• No evidence of a survival advantage yet
Biomarkers in Metastatic Disease Abstracts

Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib (G) versus carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS). M. Fukuoka, Y. Wu, S. Thongprasert, C. Yang, D. Chu, N. Saijo, C. Watkins, E. Duffield, A. Armour, T. Mok

Biomarker Data from I-PASS

- Study demonstrated survival benefit for gefitinib over carboplatin/paclitaxel in Asian light or never smokers
- Tissue samples were available for 683
- EGFR mutation analysis available for 437
- PFS was superior with gefitinib in mutation positive patients, inferior in EGFR WT
FLEX Overall survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>1-year survival</th>
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</thead>
<tbody>
<tr>
<td>CT + Cetuximab</td>
<td>11.3 months</td>
<td>47 %</td>
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<tr>
<td>(n=557)</td>
<td></td>
<td></td>
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<tr>
<td>CT</td>
<td>10.1 months</td>
<td>42 %</td>
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<td>(n=568)</td>
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</table>

HR=0.871 (95% CI 0.762-0.996), p=0.044

p-value = stratified log-rank test (2-sided)

Pirker et al, J Clin Oncol 2008, 18S (Abstract 3)
KRAS mutations in FLEX

- FLEX study showed survival benefit with addition of cetuximab to cis/vinorelbine
- Of 1125 patients, 554 samples available and results obtained from 379
- 19% harbored KRAS Mutations
- Differences in survival seen for presence of rash, but not KRAS
Conclusion from Biomarker Abstracts

• More questions than answers
• In I-PASS, since most patients will cross over at progression, is survival different?
• Is interaction between EGFR and KRAS different in NSCLC and colon cancer?
• In a study with small survival benefit with addition of a targeted agent, should biomarker correlation be expected?
Maintenance Therapy Abstracts


A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). A. Miller, P. O'Connor, C. Soh, F. Kabbinavar
Maintenance Pemetrexed

- 663 Stage IIIB/IV pts without progression after 4 cycles of platinum based rx randomized 2:1 (pemetrexed 500 mg/m²:BSC)
- 19% of patients in BSC received pemetrexed
- PFS and RR were better with maintenance
<table>
<thead>
<tr>
<th></th>
<th>Pem</th>
<th>Placeb</th>
<th>p value (HR)</th>
<th>Pem</th>
<th>Placeb</th>
<th>p value (HR)</th>
<th>Pem</th>
<th>Placeb</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall population</strong></td>
<td>13.4</td>
<td>10.6</td>
<td>0.012 (0.79)</td>
<td>4.3</td>
<td>2.6</td>
<td>&lt;0.0001 (0.50)</td>
<td>51.7</td>
<td>33.3</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Nonsquamous</strong></td>
<td>15.5</td>
<td>10.3</td>
<td>0.002 (0.70)</td>
<td>4.37</td>
<td>1.84</td>
<td>&lt;0.00001 (0.47)</td>
<td>54.3</td>
<td>26.6</td>
<td>&lt;0.001</td>
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<tr>
<td>(n=482)</td>
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<tr>
<td><strong>Adeno</strong></td>
<td>16.8</td>
<td>11.5</td>
<td>0.026 (0.73)</td>
<td>4.60</td>
<td>2.66</td>
<td>&lt;0.00001 (0.51)</td>
<td>58.2</td>
<td>29.6</td>
<td>&lt;0.001</td>
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<td>(n=329)</td>
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<td><strong>Large Cell</strong></td>
<td>8.4</td>
<td>7.9</td>
<td>0.964 (0.98)</td>
<td>4.53</td>
<td>1.45</td>
<td>0.104 (0.40)</td>
<td>30.0</td>
<td>25.0</td>
<td>0.999</td>
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<td>(n=20)</td>
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<tr>
<td><strong>Other</strong></td>
<td>11.3</td>
<td>7.7</td>
<td>0.025 (0.61)</td>
<td>4.11</td>
<td>1.58</td>
<td>0.0001 (0.44)</td>
<td>47.5</td>
<td>18.9</td>
<td>0.004</td>
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<td>(n=133)</td>
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<tr>
<td><strong>Squamous</strong></td>
<td>9.9</td>
<td>10.8</td>
<td>0.678 (1.07)</td>
<td>2.43</td>
<td>2.50</td>
<td>0.896 (1.03)</td>
<td>33.3</td>
<td>34.5</td>
<td>1.000</td>
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<tr>
<td>(n=181)</td>
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Controversy

• This should have been an immediate vs. delayed pemetrexed study.

• Although pemetrexed was not given to most patients on the control arm, the alternatives (docetaxel and erlotnib) should have had similar outcomes

• Conclusion- This is a reasonable option in selected patients
SATURN

- Nearly 2000 patients enrolled
- Approx 900 had disease that hadn’t progressed after 4 cycles of chemo
- Randomized to erlotinib 150mg vs placebo
- PFS, DCR and RR were better with rx
- OS data was not mature
PFS*: all patients (ITT)

PFS probability

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Erlotinib</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>8</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>16</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>24</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>32</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>40</td>
<td>0.00</td>
<td>0.00</td>
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</table>

HR=0.71 (0.62–0.82)
Log-rank p<0.0001

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

- Similar design to SATURN, + bevacizumab
- Treated brain mets, low molecular weight heparin and peripheral squamous cell disease was allowed
- Over 1100 patients enrolled, 750 were randomized to erlotinib 150 mg or placebo (both arms got bevacizumab maintenance)
ATLAS Study Design

Eligibility
- Stage III/IV NSCLC
- ECOG performance status 0-1

Stratification factors
- Gender
- Smoking history (never vs former/current)
- ECOG performance status (0 vs ≥1)
- Chemotherapy regimen

Primary endpoint
- PFS in all randomized pts

Secondary endpoints
- Overall survival
- Safety

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

Carbo/paclitaxel; cis/vinorelbine; carbo or cis/gemcitabine; carbo or cis/docetaxel.

Chemo-naïve Advanced NSCLC N=1,160

4 cycles of 1st-line chemotherapy* + bevacizumab

Non-PD n=768 (66%)

Bevacizumab + Erlotinib to PD

Bevacizumab + Placebo to PD

Unblind at PD

Post progression therapy
ATLAS Continued

• PFS was primary endpoint
• Study was stopped early by DSMB for improved PFS in study arm
• OS data not mature
ATLAS: Progression-Free Survival
(ITT population, investigator assessment)

No. of patients at risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>12 mo</th>
<th>9 mo</th>
<th>6 mo</th>
<th>3 mo</th>
<th>1 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bev + Placebo</td>
<td>373</td>
<td>142</td>
<td>58</td>
<td>27</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Bev + Erlotinib</td>
<td>370</td>
<td>178</td>
<td>81</td>
<td>43</td>
<td>20</td>
<td>6</td>
</tr>
</tbody>
</table>
Maintenance Abstracts

- The questions we want answered may never be answered
- Maintenance pemetrexed, particularly in adenocarcinoma is a treatment option for some patients
- Maintenance erlotinib would also be an option if OS is extended
Conclusions From ASCO 2009

- Adjuvant cisplatin based chemotherapy for lymph node positive disease is still standard.
- Pemetrexed can be combined with carbo and radiation, but efficacy unknown.
- The FDA will guide us on vandetanib.
- Interesting biomarker data is being generated. It is unclear if it will lengthen patients' lives.
- Maintenance therapy, especially pemetrexed is controversial but reasonable.