ASCOR REVIEW 2014: LUNG CANCER

Lawrence H. Einhorn
Indiana University

Off-Label Use Disclosure

I do intend to discuss an off-label use of a product during this activity.

I will discuss, as based upon evidence and ASCO presentations, several novel agents including, but not limited to, immune checkpoint inhibitors, irreversible EGFR mutation inhibitors and ALK inhibitors.
Financial Disclosure

I currently have or have had the following relevant financial relations to disclose:

- Advisory Board – Celgene
- Stock – Amgen and Biogen Idec

TOPICS TO BE COVERED

- Stage III inoperable NSCLC – role of consolidation chemotherapy following concurrent chemoXRT
- New data with EGFR inhibitors
- Molecular targeted agents combined with chemotherapy
- Immune checkpoint inhibitors
- PCI in extensive small cell lung cancer
STAGE IIIA AND IIIB DISEASE

• 40% of all cases of NSCLC
• Tri-modality therapy for select patients
• Concurrent chemoXRT (EP + XRT or carboplatin + paclitaxel weekly + XRT) achieves 10-20% 5 year survival
• Is there benefit with consolidation chemotherapy?

CONSOLIDATION DOCETAXEL AFTER CONCURRENT CHEMOXRT: SWOG 9504*

• 83 patients with T4 (non-effusion) or N3 treated with cisplatin 50 mg/M² days 1, 8, 29, and 36 plus VP-16 50 mg/M² days 1-5 and 29-33 with concurrent XRT 61 Gy starting day 1.
• Subsequently, docetaxel 75-100 mg/M2 given every 3 weeks for 3 cycles.
• Median PFS 16 months and M.S.T. 27 months with 76% 1 year, 54% 2 year and 40% 3 year survival.

HOG LUN 01-24/USO 02-033

ChemoRT

Cisplatin 50 mg/m² IV d 1,8,29,36
Etoposide 50 mg/m² IV d 1-5 & 29-33
Concurrent RT 59.4 Gy (1.8 Gy/fr)

Stratification Variables:
PS 0-1 vs 2
IIIA vs IIIB
CR vs. non-CR

Randomize

Docetaxel 75 mg/m² q 3 wk x 3
Observation

Overall Survival (ITT)
Randomized Patients (n=147)

Observation: Median: 24.2 months (18.0-34.4)
3 year survival rate: 27.6%
Docetaxel: Median: 21.6 months (17.7-34.9)
3 year survival rate: 27.2%
P-value: 0.940
There is nothing more horrible than the murder of a beautiful theory by a gang of brutal facts.

La Rochefoucauld

Study Design: Stage III NSCLC
Park et al.: ASCO 2014, abstract 7500

Cisplatin/Taxotere/XRT
Observation
Primary endpoint PFS
Secondary endpoints include OS

Cisplatin/Taxotere X 3
CISPLATIN + DOCETAXEL + XRT +/- CONSOLIDATION CISPLATIN DOCETAXEL*

- From Oct, 2005 to April, 2011, 437 patients enrolled and 419 completed chemoXRT phase
- Median PFS 8 months (observation) versus 9.1 months (p = 0.38)
- Median overall survival 20.6 months (observation) versus 21.2 months (p = 0.48)


Negative phase III trials

- Induction chemotherapy
- Consolidation therapy
  - Using same agents throughout
  - Switching agents after chemoradiation
  - Targeted/Novel therapies
  - Negative meta-analysis of 41 trials
2014 NCCN GUIDELINES FOR INOPERABLE STAGE III NSCLC

Concurrent Cisplatin/Etoposide or Cisplatin/Vinblastine with XRT “preferred”

If weekly carboplatin/paclitaxel is used…the treating physician should consider 2 cycles of full dose platinum therapy after local therapy is completed

My Thoughts

• Available evidence does not support the use of additional chemotherapy (induction or consolidation)
  – Even with weekly platinum and taxane
• Guidelines should reflect negative trials with consolidation
• New guidelines should indicate that concurrent chemoradiation alone is the standard of care in the most fit patients
EGFR INHIBITORS

OVERALL SURVIVAL IN NSCLC HARBORING EXON 19 AND EXON 21 EGFR MUTATIONS; POOLED RESULTS OF LUX3 AND LUX6 COMPARING AFATINIB WITH CHEMOTHERAPY

- LUX 3 compared afatinib with cisplatin + pemetrexed in 345 patients (worldwide study)
- LUX 6 compared afatinib with cisplatin + gemcitabine in 364 Asian patients
- Similar to other studies with EGFR-I, improved PFS, but not overall survival with afatinib
- Pooled analysis of mature overall survival for LUX 3 and LUX 6 performed
LUX 3 AND LUX 6 (cont’d)*

- 2:1 randomization; 419 received afatinib and 212 chemotherapy
- MFU 36.5 months; 64% of patients dead as of Jan, 2014
- Overall survival favored afatinib (27.3 versus 24.3 months; HR = 0.81; p = 0.0371)
- Among 355 with deletion exon 19, HR = 0.59, CI 0.45-0.77, p < 0.001, but for L858R patients, survival favored the initial chemotherapy arm (HR 1.25, CI 0.92-1.71; p = 0.16)


SHOULD AFATINIB BE THE PREFERRED EGFR-I IN EXON 19 DELETION NSCLC?

- No survival advantage individually for LUX 3 and LUX 6, but there was with combining these 2 studies
- Unknown whether there would be a similar survival advantage for gefitinib or erlotinib compared to chemotherapy for exon 19 subset
- LUX 7 phase III study of afatinib versus gefitinib completed summer 2013
- 32% of patients on chemotherapy arm never received an EGFR-I
- Cost and toxicity
SECOND-GENERATION EGFR-I (FOLLOWING ERLOTINIB/GEFITINIB)

- Continue erlotinib for slow or localized progression
- T790M
- More attractive than afatinib + cetuximab
- AZD 9291: 91 of 177 (51%) response rate; responses seen in brain metastases; lower response rate (23%) if T790M negative
  - Overall disease control rate in T790M+ patients 96% (85 of 89)
- CO-1686; 40% had > 1 prior EGFR TKI; 6 of 9 T790M+ achieved objective response
- HM61713 – 7 of 42 objective responses

SECOND LINE THERAPY COMBINING CHEMOTHERAPY WITH A VEGFR2 ANTIBODY - RAMUCIRUMAB

Abstract # LBA 8006 – Perol M et al, A randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy.
Ramucirumab

- Ramucirumab is a human IgG1 monoclonal Ab that targets the extracellular domain of VEGFR-2 preventing binding of all VEGF ligands and receptor activation.

**REVEL: Study Design**

- Stage IV NSCLC after one platinum-based chemo +/- maintenance
- Prior Bev allowed
- All histologies
- PS 0 or 1

**Randomize**

- Ramucirumab 10 mg/kg + Docetaxel 75 mg/m² q3wks N=628
- Placebo + Docetaxel 75 mg/m² q3wks N=625

**1:1**

Treatment until disease progression or unacceptable toxicity
REVEL PFS (ITT)

Garon et al., The Lancet 2014

REVEL: Overall Survival
ITT Population

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAM + DOC</td>
<td>22.9%</td>
<td>4.5 mo</td>
</tr>
<tr>
<td>PL + DOC</td>
<td>13.8% (p&lt;0.001)</td>
<td>3.0 mo (HR 0.76 p&lt;0.0001)</td>
</tr>
</tbody>
</table>
Other 2nd line trials of chemo + VEGF inhibition

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVEL</td>
<td>23 vs 14%</td>
<td>4.5 vs 3.0 mos</td>
<td>10.5 vs 9.1 mos</td>
</tr>
<tr>
<td>Nindetanib + Docetaxel</td>
<td>4.4 vs 3.3%</td>
<td>3.4 vs 2.7 mos</td>
<td>10.1 vs 9.1 mos</td>
</tr>
<tr>
<td>Nindetanib + Pemetrexed</td>
<td>9.1 vs 8.3%</td>
<td>4.4 vs 3.6 mos</td>
<td>12.2 vs 12.7 mos</td>
</tr>
<tr>
<td>Vandetanib + Docetaxel</td>
<td>17 vs 10%</td>
<td>4 vs 3.2 mos</td>
<td>10.6 vs 10.0 mos</td>
</tr>
<tr>
<td>Vandetanib + Pemetrexed</td>
<td>19 vs 8%</td>
<td>4.4 vs 2.9 mos</td>
<td>10.5 vs 9.2 mos</td>
</tr>
</tbody>
</table>

Garon et al., The Lancet 2014
Reck et al., The Lancet 2014
Hanna et al., ASCO 2013
Herbst, Lancet Oncology 2010
De Boer, JCO 2011

ASCO Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Patient Population</th>
<th>Current Baseline Median OS (months)</th>
<th>Improvement Over Current OS (months)</th>
<th>Improvement in 1-Year Survival Rate (%)</th>
<th>Improvement in PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic cancer</td>
<td>FOLFIRINOX-eligible patients</td>
<td>10 to 11**</td>
<td>4 to 5</td>
<td>0.67 to 0.85</td>
<td>44 to 63</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Gemcitabine or gemcitabine + secretory-pancreatic enzyme inhibitors</td>
<td>9 to 10**</td>
<td>3 to 4</td>
<td>0.39 to 0.76</td>
<td>36 to 90</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Non-small cell carcinoma</td>
<td>13**</td>
<td>3.2 to 4</td>
<td>0.78 to 0.96</td>
<td>33 to 61</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Squamous cell carcinoma</td>
<td>10**</td>
<td>2.5 to 3</td>
<td>0.77 to 0.86</td>
<td>44 to 53</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Metastatic hormone-sensitive, previously untreated for metastatic disease</td>
<td>10**</td>
<td>4.5 to 8</td>
<td>0.75 to 0.86</td>
<td>52 to 97</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Disease progression with all prior therapies (no new candidate for standard second- or third-line options)</td>
<td>4 to 6**</td>
<td>3 to 5</td>
<td>0.67 to 0.67</td>
<td>25 to 25</td>
</tr>
</tbody>
</table>

*Oncologists’ intended target.

“This phase III trial fails to meet these criteria”

My Thoughts

- This is financially toxic!
- $8,920 per Ramucirumab DOSE!
Is The Glass Half Full or Half Empty?

HALF FULL
- Met its endpoint
- Improved ORR, Median PFS & OS
- 1st VEGFR inhibitor to benefit Squamous pts

HALF EMPTY
- Modest survival benefit
- Need more info on benefit in pts with prior VEGF Rx
- Lack of biomarker – Info coming

• A pessimist always thinks the glass is half empty
• A pessimist *always* thinks the glass is half empty

• An optimist thinks the glass is half full when it is empty
**UPDATE ON NIVOLUMAB – PREVIOUSLY TREATED**

- 129 patients, 54% with 3 or more prior therapies
- Response rate 17% with MDR 17 months
- Activity in all histologies and lines of prior therapy
- MST PD-L1+ 7.8 months and 10.5 months PD-L1 negative
- PFS 3.6 months PD-L1+ versus 1.8 months
- Ongoing phase III trials evaluating 3 mg/kg IV q 3 week dosage and PD-L1 as a potential predictor of clinical outcomes


**MK-3475 AS INITIAL THERAPY IN NSCLC**

- Patients with no prior systemic therapy whose tumors expressed PD-L1 by IHC received MK-3475 every 2 or 3 weeks IV
- 57 of 84 (68%) PD-L1
- Objective response rate 36% (45 patients evaluable)
- Therapy well tolerated

NIVOLUMAB MONOTHERAPY AS FIRST-LINE THERAPY IN NSCLC

- Dosage 3 mg/kg IV q 2 weeks
- Elevated LFTs, hyperglycemia and rash observed; no pneumonitis
- 6 of 20 (30%) response rate, but 6 of 9 in PD-L1 + and 0 of 6 in tumors evaluated that were PD-L1 negative

SCLC

- Brain metastases are common with SCLC
  - Usually cause substantial symptoms

- PCI is a standard for some patients with LD
  - Reduces incidence of brain mets in lifetime
  - Appears to improve chances of cure by 5%

- A randomized trial from 2007 suggested PCI may have a role in patients with ED SCLC
Symptomatic Brain Metastases
Slotman et al.: NEJM 2007

Control
PCI

Survival from Randomization
Slotman et al.: NEJM 2007

Control
PCI

1 year: 14.6% vs. 40.4%
HR: 0.27 (0.16-0.44); \textbf{p}<0.001

1 year: 27.1% vs. 13.3%
HR: 0.68 (0.52-0.88); \textbf{p}=0.003
Phase III trial: PCI vs. Observation in ED SCLC
Seto et al.: ASCO 2014, abstract 7503

- Randomized 163 patients to PCI vs. Observation

- Eligibility included:
  - Response to 2 or more cycles of platinum-based doublets
  - Absence of BM by MRI assessment within 4 weeks at enrollment
  - Absence of tumor regrowth within 4 weeks at enrollment

Significant reduction in brain mets reported

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td>BM at 12 months</td>
<td>32.4%</td>
<td>58.0%</td>
</tr>
</tbody>
</table>

Gray's test: P < 0.001 (2-sided)
Progression-Free Survival

<table>
<thead>
<tr>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=84</td>
<td>n=79</td>
</tr>
<tr>
<td>No. of PFS Events</td>
<td>82</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.12 (0.82-1.54)</td>
</tr>
<tr>
<td>Median PFS (95%CI), mo</td>
<td>2.2 (2.0-2.6)</td>
</tr>
</tbody>
</table>

Overall Survival favors NO PCI

<table>
<thead>
<tr>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=84</td>
<td>n=79</td>
</tr>
<tr>
<td>No. of OS Events</td>
<td>61</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.38 (0.95-2.02)</td>
</tr>
<tr>
<td>Median OS (95%CI), mo</td>
<td>10.1 (8.5-13.2)</td>
</tr>
</tbody>
</table>

Stratified log-rank test: P=0.091 (2-sided)
Bayesian predictive probability: < 0.1%
CONCLUSIONS

- ChemoXRT for stage III NSCLC
- EGFR-I
- Immune checkpoint inhibitors
  - 21% 2 year survival as third to fourth-line therapy

TOBACCO WARNING

“Cigarette smoking is a health hazard of sufficient importance in the U.S. to warrant appropriate remedial action.”

Advisory Committee to the Surgeon General of the Public Health Service, 1964