Optimal Application of Adjuvant Therapy in NSCLC

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University of Southern California
Keck School of Medicine
Presentation Overview

- Current Evidence for the Role of Adjuvant Chemotherapy in NSCLC
- Integration of Targeted Agents
- Integration of Biomarkers
Optimal Application

- WHO HAS THE HIGHEST MAGNITUDE OF BENEFIT?
- IS ANYONE "HARMED"?
- HOW CAN WE MOVE ON AND IMPROVE?
Adjuvant Chemotherapy for NSCLC
ALPI: Cisplatin + Mitomycin + Vindesine

- Stages I-IIIA
- Failed to confirm significant role for adjuvant CDDP chemo
- Poor compliance with chemo
- High toxicity with triplet regimen (MVP)

N = 1209
IALT: Cisplatin-Based Adjuvant Therapy for NSCLC After Complete Resection

Patients with stage I-IIIA NSCLC aged 18-75 yrs after complete surgical resection* (N = 1867)

- Cisplatin-based chemotherapy† (n = 932)
- No chemotherapy (n = 935)

*Postoperative radiotherapy performed at discretion of institution.
†Chemotherapy regimens: etoposide: 56.5%; vinorelbine: 26.8%; vinblastine: 11.0%; vindesine: 5.8%.

Adjuvant Chemotherapy for NSCLC
IALT: Cisplatin + a Vinca or Etoposide

4% Benefit at 5 years

Survival rates for surgery and surgery + chemotherapy.

HR = 0.86; 95% CI 0.76-0.98; \( P < 0.03 \)

N = 1867

IALT: Interaction With Pathologic Stage

Stage I

Stage II

Stage III

Total effect

Chemotherapy Better  0.86  1.00  Control Better

JBR.10: Adjuvant Vinorelbine + Cisplatin for Resected NSCLC (NCI Canada)

Patients with completely resected T2N0, T1N1, or T2N1 NSCLC; ECOG PS 0/1 (N = 482)

Vinorelbine 25 mg/m$^2$* wkly for 16 wks + Cisplatin 50 mg/m$^2$ on Days 1, 8 every 4 wks for 4 cycles (n = 242)

Observation (n = 240)

*Dose of 30 mg/m$^2$ for first 18 patients; reduced due to hematologic toxicity.

JBR.10: Survival Advantage of Vinorelbine Plus Cisplatin for Resected NSCLC

Survival Probability (%)

Vinorelbine + cisplatin
Observation

Median Survival 94 months vs 73 months
(HR = 0.69; 95% CI 0.52-0.91; P = 0.04)
5y OS 69% vs. 54% = 15% improvement

Survival Within Stage 1B By Tumor Size < 4cm

HR 0.66; (0.39 to 1.14) \( P = .13 \)
5yr survival 79% vs 59%

Butts CA, et al (and Frances Shepherd, David Gandara)
JCO 2010
ANITA: Adjuvant Vinorelbine + Cisplatin vs Observation

- Open, multicenter study

Patients with stage IB-IIIA NSCLC aged 18-75 yr after complete surgical resection*
(N = 840)

Vinorelbine 30 mg/m² IV wkly x 16 + Cisplatin 100 mg/m² IV on Days 1, 29, 57, 85
4 cycles (n = 407)

Observation (n = 433)

*Postoperative radiotherapy performed at discretion of institution.
ANITA OS and DFS

Median 65.7m vs. 43.7m
HR 0.80 (0.66-0.96)

Overall survival at 5y improved by 8.6%

Median DFS 36.3m vs. 20.7m
HR 0.76 (0.64-0.91)

Douillard
Lancet Oncology
2006; 7: 719-727
# ANITA

## 5-yr OS according to stage & LN status

<table>
<thead>
<tr>
<th>Stage</th>
<th>Chemotherapy</th>
<th>Control</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>62%</td>
<td>64%</td>
<td>1.10 [0.76-1.57]</td>
</tr>
<tr>
<td>II</td>
<td>52%</td>
<td>39%</td>
<td>0.71 [0.49-1.03]</td>
</tr>
<tr>
<td>IIIA</td>
<td>42%</td>
<td>26%</td>
<td>0.69 [0.523-0.90]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal status</th>
<th>Chemotherapy</th>
<th>Control</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>58%</td>
<td>61%</td>
<td>1.14 [0.83-1.57]</td>
</tr>
<tr>
<td>N1</td>
<td>52%</td>
<td>36%</td>
<td>0.67 [0.47-0.94]</td>
</tr>
<tr>
<td>N2</td>
<td>40%</td>
<td>19%</td>
<td>0.60 [0.44-0.82]</td>
</tr>
</tbody>
</table>
CALGB 9633: Adjuvant Chemotherapy in Stage IB NSCLC

Patients with completely resected T2N0M0, stage IB NSCLC
(N = 344)

Adjuvant Chemotherapy
Paclitaxel 200 mg/m² IV + Carboplatin AUC 6
4 cycles over 12 wks
(n = 173)

Observation
(n = 171)

CALGB 9633: Adjuvant Chemotherapy in Stage IB NSCLC

Chemotherapy (n = 173)  Control (n = 171)

<table>
<thead>
<tr>
<th>Survival Probability (%)</th>
<th>1.0</th>
<th>0.8</th>
<th>0.6</th>
<th>0.4</th>
<th>0.2</th>
<th>0</th>
<th>0</th>
<th>40</th>
<th>80</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median OS, mos
- Chemotherapy: 95 mos
- Observation: 78 mos

P value
- Chemotherapy: 0.125
- Observation: 0.125

HR (90% CI)
- Chemotherapy: 0.83 (0.64-1.08)
- Observation: 0.83 (0.64-1.08)

CALGB 9633: Survival by Tumor Size

### Post 1995 Meta-Analysis: Randomized Adjuvant Platinum-Based Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>n</th>
<th>Chemo</th>
<th>↑ 5 yr Survival</th>
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</thead>
<tbody>
<tr>
<td>E3590</td>
<td>II-III A</td>
<td>488</td>
<td>Cis/VP16</td>
<td>No</td>
</tr>
<tr>
<td>ALPI</td>
<td>I-III</td>
<td>1209</td>
<td>Cis/MVd</td>
<td>No</td>
</tr>
<tr>
<td>BLT</td>
<td>I-III</td>
<td>381</td>
<td>Cis/4 options</td>
<td>No</td>
</tr>
<tr>
<td>IALT</td>
<td>I-III</td>
<td>1867</td>
<td>Cis/Vinca or VP16</td>
<td>Yes</td>
</tr>
<tr>
<td>JBR.10</td>
<td>IB-II</td>
<td>482</td>
<td>Cis/Vin</td>
<td>Yes</td>
</tr>
<tr>
<td>CALGB</td>
<td>IB</td>
<td>344</td>
<td>Carbo/Pac</td>
<td>No</td>
</tr>
<tr>
<td>ANITA</td>
<td>I-III A</td>
<td>840</td>
<td>Cis/Vin</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Meta-analyses ~ 5% survival advantage at 5 yr**

- NEJM 00; JNCI 03; EuroJTS 04, NEJM 04; NEJM 05; JCO 2008; Lancet Oncology 06
Adjuvant Chemotherapy for NSCLC
LACE: Pooled Data Overall Survival

5.3% survival advantage at 5 years
HR = 0.89
95% CI 0.82-0.96
P = 0.005

### Adjuvant Chemotherapy for NSCLC

#### LACE Analysis by Stage

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard Ratio (Chemotherapy / Control)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>104 / 347</td>
<td></td>
<td>1.41 [0.96;2.09]</td>
</tr>
<tr>
<td>Stage IB</td>
<td>515 / 1371</td>
<td></td>
<td>0.92 [0.78;1.10]</td>
</tr>
<tr>
<td>Stage II</td>
<td>893 / 1616</td>
<td></td>
<td>0.83 [0.73;0.95]</td>
</tr>
<tr>
<td>Stage III</td>
<td>878 / 1247</td>
<td></td>
<td>0.83 [0.73;0.95]</td>
</tr>
</tbody>
</table>

Test for trend: $P = 0.051$

Adjuvant chemo has greatest benefit for stage II and III and may be detrimental for stage IA

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Adjuvant Chemotherapy:

Does The Effect Last In Long Term Follow Up?
Any Long Term Safety Signals?

I Want to Know!
IALT: Cisplatin + a Vinca or Etoposide Update: 7.5-Year Median Follow-Up

chemotherapy: 578 deaths
- 495 deaths before 5 years
- 83 deaths after 5 years

control 590 deaths
- 534 deaths before 5 years
- 56 deaths after 5 years

HR: 0.91 (0.81-1.02, $P = 0.10$)

Arriagada R. et al JCO 2010
IALT Long-term Results:

<table>
<thead>
<tr>
<th>Outcome at 8.0 Yrs, Events</th>
<th>Chemotherapy (n = 932)</th>
<th>Control (n = 935)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant metastases</td>
<td>338</td>
<td>378</td>
<td>.02</td>
</tr>
<tr>
<td>Local Recurrence Rate</td>
<td>181</td>
<td>230</td>
<td>.002</td>
</tr>
<tr>
<td>Second malignancies</td>
<td>50</td>
<td>57</td>
<td>.54</td>
</tr>
</tbody>
</table>

Non-significant trend toward increased non-NSCLC mortality in CT arm vs control arm (HR: 1.34; \( P = .06 \)) (chemotherapy related, cardiopulmonary and secondary non-nsclc malignancy)

LACE Meta-Analysis
More non–lung cancer deaths for chemotherapy (HR = 1.36; \( P = .004 \))
1st 6mo HR 2.41 \( p<0.001 \), follow up HR 1.06

Pignon, et al JCO 2008

JBR.10 Updated Survival

Median F/U 9.3 yrs range (3.2-13.8)
All Pts HR 0.78 (p = .04)
11% improvement at 5yrs (67% vs 56%)

Stage II HR 0.68 p=0.01 3.6 vs 6.8yrs
No Benefit for Stage IB (except >4cm)

Non-disease-related death rates similar between arms (\(P = .660\))

Butts C, et al. JCO 2010
## ANITA OS Update

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Control</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Survival</strong></td>
<td>65.7 m</td>
<td>43.7 m</td>
<td>0.80 [0.66-0.96]</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>1-yr survival benefit</strong></td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2-yr survival benefit</strong></td>
<td>4.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5-yr survival benefit</strong></td>
<td>8.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>7-yr survival benefit</strong></td>
<td>8.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Adjuvant Therapy for NSCLC

- Optimal regimen for adjuvant therapy?
  - Substitutions are often made

Non-Small Cell Lung Cancer

Published Chemotherapy Regimens

- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles
- Cisplatin 100 mg/m² on day 1; vinorelbine 30 mg/m² days 1, 8, 15, 22; every 28 days for 4 cycles
- Cisplatin 75-80 mg/m² day 1; vinorelbine 25-30 mg/m² days 1 + 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² on day 1; etoposide 100 mg/m² days 1-3, every 28 days for 4 cycles
- Cisplatin 80 mg/m² on day 1, 22, 43, 64; vinblastine 4 mg/m² days 1, 8, 15, 22 then every 2 wks after day 43, every 21 days for 4 cycles

Other Acceptable Cisplatin-based Regimens

- Cisplatin 75 mg/m² on day 1; gemcitabine 1250 mg/m² on days 1, 8 every 21 days
- Cisplatin 75 mg/m²; docetaxel 75 mg/m² every 21 days
- Pemetrexed 500 mg/m² on day 1; cisplatin 75 mg/m² on day 1 for adenocarcinoma and large cell carcinoma and NSCLC NOS (without specific histologic subtype) every 21 days for 4 cycles

Chemotherapy Regimens for patients with comorbidities or patients not able to tolerate cisplatin

Paclitaxel 200 mg/m² on day 1, carboplatin AUC 6 on day 1, every 21 days
Trial on Refinement of Early stage NSCLC Adjuvant Therapy (TREAT)

• Randomized phase II study
  – Trial on Refinement of Early stage NSCLC Adjuvant Therapy (TREAT) (n=132) (1B-3A T3N1)
  – Primary endpoint: Feasibility
    • Cisplatin/Vinorelbine vs. Cisplatin/Pemetrexed
      – Cisplatin/Vinorelbine standard arm
        » Cisplatin 50mg/m² days 1 and 8
        » Vinorelbine 25mg/m² weekly
        » 28 day cycles x 4
      – Cisplatin/Pemetrexed experimental arm
        » Cisplatin 75mg/m² day 1
        » Pemetrexed 500mg/m² day 1
        » 21 day cycles x 4

Kreuter et al, ASCO Annual Meeting 2011
Adjuvant Therapy for NSCLC

• Adjuvant TREAT trial (Cis/Vb vs. Cis/Pem)

<table>
<thead>
<tr>
<th></th>
<th>Cis/Vb</th>
<th>Cis/Pem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion of Therapy</td>
<td>36.9%</td>
<td>77.6%</td>
</tr>
<tr>
<td>Early Termination of Therapy</td>
<td>63.1%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Reasons for Early Termination (events)</td>
<td>(n=41)</td>
<td>(n=15)</td>
</tr>
<tr>
<td>Unacceptable Toxicity (per protocol)</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Unacceptable Toxicity (per patient)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Relapse of Disease</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawal of Consent</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dose Delivery (% Planned)</td>
<td>Cis 66%</td>
<td>Cis 90%</td>
</tr>
<tr>
<td></td>
<td>Vb 64%</td>
<td>Pem 90%</td>
</tr>
</tbody>
</table>

*Kreuter et al, ASCO Annual Meeting 2011*
Adjuvant Chemotherapy: Lessons Learned From 1\textsuperscript{st} Generation Trials

Agents
- Platinum agents important \textbf{Probably Cisplatin}
- Not enough data available on Carboplatin in an appropriately powered study
- Vinorelbine, Etoposide (Level I Evidence): Not enough data on other drugs
- \textbf{We Need Better Drugs}

Stage
- II-III\textsubscript{A} (R0 resections)
- IB is still a question: But convincing evidence of benefit in subgroup analysis \textgreater{} 4cm (JBR.10, CALGB).

Selection
- Fit Elderly have benefit although not much data on age \textgreater{} 80yrs
- Benefit regardless of histology
- NEED BIOMARKERS PROGNOSTIC and PREDICTIVE
Phase III Adjuvant Trials
Incorporating Targeted agents
JBR.19: Adjuvant Gefitinib in Resected Stage I-IIIA NSCLC

Patients with completely resected stage IB-IIIA NSCLC
(N = 503)

- Gefitinib 250 mg/day (n = 251)
- Placebo (n = 252)

*Protocol amended in January 2003 to permit adjuvant chemotherapy.

BR.19 - Overall Survival

NOT Improved by Gefitinib

HR : 1.23 (95% CI 0.94-1.64)
p=0.136

Median survival: Gefitinib - 5.1 yrs
Placebo - N.E.

Goss PASCO 2010, abstr 7005

*Stratified Log Rank
### JBR.19: Association Between EGFR Mutation and OS

<table>
<thead>
<tr>
<th>Median OS, Yrs</th>
<th>Gefitinib (n = 251)</th>
<th>Placebo (n = 252)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>5.0</td>
<td>NR</td>
<td>1.21 (0.84-1.73)</td>
<td>.301</td>
</tr>
<tr>
<td>Mutated</td>
<td>3.7</td>
<td>5.1</td>
<td>1.58 (0.83-3.00)</td>
<td>.160</td>
</tr>
</tbody>
</table>

#### Sensitizing mutation

- **Placebo**
- **Gefitinib**

![Graph showing survival rates for Placebo and Gefitinib with EGFR mutations](image-url)
ECOG-E1505: Adjuvant Chemotherapy ± Bevacizumab for Stage IB-IIIA NSCLC

Randomized, multicenter phase III trial

PI Heather Wakelee

Patients with completely resected stage IB-IIIA (IB ≥ 4 cm) NSCLC; ECOG PS 0-1; no previous systemic chemotherapy; no planned radiotherapy

- (Expected N = 1500)

Adjuvant Chemotherapy*

Four 21-day cycles

Adjuvant Chemotherapy* + Bevacizumab 15 mg/kg IV on Day 1

Continue Bevacizumab for up to 1 yr

*Cisplatin/vinorelbine, or cisplatin/docetaxel, or cisplatin/gemcitabine, or cisplatin/pemetrexed (nonsquamous histology only).

ClinicalTrials.gov. NCT00324805.
E1505 a “Treasure Chest” Study

Dr Wakelee an Adjuvant
NSCLC Crusader
ECOG-E1505: Further Eligibility Criteria

- Complete resection within previous 6-12 wks
- Preoperative or intraoperative mediastinal lymph node samples
  - Levels 7 and 4 for right-sided tumors or level 7 and 5 and/or 6 for left-sided tumors
- No chemotherapy
- Acceptable lab values
- Therapeutic anticoagulation allowed
- No cancer within 5 yrs
- No MI, ATE for 12 mos
- No CVA, TIA ever
- No coagulopathy
- No uncontrolled hypertension (≥ 150/90)
- No active hemoptysis

ClinicalTrials.gov. NCT00324805.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Total</th>
<th>Arm A</th>
<th>Arm B (BEV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB T2N0</td>
<td>156(23%)</td>
<td>82(24%)</td>
<td>74(23%)</td>
</tr>
<tr>
<td>IIA T1N1</td>
<td>77(12%)</td>
<td>43(13%)</td>
<td>34(10%)</td>
</tr>
<tr>
<td>IIB T2N1</td>
<td>190(29%)</td>
<td>91(27%)</td>
<td>99(31%)</td>
</tr>
<tr>
<td>IIB T3N0</td>
<td>29(4%)</td>
<td>8(2%)</td>
<td>21(6%)</td>
</tr>
<tr>
<td>IIIA T1-3N2</td>
<td>186(28%)</td>
<td>101(30%)</td>
<td>85(27%)</td>
</tr>
<tr>
<td>IIIA T3N1</td>
<td>26(4%)</td>
<td>15(4%)</td>
<td>11(3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adenocarcinoma</td>
<td>358(54%)</td>
<td>172(51%)</td>
<td>186(57%)</td>
</tr>
<tr>
<td>Squamous</td>
<td>206(31%)</td>
<td>109(32%)</td>
<td>97(30%)</td>
</tr>
<tr>
<td>Large Cell</td>
<td>17(3%)</td>
<td>9(3%)</td>
<td>8(2%)</td>
</tr>
<tr>
<td>BAC</td>
<td>8(1%)</td>
<td>6(2%)</td>
<td>2(1%)</td>
</tr>
<tr>
<td>Combined/Mixed</td>
<td>47(7%)</td>
<td>27(8%)</td>
<td>20(6%)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>9(1%)</td>
<td>3 (&lt;1%)</td>
<td>6(2%)</td>
</tr>
</tbody>
</table>
# Types of Resection/Chemotherapy

<table>
<thead>
<tr>
<th>Resection</th>
<th>Total</th>
<th>Arm A</th>
<th>Arm B (Bev)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>670 (100%)</td>
<td>341</td>
<td>329</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>88 (13%)</td>
<td>45 (13%)</td>
<td>43 (13%)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>492 (74%)</td>
<td>253 (74%)</td>
<td>239 (73%)</td>
</tr>
<tr>
<td>Bi-lobectomy</td>
<td>46 (7%)</td>
<td>23 (7%)</td>
<td>23 (7%)</td>
</tr>
<tr>
<td>Complex Lobectomy</td>
<td>30 (4%)</td>
<td>13 (4%)</td>
<td>17 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (2%)</td>
<td>7 (2%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Pre-op Mediastinoscopy</td>
<td>201 (30%)</td>
<td>103 (31%)</td>
<td>98 (30%)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Total</th>
<th>Arm A</th>
<th>Arm B (BEV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin +</td>
<td>670</td>
<td>341</td>
<td>329</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>179 (27%)</td>
<td>88 (26%)</td>
<td>91 (28%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>213 (32%)</td>
<td>110 (32%)</td>
<td>103 (31%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>164 (25%)</td>
<td>85 (25%)</td>
<td>79 (24%)</td>
</tr>
<tr>
<td>Pemetrexed* (non-sq only)</td>
<td>112 (17%)</td>
<td>57 (17%)</td>
<td>55 (17%)</td>
</tr>
</tbody>
</table>
Integration of Biomarkers!

THE WAY FORWARD?!

How an individual will do independent of treatment
PROGNOSTIC Marker
Who benefits from a specific drug therapy?
PREDICTIVE Marker
# Early Stage NSCLC Predictive Biomarkers (Who Benefits From a Particular Therapy)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Marker</th>
<th>Trial</th>
<th>N</th>
<th>Marker Status</th>
<th>HR for Survival (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fouret 2009[1]</td>
<td>MSH2</td>
<td>IALT</td>
<td>768</td>
<td>Negative</td>
<td>0.76 (.03) 1.12 (.48)</td>
</tr>
<tr>
<td>Olaussen 2006[2]</td>
<td>ERCC1</td>
<td>IALT</td>
<td>761</td>
<td>Negative</td>
<td>0.65 (.002) 1.14 (.40)</td>
</tr>
<tr>
<td>Filipits 2007[3]</td>
<td>p27Kip1</td>
<td>IALT</td>
<td>778</td>
<td>Negative</td>
<td>0.66 (.006) 1.09 (.54)</td>
</tr>
<tr>
<td>Tsao 2007[4]</td>
<td>p53</td>
<td>JBR.10</td>
<td>253</td>
<td>Positive</td>
<td>0.54 (.02) 1.40 (.26)</td>
</tr>
<tr>
<td>Seve 2007[5]</td>
<td>β-tubulin III</td>
<td>JBR.10</td>
<td>265</td>
<td>Positive</td>
<td>0.64 (.07) 1.00</td>
</tr>
<tr>
<td>Pirker 2007[6]</td>
<td>ERCC1/p27Kip1</td>
<td>IALT</td>
<td>778</td>
<td>Both negative</td>
<td>0.52 (95% CI: 0.36-0.74) 1.27 (95% CI: 0.87-1.84)</td>
</tr>
<tr>
<td>Fouret 2009[1]</td>
<td>MSH2/ERCC1</td>
<td>IALT</td>
<td>658</td>
<td>Both negative</td>
<td>0.65 (.01) 1.30 (.19)</td>
</tr>
</tbody>
</table>

### Early Stage NSCLC
#### Prognostic Biomarkers
(Who Needs Adjuvant therapy)

<table>
<thead>
<tr>
<th>Reference</th>
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<td>Olaussen 2006[2]</td>
<td>ERCC1</td>
<td>IALT</td>
<td>761</td>
<td>Positive</td>
<td>0.66 (.009)</td>
</tr>
<tr>
<td>Filipits 2007[3]</td>
<td>MRP2</td>
<td>IALT</td>
<td>782</td>
<td>Positive</td>
<td>1.37 (.007)</td>
</tr>
<tr>
<td>Cappuzzo 2009[6]</td>
<td>MET</td>
<td>Retrospective</td>
<td>447</td>
<td>Negative</td>
<td>0.66 (.04)</td>
</tr>
<tr>
<td>Rosell 2007[7]</td>
<td>BRCA1</td>
<td>Retrospective</td>
<td>126 58</td>
<td>Positive</td>
<td>1.98 (.02) 2.4 (.04)</td>
</tr>
</tbody>
</table>

IALT: Prognostic and Predictive Value of ERCC1 in Adjuvant Treatment of NSCLC

Patients With ERCC1-Negative Tumors[1]

Chemotherapy

Control

HR: 0.65 (95% CI: 0.50-0.86; \(P = .002\))

OS (%)

Yrs

0 1 2 3 4 5

(2008) HR: 0.76 (95% CI: 0.59-0.98)[2]

Patients With ERCC1-Positive Tumors[1]

Chemotherapy

Control

HR: 1.14 (95% CI: 0.84-1.55; \(P = .40\))

OS (%)

Yrs

0 1 2 3 4 5

(2008) HR: 1.20 (95% CI: 0.91-1.59)[2]

JBR.10: Adjuvant Vinorelbine + Cisplatin for Resected NSCLC

Patients with completely resected T2N0, T1N1, or T2N1 NSCLC; ECOG PS 0/1
(N = 482)

Vinorelbine 25 mg/m²* wkly for 16 wks + Cisplatin 50 mg/m² on Days 1, 8 every 4 wks for 4 cycles (n = 242)

Observation (n = 240)

Median follow-up: 5.1 yrs

Median follow-up: 5.3 yrs

*Dose of 30 mg/m² for first 18 patients; reduced due to hematologic toxicity.

15-gene Signature is Prognostic in Stage I and Stage II Observation Patients

HR 13.32 (95% CI 2.86-62.11)  
p<0.0001

HR 13.47 (95% CI 3.00-60.43)  
p<0.0001

Zhu CQ, Shepherd FA et al JCO 2010
Chemotherapy Benefits JBR.10 High Risk but Not Low Risk Patients

JBR.10, high risk (n=67)

HR 0.33 (95% CI 0.17-0.63)

p=0.0005

JBR.10, low risk (n=66)

HR 3.67 (95% CI 1.22-11.06)

p=0.0133

Interaction p = 0.0001

National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques
CALGB 30506
NCT00863512

Patients with NSCLC
≥ 2.0 cm but ≤ 7.0 cm
(T1a, T1b, T2a, or T2b)
ode negative
(N = 1525)

Cisplatin-based chemotherapy \( \times 4 \) cycles
Vinorelbine, gemcitabine, docetaxel, pemetrexed

Observation

Primary Objectives:
• overall survival benefit
• To collect and process high-quality fresh frozen lung cancer tumor tissue for gene expression array generation from multiple institutions.

Secondary
• To evaluate selected genomic-based lung cancer prognostic models using data from the patients randomized to observation after resection.
• Toxicity, QOL
A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies

Johannes R Kratz*, Jianxing He*, Stephen K Van Den Eeden, Zhi-Hua Zhu, Wen Gao, Patrick T Pham, Michael S Mulvihill, Fatemeh Ziaei, Huanrong Zhang, Bo Su, Xuyi Zhi, Charles P Quesenberry, Laurel A Habel, Qiuhua Deng, Zongfei Wang, Jiangfen Zhou, Huiing Li, Mei-Chun Huang, Che-Chung Yeh, Mark R Segal, M Roshni Ray, Kirk D Jones, Dan J Raz, Zhidong Xu, Thierry M Jahan, David Berryman, Biao He, Michael J Mann, David M Jablons

University of California, San Francisco, CA,
Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical College, State Key Laboratory of Respiratory Disease, Guangzhou, China
Kaiser Permanente Dept of Research, Northern California, Oakland, CA,
Department of Thoracic Oncology, Cancer Centre of Sun Yat-Sen University, Guangzhou, China
Shanghai Pulmonary Hospital, Shanghai, China
Beijing Lung Cancer Centre, Capital Medical University, Beijing, China
Pinpoint Genomics, Mountain View, CA
Pinpoint™ Assay Development

361 stage I-IV non-squamous FFPE samples (UCSF Training Cohort) → paraffin-tissues

Measure expression of 14 cancer pathway + reference genes (CLIA-certified Laboratory) → qPCR

L2-penalized Cox Proportional Hazards Modeling

Prognostic Algorithm

Analytical Assay Validation (CLIA-certified Laboratory)

Kaiser Northern California

433 stage I samples

Independent Validation

China Clinical Trials Consortium

1006 stage I-III samples

blinded
First practical, validated molecular prognostic for early-stage lung cancer

- Large-scale validation studies: ~1,500 Patients

China Clinical Trials Consortium: 967 patients (Stages I-IIla)

Kaiser Northern California: 420 patients (Stage I)

# Prospective Adjuvant Trials Utilizing Biomarkers

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Therapy</th>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 0720</td>
<td>I</td>
<td>± Chemotherapy (cis/gem)</td>
<td>ERCC1/RRM1</td>
</tr>
<tr>
<td>ITACA</td>
<td>II-III</td>
<td>Cisplatin/Pemetrexed</td>
<td>ERCC1/TS</td>
</tr>
<tr>
<td>SCAT</td>
<td>II-III A</td>
<td>Platinum/Docetaxel</td>
<td>BRCA1</td>
</tr>
<tr>
<td>MAGRIT</td>
<td>IB-III A</td>
<td>MAGE A3 Vaccine</td>
<td>MAGE-A3</td>
</tr>
<tr>
<td>RADIANT</td>
<td>IB-III A</td>
<td>Erlotinib vs Placebo</td>
<td>EGFR FISH or IHC+</td>
</tr>
<tr>
<td>TASTE</td>
<td>II-III A</td>
<td>Erlotinib vs CDDP Pem</td>
<td>ERCC1/EGFR mut</td>
</tr>
<tr>
<td>SELECT</td>
<td>I and I N0</td>
<td>Erlotinib</td>
<td>EGFR mutation</td>
</tr>
<tr>
<td>GACT</td>
<td>II-III A N+</td>
<td>Gefitinib vs CDDP Vinorelbine</td>
<td>EGFR mutation</td>
</tr>
</tbody>
</table>
SWOG-0720
Biomarker (ERCC1 and RRM1)-based decision-making algorithm for adjuvant chemotherapy in stage I non-small-cell lung cancer

Ralph Zinner, James Moon, Gerold Bepler, Royce Calhoun Kemp Kernstine, Charles Williams, Philip C. Mack, Vasco Oliveira & David R. Gandara
Chemo or Active Monitoring Must Begin ≤ 84 Days of Surgery

1. Surgery and resected tumor specimen
2. Ship Specimen to SWOG Tissue Repository
3. Assessment of RRM1 and ERCC1 expression by AQUA (Karmanos Cancer Inst.)

- Both higher expression
  - $RRM1 \geq 40$ and $ERCC1 \geq 65$
  - Active Monitoring $x$ 2 yrs

- Either lower expression
  - $RRM1 < 40$ and/or $ERCC1 < 65$
  - Cisplatin 80mg/m2
  - Gemcitabine 1000mg/m2
  - $x$ 4 courses
Conclusions

Met Primary Endpoint of Feasibility
• Gene expression analysis for all 83 eligible pts
• 72/83 (87%) treatment assignment met requirements
• 64/83 (77%) evaluated pts assigned to chemo;
• 14/64 pts (22%) declined treatment assignment

Biomarker
• RRM1 and ERCC1 levels correlated
• Neither correlated with gender, age, histology
• EGFR altered (either FISH + or EGFR mutant) conferred favorable event free survival advantage

Zinner R et al. WCLC 2011
International Tailored Chemotherapy Adjuvant Trial (ITACA)

- Patients with histologically confirmed lung cancer who received standard platinum-containing doublet chemotherapy followed by EGFR tyrosine kinase inhibitors
  - Tumors tested for ERCC1 and TS

ERCC1 (Planned N = 700)

- High/Low ERCC1 and TS selected according to median level of mRNA expression in historical series

*Control arm: investigator choice of a DDP-based doublet.
RADIANT: Adjuvant Chemotherapy ± Erlotinib for EGFR-Positive NSCLC

- Randomized, multicenter phase III trial
- Primary endpoint: DFS

Stratified by histology, age, sex, adjuvant chemotherapy, smoking status

Patients with stage IB-IIIA NSCLC; EGFR-positive tumor by IHC or FISH
(N = 945)

Up to 4 cycles adjuvant chemotherapy
2:1

Erlotinib 150 mg/day
Placebo

ClinicalTrials.gov. NCT00373425.
Tailored Postsurgical Therapy in Early Stage NSCLC (TASTE)

Control Arm
CDDP-Pemetrexed

Experimental Arm
Customized

NSCLC stage II and IIIA (non-N2); max 2 mos from surgery to therapy NON-SQUAMOUS

EGFR mutated

EGFR WT and ERCC1+

EGFR wild type and ERCC1-

Erlotinib

Observation

CDDP-Pemetrexed

ClinicalTrials.gov. NCT00775385.
The SELECT Trial

Primary Endpoint DFS (ASCO 2011 preliminary: 94% 2 yr DFS)
Biopsy at Recurrence: EGFR Sequencing/EGFR, MET amplification (FISH)
Sequist, L et al. ASCO 2011
Current State of Evidence for the Role of Adjuvant Chemotherapy
CONCLUSIONS

- We know the benefit of adjuvant chemotherapy because of clinical trial participation.
- We only offer a 5% to 15% survival benefit with the best adjuvant chemotherapy.
- We can improve upon that plateau with better selection of patients (Prognostic Markers); better selection of drugs: (Predictive Markers) and better drugs!
- But ONLY with clinical trial participation, including tissue analysis. This is the only way forward!
The End
Thank You For Listening!
Thank You For Inviting me to Speak!

“Can We Go to the Park Now?”