Optimal Application of Adjuvant Therapy in NSCLC

Heather Wakelee, MD
Stanford University, Stanford Cancer Institute
### Post 1995 Meta-Analysis: NSCLC Randomized Adjuvant Platinum Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>n</th>
<th>Chemo</th>
<th>↑Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>E3590</td>
<td>II-IIIA</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>Yes⇒No</td>
</tr>
<tr>
<td>ANITA</td>
<td>I-IIIA</td>
<td>840</td>
<td>Cis/Vin</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Meta-analyses ~ 5% survival advantage at 5 yr, stage dependent
Lung adjuvant cisplatin evaluation (LACE)

- 5 trials - 4,584 patients
- Median follow-up: 5.1 years
- OS HR 0.89 [0.82-0.96], p = .005
- 5% OS benefit at 5 yrs

- Stage IA HR 1.40 [0.95, 2.06]
- Stage IB HR 0.93 [0.78, 1.10]
- Stage II/III HR 0.83 [0.73, 0.95]

Pignon JCO 26:3552, 2008
Long Term Adjuvant Benefit?

- IALT - yes at 5 yrs, no at 7.5 yrs
- ANITA - yes at 6.3 years
- JBR.10 yes at 5 yrs, YES at > 9 yrs
- All show benefit in stage II+

- Stage IB benefit? Overall NO:
  - Yes if >4cm in CALGB 9633
  - Probably if >4cm in JBR.10
## Stage IB T size analysis

<table>
<thead>
<tr>
<th></th>
<th>T &lt; 4 cm</th>
<th></th>
<th>T ≥ 4 cm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR OS</td>
<td>p</td>
<td>HR OS</td>
<td>p</td>
</tr>
<tr>
<td>CALGB 9633</td>
<td>1.02</td>
<td>.51</td>
<td>0.66</td>
<td>.04</td>
</tr>
<tr>
<td>JBR.10</td>
<td>1.73</td>
<td>.07</td>
<td>0.66</td>
<td>.13</td>
</tr>
<tr>
<td>No Chemo Benefit</td>
<td></td>
<td></td>
<td>Potential Chemo Benefit</td>
<td></td>
</tr>
</tbody>
</table>

Strauss *JCO* 2008, Vincent PASCO 2009
Which Chemotherapy?

- Strongest evidence for adjuvant chemotherapy in NSCLC is with cisplatin/vinorelbine
- TREAT trial at ASCO gives some evidence to support common practice of substituting other cisplatin doublets
- Definitively showed improved feasibility and drug delivery with cis/pemetrexed vs cis/vinorelbine; no efficacy endpoints

Kreuter PASCO 2011, abstr 7002
A simple proof in adjuvant chemotherapy

• So IF in metastatic disease:
  • Cis/Vin < Cis/Doce
  • Cis/Doce = Cis/Gem
  • Cis/Gem < Cis/Pem (non-squam)

• Then: either cis/doce, cis/gem or cis/pem (non-squam) > cis/vin for adjuvant therapy
• But this is BIOLOGY, not simple math

Wakelee, ASCO discussion 2011
NCCN Guidelines

- Adjuvant Chemotherapy, NSCL-D
- Includes 5 published cisplatin regimens
  - Cis 50 d 1,8 + Vin 25 d 1, 8, 15, 22 q 28
  - Cis 100 d 1 + vin 30 d 1, 8, 15, 22 q 28
  - Cis 75-80 d 1 + vin 25-30 day 1, 8 q 21
  - Cis 100 d 1 + etop 100 day 1-3, q 28
  - Cis 80 d 1 + vinblastine 4 q wk - q 2 wk q 21
- Includes 3 other regimens – all cis 75 q 21
  - Gem 1250 d 1,8: Doce 75 d 1, Pem 500 d 1
Other regimens being used:

E1505 - Chemo Choices to date

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Arm A</th>
<th>Arm B (BEV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin +</td>
<td>636</td>
<td>320</td>
<td>316</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>170(27%)</td>
<td>82(26%)</td>
<td>88(28%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>207(33%)</td>
<td>105(33%)</td>
<td>102(32%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>158(25%)</td>
<td>82(26%)</td>
<td>76(24%)</td>
</tr>
<tr>
<td>Pemetrexed*</td>
<td>99(16%)</td>
<td>50(16%)</td>
<td>49(16%)</td>
</tr>
</tbody>
</table>

*option only since 2009, non-squamous histology only

Wakelee abstr 7013, ASCO 2011
Adjuvant Elderly Analysis

- NCIC-CTG JBR.10
  - Analyzed young ≤ 65 yo (n=327) vs elderly > 65 (n=155)
  - Overall Survival HR 0.61 [0.38-0.98], p = .04 in elderly
- LACE elderly analysis
  - Analyzed ≤ 65 yo (n=3269) vs 65-69 (n=901) vs ≥ 70 (n=414)
  - Overall Survival HR 0.90 [0.7-1.16], ≥ 70 yo

- Elderly received less chemotherapy overall
- Toxicity differences not seen by age group, but more non-lung cancer deaths in elderly groups in LACE

- Adjuvant chemo should be offered to the fit elderly

Adjuvant Therapy in the Elderly - 2011

• Ontario- population study 2001-2006
  – 2001-3 vs 2004-6, 2763 cases >70 yo
  – 3.3% vs 16.2% -ACT; 4yr OS 47% vs 50%
  – 70% cis vs 28% carbo

• SEER data 1992-2005
  – 3,324 pts 65 yo+
  – 19% had adj chemo
  – 16% (105 pts) Cis, 77% carbo, HR 0.91, NS

Cuffe PASCO 2011, abstr 7012; Gu PASCO 2011, abstr 7014
Patient preferences: Adjuvant therapy

- Meta-analysis of 23 papers, 1987-2003
- Patients accept adjuvant therapy more if:
  - larger benefits (10% vs. 5% significant)
  - less toxicity
  - personal experience of a particular treatment
  - having dependents at home
- Age did not affect decisions
- Therapy acceptance higher if framed in terms of increased probability of survival versus survival prolongation

Jansen et al. JCO 22: 3181, 2004
Patient Selection
Prognostic vs Predictive

• Prognostic Marker:
  – Indicates survival benefit/detriment regardless of therapy
  – Stage, tumor size, sex
  – > 10 LNs resected
    • SEER -5 yr OS 58% vs 42% p<.0001 if 10+ LNs resected

• Predictive Marker:
  – Predicts for differential benefit from a particular therapy

Varlotto Cancer;115:851, 2009
IALT Bio - ERCC1 Testing

Results

• 761 tumors of 1867 total pts on trial
  – Adjuvant cis-based chemo: 389 (51%)
  – Control: 372 (49%)

  – 335 (44%) were ERCC1 positive
  • Chemo: 165        Control: 170

  – 426 (56%) were ERCC1 negative
  • Chemo: 224        Control: 202

Olaussen KA. *NEJM* ;355:983, 2006
IALT: Prognostic and Predictive Value of ERCC1 in Adjuvant Treatment of NSCLC

Patients With ERCC1-Negative Tumors

- Chemotherapy (105 deaths)
  - Control (113 deaths)
  - HR = 0.65 (0.50-0.86)
  - $P=0.002$

Patients With ERCC1-Positive Tumors

- Chemotherapy (92 deaths)
  - Control (80 deaths)
  - HR = 1.14 (0.84-1.55)
  - $P=0.40$

2008: HR 0.76 [0.59-0.98]  
2008: HR 1.20 [0.91-1.59]

Olaussen KA. *NEJM* ;355:983, 2006
# Early stage NSCLC Prognostic Biomarkers

<table>
<thead>
<tr>
<th>Reference</th>
<th>Marker</th>
<th>Trial</th>
<th>N</th>
<th>HR-survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fouret 2009</td>
<td>MSH2</td>
<td>IALT</td>
<td>768</td>
<td>HR 0.66, p. 01- high</td>
</tr>
<tr>
<td>Olaussen 2006</td>
<td>ERCC1</td>
<td>IALT</td>
<td>761</td>
<td>HR 0.66, p.009 -high</td>
</tr>
<tr>
<td>Filipits 2007</td>
<td>MRP 1</td>
<td>IALT</td>
<td>782</td>
<td>HR 1.37, p.007 -high</td>
</tr>
<tr>
<td>Tsao 2007</td>
<td>p53 expression</td>
<td>JBR.10</td>
<td>253</td>
<td>HR 1.89, p.03 - high</td>
</tr>
<tr>
<td>Seve 2007</td>
<td>B-tubulin III</td>
<td>JBR.10</td>
<td>256</td>
<td>HR 1.72 p. 04-high</td>
</tr>
<tr>
<td>Cappuzzo 2009</td>
<td>MET</td>
<td>Retrospective</td>
<td>447</td>
<td>HR 0.66, p.04 – neg</td>
</tr>
<tr>
<td>Rosell 2007</td>
<td>BRCA1</td>
<td>Retrospective</td>
<td>126</td>
<td>HR 1.98, p.02 -high</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>58</td>
<td>HR 2.4, p.04 - high</td>
</tr>
</tbody>
</table>

Others: VEGF, CRMP, CYFRA, CEA, BCL-2, FAS, epigenetic factors (p16, CDH13)…
Multiple Gene Expression Profiles: Including JBR.10 analysis…
# Early Stage NSCLC
## Predictors of Adj Chemo Benefit

<table>
<thead>
<tr>
<th>Reference</th>
<th>Marker</th>
<th>Trial</th>
<th>N</th>
<th>Overall survival-HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fouret 2009</td>
<td>MSH2</td>
<td>IALT</td>
<td>768</td>
<td>HR 0.75, p.03 - low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 1.14, p.44 - high</td>
</tr>
<tr>
<td>Olaussen 2006</td>
<td>ERCC1</td>
<td>IALT</td>
<td>761</td>
<td>HR 0.73, p.03 - low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 1.11 p.049 - high</td>
</tr>
<tr>
<td>Filipits 2007</td>
<td>p27$^{\text{Kip1}}$</td>
<td>IALT</td>
<td>778</td>
<td>HR 0.66, p.006 – neg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 1.09, p.54 - positive</td>
</tr>
<tr>
<td>Tsao 2007</td>
<td>p53 expression</td>
<td>JBR.10</td>
<td>253</td>
<td>HR 0.54, p.02 – pos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 1.40, p.26 - neg</td>
</tr>
<tr>
<td>Seve 2007</td>
<td>B-tubulin, III</td>
<td>JBR.10</td>
<td>133</td>
<td>HR 0.64, p.07-high - HR 1-low</td>
</tr>
<tr>
<td>Pirker 2007</td>
<td>ERCC1/p27$^{\text{Kip1}}$</td>
<td>IALT</td>
<td>778</td>
<td>HR 0.52 [0.36-0.74] both low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 1.27, NS both high</td>
</tr>
<tr>
<td>Fouret 2009</td>
<td>MSH2/ERCC1</td>
<td>IALT</td>
<td>658</td>
<td>HR 0.65, p.01 both low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 1.32, p.19 both high</td>
</tr>
</tbody>
</table>
Other Predictive Markers

• 15 gene signature from JBR.10 +/- chemo
  – High risk HR 0.33, p.0005 vs low risk HR 3.67, p.013
• To date these Prognostic + Predictive Factors in early stage are RETROSPECTIVE analyses
• PREDICTIVE markers in advanced NSCLC
• In general low levels = sensitivity
  – ERCC1 - platinum
  – Thymidylate Synthase (TS) - pemetrexed
  – RRM1 - Gemcitabine
  – BRCA 1 - low platinum, but HIGH for taxanes
  – EGFR mutation - EGFR-TKIs
  – KRAS mutation - No EGFR-TKI benefit
<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Therapy</th>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>C30506</td>
<td>Stage I</td>
<td>+/- Chemotherapy</td>
<td>Multiple</td>
</tr>
<tr>
<td>SWOG 0720</td>
<td>Stage I</td>
<td>+/- Chemotherapy (Cis/Gem)</td>
<td>ERCC1/RRM1</td>
</tr>
<tr>
<td>ITACA</td>
<td>Stage I-IIIA</td>
<td>Standard vs Selected Chemo (cis/pem)</td>
<td>ERCC1/TS</td>
</tr>
<tr>
<td>TASTE</td>
<td>Stage I-IIIA</td>
<td>Standard vs selected therapy (Cis vs Erlotinib)</td>
<td>ERCC1/EGFR mut</td>
</tr>
<tr>
<td>SCAT</td>
<td>Stage I-IIIA</td>
<td>Standard vs selected Platinum / Docetaxel</td>
<td>BRCA1/ RAP80</td>
</tr>
</tbody>
</table>
### S0720: Pharmacogenomic-directed Adjuvant Therapy of NSCLC

**Assignment**

<table>
<thead>
<tr>
<th>RRMI ≥ 40.5 AND ERCC1 &gt; 66.0</th>
<th>All Others (RRM1 &lt; 40.5 OR ERCC1 &lt; 66.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active Monitoring</strong></td>
<td><strong>Cisplatin-Gemcitabine</strong></td>
</tr>
</tbody>
</table>

- **Good Prognosis**
  - Less benefit from Chemotherapy

- **Poor Prognosis**
  - More benefit from Chemotherapy

**Primary Endpoint:** Feasibility measured as % of patients in whom treatment assignment can be made (>75%=success)
S0720 RRM1 and ERCC1 (AQUA) 64/83 (77%) eligible for chemo

$r = 0.40 (p = 0.0002)$

<table>
<thead>
<tr>
<th>RRM1</th>
<th>ERCC1</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;65</td>
<td>≥65</td>
<td>Total</td>
</tr>
<tr>
<td>≥ 40</td>
<td>22</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>31</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>30</td>
<td>83</td>
</tr>
</tbody>
</table>

Zinner WCLC 2011
Met Primary Endpoint of Feasibility

- 72/83 (87%) treatment assignments met requirements
- 64/83 (77%) evaluated pts assigned to chemo
- 14/64 pts (22%) declined treatment assignment

Biomarker

- RRM1 and ERCC1 levels correlated with each other
- Neither correlated with gender, age, histology
ITACA: Pharmogenomic-Driven Adjuvant Study of ERCC1 & TS

High/Low ERCC1 & TS selected according to median level of mRNA expression in historical series; * Control arm – Investigator choice of a DDP-based doublet.
**TASTE design**

**Control Arm**
CDDP - pemetrexed

**Experimental Arm**
Customized

- **EGFR mutated**
  - Erlotinib
- **EGFR wt**
  - **ERCC1+**
    - Observation
  - **ERCC1-**
    - CDDP-Pemetrexed

**Non-SCC NSCLC stage II and IIIA (non-N2)**

*Intergroupe Francophone de Cancérologie Thoracique*
Spanish Customized Adjuvant Therapy in completely resected N1 & N2 NSCLC

Genotyping for EGFR & K-ras mutations

CONTROL

Docetaxel/Cis

Docetaxel/Cis

T1 RAP80 (T1-T3 BRCA1)

Docetaxel/Cis

T2-T3 RAP80 (T1-T2 BRCA1)

Docetaxel

T2-T3 RAP80 (T3 BRCA1)

Resected NSCLC pN1 / pN2

1:1

EXPERIMENTAL
## Phase III “Targeted” Therapy Adjuvant Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Therapy</th>
<th>Target</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>RADIANT</td>
<td>I-IIIA</td>
<td>Erlotinib x 2 yr</td>
<td>EGFR-IHC+</td>
<td>945</td>
</tr>
<tr>
<td>MAGRIT</td>
<td>IB-IIIA</td>
<td>Vaccine x 27 mo</td>
<td>MAGE-A3</td>
<td>2270</td>
</tr>
<tr>
<td>E1505</td>
<td>IB(≥4cm)-IIIA</td>
<td>Chemo +/- Bevacizumab</td>
<td>?</td>
<td>1500</td>
</tr>
</tbody>
</table>

DFS: Disease-free survival; OS: Overall survival
Pts with completely resected stage IB, II, and IIIA NSCLC

Stratified by
- stage
- histology
- post-op RT
- sex
- adjuvant chemotherapy*

Gefitinib
250 mg po daily x 2 yrs

Placebo
po daily x 2 yrs

Randomized 1:1

Goss PASCO 2010, abstr 7005
BR.19 - Overall Survival

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
BR.19 Overall Survival by *EGFR* Mutation Status and Treatment

### Wild type

- **Placebo**
  - # at Risk: 145, 126, 118, 105, 91, 77
  - Percentage at each time point: 100, 80, 60, 40, 20, 0
- **Gefitinib**
  - # at Risk: 136, 121, 110, 99, 89, 74
  - Percentage at each time point: 100, 80, 60, 40, 20, 0

**HR (95% C.I.)**
- Gefitinib/Placebo: 1.21 (0.84, 1.73)
- Log Rank: *p*=0.301

**Median (95% C.I.)**
- Placebo: Not reached (5.1, inf.)
- Gefitinib: 5.0 (4.3, inf.)

### Sensitizing mutation

- **Placebo**
  - # at Risk: 40, 38, 32, 30, 26, 21
  - Percentage at each time point: 100, 80, 60, 40, 20, 0
- **Gefitinib**
  - # at Risk: 36, 29, 26, 17, 7, 0
  - Percentage at each time point: 100, 80, 60, 40, 20, 0

**HR (95% C.I.)**
- Gefitinib/Placebo: 1.58 (0.83, 3.00)
- Log Rank: *p*=0.160

**Median (95% C.I.)**
- Placebo: 5.1 (4.4, inf.)
- Gefitinib: 3.7 (2.6, inf.)

Goss PASCO 2010, abstr 700
RADIANT
Adjuvant NSCLC +/- Erlotinib

ELIGIBLE:
N=945
Resected I-IIIA
≥Lobectomy
Required IHC/FISH for EGFR
Chemo optional

STRATIFIED:
-Histology
-Gender
-Age
-EGFR Status
-Smoking
-Adj Chemo

RANDOMIZE
2:1
 DFS as primary endpoint

Erlotinib 150 mg po qd X 2 yrs
Observation
RADIANT - biomarker outcomes

- 974 pts enrolled
- 17% w/ EGFR mut
  - 27% F, 10% M
  - 46% Asian, 4% Black, 11% Caucasians
  - 53% NS, 4% current smoker (CS), 9% former smoker (FS)
  - 28% adenocarcinoma, 4% Squamous cell
- 16% KRAS mut
  - 6% NS, 14% CS, 20% FS

Richardson WCLC 2011 O28.01
MAGRIT Adjuvant NSCLC (+/- Chemo)+/-MAGE-A3 vaccine

ELIGIBLE:
N=2270 screened
Resected IB-IIIA
≥Lobectomy
Required MAGE-A3 Expression (<40%)
Chemo optional/
Pts stratified by +/- chemo

RANDOMIZE

MAGE-AE ASCI x 13 Injections over 27 mo

placebo injections

DFS as primary endpoint
ECOG 1505
Adjuvant NSCLC Chemo+/ - Bevacizumab

ELIGIBLE:
N=1500
Resected IB-IIIA (1B ≥ 4cm)
≥Lobectomy
No prior chemo
No planned XRT

STRATIFIED:
-Stage
-Histology
-Gender
-Chemo*

RANDOMIZE
Chemotherapy
X 4 cycles
Chemotherapy
X 4 cycles
Plus
Bevacizumab
X 1 year

* Investigator Choice of 4 chemo: Cis/Vin, Cis/Docetaxel, Cis/Gem, Cis/Pem

Overall Survival
Primary Endpoint
E1505 Eligibility

- Adequate Resection*
- 6-12 wks postop
- Anticoagulation OK (INR $\leq 3$)
- No prior chemotherapy
- No MI, ATE for 12 mo
- No CVA, TIA ever
- No uncontrolled HTN ($<150/90$)
- No planned PORT

*Surgical resection minimum lobectomy
Med LN sampling required:
L sided level 7 + level 5 or 6
R sided level 7 + level 4
## E1505 Significant Tox Differences

<table>
<thead>
<tr>
<th>Condition</th>
<th>Arm A n=341 Gr 3/4</th>
<th>Arm B (Bev) n=329 Gr 3/4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>57(17%) / 69(21%)</td>
<td>68(21%)/ 76(24%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7(2.1%) / 0(0%)</td>
<td>64(20.1%)/ 3(0.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 (0.6%) / 0</td>
<td>8(2.5%) / 1 (0.3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (0.3%) / 0</td>
<td>12 (3.8%) / 2 (0.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>21(6.3%)/1(0.3%)</td>
<td>31(9.7%)/5(1.6%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>1(0.3%)/0</td>
<td>6(1.9%)/0/1 gr 5 (0.3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Worst grade - any</td>
<td>130 (38%) / 95 (28%)</td>
<td>160 (50%) / 107 (34%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 5</td>
<td>8 (2.4%)</td>
<td>10 (3.1%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Wakelee et al; WCLC 2011: Abstract O42.03
## E1505 Other Grade 3/4 Toxicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Arm A n=341 Gr 3/4</th>
<th>Arm B (Bev) n=329 Gr 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>19(5.7%)/3(0.9%)</td>
<td>14(4.4%)/6(1.9%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11(3.3%)/8(2.4%)</td>
<td>17(5.3%)/4(1.3%)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>11 (3.3%)/11 (3.3%)/2*</td>
<td>10(2.8%)/11(3.1%)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>11(3.3%)/2(0.6%)</td>
<td>15(4.7%)/2(0.6%)/1*</td>
</tr>
<tr>
<td>CNS ischemia</td>
<td>1(0.3%)/2(0.6%)</td>
<td>3(0.9%)/2(0.6%)</td>
</tr>
<tr>
<td>Hemorrhage#</td>
<td>3(0.9%)/1(0.3%)</td>
<td>5(1.6%)/0/1*</td>
</tr>
</tbody>
</table>

*Gr 5 Thrombosis, Gr 5 Febrile neutropenia, other Gr 5 in results listed separately

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Only 1 bronchopleural fistula seen (non-fatal)
GI perforations 1 arm A, 2 arm B

#Arm A: CNS (Gr 4), GI (Gr 3, N=2), nose (Gr 3)
Arm B: CNS (Gr 3), GI (Gr 3, N=2), lung (Gr 3 N=1, Gr 5 N=1), nose (Gr 3)

Wakelee et al; WCLC 2011: Abstract O42.03
Conclusions

• Adjuvant cisplatin chemotherapy SOC for pts w/resected stage II/IIIA NSCLC
• Pts w/larger stage I tumors may benefit
• Neo-adjuvant therapy vs adjuvant unresolved
• Long term follow-up important
• More critical issues are:
  • Better patient selection (ERCC1, MSH2, gene analysis, etc.) with ongoing trials
  • Better drugs are needed (targeted)
    – EGFR, VEGF, VACCINES