Southwest Oncology Group (SWOG)
Lung Committee:
Current Trials & Future Directions

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UC Davis Cancer Center
SWOG Lung Committee: Stage I-III NSCLC

- **NSCLC, Stage I**
  - **S0720**: ERCC1/RRM1 Adjuvant Trial Zinner/Bepler
  - **CALGB 140503**: Lobectomy vs Sublobar Resection in Small Peripheral NSCLC

- **NSCLC, Stage IB-IIIA**
  - **E1505**: Chemo +/- Bevacizumab
S0720: Biomarker-directed Adjuvant Chemotherapy of Stage I NSCLC (ERCC1 & RRM1)

NSCLC Stage I pT1(≥2cm) pT2N0M0

R0 resection
PS 0-1
N=55

Assignment
Cisplatin-Gemcitabine Vs Observation

ERCC1 & RRM1 AQUA testing

ERCC1: Excision Repair Cross-Complementing Group 1
RRM1: Ribonucleotide Reductase M1

ERCC1-RRM1 Combination Index: Superiority in Predictive Value for Platinum-based Chemotherapy

**S0720: Biomarker-directed Adjuvant Therapy of Stage I NSCLC**

<table>
<thead>
<tr>
<th>Assignment</th>
<th>RRMI $\geq 40.5$ AND ERCC1 $\geq 66.0$</th>
<th>All Others (RRMI $&lt; 40.5$ OR ERCC1 $&lt; 66.0$)</th>
</tr>
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<tbody>
<tr>
<td>Observation</td>
<td></td>
<td>Cisplatin-Gemcitabine</td>
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**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 Eligibility

- Stage I by 6th edition staging system (Stage I, no positive lymph nodes)
  - T1a ≥ 2cm
  - T1b
- Open or VATS: Lobectomy, bi-lobectomy, pneumonectomy
- At least 2 LN stations must be sampled
  - If Right; 4R, 7, 8, 9 and 10R
  - If Left; 4L, 5, 6, 7, 8, 9 and 10L
- Tumor tissue available
- No prior chemotherapy or radiation
- PS 0-1

Zinner, Bepler, Gandara et al: IASLC WCLC 2011
Phase II Pharmacogenomics-Based Adjuvant Therapy Trial in Stage I NSCLC

Started Accrual April 2009. 85 pts enrolled. 83 eligible.

- Met Primary Endpoint of Feasibility
- Expression analysis for all 83 eligible pts
- 72/83 (87%) treatment assignment met requirements
- Pre-specified target was at least 85%

- 64/83 (77%) evaluated pts assigned to chemo (95% CI: 67%-86%)
  Expected: 70%
- 14/64 pts (22%) declined treatment assignment

Zinner, Bepler, Gandara et al: IASLC WCLC 2011
RRM1 and ERCC1 (AQUA)

64/83 (77%) eligible for chemo

$r = 0.40 (p = 0.0002)$

<table>
<thead>
<tr>
<th>RRM1</th>
<th>ERCC1 &lt;65</th>
<th>≥65</th>
<th>Total</th>
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<tbody>
<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>
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</table>

S0720 Conclusions

Met Primary Endpoint of Feasibility
- 72/83 (87%) treatment assignments met requirements
- 64/83 (77%) patients assigned to chemotherapy
- 14/64 pts (22%) declined treatment assignment

Biomarker
- RRM1 and ERCC1 levels correlated with each other
- Neither correlated with gender, age, histology

Future Directions
- Expand accrual to cross-compare different biomarker methodologies

Zinner, Bepler, Gandara et al: IASLC WCLC 2011
Expansion of a Phase II Pharmacogenomics-Based Adjuvant Therapy Trial in Patients with Stage I Non-Small Cell Lung Cancer (NSCLC) S0720

- Increase from current 83 to total 125 patients
- Further Characterization of ERCC1/RRM1. The Main Goal is to correlate Protein and mRNA expression levels to determine comparability
  - Endpoints (all on formalin fixed paraffin embedded tissue)
  - RRM1: AQUA current polyclonal and AQUA a new mAbs
  - RRM1 & ERCC1:
    - AQUA current reagents vs. RT-PCR proprietary (Response Genetics Inc.)
    - AQUA current reagents vs. RTPCR commercial
    - RTPCR: (Response Genetics Inc.) vs. commercially available
    - AQUA current reagents vs. AQUA mAbs vs. mRNA by both techniques
SWOG Lung Committee Trials:
Advanced NSCLC (Active Trials)

• NSCLC, First Line Advanced Stage
  – S0819: Paclitax/Carbo +/- Cetux ( +/- Bev eligible) Herbst/Kim

• NSCLC, First Line Adv Stage PS 2
  – S0709: PS2 adv: Proteomics + : Erlotinib +/- Chemo Lara
S0819: Phase III Trial of Chemotherapy +/- Cetuximab

**NSCLC Adv Stage**

**Tumor Tissue available**

**Co-Primary Endpoints:** 1545 patients (618 FISH +)

**Primary Endpoints:** OS (entire study), PFS (EGFR FISH)

**Correlative Science:**
- **Tumor:** EGFR/HER pathways; KRAS
- **Genomic DNA:** EGFR polymorphisms
- **Plasma:** Proteomic predictor

*In Bevacizumab Eligible: as piloted in S0536*
FLEX: Cetuximab + Chemotherapy Improves Overall Survival

HR = 0.871, 0.762–0.996
Log-rank $P = .044$

1-year OS 47% vs 42%

Pirker: ASCO, 2008
FLEX: Response rate by EGFR expression levels (quantitative IHC Score)

Low EGFR expression (<200)
- n=776 (69%)

High EGFR expression (≥200)
- n=345 (31%)

Treatment interaction test p=0.040

O’Byrne et al. JTO 2010, 12 (suppl), S558 (LBOA1)
Predictive value of high EGFR for Survival benefit with CT + cetuximab

Low EGFR H score

HR 0.99 [95% CI 0.84–1.16]

High EGFR score

HR 0.73 [95% CI 0.58–0.93]

Interaction p-value=0.044

Pirker et al. WCLC 2011, # O 01.06
S0342 Phase II Selection Design:
Chemotherapy plus Concurrent or Sequential Cetuximab

Paclitaxel
Carboplatin
Cetuximab
X 4 cycles

Cetuximab
weekly x
1 year

Concurrent

Sequential

Paclitaxel
Carboplatin
Cetuximab
X 4 cycles

Cetuximab
weekly x
1 year

Progression-Free Survival

Overall Survival

Herbst: et al  JCO 2010 (in press)
S0342: Concurrent or Sequential Chemotherapy + Cetuximab: Analysis by EGFR FISH

<table>
<thead>
<tr>
<th>EGFR FISH</th>
<th>OR (CR/PR)</th>
<th>DCR (CR/PR/SD)</th>
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<tbody>
<tr>
<td>FISH-</td>
<td>26%</td>
<td>55%</td>
</tr>
<tr>
<td>FISH+</td>
<td>45%</td>
<td>81%** (p=0.02)</td>
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**Hirsch: JCO, 2008**
S0342: KRAS Mutation Analysis

KRAS in Tissue/Plasma

Progression-free survival by KRAS in plasma or tissue

Overall survival by KRAS in plasma or tissue

Mack et al: ASCO 09
S0536: Paclitaxel/Carboplatin + Cetuximab/Bevacizumab

- Partial Response: 54%
- Stable Disease: 23%
- Disease Control Rate: 77%
- Progression-free survival: 7 months
- Overall survival: 15 months

Kim et al: manuscript in preparation
S0819: Phase III Trial of Chemotherapy +/- Cetuximab (builds on S0342 & S0536)

**NSCLC Adv Stage**

**Tumor Tissue available**

**Co-Primary Endpoints:**
- 1545 patients (618 FISH +)

**Primary Endpoints:**
- OS (entire study)
- PFS (EGFR FISH)

**Randomize**

- Paclitaxel
- Carboplatin
- *Bevacizumab

*In Bevacizumab Eligible: as piloted in S0536

**Correlative Science:**
- **Tumor:** EGFR/HER pathways; KRAS
- **Genomic DNA:** EGFR polymorphisms
- **Plasma:** Proteomic predictor
Advanced NSCLC: In Development

- (S10XX) ALK fusion NSCLC:
  - Study 1: ALK Biomarker comparisons in Crizotinib-naïve NSCLC
  - Study 2: Crizotinib +/- Pemetrexed in ALK-positive NSCLC at time of PD to Crizotinib

Li/Camidge
Identification of the transforming \textit{EML4–ALK} fusion gene in non-small-cell lung cancer

Manabu Soda$^{1,2}$, Young Lim Choi$^1$, Munehiro Enomoto$^{1,2}$, Shuji Takada$^1$, Yoshihiro Yamashita$^1$, Shunpei Ishikawa$^5$, Shin-ichiro Fujiwara$^1$, Hideki Watanabe$^1$, Kentaro Kurashina$^1$, Hisashi Hatanaka$^1$, Masashi Bando$^2$, Shoji Ohno$^2$, Yuichi Ishikawa$^6$, Hiroyuki Aburatani$^{5,7}$, Toshirō Niki$^3$, Yasunori Sohara$^4$, Yukihiko Sugiyama$^2$ & Hiroyuki Mano$^{1,7}$

\textbf{EML4–ALK} frequency:

$\sim 4\%$ NSCLC (64/1709) adenocarcinoma (acinar subtype)

\textit{Soda et al., Nature, 2007}
Responses to Crizotinib in ALK fusion-positive NSCLC

- ORR = 64%
- DCR = 90%
- Median duration of treatment = 19+ wks (3-64+)
- Median PFS not reached (>75% still on treatment)

• Is break-apart FISH the best test to identify who will respond to Crizotinib?
• How do we handle acquired resistance to crizotinib?
Study 1: ALK Screening Test Trial (SWOG & N. American Intergroup): Comparisons of FISH, RT-PCR & IHC

**Tumor** sample sent to SWOG central pathology lab

Abbott break-apart FISH screening (positive if >15% of scored tumor cells have split ALK 5' and 3' probe signals or single 3' red signals)

- **FISH positive**
  - Retrospective

- **FISH negative**
  - IHC and RT-PCR assays
    - IHC or RT-PCR positive
    - Negative for both IHC and RT-PCR = screen failure

Study Entry: Crizotinib Treatment

PIs: T. Li, R. Camidge
Study 2: Proposed SWOG Phase II Trial in ALK-positive NSCLC after PD on Crizotinib

Recurrent NSCLC
One prior platinum based therapy
EGFR - and VEGF- directed therapy allowed
ALK-positive by FISH
PD after Crizotinib therapy

PF-1066 + Pemetrexed

Pemetrexed

Phase III if meets endpoints

Endpoints:
PFS
ORR, DCR, OS,
Toxicity

Pls: T. Li
R. Camidge
SWOG Lung Committee Trials: SCLC

• SCLC, Limited Stage
  – CALGB: Ph III: High vs Standard RT +/- Cetux

• SCLC, Extensive
  – (S1114): Ph II/III: PE +/- AZ2171 Heymach/Glisson
  – S0802: Ph II 2nd line: VEGF Trap + Topotecan Allen/Jahanzeb
  – (S10XX): Ph II 2nd line: MK2206 (AKT-I) Huang/Kelly
S1114: Phase II/III Trial in Extensive SCLC

- **E-SCLC**
  - Chemo naïve
  - PS 0-1
  - No CNS mets
  - No hemoptysis

**Randomizer**

- **EP + AZ2171**
  - 20 mg daily
- **AZ2171**
  - 20 mg daily
- **EP + Placebo**
- **Placebo**

**Biomarker-embedded design:** Randomized, adaptive phase III design

**PIs:** J. Heymach, B. Glisson
S0124: PE (Cisplatin/Etoposide) vs PI (Cisplatin/Irinotecan)

- **Response**: 60% vs 57%, p-value 0.56
- **PFS (mos)**: 5.7 vs 5.2, p-value 0.07
- **OS (mos)**: 9.9 vs 9.1, p-value 0.71

S0124 did not confirm results of J9511
Efficacy of Irinotecan greater in Japanese patients
Toxicity greater in Japanese patients
Pharmacogenomics may have influenced results

*Lara: JCO, 2009*
Phase I Trial of AZD2171 (Cediranib) + Etoposide/Cisplatin in Ext-SCLC

Figure 1. Study design

Heymarch et al: ASCO 2010
Phase I Trial of AZD2171 + Etoposide/Cisplatin in Ext-SCLC

Waterfall Plot of Response (ORR=71%)

Preliminary PFS: Median=8.9 mos

Heymachi et al: ASCO 2010
S1114: Biomarker-embedded design: Randomized Adaptive Design

- **Stage 1: Marker training**
  - randomly select 1/2 pts
  - test markers
  - define predictive marker

- **Stage 2: Marker validation**
  - classify remaining 1/2 pts by marker
  - unblind outcome

- **Primary Endpoint:** Improved OS Overall study (EP/2171 vs EP arm)
  - $\alpha=0.04$

- **Co-Primary Endpoint:** Improved OS Marker+ group
  - $\alpha=0.01$

Note: patient numbers are projected based on statistical modeling
SWOG Lung Committee Trials: Mesothelioma

- **S0905**: Ph II: Pemetrexed/Cis +/- AZD2171  
  Tsao/Vogelzang

- **S0722**: RAD001  
  Ou

- (S10XX): EPP vs Pleurectomy in Meso  
  Kernstine

- (S10XX): Ph II: Gem/Cis +/- ABT888  
  Garland

- (S10XX): BIBW1120 (VEGFR-I)  
  Wozniak
S0905: Phase I/II Trial of Pemetrexed-Cisplatin +/- AZ2171 in first line therapy of Advanced Mesothelioma

Run In Phase I
Cohort 1: 30 mg
Cohort 2: 20 mg

RANDOMIZE

Pemetrexed
Cisplatin
+ Placebo

AZ2171

Placebo
### S0509: AZ2171 in Second Line Therapy of Mesothelioma

<table>
<thead>
<tr>
<th>Response</th>
<th>N=46</th>
<th>Percent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Partial Response</td>
<td>4</td>
<td>9%</td>
<td><strong>Two patients with bulky disease: 91% and 56% tumor shrinkage</strong></td>
</tr>
<tr>
<td>Stable Disease</td>
<td>15</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>19</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>19</td>
<td>41%</td>
<td></td>
</tr>
</tbody>
</table>

*Garland: ASCO 2009*
S0509: AZ2171 in Second Line Mesothelioma

Overall Survival

OS  Events / N  Median in Months
36 / 46  9.8 (5.6,11.8)

1 yr. Surv: 37% (22-51%)
2 yr. Surv: 11% (3-24%)

Garland: ASCO 2009
SWOG Malignant Pleural Mesothelioma: QOL Concept
Extra-Pleural Pneumonectomy (EPP) vs Pleurectomy-Decortication (PD)

**Phase II Trial Design**

- **Histo Confirmed, Stages I-IIIA, Standardized PreOp Evaluation**

**Stratify:**
- Histology
- Stage
- Nodes & Histology
- PreOp Therapy
- Adj Thx

**Assignment**
- Standard EPP
- Standard P/D

**Primary Endpoint:**
- % return to baseline QOL at 3, 6, 9, 12, 18, 24 months

**Secondary Endpoints:**
- Cost of Care at 3, 6, 9 and 12 months
- % Ready for adjuvant 2-year DF and O survival

*Kernstine et al*