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

David R. Gandara, MD
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SWOG Lung Committee:
Stage I-III NSCLC

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

- NSCLC, Stage IB-IIIA
  - E1505: Chemo +/- Bevacizumab
  - ...

Slide 3

S0720: Biomarker-directed Adjuvant Chemotherapy of Stage I NSCLC (ERCC1 & RRM1)

- NSCLC, Stage I
- pT1(>2cm)
- pT2N0M0
- R0 resection
- PS 0-1
- N=55
- Enrollment
- Assignment
- Cisplatin-Gemcitabine
- Surgery
- Observation
- ERCC1 & RRM1:

Slide 1

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

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- NSCLC, Stage I
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- Cisplatin-Gemcitabine
- Surgery
- Observation
- ERCC1 & RRM1:
ERCC1-RRM1 Combination Index: Superiority in Predictive Value for Platinum-based Chemotherapy


### Slide 5

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

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Observation</th>
<th>Cisplatin-Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRM1 &gt; 40.5 AND ERCC1 &gt; 66.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Others</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Less benefit from chemotherapy</th>
<th>More benefit from chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
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</table>

**Primary Endpoint:** Feasibility measured as % of patients in whom treatment assignment can be made (>75%=success)

**Zinner, Bepler, Gandara et al: IASLC WCLC 2011**

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**S0720 Eligibility**

- Stage I by 6th ed staging system (Stage I, no positive lymph nodes)
  - T1a ≤ 2cm
  - T1b
- Open or VATS: Lobectomy, bilobectomy, 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: 75%
- 14/64 pts (22%) declined treatment assignment

Zinner, Bepler, Gandara et al: IASLC WCLC 2011

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RRM1 and ERCC1 (AQUA)

64/83 (77%) eligible for chemo

\[ r = 0.40 \text{ (p = 0.0002)} \]


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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
  - RRMI & ERCC1:
    - AQUA current reagents vs. RT-PCR proprietary (Response Genetics Inc.)
    - AQUA current reagents vs. RTPCR commercial
    - RT-PCR, (Response Genetics Inc.) vs. commercially available
    - AQUA current reagents vs. AQUA mAbs vs. mRNA by both techniques

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**SWOG Lung Committee Trials: Advanced NSCLC (Active Trials)**

- NSCLC, First Line Advanced Stage
  - **S0819**: Paclitaxel/Carbo +/- Cetux (+/- Bev eligible)
  
  - Herbst/Kim

- NSCLC, First Line Adv Stage PS 2
  - **S0709**: PS2 adv: Proteomics + : Erlotinib +/- Chemo

  - Lara

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**S0819: Phase III Trial of Chemotherapy +/- Cetuximab**

<table>
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<tr>
<th>NSCLC Adv Stage</th>
<th>Paclitax + Carb +/− Cetuximab +/− Bevacizumab</th>
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<tr>
<td>Tumor Tissue available</td>
<td>Paclitax + Carb +/− Cetuximab +/− Bevacizumab</td>
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<tr>
<td>Co-Primary Endpoints: 1545 patients (618 FISH +)</td>
<td>Correlative Science: EGFR/HER pathways; KRAS</td>
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<tr>
<td>Randomize:</td>
<td>Response: EGFR polymorphisms</td>
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<tr>
<td>OS (entire study), PFS (EGFR FISH)</td>
<td>EGFR/HER predictor</td>
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FLEX: Cetuximab + Chemotherapy Improves Overall Survival

- Patients surviving, %
  - Cetuximab + CT
  - CT

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

FLEX: Cetuximab + Chemotherapy Improves Overall Survival

Pirker: ASCO, 2008

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FLEX: Response rate by EGFR expression levels (quantitative IHC Score)

- Low EGFR expression (≤200)
- High EGFR expression (≥200)

- CT
- CT + cetuximab

- Response rate (%)
- Interaction p-value = 0.040
- O’Byrne et al. JTO 2010, 12 (suppl), S558 (LBOA1)

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Predictive value of high EGFR for Survival benefit with CT + cetuximab

- Low EGFR score
- High EGFR score

- Interaction p-value = 0.040

Pirker et al. WCLC 2011, # O 01.06
Progression-free survival by KRAS in tissue

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<tr>
<th>Months After Registration</th>
<th>Mutant</th>
<th>Other</th>
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Progression-free survival by KRAS in plasma or tissue

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Overall survival by KRAS in plasma or tissue

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<th>Mutant</th>
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<tr>
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<td>69</td>
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<tr>
<td></td>
<td>27</td>
<td>23</td>
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</table>

S0342 Phase II Selection Design:
Chemotherapy plus Concurrent or Sequential Cetuximab

Chemotherapy
Concurrent
Sequential
Cetuximab
FISH+
FISH

S0342: KRAS Mutation Analysis

KRAS in Tissue/Plasma

Hirsch: JCO, 2008

Herbst: et al JCO 2010 (in press)
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**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

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**S0819: Phase III Trial of Chemotherapy +/- Cetuximab (builds on S0342 & S0536)**

**NSCLC Adv Stage**

**Tumor Tissue available**

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

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

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

In Bevacizumab Eligible: as piloted in S0536

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**Advanced NSCLC: In Development**

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

Li/Camidge
**Slide 22**

**EML4-ALK Translocations in NSCLC**

Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer

- **EML4-ALK frequency:**
  - ~4% NSCLC (64/1709) adenocarcinoma (acinar subtype)


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**Responses to Crizotinib in ALK fusion-positive NSCLC**

- **Responses**: ORR = 64%, DCR = 90%
- **Median duration of treatment**: 19+ wks (3-64+)
- **Median PFS**: Not reached (>75% still on treatment)

- **Questions**:
  - Is break-apart FISH the best test to identify who will respond to Crizotinib?
  - How do we handle acquired resistance to crizotinib?

**Slide 24**

**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**
  - Study Entry: Crizotinib Treatment
  - FISH negative
  - IHC or RT-PCR positive
  - Negative for both IHC and RT-PCR = screen failure

- **Retrospective**
  - PIs: T. Li, R. Camidge
**Slide 25**

**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

**Endpoints:**
- PFS
- ORR, DCR, OS
- Toxicity

**Study 2: Proposed SWOG Phase II Trial**

- in ALK-positive NSCLC after PD on Crizotinib
  - Phase III if meets endpoints

**PIs:** T. Li, R. Camidge

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**SWOG Lung Committee Trials: SCLC**

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

- **SCLC, Extensive**
  - (S1114): Ph II/III: PE +/- AZ2171
  - S0802: Ph II 2nd line: VEGF Trap + Topotecan
  - Allen/Jahanzeb
  - (S10XX): Ph II 2nd line: MK2206 (AKT-I)

**SWOG Lung Committee Trials: SCLC**

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**S1114: Phase II/III Trial in Extensive SCLC**

- E-SCLC
- Chemonaive
- PS 0-1
- No CNS mets
- No hemoptysis

**Randomize**

- EP + AZ2171
  - 20 mg daily
- AZ2171
  - 20 mg daily

**Randomize, adaptive phase II design**

**PIs:** J. Heymach, B. Glisson
**Slide 28**

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

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Phase I Trial of AZD2171 (Cediranib) + Etoposide/Cisplatin in Ext-SCLC

Heymach et al: ASCO 2010

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Phase I Trial of AZD2171 + Etoposide/Cisplatin in Ext-SCLC

Waterfall Plot of Response (ORR=71%)
Preliminary PFS:
Median=8.9 mos

Heymach et al: ASCO 2010
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**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

**α = 0.04**

Note: patient numbers are projected based on statistical modeling.

**SWOG Lung Committee Trials: Mesothelioma**

- **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

**S0905:** Phase III 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**
  - + AZ2171
  - + Placebo
  - **AZ2171**
  - **Placebo**

**SWOG Lung Committee Trials:**

- **Mesothelioma**
  - **S0905:** Ph II: Pemetrexed/Cis +/- AZ2171
  - Taieb-Vogelzang
  - **S0722:** RAD001
  - Ou
  - **(S10XX):** EPP vs Pleurectomy in Meso
  - Kernstine
  - **(S10XX):** Ph II: Gem/Cis +/- ABT888
  - Garland
  - **(S10XX):** BIBW1120 (VEGFR-I)
  - Wozniak

**SWOG Lung Committee Trials:**

- **Mesothelioma**
  - **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
  - **Pemetrexed Cisplatin**
    - + Placebo
    - + AZ2171
  - **AZ2171**
  - **Placebo**
S0509: AZ2171 in Second Line Therapy of Mesothelioma

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>4</td>
<td>9%</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>15</td>
<td>32%</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>19</td>
<td>41%</td>
</tr>
</tbody>
</table>

Two patients with bulky disease: 91% and 56% tumor shrinkage

Disease Control Rate 19 (42%)

Glanz: ASCO 2009

S0509: AZ2171 in Second Line Mesothelioma

Overall Survival

OS

Events / N
36 / 46

Median in Months
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)

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

Assignment

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

Secondary Endpoints:
- Cost of Care at 3, 6, 12 and 24 months
- % Ready for adjuvant 2-year OS and D survival

Kernstine et al