Lung Cancer Program

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Using the right treatment for the right patient

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Clinical and Translational Program

• Genetic studies on large retrospective series, with the goal to identify molecular prognostic and predictive markers and druggable genetic alterations in:
  – Lung cancer
  – Thymomas
• Prospective Molecular Profiling in patients visiting NCI/MOB
• Clinical studies of targeted agents for molecularly defined patients
Biomarker discovery and molecular characterization studies in clinical specimens

Integrated database

Clinical specimen

Standardized processing and storage

Biospecimen

DNA

RNA

primary culture

array CGH mutation analysis

microRNA expression/ISH

Cancer stem cell (in vitro/in vivo)
IALT-BIO collaboration

**AIM:** microRNA expression profiling to determine prognostic biomarkers and to predict benefit adjuvant chemotherapy in resectable non-small cell lung cancer (NSCLC)

**Material:** Formalin Fixed Paraffin Embedded Tissue Sections (n = 783)

1. **FFPE section**
2. RNA extraction
3. Real-Time PCR
4. **predictive/prognostic microRNA validation**
5. **clinical parameters/statistical analysis**
6. In Situ Hybridization
Molecular characterization of small cell lung cancer (SCLC)

AIMS:  
- molecular characterization of small cell lung cancer  
- comparison with other neuro-endocrine tumors  
- drug target discovery

Material: FFPE Tissue/ archival FNA smears

[Diagram showing process flow from FFPE Tissue to Biomarkers and Validation studies via DNA extraction, array CGH, mutation analysis, and bio-informatics]
Array CGH of small cell lung cancer and neuro-endocrine tumors

**Array CGH data**

Cluster analysis

Cluster 3
Mix

Cluster 2
80% NET

Cluster 1
80% SCLC

**Comparison of clusters**

Molecular classification
Thymoma

- Thymoma is a tumor of the epithelial cell of the thymus
- Thymoma is the most common cancer of the anterior mediastinum
- There are different histotypes with different outcome

Chen G et al. Cancer 2002 (N=200)
Thymoma Samples

- FFPE blocks from a series of 134 thymoma patients.
- CGH is feasible only when cancer cell are >50%.
- 66 samples match the criteria for cancer cell concentration
- 68 samples have too many lymphocytes
- Actually we analyzed the results of 26 samples.
Defining histotype specific genome aberration
Genome imbalance differences
## Cluster Analysis

<table>
<thead>
<tr>
<th>sample</th>
<th>WHO subtype</th>
<th>Cluster</th>
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<td>I-Thy 027</td>
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<tr>
<td>I-Thy 103</td>
<td>B3</td>
<td>cluster1</td>
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<td>cluster2</td>
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<td>I-Thy 109</td>
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<td>I-Thy 7</td>
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<tr>
<td>I-Thy 78</td>
<td>B3</td>
<td>cluster3</td>
</tr>
</tbody>
</table>
Case Presentation

• 52 y/o AA male
  – Never smoker
  – Diagnosed with NSCLC adenocarcinoma
  – Stage IV, multiple lesions in LLL and RUL

– No Past Medical History
– No Family History

– Treatment:
  – carboplatin/paclitaxel/bevacizumab
    • 8 cycles, initial Partial Response (PR) then Progressive Disease (PD)
  – erlotinib 150 mg PO daily, (6 weeks) PD
  – Referred for evaluation at NCI
Treatment Course

• Screened for PF-00299804 trial:
  – KRAS wild type (wt)
  – [EGFR wt]

• Enrolled on trial PF-00299804 for patients who have failed EGFR TKIs

• Started on PF-00299804
  – 45 mg PO daily
PF-00299804

- Apoptosis resistance
- Proliferation
- Transcription
- Angiogenesis
- Metastasis
Maximum percentage change in target lesions per RECIST in 41 patients with both a baseline and at least one on-study measurement (March 31, 2009)

PD = progressive disease; PR = partial response; SD = stable disease.

P. Janne….G. Giaccone, ASCO 2009
Pretreatment and after 4 cycles of PF-00299804

October 21, 2008

January 16, 2009
Serum HER-2 levels at baseline and through 4 cycles of PF-00299804 therapy

C = cycle; D = day; ECD = extracellular domain; EGFR = epidermal growth factor receptor; WT = wild type.
Stain Tumor for Her2/Neu

**HER2/Neu FISH**

**PATHOLOGY**

- IHC 2+
- Her2/Neu Amplified
  - Cells counted 20
  - HER2 = 10.3
  - CEP17 = 2.4
  - HER2/CEP17 Ratio: 4.3
Prospective Molecular Profiling

Background

• The treatment of lung cancer and thymic malignancies is based on histopathology and clinical stage.

• Existing classifications and staging systems have reached their limit in providing information that may influence management or improve outcome.

• Molecular characterization of tumors has the potential ability to classify more accurately than histology and indicate specific treatments for subsets of patients.
Prospective Molecular Profiling

General Outline

• Prospective collection of fresh frozen and PEFF tumor and circulating tumor material from patients with lung cancer and thymic malignancies coming to the clinical center.

• Extensive molecular profiling:
  – Limited profile for treatment decision
  – Exploratory investigations

• Allow treatment based on molecular profiling
  – Set up mechanism for access to experimental drugs for single patient studies
Subgroups of specific interest

- Lung cancer in never-smokers
- Lung cancer in women
- Lung cancer in younger than 40
- Familial forms of lung cancer
- Rare histological forms of lung cancer
- Lung cancer in HIV patients
- Thymomas
- Thymic carcinoma
Targeted Therapy

- **EGFR-exon 19 or 21 mutation**
  - Gefitinib (CTEP) or erlotinib
- **EGFR-exon 20 (i.e. T790M)**
  - PF-00299804 or BIBW-2292 (Drug Company)
- **MET amplification**
  - Met TKI or anti-Met ab (CTEP)
- **Alk translocation**
  - Alk inhibitor (Drug Company)
- **Trk mutation**
  - Trk inhibitor (Drug Company)
- **Her2 amplification**
  - Herceptin or pertuzumab (CTEP)
- **PDGFRA amplification**
  - Sunitinib (CTEP)
- **N-Ras, K-ras, BRAF or MEK mutations**
  - Mek inhibitor (CTEP)
- **PI3KCA mutation**
  - Akt or mTOR inhibitor
  - Temsirolimus, perifosine (CTEP)
Molecular Profiling

- **Mutations**
  - EGFR, ERBB2, KRAS, NRAS, BRAF, PIK3CA, AKT1, CTNNB1, C-MET, TRK, MEK, FGFR4, LKB1, P53, PTEN, RB

- **FISH**
  - EML4/ALK translocation
  - MET, EGFR, HER-2 and PDGFRA amplification

- **Genome-wide screening**
  - Comparative genomic hybridization
  - Solexa sequencing

- **Blood samples analysis**
  - Circulating tumor cells
  - Circulating tumor DNA of targeted genes by Fluidigm analysis
  - Circulating miRNAs by Solexa sequencing
Belinostat, a pan-HDACi - Phase I Clinical Data: Solid Tumours

Five patients (all treated at ≥ 900 mg/m²/day) had longer treatment duration on belinostat monotherapy than on their previous treatment.

Phase Ib/II soft-tissue sarcoma trial underway based on interesting patient data:
- Belinostat + doxorubicin

Patient with epithelial thymoma receiving belinostat 900 mg/m² as 5th line treatment during a period of 17 months:
- SD until PD at 30.7 months after belinostat treatment initiation
- 4th line therapy treatment period was 1 month
- 12% tumour size reduction was achieved

### Characteristics of patients who derived apparent clinical benefit from belinostat

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumour type</th>
<th>No of prior therapies</th>
<th>Treatment duration on most recent prior therapy (months)</th>
<th>Response to belinostat</th>
<th>Treatment duration on belinostat (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Epithelial thymoma</td>
<td>4</td>
<td>1</td>
<td>SD (12% reduction)</td>
<td>17</td>
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<td>2</td>
<td>Soft –tissue sarcoma</td>
<td>1</td>
<td>2</td>
<td>SD (9% reduction)</td>
<td>14</td>
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<tr>
<td>3</td>
<td>Soft –tissue sarcoma</td>
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<td>1</td>
<td>SD</td>
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<tr>
<td>4</td>
<td>Melanoma</td>
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<td>1</td>
<td>SD</td>
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<tr>
<td>5</td>
<td>Renal carcinoma</td>
<td>3</td>
<td>1</td>
<td>SD (14% reduction)</td>
<td>4</td>
</tr>
</tbody>
</table>

Pre-belinostat

Locally advanced epithelial mediastinal thymoma

Baseline CT scan

CT scan post cycle 16.
# Patient Characteristics

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>n</th>
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<tbody>
<tr>
<td>Accrual start:</td>
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<tr>
<td>December 17, 2007</td>
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<tr>
<td>Number of patients enrolled</td>
<td>31</td>
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<tr>
<td>National Cancer Institute (NCI)</td>
<td>22</td>
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<tr>
<td>Indiana University (IU)</td>
<td>9</td>
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<tr>
<td>Mean Age (range), years</td>
<td>53.5 years (24 – 84 years)</td>
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<tr>
<td>Gender, M : F</td>
<td>18:13</td>
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<tr>
<td>Histology</td>
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<tr>
<td>Thymoma</td>
<td>21</td>
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<tr>
<td>Thymic Carcinoma</td>
<td>10</td>
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<tr>
<td>Paraneoplastic syndromes</td>
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<tr>
<td>Myasthenia Gravis</td>
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<tr>
<td>Schulman’s syndrome</td>
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<tr>
<td>Infections (Candida mucositis)</td>
<td>1</td>
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</tbody>
</table>
Duration of Therapy

[Graph showing duration of therapy for different cases, with green bars for Thymoma and red bars for Thymic carcinoma, and arrows indicating patients on study.]
Maximum percentage change in target lesions from baseline

* Non-target lesions did not regress
Plan on attending the upcoming

1st International Conference on Thymic Malignancies
August 20-21, 2009

Hosted by the National Cancer Institute, Medical Oncology Branch
Bethesda, Maryland

http://web.ncifcrf.gov/events/thymic/program.asp

Natcher Conference Center, NIH
Lung Cancer: Family of Distinct Diseases

• Emerging etiologic, clinical and molecular data reveal lung cancer to be a family of related but distinct diseases. The implications are that clinical trials will require studies in select subsets of patients. Given the challenges in accruing patients to lung cancer studies, how will we complete future trials that include the obligatory subsets?
Questions

• How can we assure adequate patient accrual in key lung cancer populations?  
  – i.e. health disparities, former/nonsmokers, women, and different molecular profiles

• How can we better integrate patient accrual and tissue availability with detailed patient characterization to fully exploit the unique challenges of molecularly defined subgroups for prevention, screening, detection, diagnosis, treatment, and follow-up?

• What preclinical models and approaches for lung cancer subgroups can be used/developed to accelerate translation?

• How can we capitalize on the implications of emerging lung cancer and smoking susceptibility genes?