NCAB
June 11 2009

Lung Cancer Program

- Neil Caporaso – Genetic Epidemiology Branch (DCEG)
- Phil Dennis – Medical Oncology Branch
- Giuseppe Giaccone – Medical Oncology Branch

Using the right treatment for the right patient

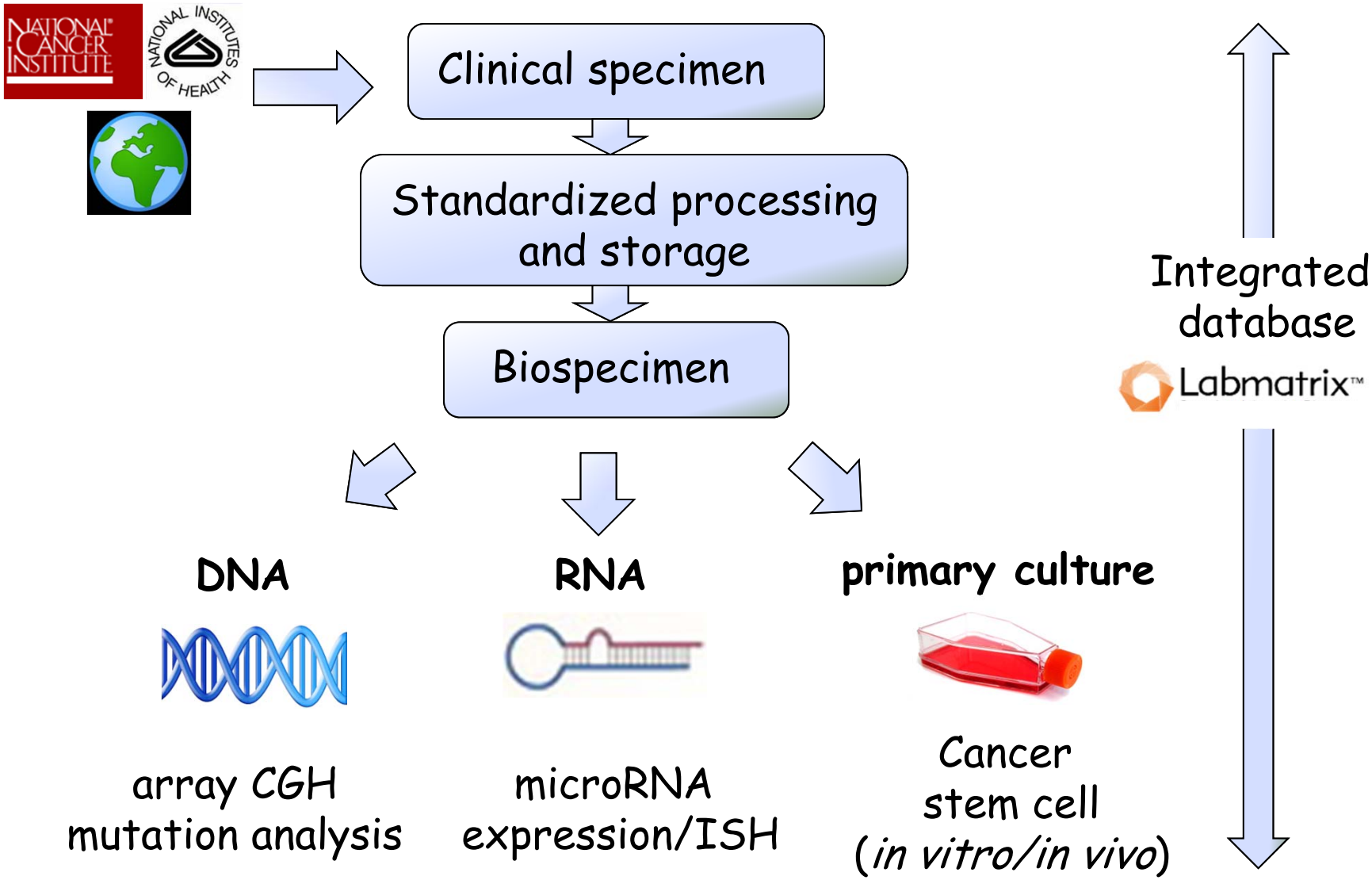
Giuseppe Giaccone, MD PhD

Chief, Medical Oncology Branch

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

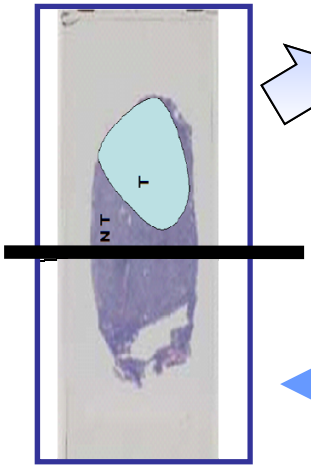


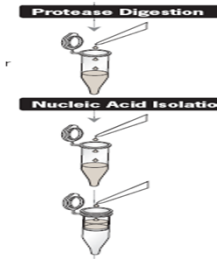
IALT-BIO collaboration

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

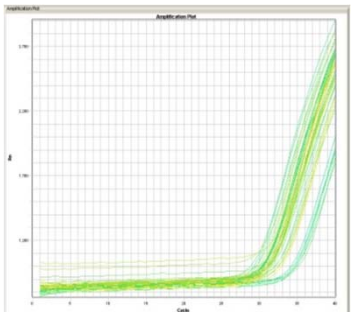
Material: Formalin Fixed Paraffin Embedded Tissue Sections (n = 783)

FFPE section





RNA extraction

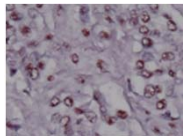


Real-Time PCR

clinical parameters/ statistical analysis

predictive/ prognostic microRNA

validation



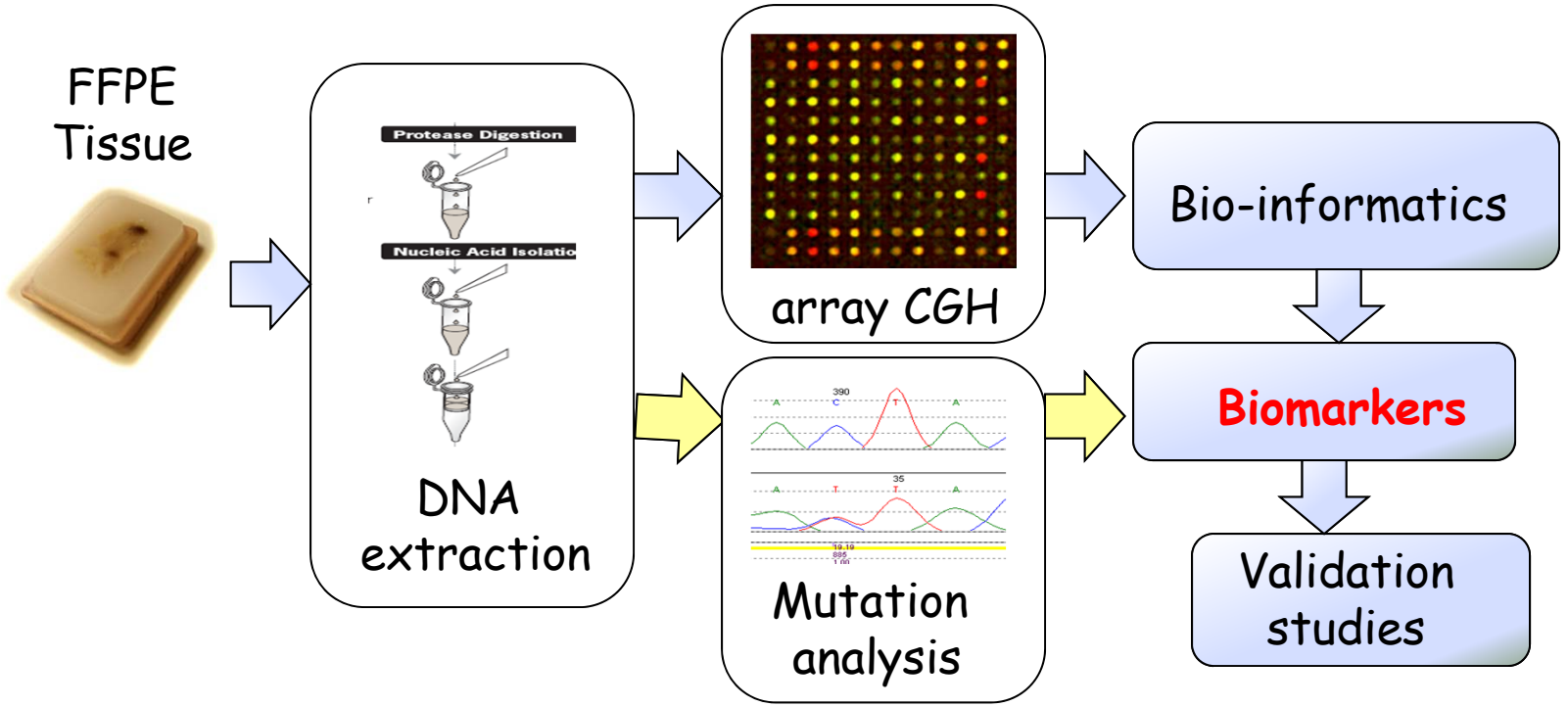
In Situ Hybridization

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

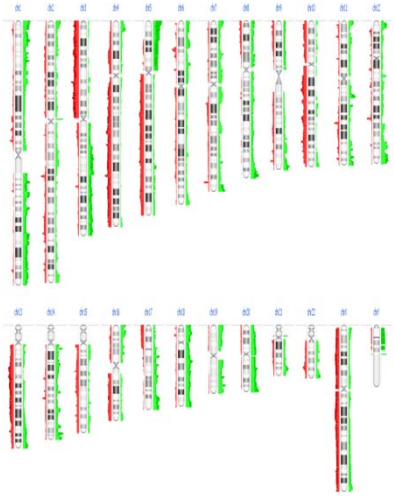
Genetics Branch/ CMPC

Material: FFPE Tissue/ archival FNA smears

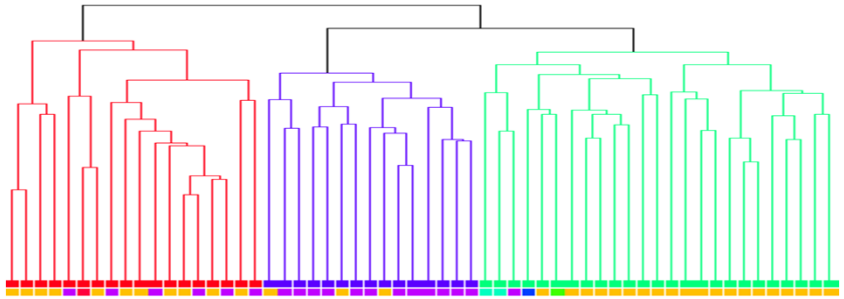


Array CGH of small cell lung cancer and neuro-endocrine tumors

Array CGH data



cluster analysis



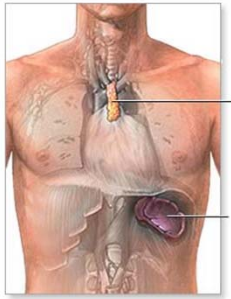
Cluster 3 | Cluster 2 | Cluster 1

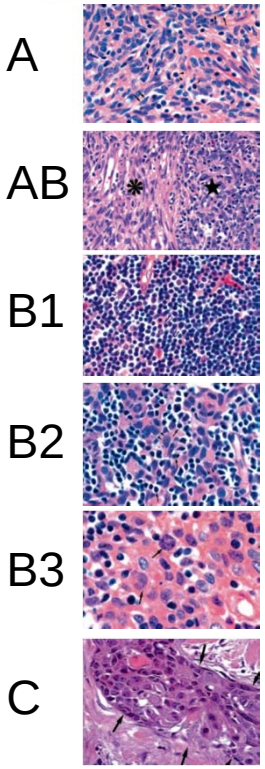
Mix | 80% NET | 80% SCLC

Comparison of clusters

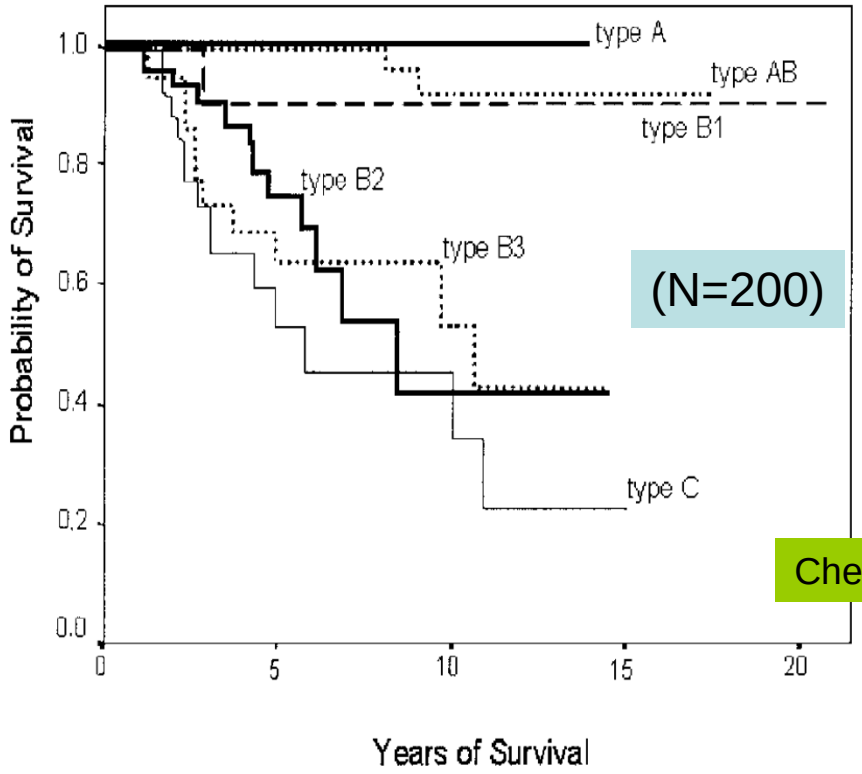
Molecular classification

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

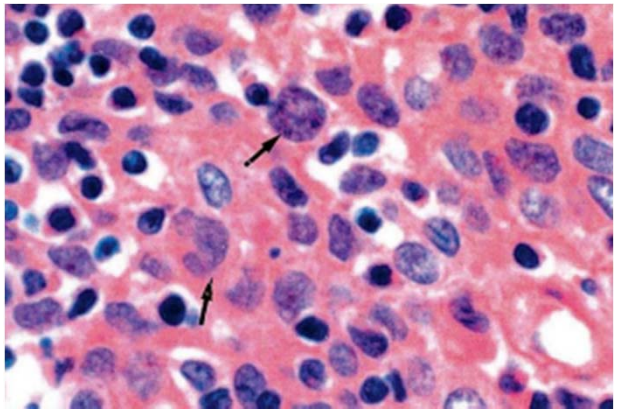


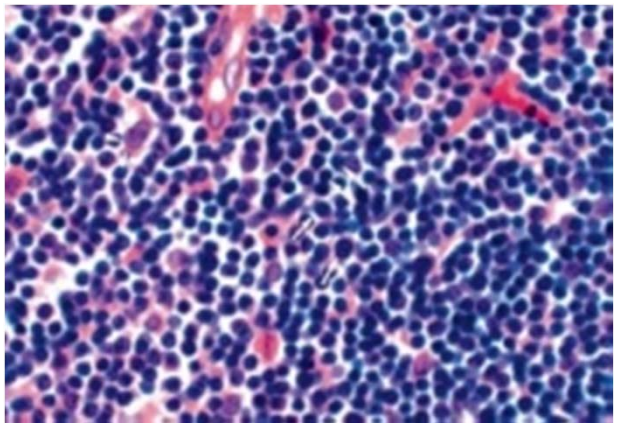
(N=200)

Chen G et al. Cancer 2002

Thymoma Samples

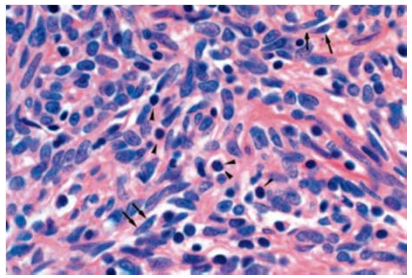
- FFPE blocks from a series of 134 thymoma patients.
- CGH is feasible only when cancer cell are >50%.
- 66 samples match the criteria for cancer cell concentration
- 68 samples have too many lymphocytes
- Actually we analyzed the results of 26 samples.

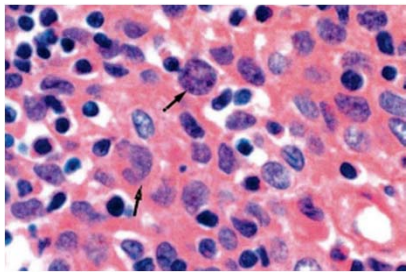


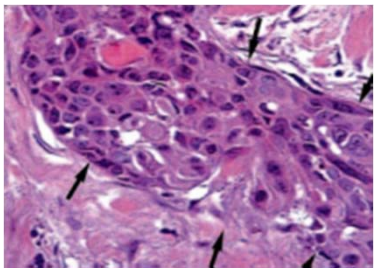


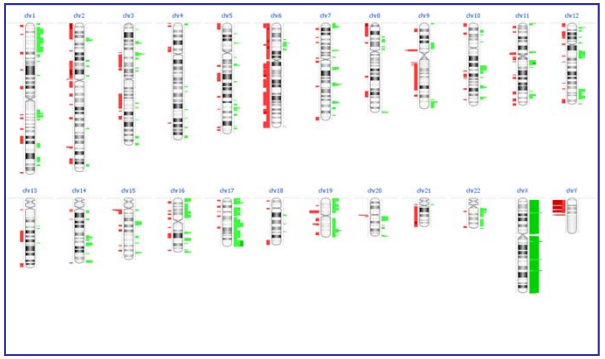
Defining histotype specific genome aberration

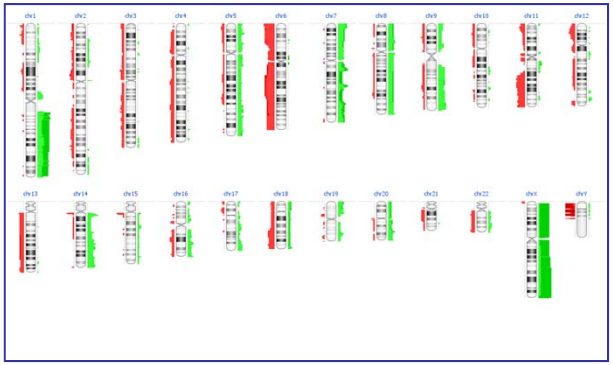
A B3 C

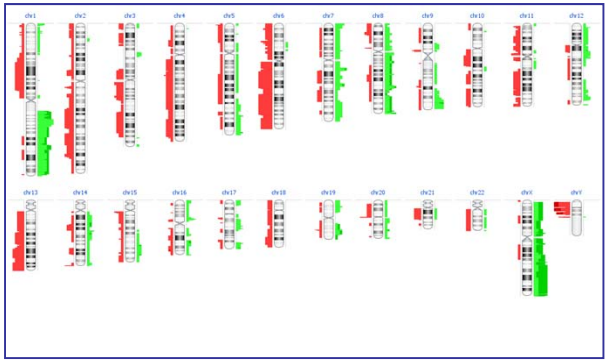




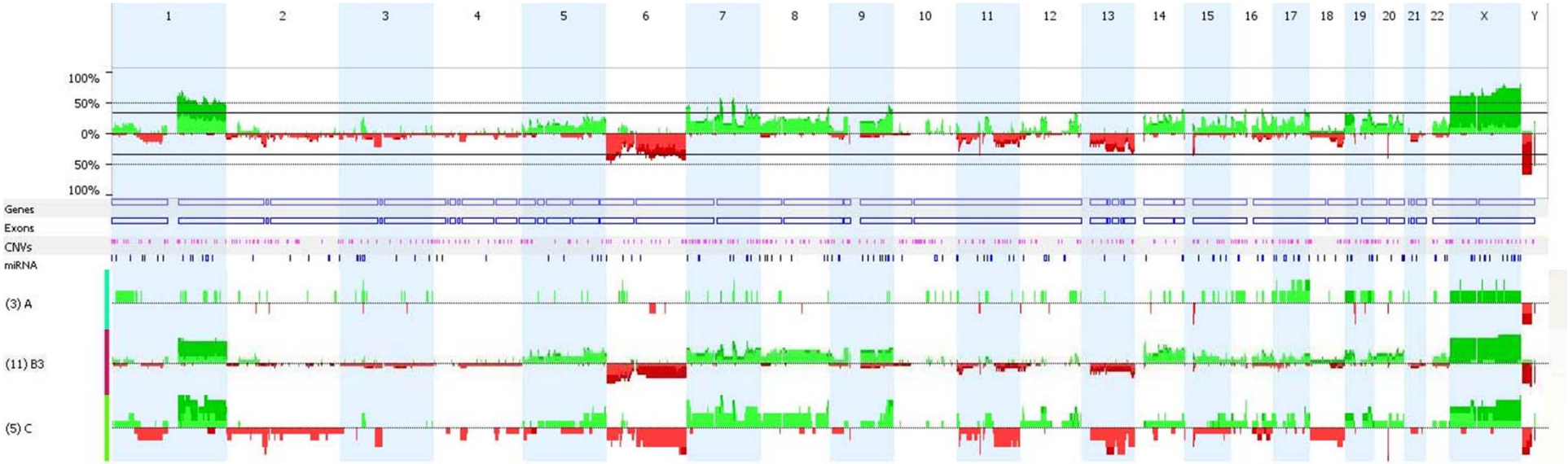




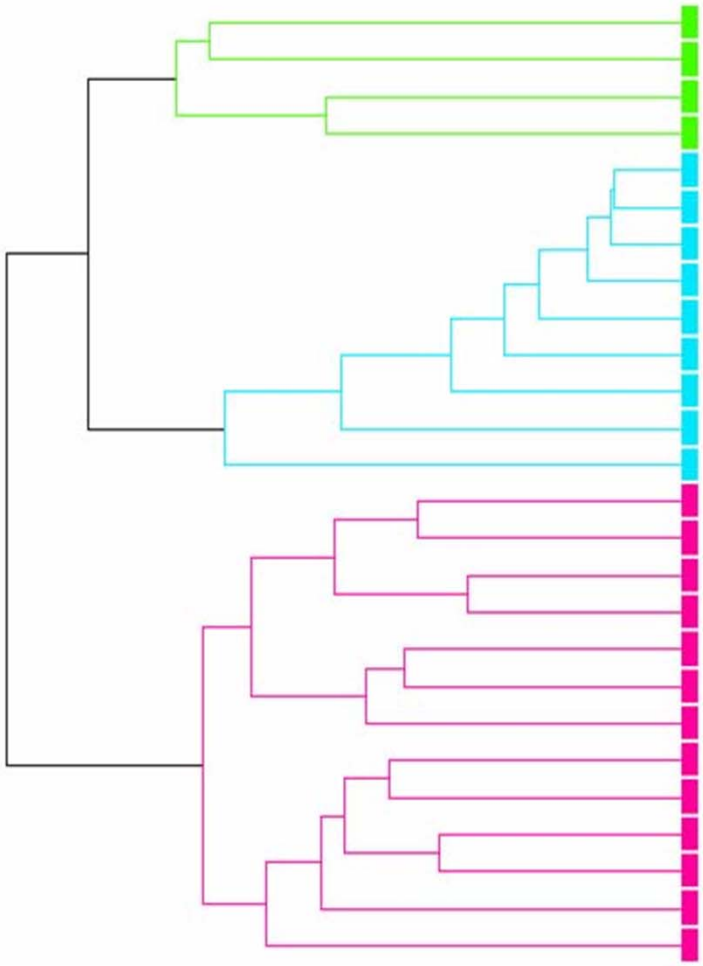




Genome imbalance differences



Cluster Analysis



sample	WHO subtype	Cluster
I-Thy 027	A	cluster1
I-Thy 032	AB	cluster1
I-Thy 100	C	cluster1
I-Thy 103	B3	cluster1
I-Thy 020	AB	cluster2
I-Thy 030	AB	cluster2
I-Thy 049	B3	cluster2
I-Thy 054B	B2	cluster2
I-Thy 070	B3	cluster2
I-Thy 102	A	cluster2
I-Thy 130	B3	cluster2
I-Thy 6	A	cluster2
I-Thy 97	AB	cluster2
I-Thy 016A	B3	cluster3
I-Thy 024	B3	cluster3
I-Thy 026	AB	cluster3
I-Thy 046	B3	cluster3
I-Thy 056	C	cluster3
I-Thy 064	B3	cluster3
I-Thy 086A	C	cluster3
I-Thy 101	B3/B2	cluster3
I-Thy 109	B3	cluster3
I-Thy 4	B3	cluster3
I-Thy 7	C	cluster3
I-Thy 83A	C	cluster3
I-Thy78	B3	cluster3

Case Presentation

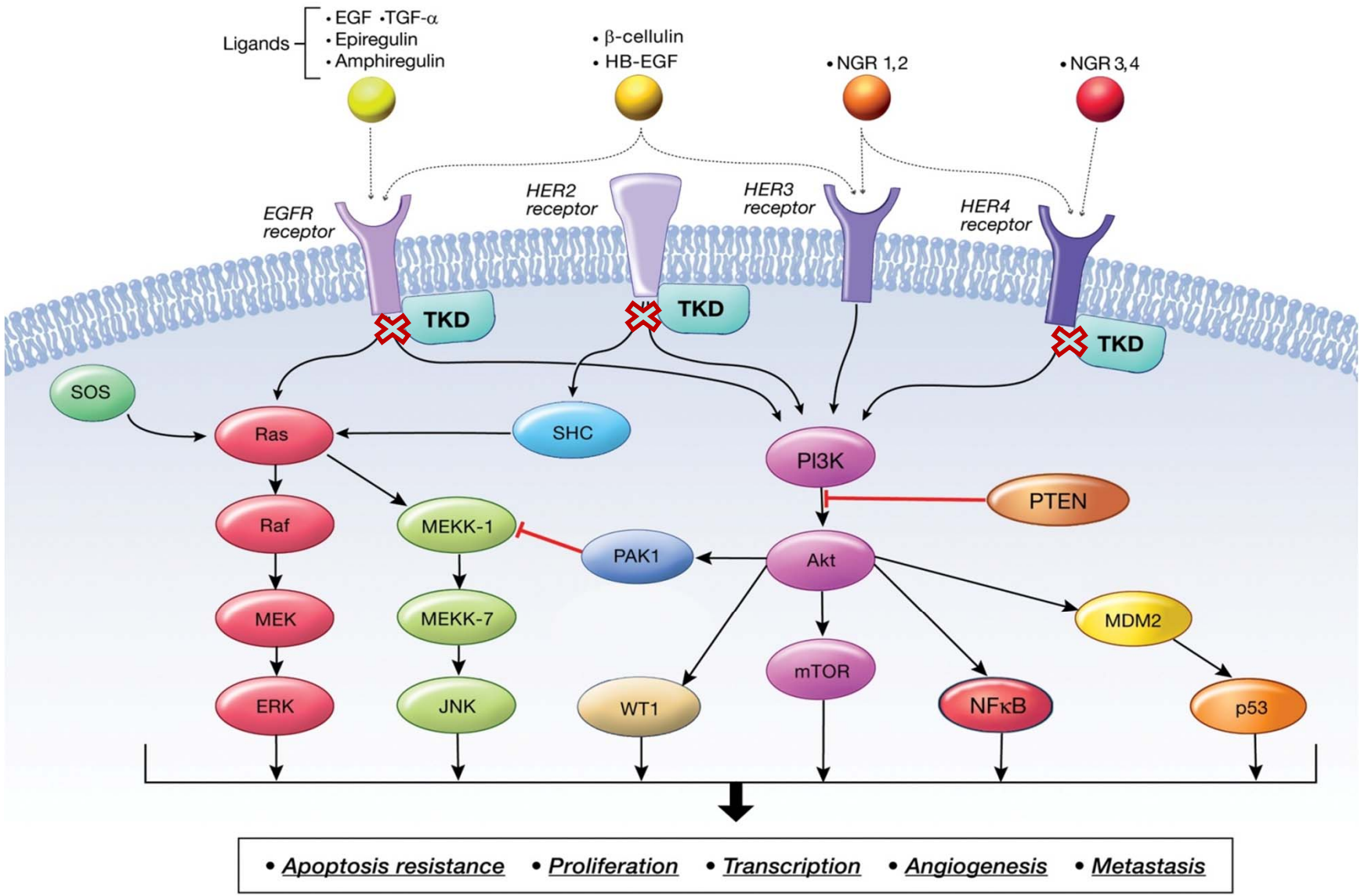
- 52 y/o AA male
  - Never smoker
  - Diagnosed with NSCLC adenocarcinoma
  - Stage IV, multiple lesions in LLL and RUL
- No Past Medical History
- No Family History

- 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

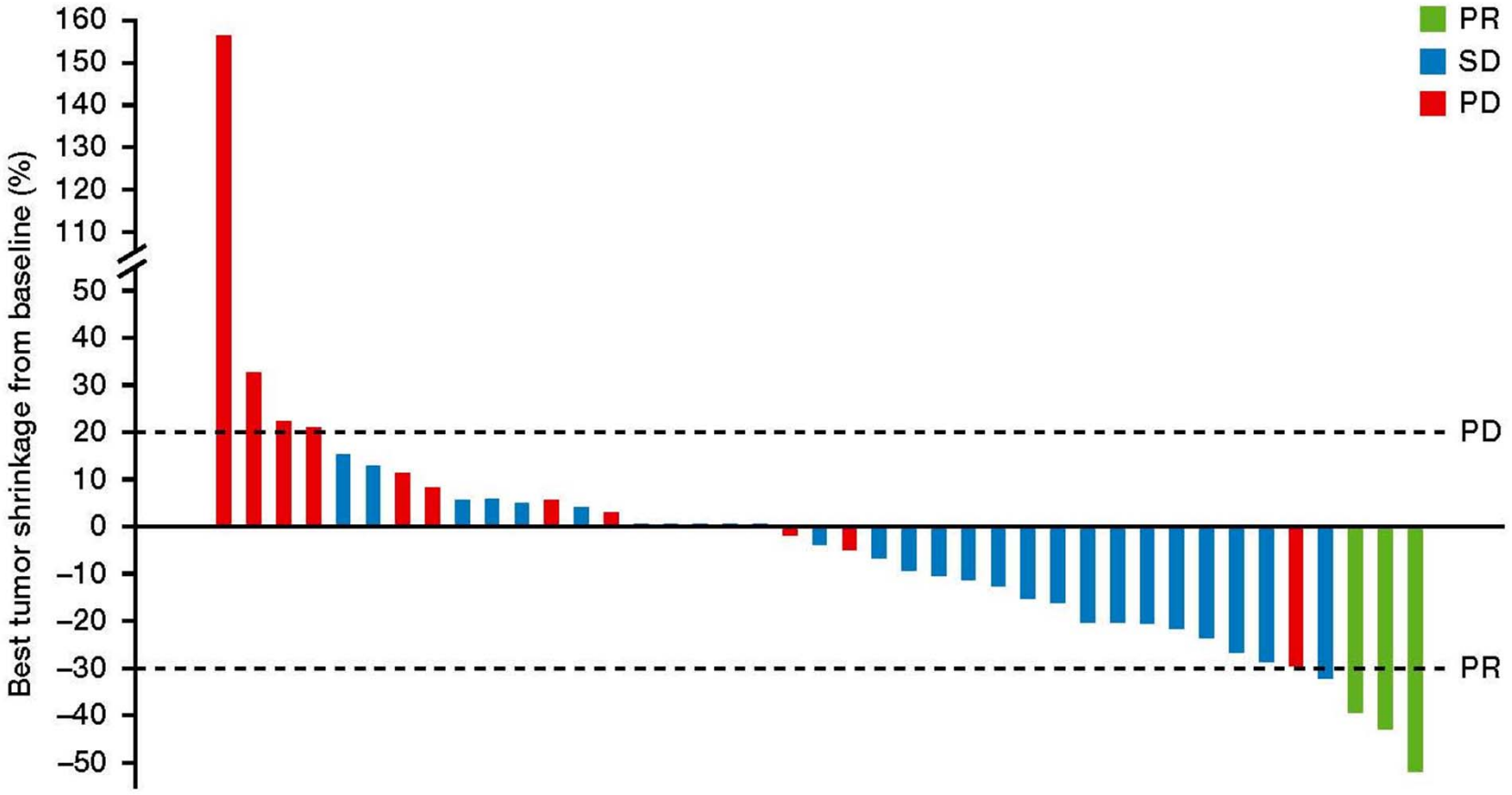
Treatment Course

- 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


Ligands
• EGF • TGF-α
• Epiregulin
• Amphiregulin
• β-cellulin
• HB-EGF
• NGR 1,2
• NGR 3,4
EGFR receptor
HER2 receptor
HER3 receptor
HER4 receptor
TKD
TKD
TKD
SOS
Ras
SHC
PI3K
PTEN
Raf
MEKK-1
PAK1
Akt
MEK
MEKK-7
MDM2
mTOR
ERK
JNK
WT1
NFκB
p53
• Apoptosis resistance • Proliferation • Transcription • Angiogenesis • Metastasis

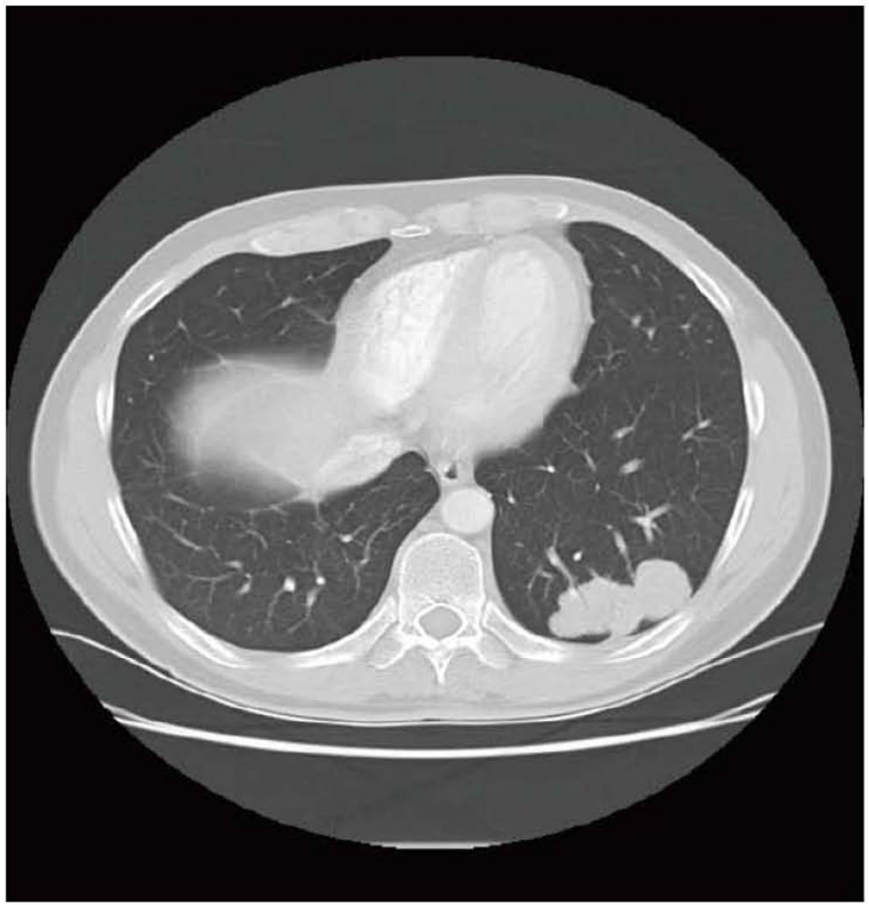
Maximum percentage change in target lesions per RECIST in 41 patients with both a baseline and at least one on-study measurement (March 31, 2009)



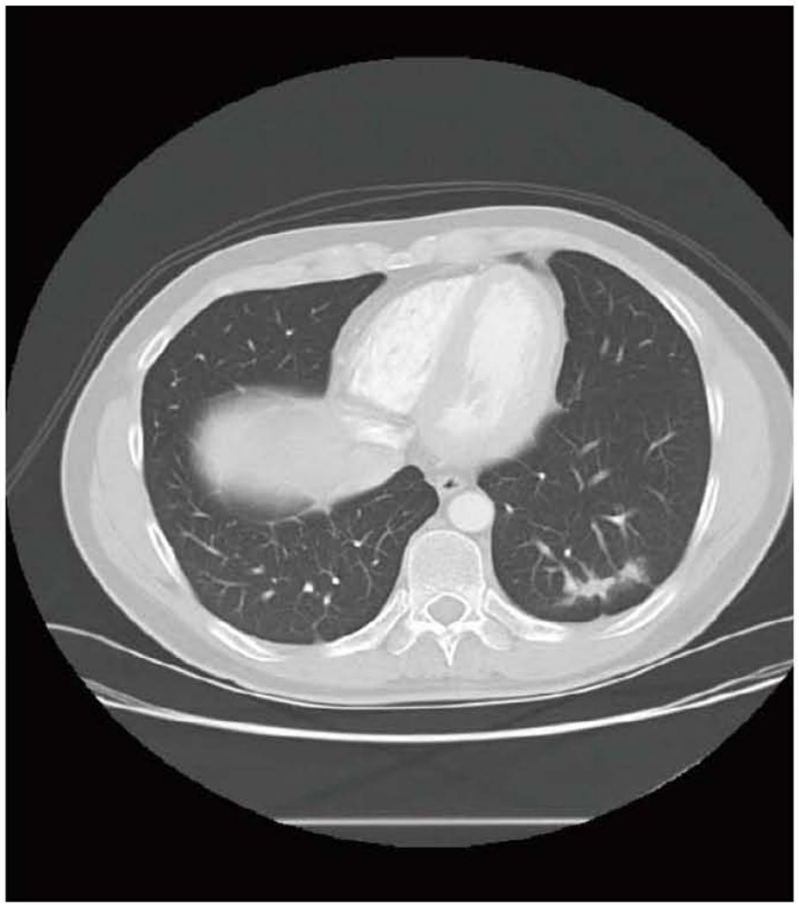
PD = progressive disease; PR = partial response; SD = stable disease.

P. Janne….G.Giaccone, ASCO 2009

Pretreatment and after 4 cycles of PF-00299804

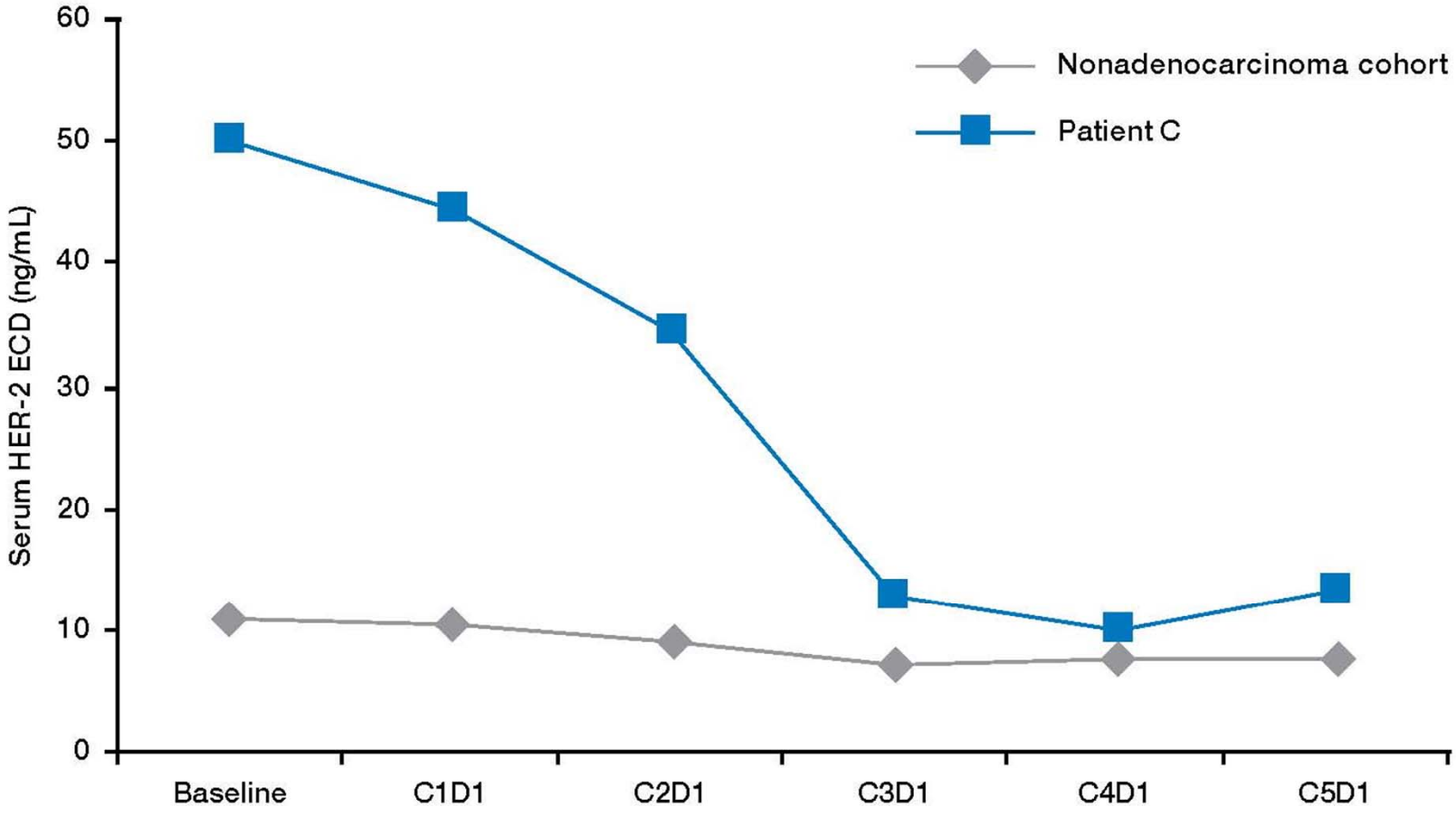


October 21, 2008



January 16, 2009

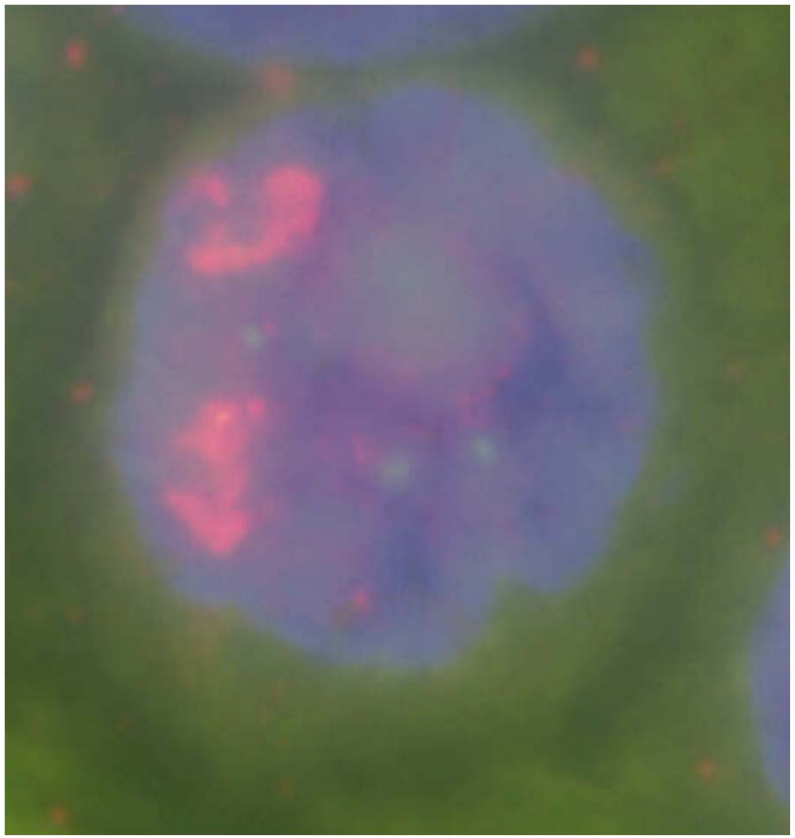
Serum HER-2 levels at baseline and through 4 cycles of PF-00299804 therapy



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

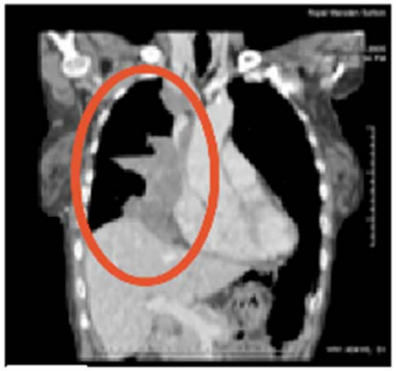
Characteristics of patients who derived apparent clinical benefit from belinostat					
Patient	**Tumour type**	**No of prior therapies**	**Treatment duration on most recent prior therapy (months)**	**Response to belinostat**	**Treatment duration on belinostat (months)**
1	Epithelial thymoma	4	1	SD (12% reduction)	17
2	Soft –tissue sarcoma	1	2	SD (9% reduction)	14
3	Soft –tissue sarcoma	3	1	SD	7
4	Melanoma	1	1	SD	3
5	Renal carcinoma	3	1	SD (14% reduction)	4

- Five patients (all treated at ≥ 900 mg/m^2/day) had longer treatment duration on belinostat monotherapy than on their previous treatment

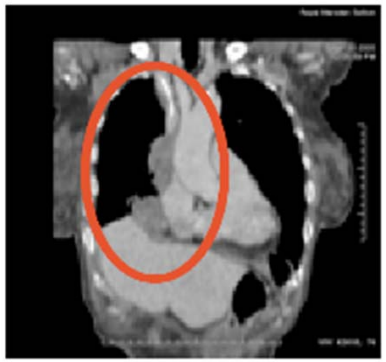
} Phase Ib/II soft-tissue sarcoma trial underway based on interesting patient data
  - Belinostat + doxorubcin

Pre-belinostat **Post-belinostat**

Locally advanced epithelial mediastinal thymoma



Baseline CT scan



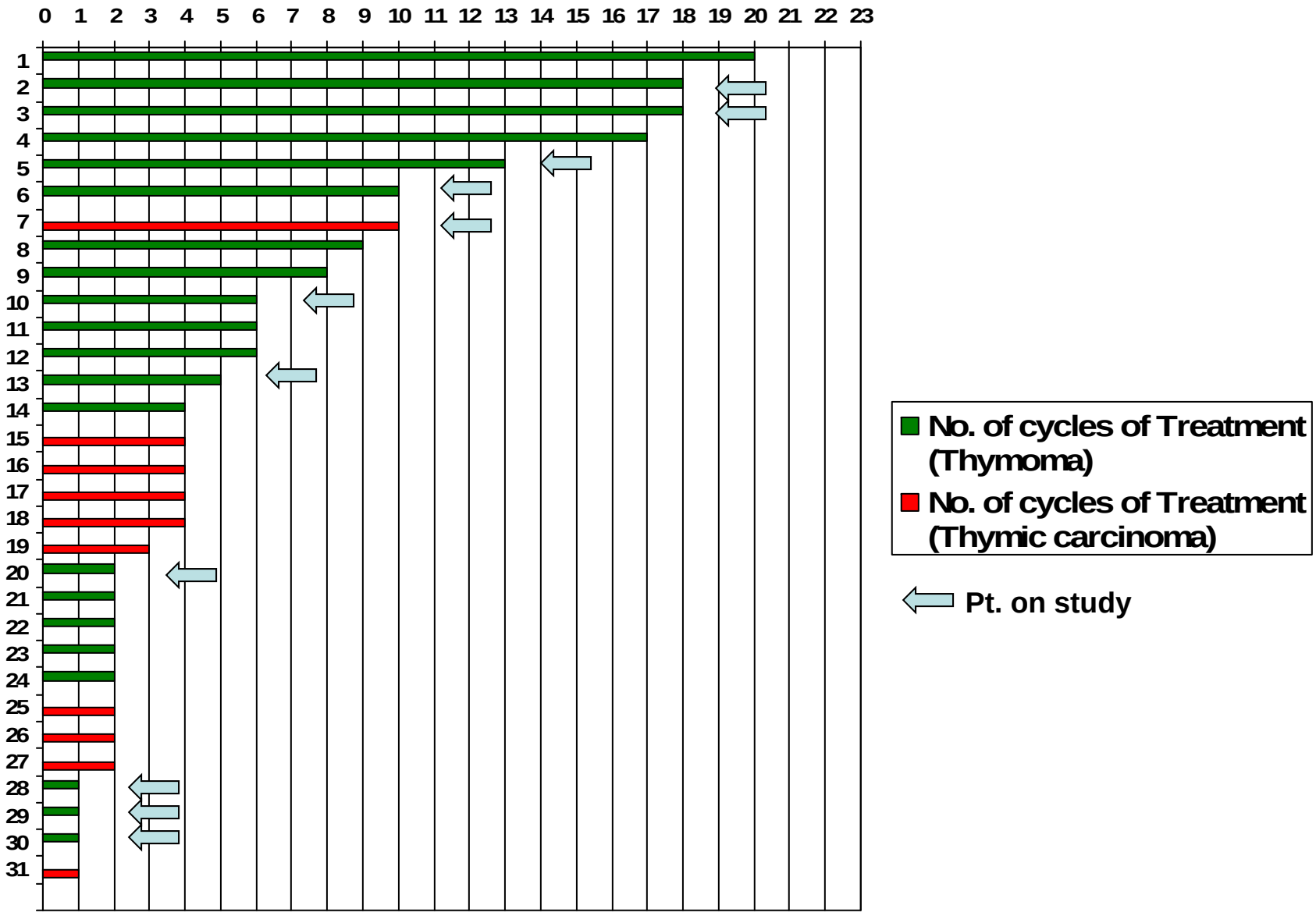
CT scan post cycle 16.

- Patient with epithelial thymoma receiving belinostat 900 mg/m^2 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

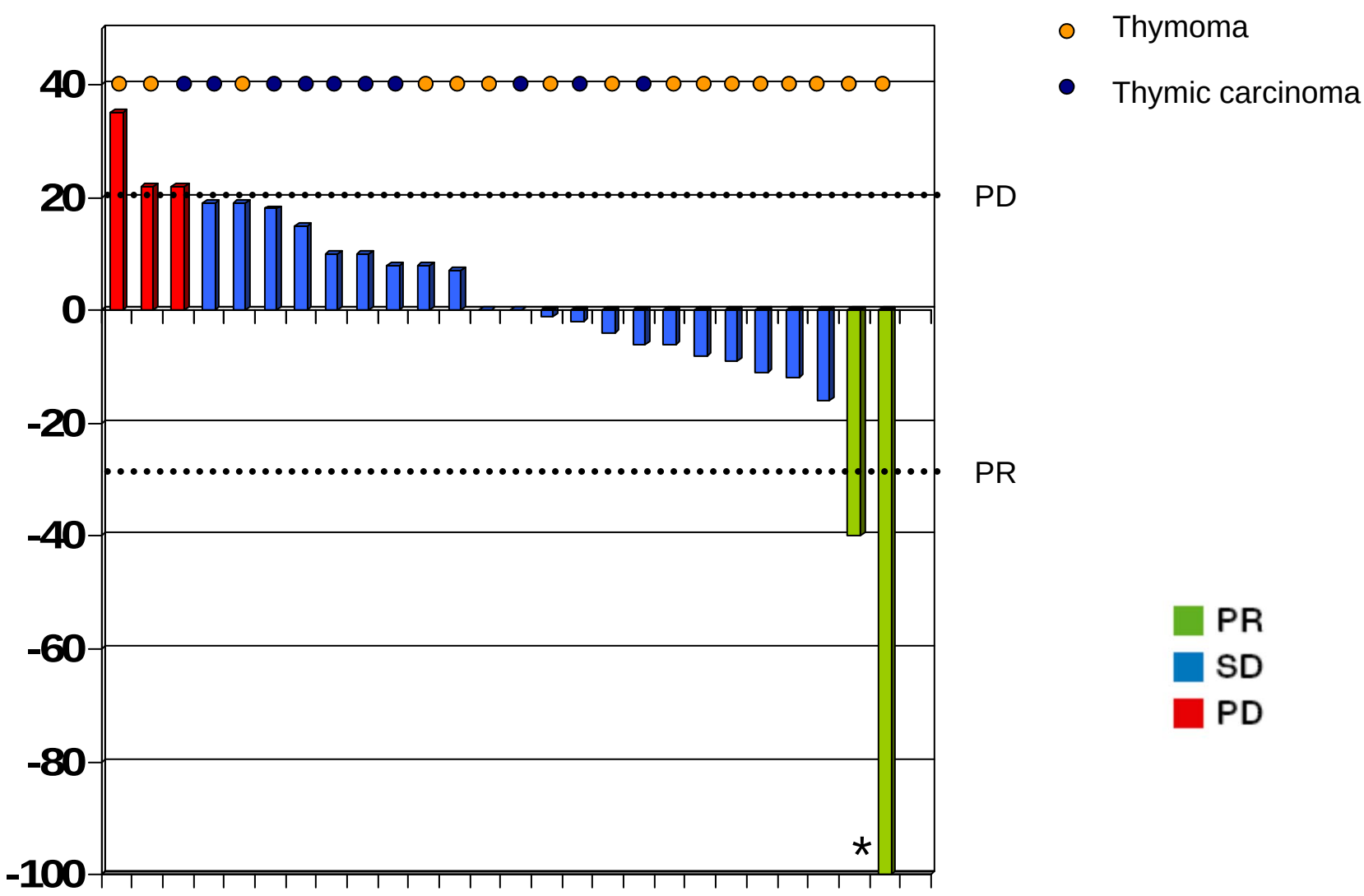
Patient Characteristics

Clinical Parameter	**n**
Accrual start: December 17, 2007	
Number of patients enrolled	31
National Cancer Institute (NCI)	22
Indiana University (IU)	9
Mean Age (range), years	53.5 years (24 – 84 years)
Gender, M : F	18:13
Histology	
Thymoma	21
Thymic Carcinoma	10
Paraneoplastic syndromes	
Myasthenia Gravis	4
Schulman's syndrome	1
Infections (Candida mucositis)	1

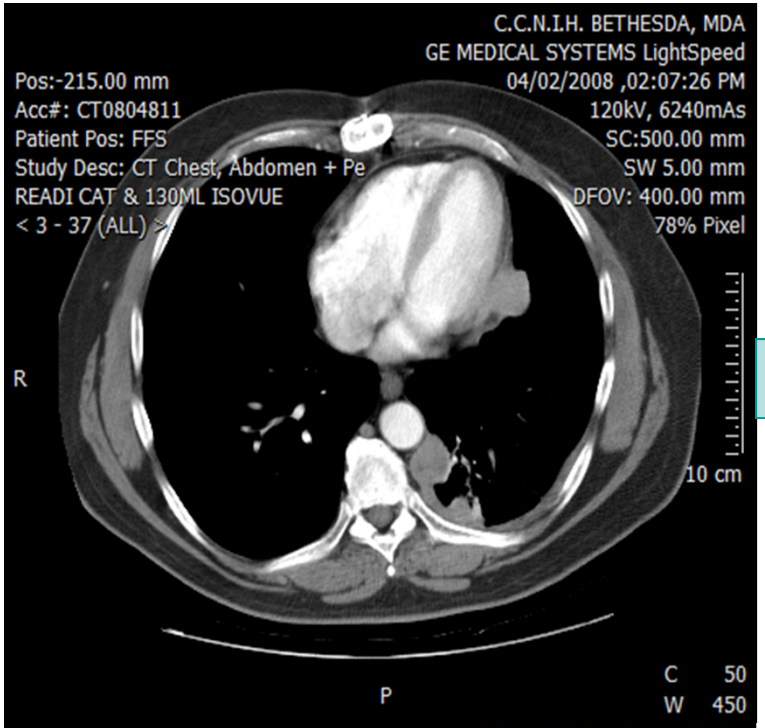
Duration of Therapy



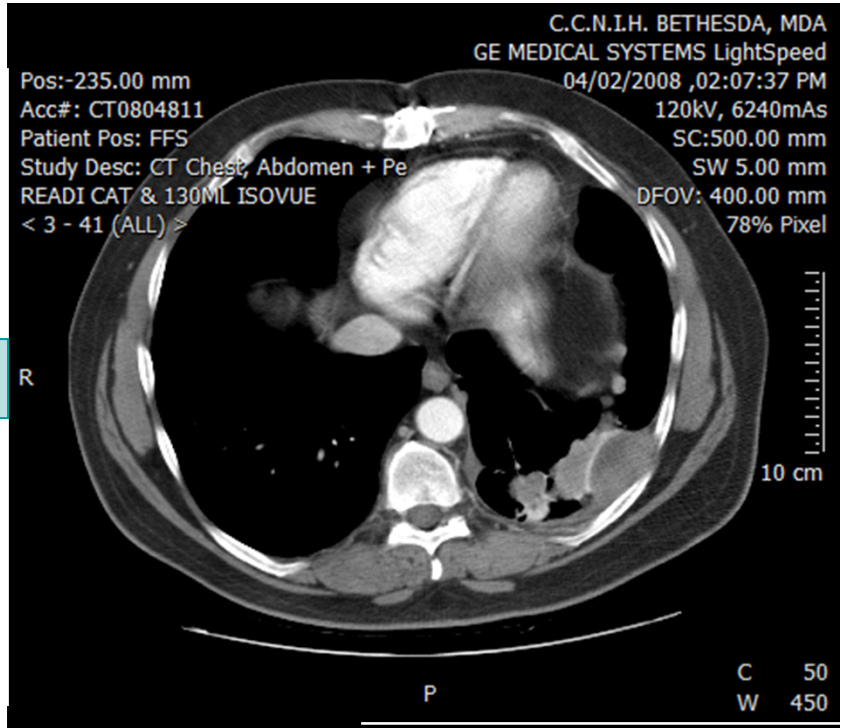
Maximum percentage change in target lesions from baseline

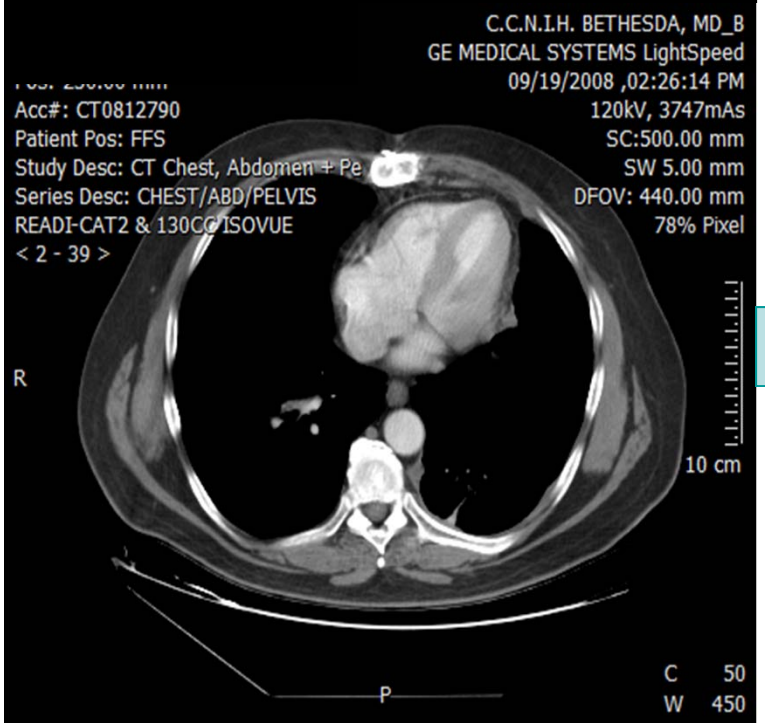


* Non-target lesions did not regress

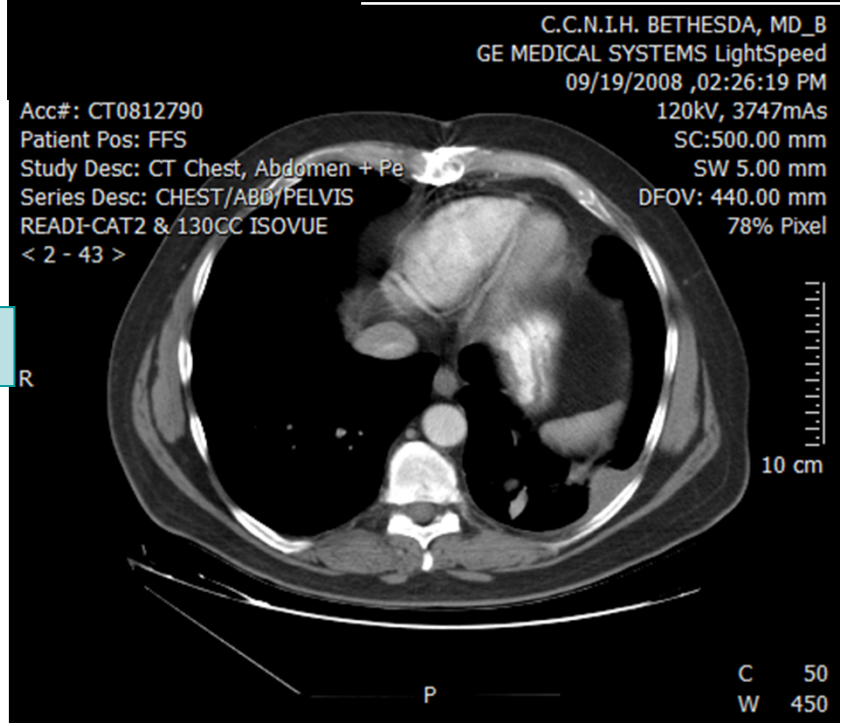


April 08





September 08



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

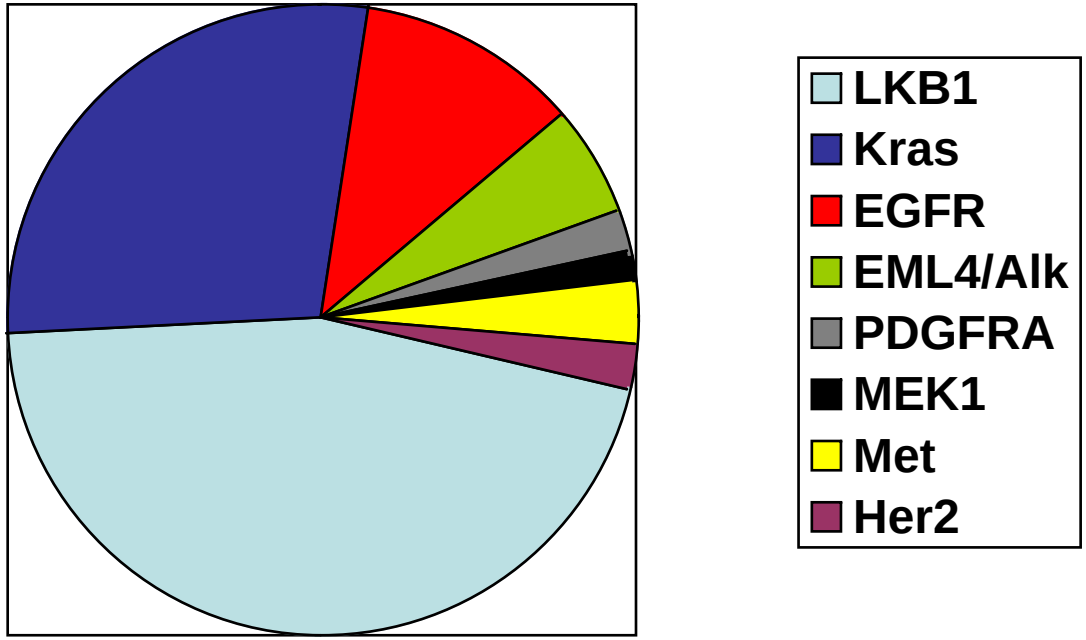
Natcher Conference Center, NIH

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?


LKB1
Kras
EGFR
EML4/Alk
PDGFRA
MEK1
Met
Her2