Biology and treatment of thymoma

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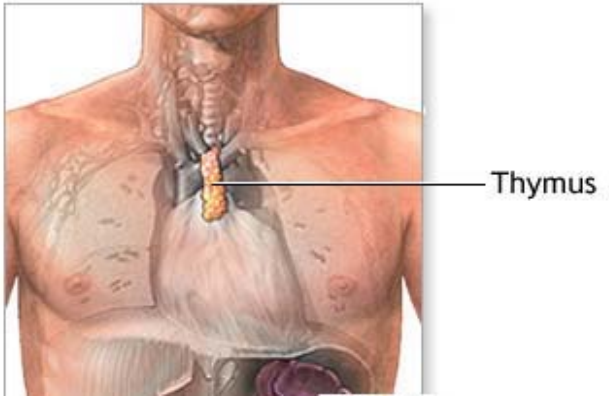
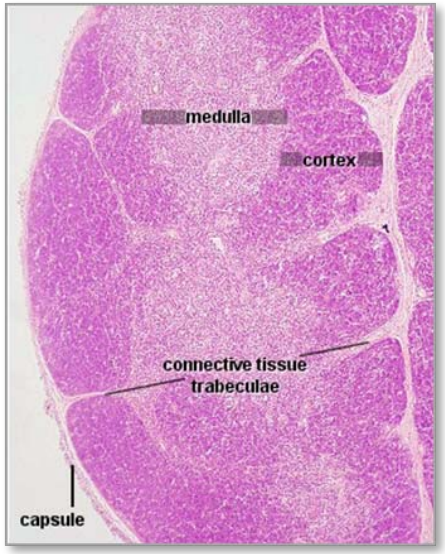
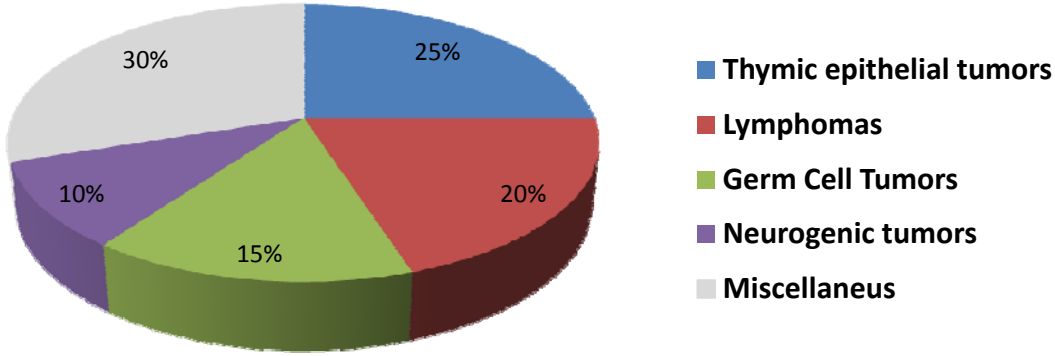
Brown Bag Seminar
April 13, 2011

Thymus and thymic tumors





Primary Mediastinal Tumors (<1% of all cancers)

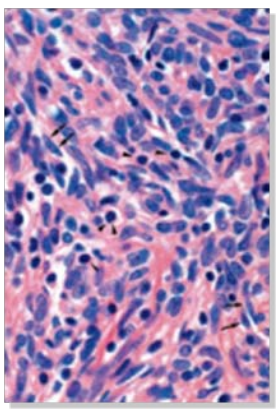


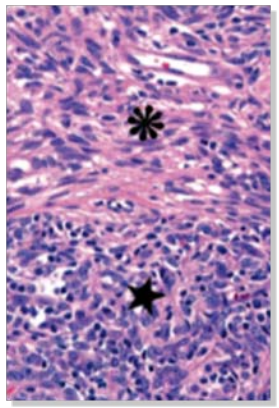
Muller-Hermelink *et al* WHO classification 2004

Thymic Epithelial Tumors

- Tumors originating from epithelial cells of thymus
- Rare (600/year in US), but the most frequent tumors of the anterior mediastinum in adults
- Thymoma often associated with paraneoplastic syndromes (e.g. Myasthenia Gravis)
- Prognostic factors: Stage and Completeness of resection
- There are different histotypes with different outcome

WHO 2004 histological classification of Thymic Epithelial Tumors


A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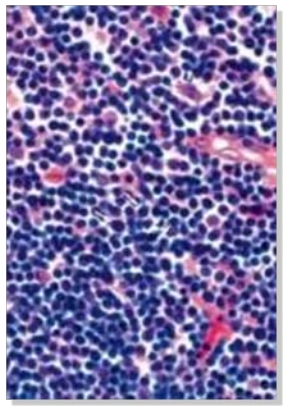
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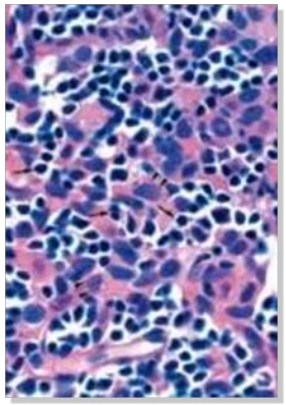
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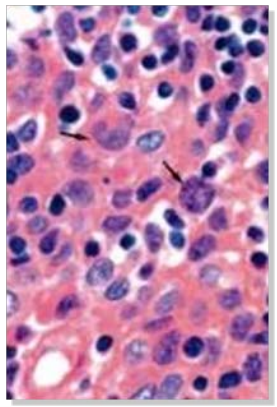
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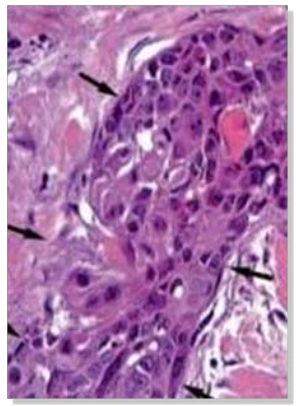

Thymic Carcinoma

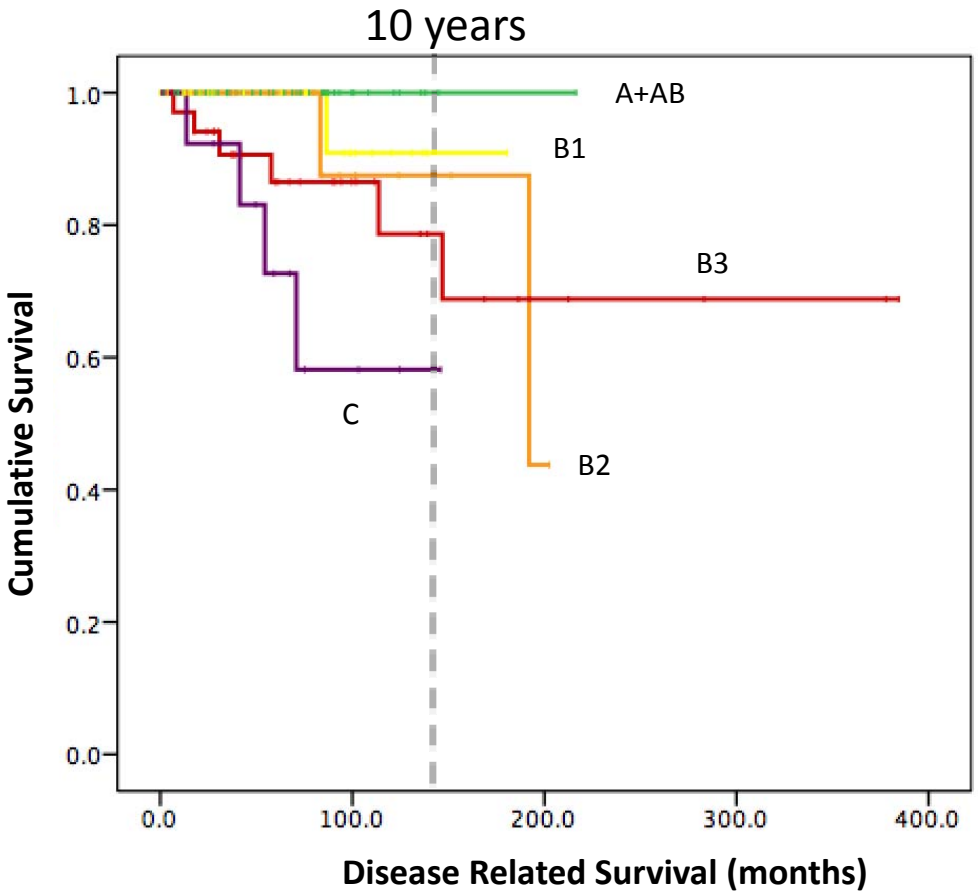
Reproduce medullary structure

Reproduce Cortex structure

Reproduce structure of carcinomas from organs other than thymus

Muller-Hermelink *et al* WHO classification 2004

WHO classification: survival implications



10-year DRS

A 100%

AB 100%

B1 93%

B2 89%

B3 80%

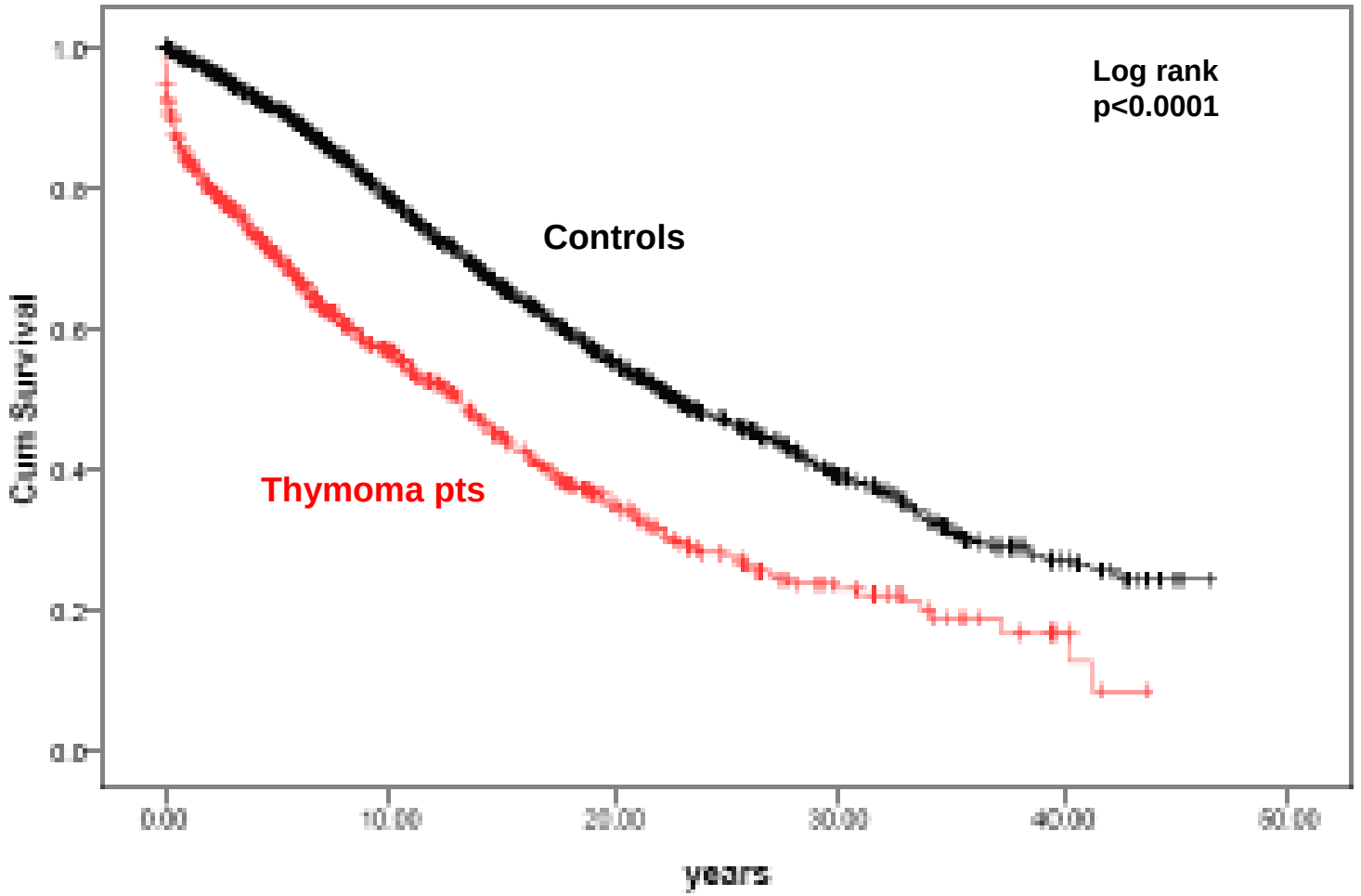
C 60%

Petrini I. *et al.* JTO 2010, Jul 21

Thymomas : General Characteristics

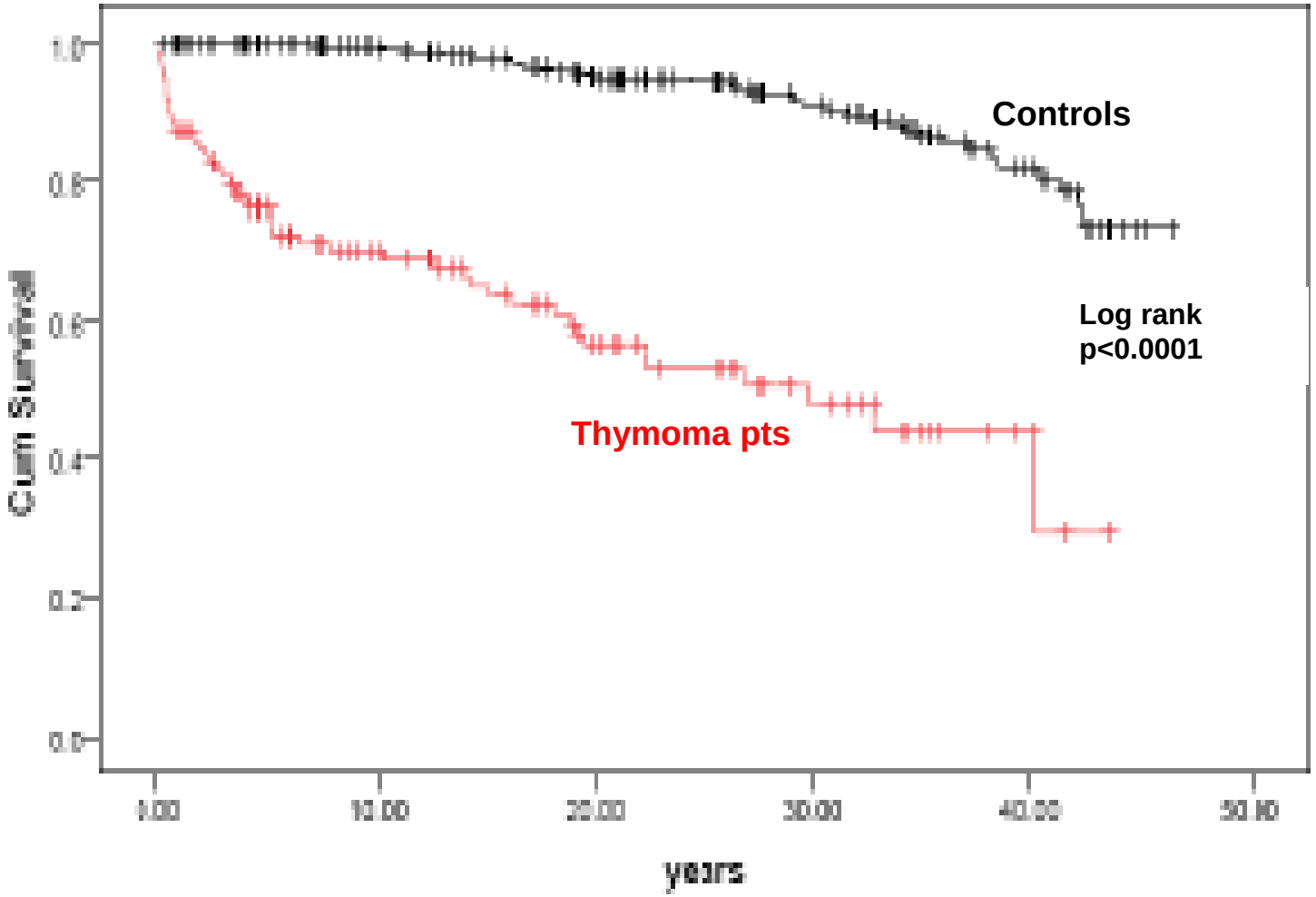
- 17% of mediastinal enlargements
- Higher incidence at 40-60 years of age
- Equal gender distribution
- 30-65% associated with myasthenia gravis
- 10-15% cases of myashenia gravis are associated with thymoma
- 70% well encapsulated
- Rare (1%) extrathoracic progression

681 thymomas and 2719 matched controls (1958-2004) - overall survival



Gadalla et al Int J Cancer 2010

Results – overall survival, age ≤40



Paraneoplastic syndromes associated with thymoma (1 of 3)

- myasthenia gravis
- pure red cell aplasia
- acquired hypogamma-globulinemia
- Eaton-Lambert syndrome
- peripheral neuropathy
- limbic encephalitis
- myeloradiculopathy
- Isaac's syndrome
- hyperthyroidism
- panhypopituitarism
- Addison's disease
- macrogenitosomia precox
- rheumatoid arthritis
- systemic lupus erythematosus
- systemic sclerosis
- dermatomyositis
- Whipple's disease
- inflammatory bowel disease
- nontropical sprue
- nephrotic syndrome

Lara PN Jr, Ca Tr Rev 26:127, 2000

Thymoma - surgery

- Surgery is the mainstay treatment of thymoma
- pre-operative biopsy is not considered necessary in well encapsulated tumors
- complete median sternotomy necessary
- cervical approach may lead to local recurrence
- total thymectomy necessary also in case of intrathymic thymomas (multifocal disease)
- Radical resection is the best prognostic factor
- debulking surgery indicated in case of invasive thymoma
- re-operation indicated in case of local recurrence

Masaoka Staging System

Stage I	Macro and microscopically encapsulated (tumors invading into but not through the capsule)
Stage II	A. Microscopic transcapsular invasion B. Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organs (i.e. pericardium, great vessels, lung) A. without invasion of great vessels B. with invasion of great vessels
Stage IV	A. Pleural or pericardial dissemination B. Lymphogenous or hematogenous metastases

Masaoka et al, Cancer 1981

Thymoma - 5-year survival

- Stage I: 93%
- stage II: 86%
- stage III: 70%
- Stage IV: 50%

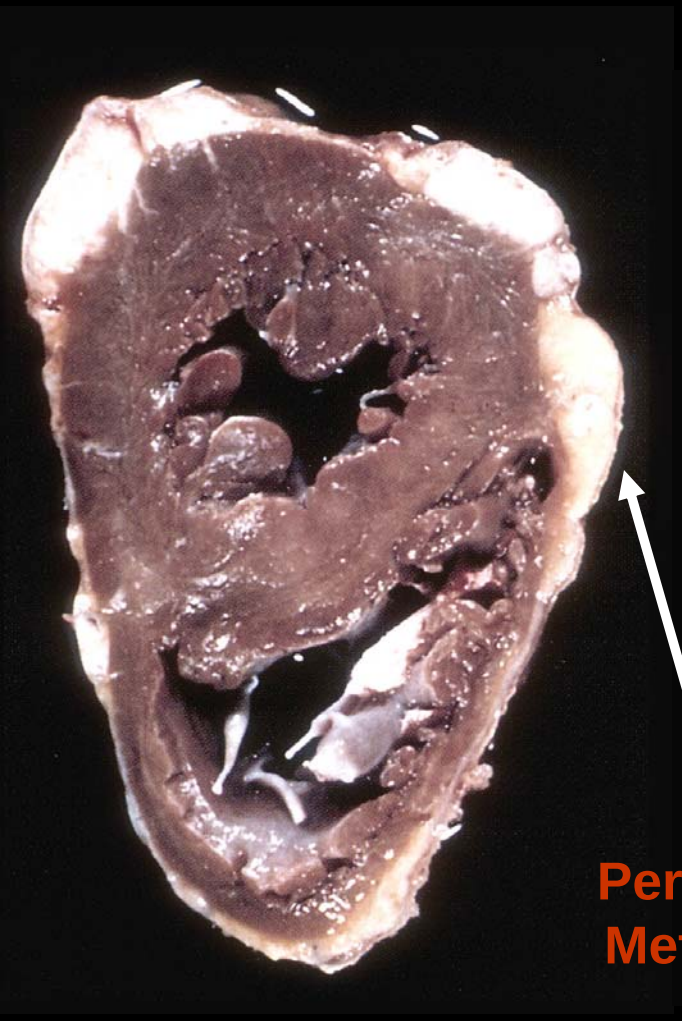
World Health Organization (WHO) classification (1)

- several types of thymomas are distinguished based on histological criteria:
- type A thymomas (also called medullary or spindle-cell thymoma)
- type AB thymomas (also called mixed thymoma)

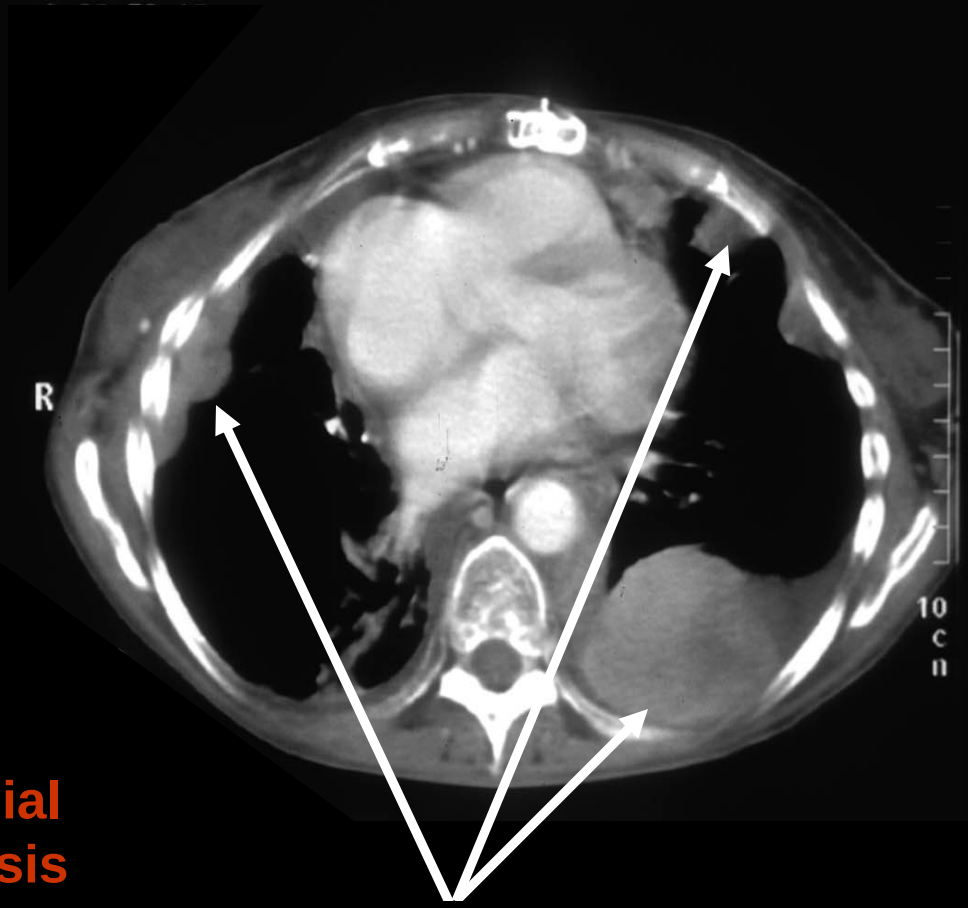
World Health Organization (WHO) classification (2)

- type B thymomas which are subclassified as:
  - type B1 thymomas (also called lymphocyte-rich thymoma, lymphocytic thymoma, predominantly cortical thymoma, or organoid thymoma)
  - type B2 thymomas (also called cortical thymoma) and
  - type B3 thymomas (also called epithelial, atypical, or squamoid thymoma or well-differentiated thymic carcinoma, respectively))
- 4) type C thymomas (thymic carcinomas)

Stage IVa Thymoma



Pericardial Metastasis



Pleural Metastasis

Thymoma - radiotherapy

- Post-operative radiotherapy: 30-60 Gy in 1.8-2.0 Gy/fraction in 3-6 weeks
- Recommended in Masaoka stage III
- may help in stage II (recurrence rate 30%)
- not indicated in stage I (recurrence rate 1.5%)

Thymoma: Single Agent Activity

	Responses/No. Pts
Cisplatin	7/28 (25%)
Ifosfamide	6/13 (46%)
Maytansine	5/7 (71%)
Interleukin-2	0/14
Octreotide	4/38 (11%)
- plus prednisone	9/38 (24%)*
Pemetrexed	5/27 (19%)

Combination Chemotherapy

- ***Anthracycline Regimens:***

	Regimen	Stage	No.Pts.	CR + PR
• Loehrer et al	PAC	IV	30	50%
• Loehrer et al	PAC*	III	23	70%
• Fornasiero et al	ADOC	III/IV	32	90%
• Lucchi et al	PEpiVP-16	III/IV	7	100%
• Venuta et al	PAC	III	15	69%
• Kim et al	PAC+Pred*	$III/IV_{A\&B}$	22	77%

- ***Non-Anthracycline Regimens:***

• Giaccone et al	PE	IV	16	56%
• Loehrer et al	VIP	III/IV	28	32%
• Lemma et al:				
– Thymoma	Carbo/Pac	III/IV	23	35%
– Thymic CA	Carbo/Pac	III/IV	21	29%

- *Radiotherapy to limited disease

Targeted therapy Anectodal activities

- Erlotinib
- Cetuximab
- Sorafenib
- Imatinib
- Dasatinib
- ZD2171
- AMG706
- SU14813: 2 PR/4 in a phase I study
- etc..

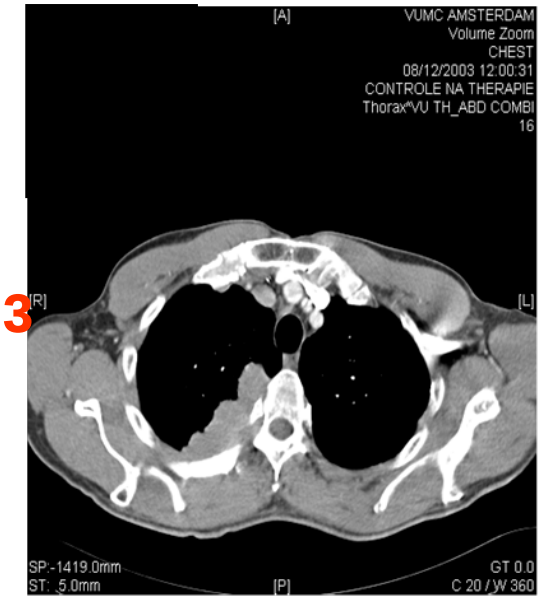
Octreotide +/- prednisone

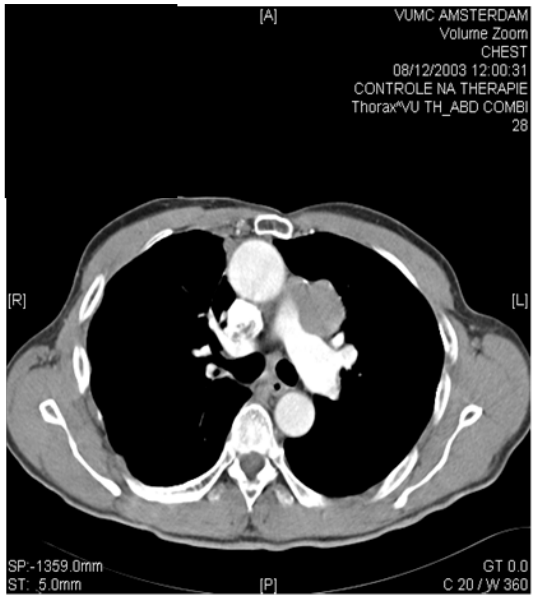
- 38 eligible patients
- 32 thymomas
- 5 thymic carcinomas and 1 carcinoid
- Octreotide: 4 PRs / 38 (10.5%)
- Octreotide + prednisone: 2 CR+6 PRs / 21 (31.6%)
- Overall: 2 CR + 10 PR / 38 (31.6%)
- No responses in non-thymomas

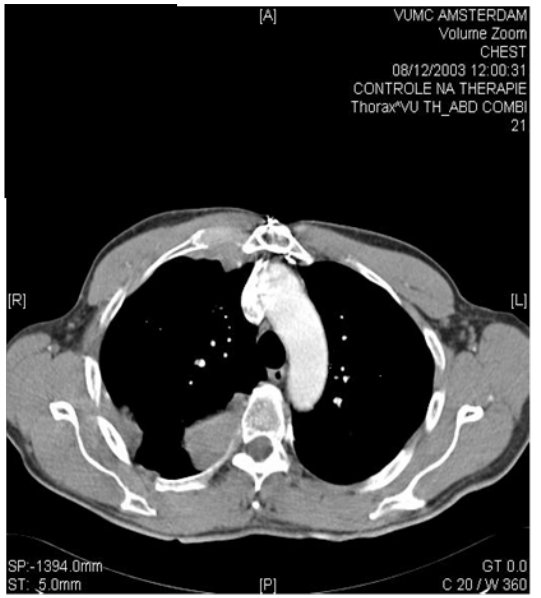
Loehrer et al. JCO 22, 293-299, 2004

Somatostatin + prednisone in a patient with metastatic thymoma

8 Dec 03







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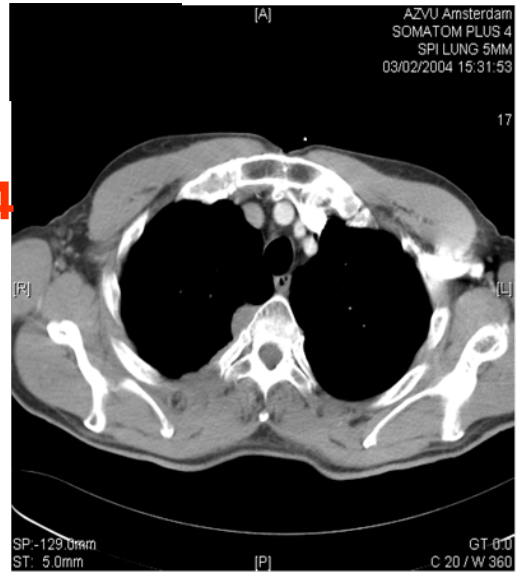
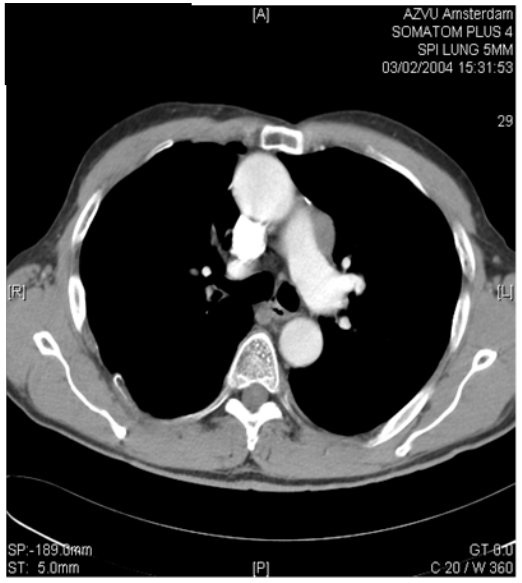
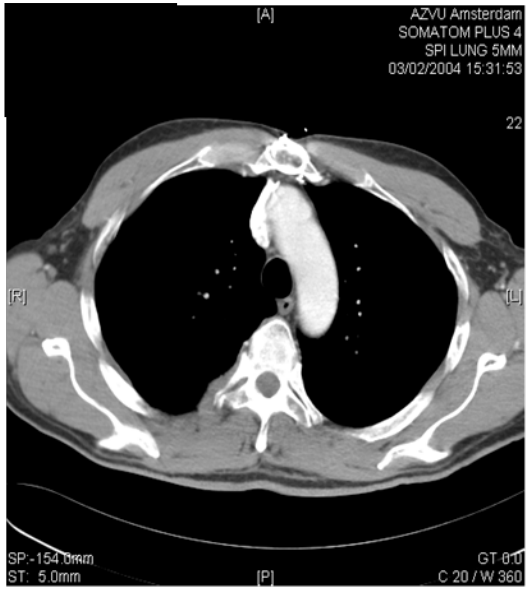






Phase II of Gefitinib in previously treated thymomas

- 26 enrolled
  - 19 thymomas
  - 7 thymic carcinomas
- 1PR (5m)
- 14 NC
- In 5 patients : no EGFR or K-Ras mutation

Kurup A et al. ASCO 2005, abstract 7068

Phase II of erlotinib and bevacizumab in previously treated thymomas

- 18 enrolled
  - 11 thymomas
  - 7 thymic carcinomas
- No responses; 11 NC, 7 PD

Bedano PM et al. ASCO 2008, abstract 19087

EGFR summary

	IHC	**Mutations**
Thymoma	135/176 (77%)	2/114 (2%)
Thymic carcinoma	23/36 (64%)	0/22 (0%)

Phase II imatinib in WHO thymoma B3 and C

- 400 - 800 mg/day
- 7 patients
  - 3 no prior chemotherapy
- Gender:
  - 6 man
  - 1 woman
- Performance status:
  - 3 PS 1
  - 4 PS 2

- Histology:
  - –2 Thymoma B3
  - –5 Thymus carcinoma C
- Stage:
  - –2 IVA
  - –5 IVB

- 2 NC, 5 PD

No mutations in cKit or PDGFRA in 3 patients tested

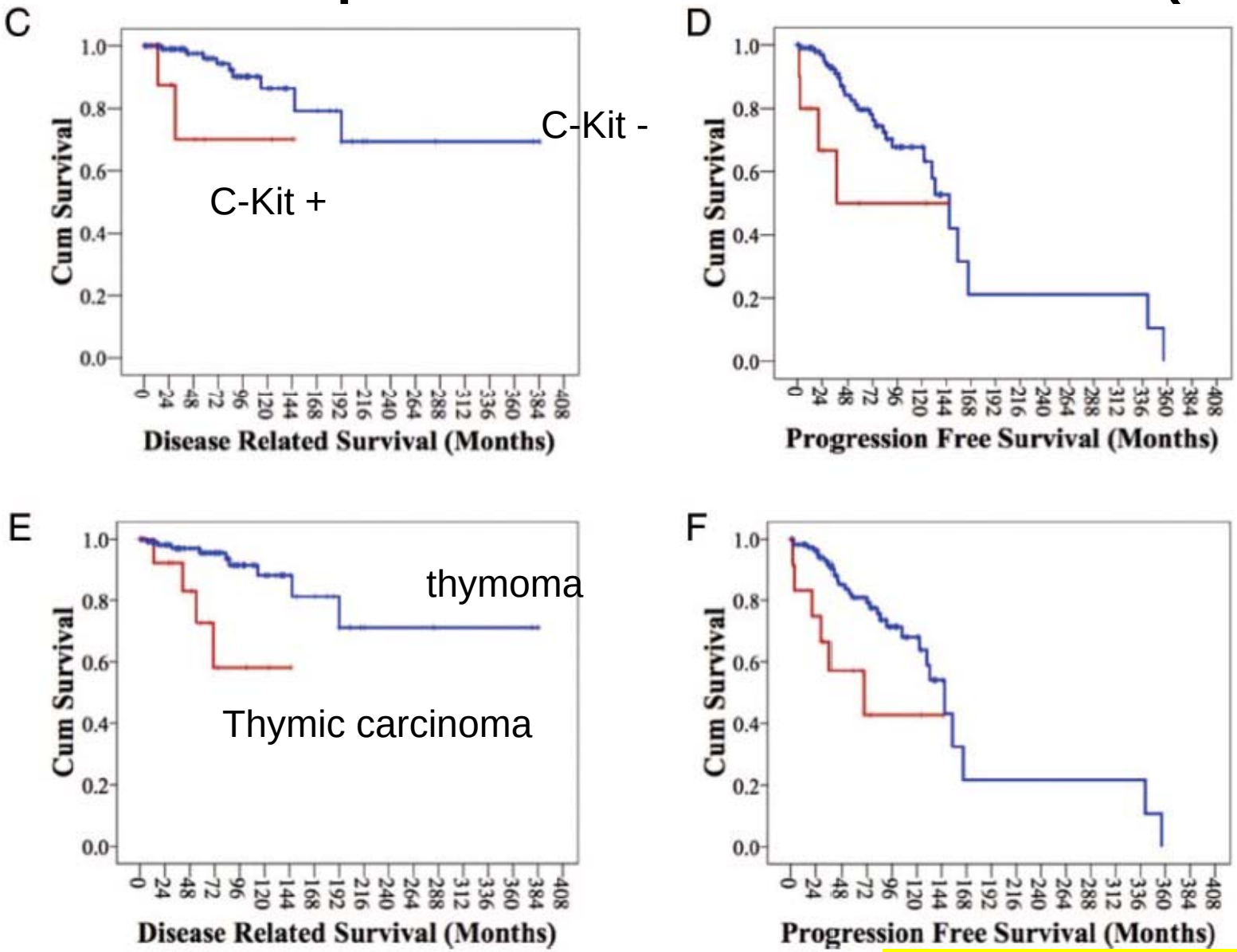
Giaccone G et al. JTO 4, 1270, 2009

Imatinib in thymic carcinomas

- 11 previously treated thymic carcinoma
  - IHC positive for C-KIT (9 cases)
  - or PDGFR (2 cases)
- 3 NC, 4 PD, 3 toxicity discontinuations

Salter et al. ASCO 2008, abstract 8116

C-Kit expression and survival (n=120)



Petrini et al JTO 5, 1447, 2010

C-Kit summary

	IHC	**Mutations**
Thymoma	7/366 (2%)	0/67 (0%)
Thymic carcinoma	95/127 (75%)	5/59 (8%)

Petrini et al JTO 5, 1447, 2010

Phase II study of Belinostat

- Background:
  - No standard treatment for patients with advanced thymoma who progressed after platinum-based chemotherapy
  - One minor long lasting response in a phase I study of the pan-HDAC inhibitor belinostat
- Eligibility:
  - Recurrent thymoma or thymic carcinoma failing chemotherapy
  - Measurable disease
  - ECOG PS $\leq$ 2
  - Baseline QTc interval > 500 msec was an exclusion criterion
- Schedule:
  - 1 g/m^2 x 5 days q3w until progression or development of unacceptable adverse events

Phase II of Belinostat Patient Characteristics

Clinical Parameter	n
Accrual: December 17, 2007 - January 5, 2010	
Number of patients enrolled	41
Median Age (range), years	53 years (23 – 83 years)
Gender, M : F	20:21
Histology	
Thymoma	25
Thymic Carcinoma	16
Paraneoplastic syndromes	
Myasthenia Gravis	4
Schulman's syndrome	1
Infections (Candida mucositis)	2
Median number of prior regimens (range)	2 (1 – 10)

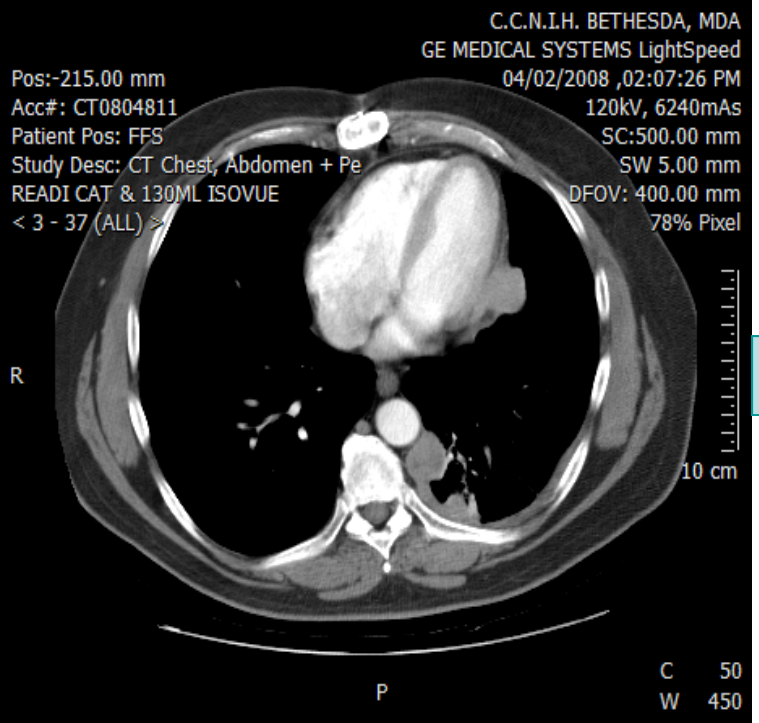
Giaccone et al. JCO (in press)

Belinostat Study - outcome

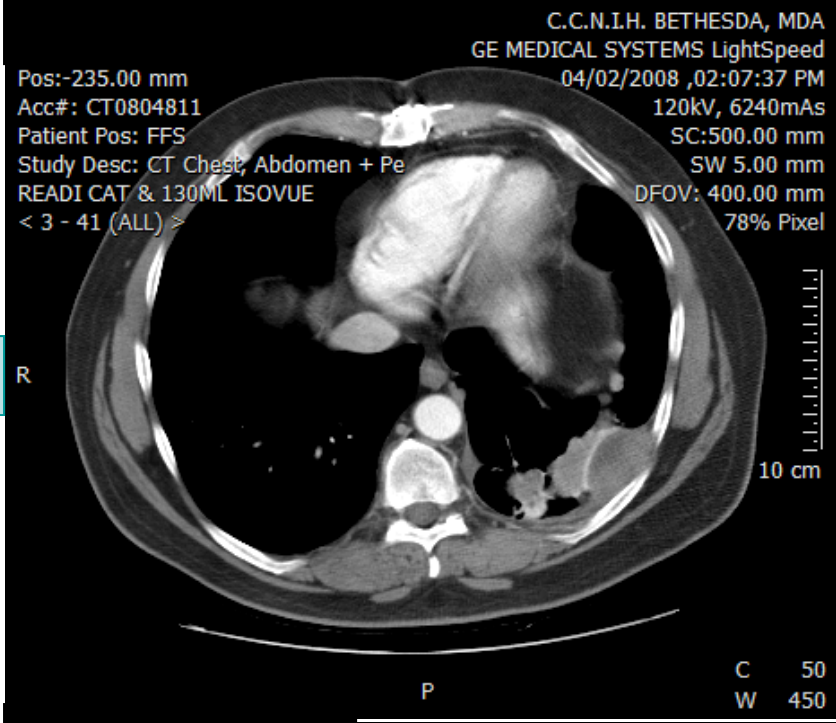
- Patients evaluable for response: 40 (24 T; 16 TC)
  - Thymoma: 2 PR; 17 SD; 5 PD
  - Thymic Carcinoma: 0 PR; 8 SD; 8 PD

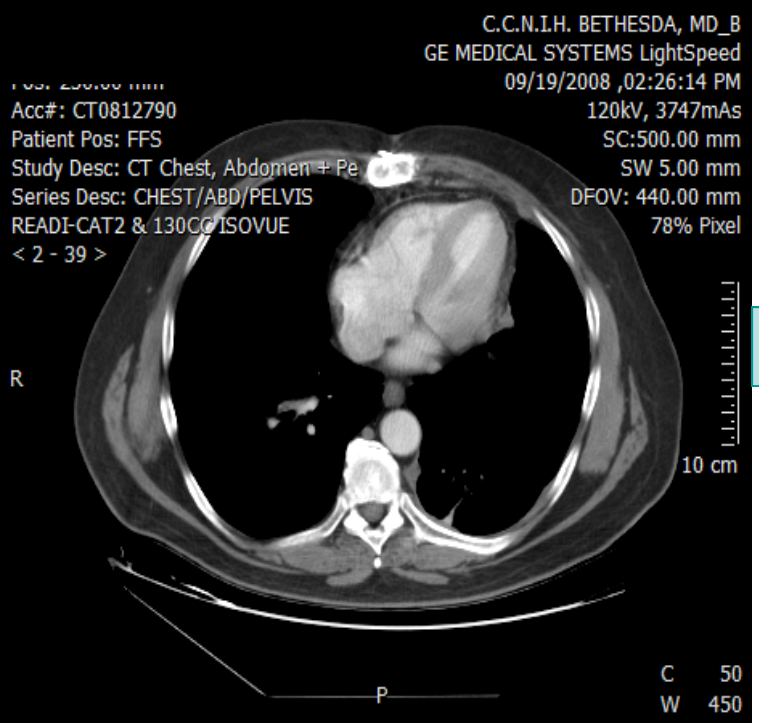
- Median Time To Progression (TTP)
  - Thymoma: 343 days
  - Thymic carcinoma: 82 days

- Median Survival
  - Thymoma: Not reached
  - Thymic carcinoma: 371 days

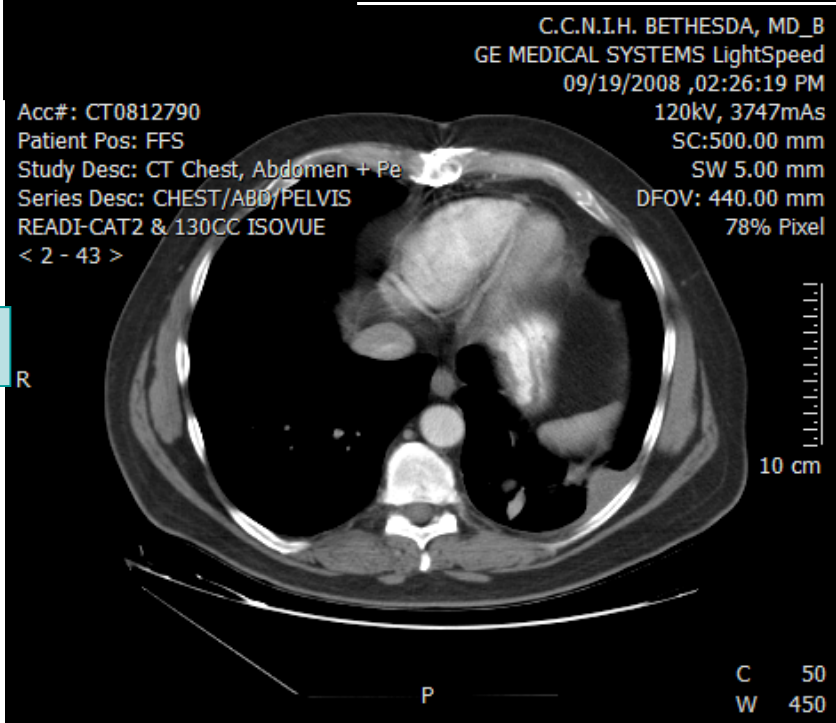


April 08



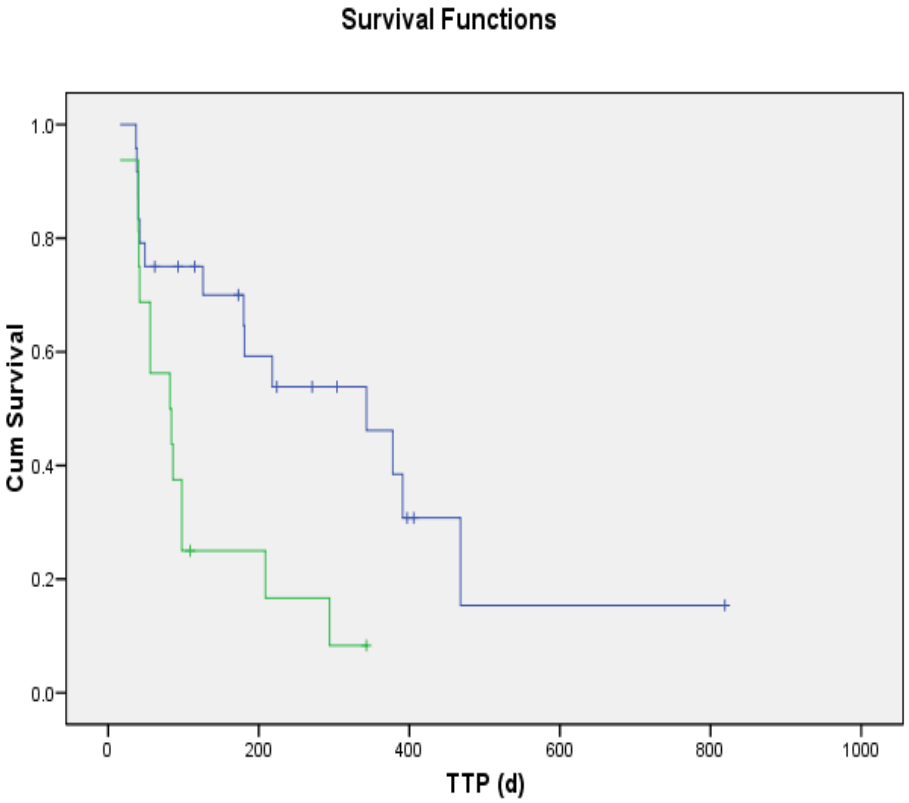


September 08

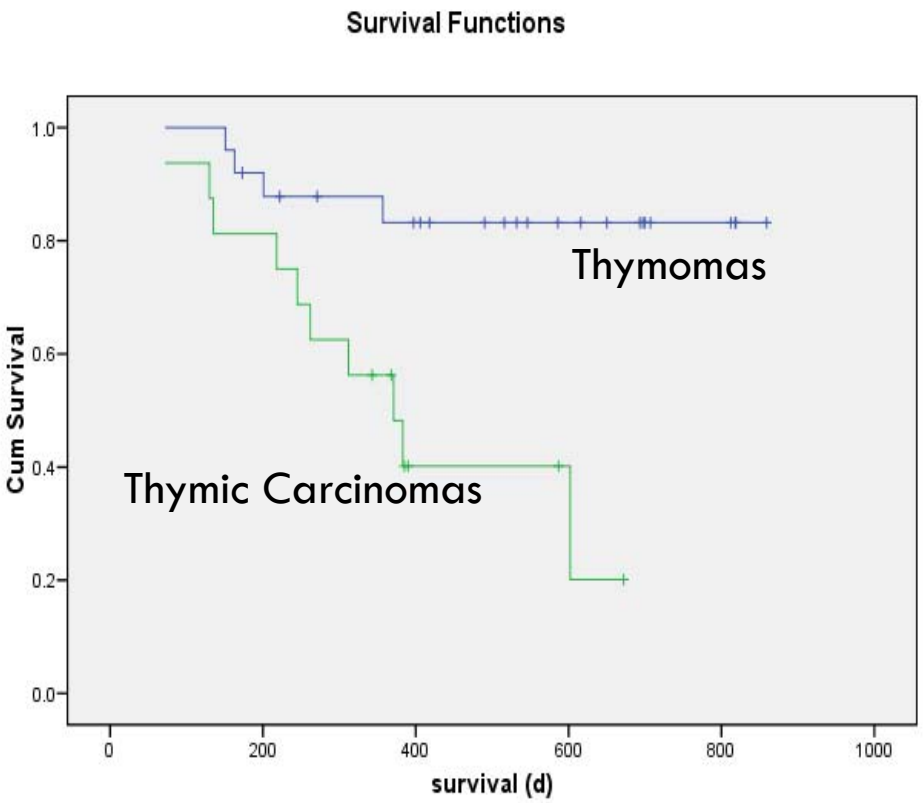


Thymoma vs thymic carcinoma

Time to progression



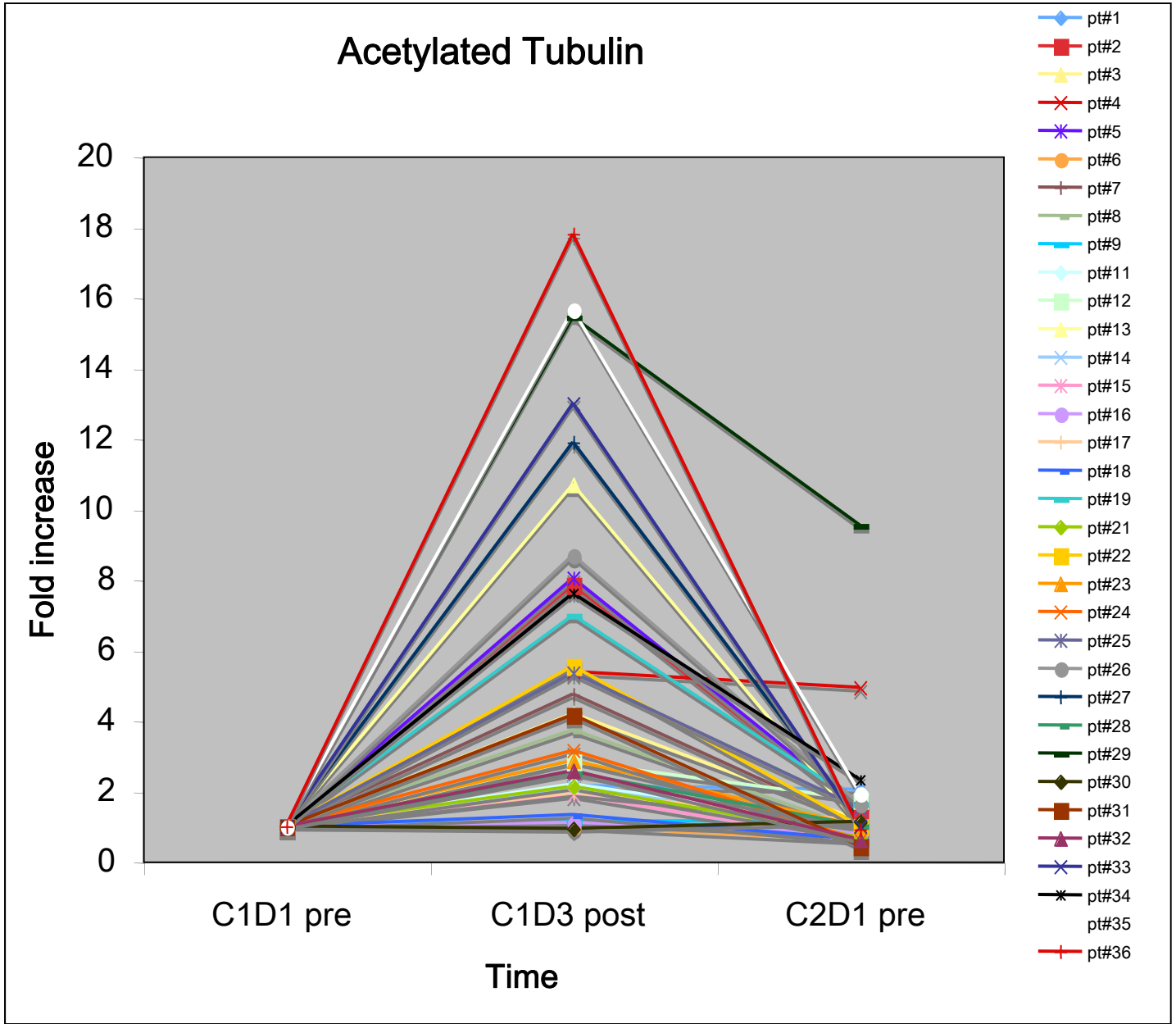
Survival



Belinostat Study

- Common toxicities:
  - Nausea
  - Flushing
  - Transient hypotension
- Uncommon but potentially serious toxicity:
  - Prolongation of QT interval

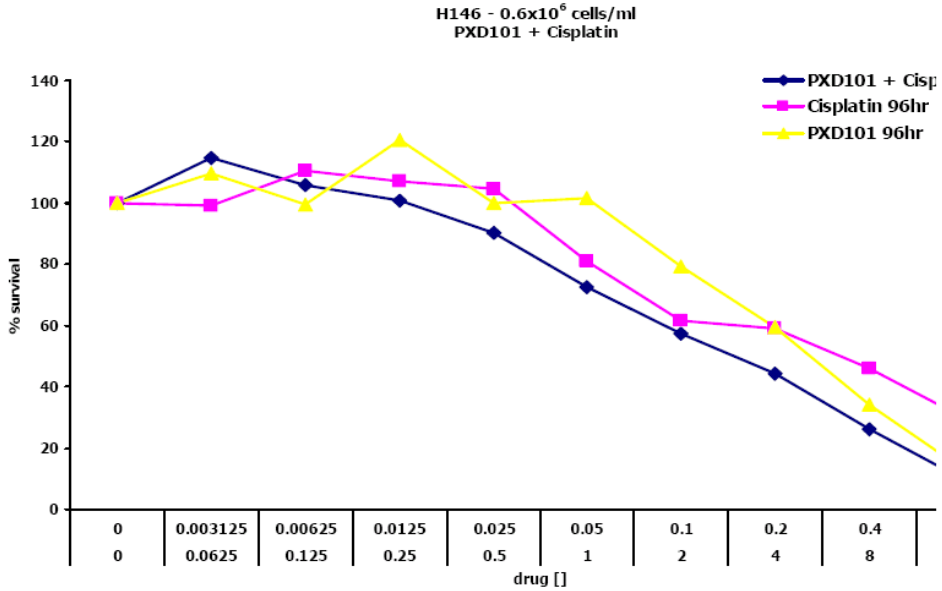
PBMCs

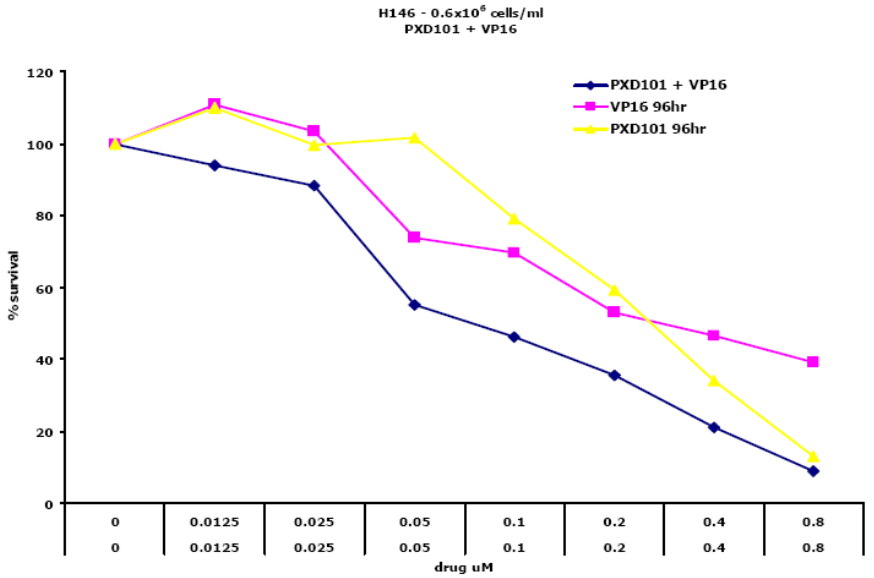


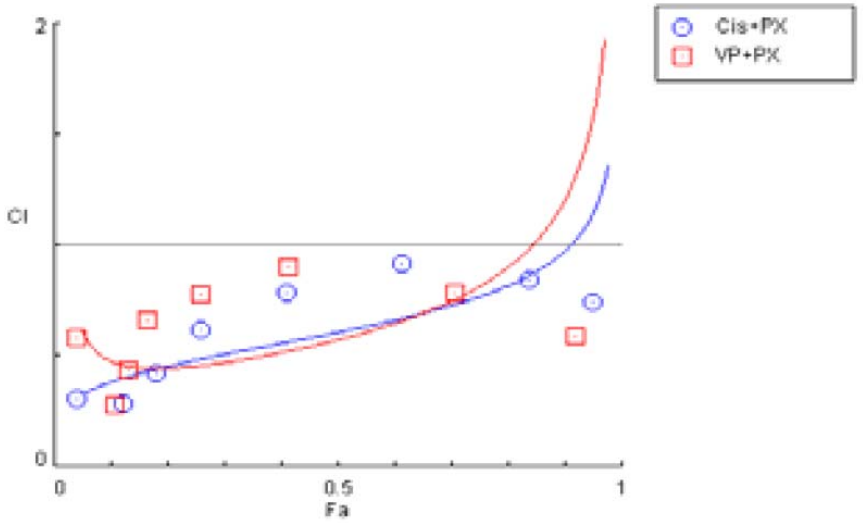
J.Trepel

Rationale for combinations

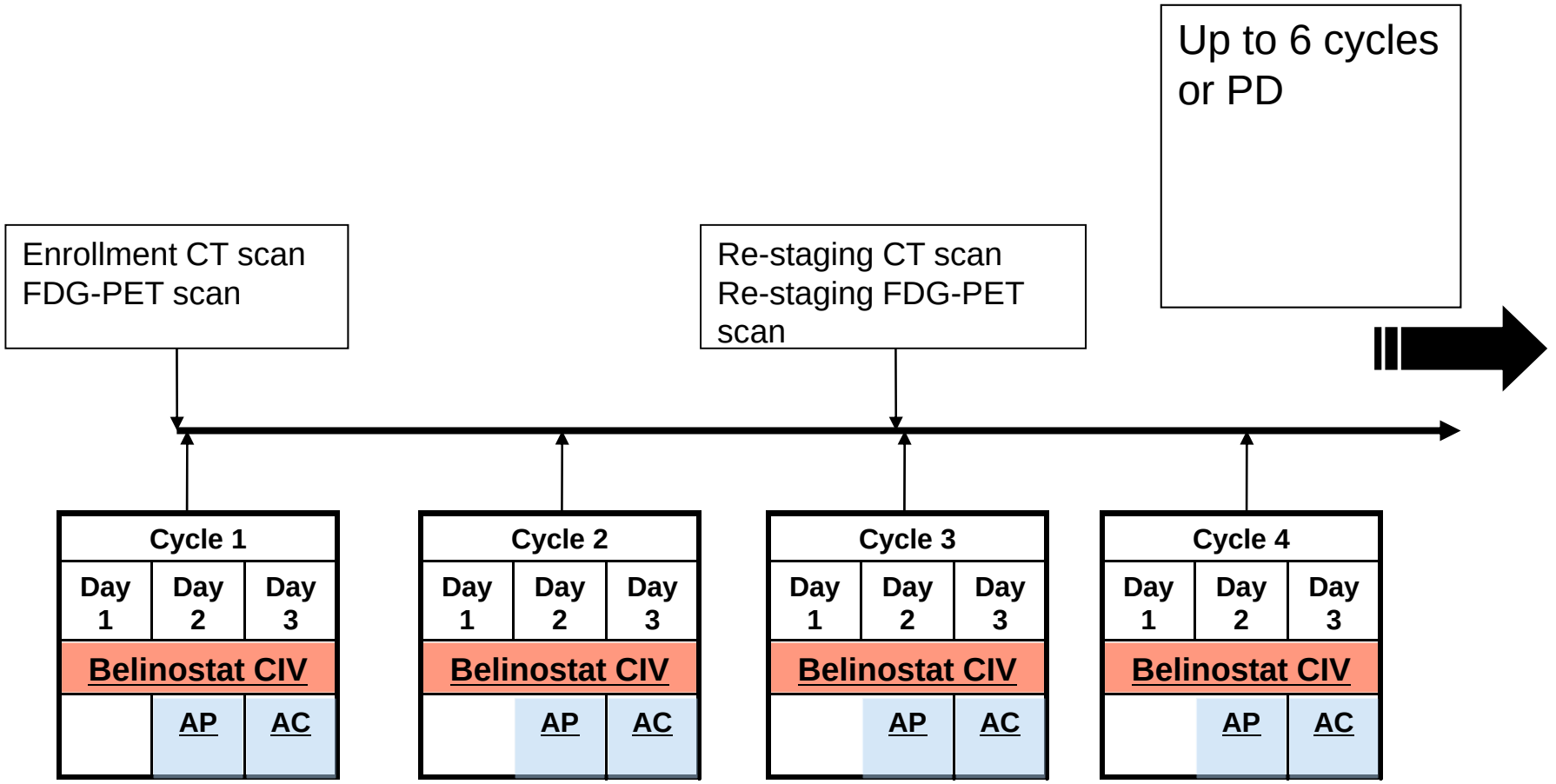
Sim: PXD+Cis; PXD+VP: Synergistic at most doses





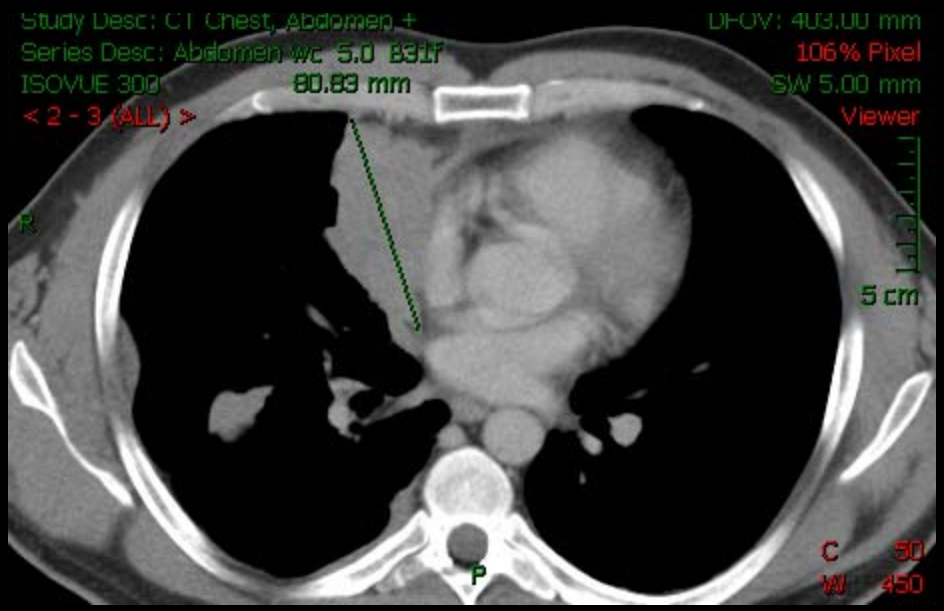


Phase I/II of B-PAC - Schema

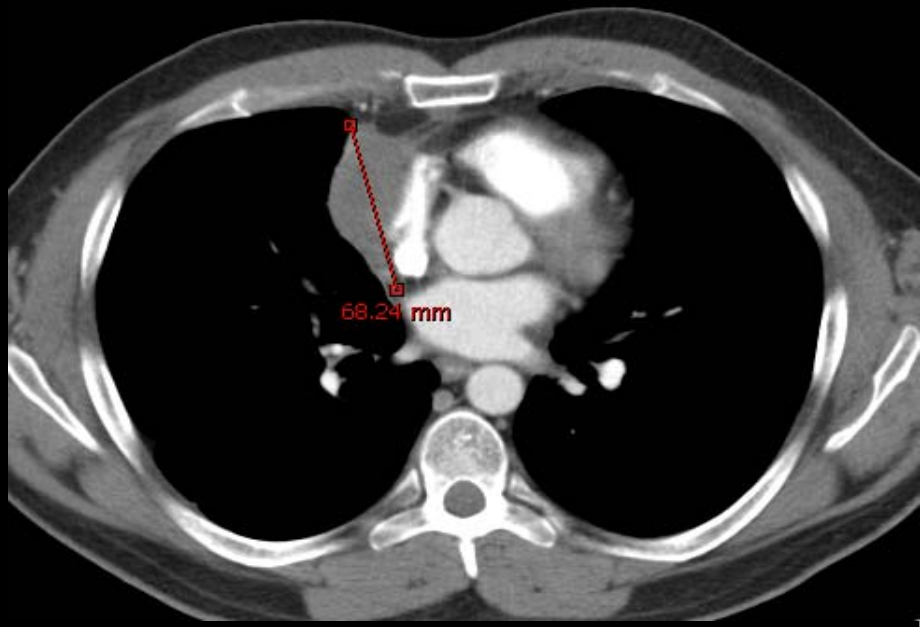


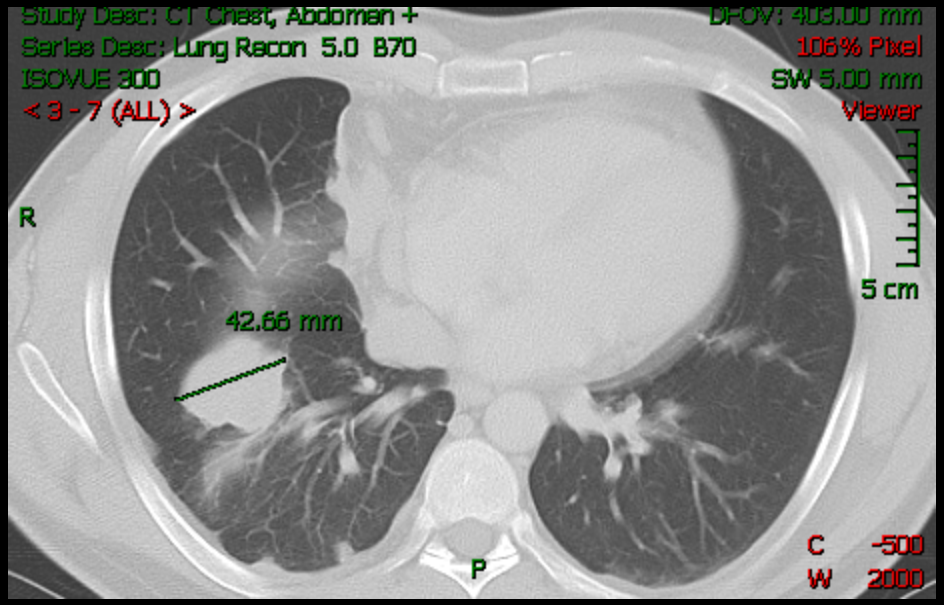
cyclophosphamide(C), doxorubicin (A), cisplatin (P)

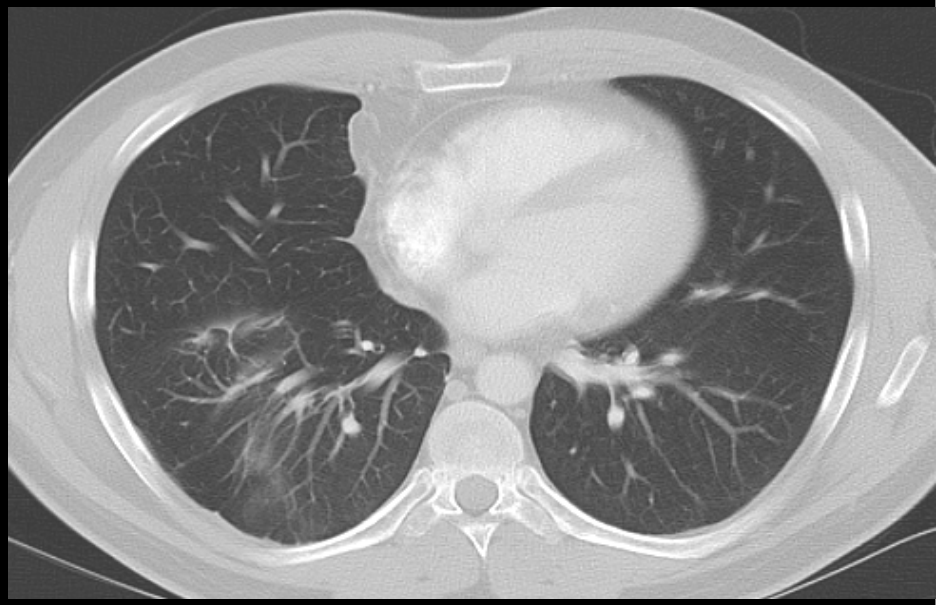
Study Patient 1
Baseline



s/p 2 cycles



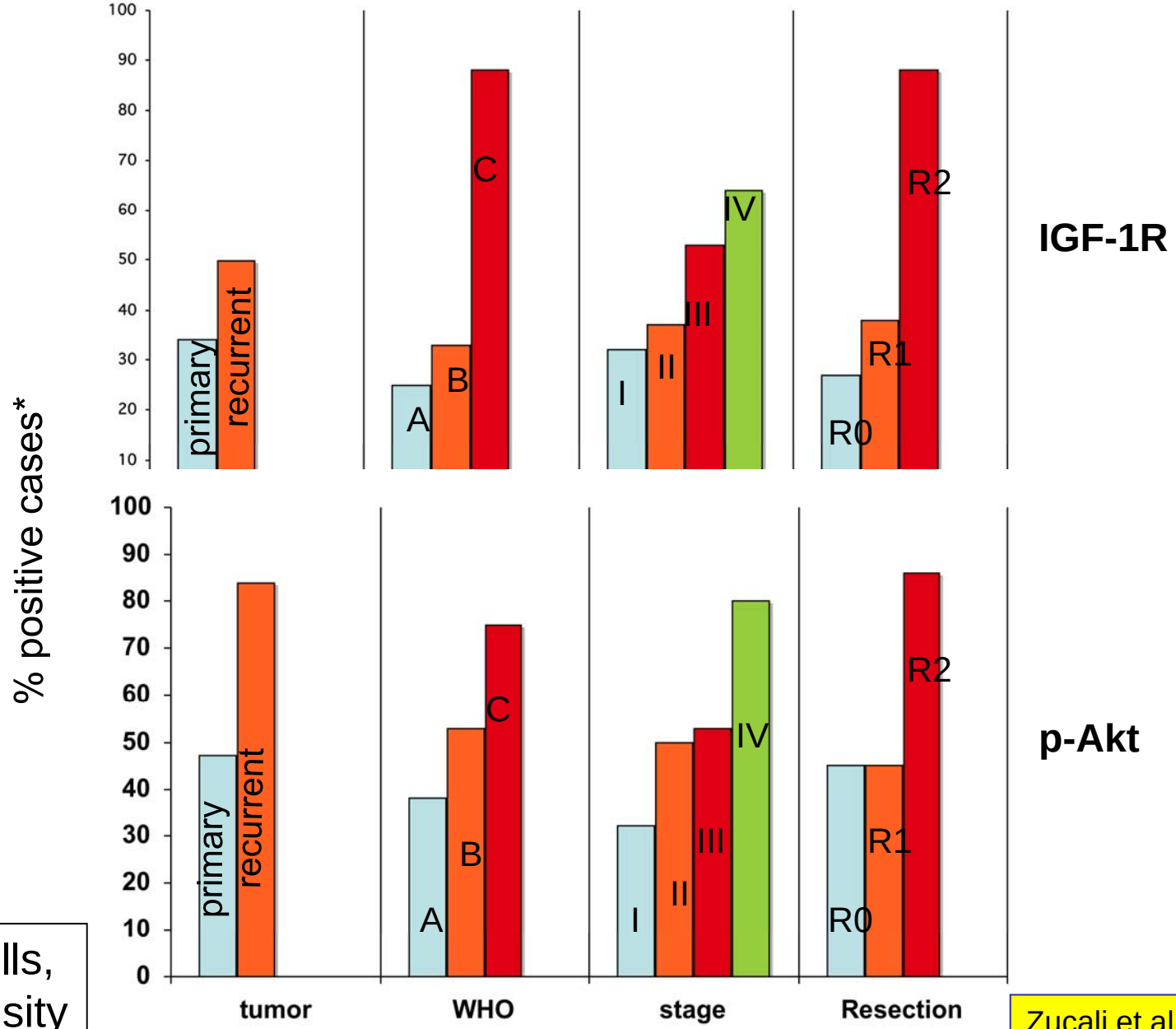




Phase II of IMC-A12, an IGF-1R MoAb in Thymic Malignancies

- Rationale:
  - IGF-1R identified in rat thymocytes
  - Increased expression of IGF-1 and IGF-1R in thymic epithelial cells of patients with thymic-hyperplasia associated MG
  - One thymoma patient with reduction of 10% in a phase I study figitumumab for over 1 year
  - Increased IGF1R expression in higher grade and stage thymic malignancies

IGF-1R and p-Akt expression in resected thymomas (n=111)



* >5% cells, any intensity

Zucali et al Cancer 2010

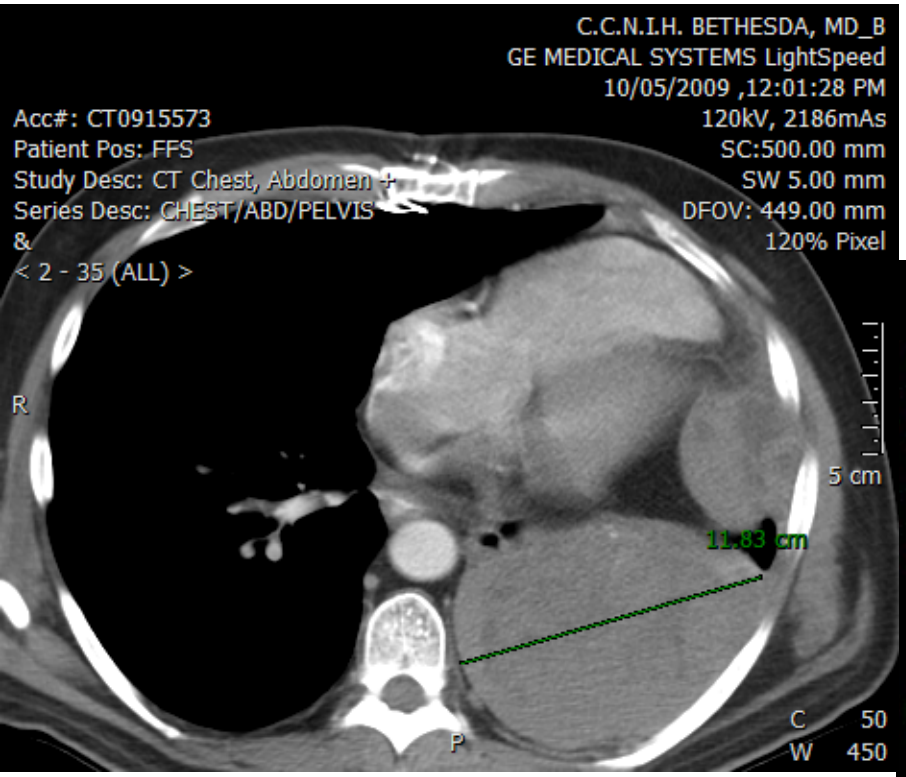
Phase II study of IMC-A12 in thymic malignancies

Single center study: open August 2009

	Thymoma	Thymic carcinoma
Accrued	15	12
Male : female	8 : 7	5 : 7
Median age (range)	55 (36 – 69)	47 (26 – 71)
Response: PR	2	
NC	11	4
PD	2	8

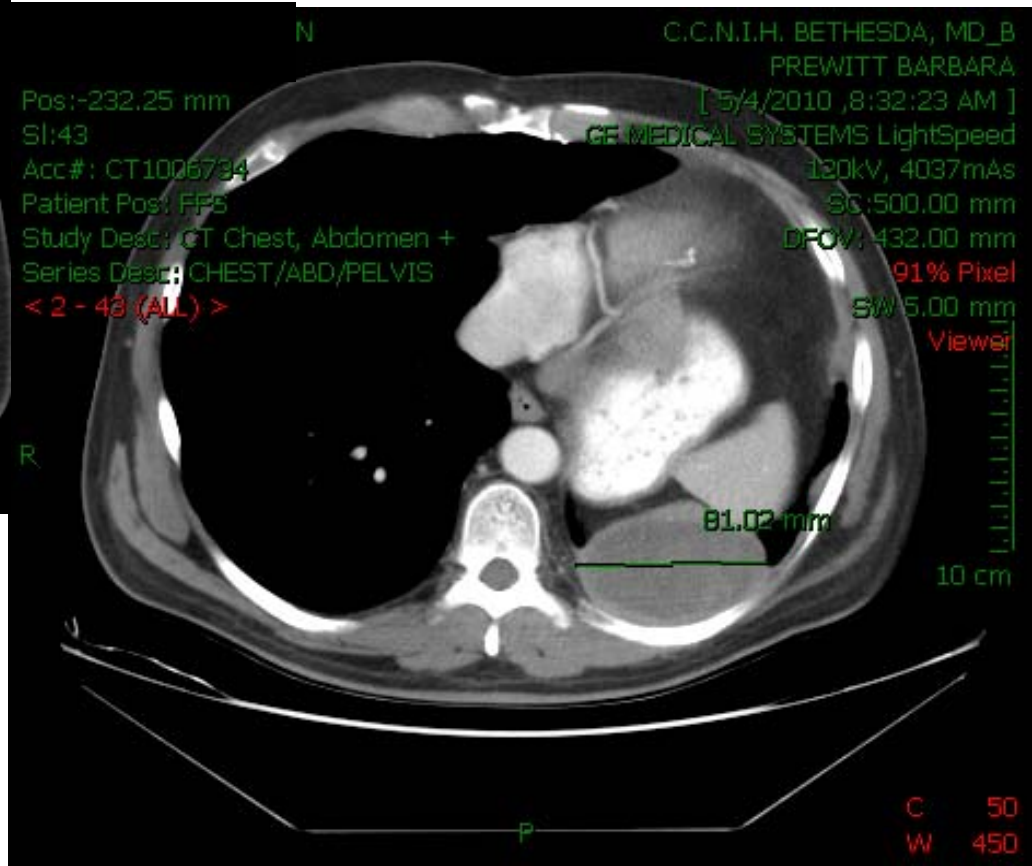
09-C-

CT scans demonstrating a Partial Response in a patient with thymoma



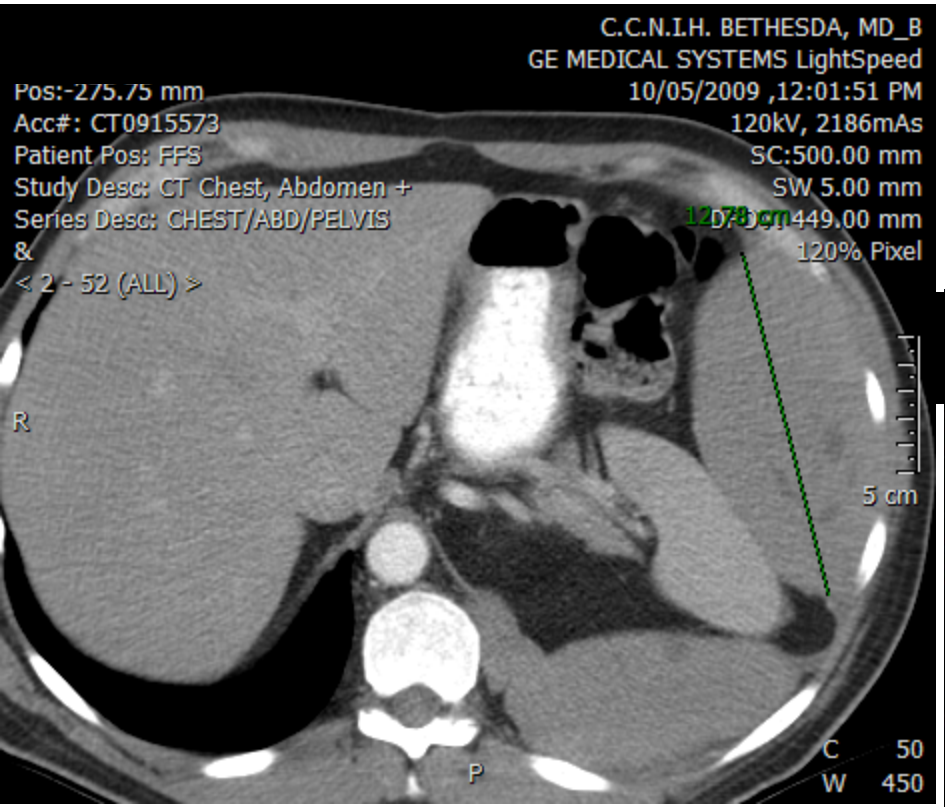
Baseline – Oct 2009

May 2010



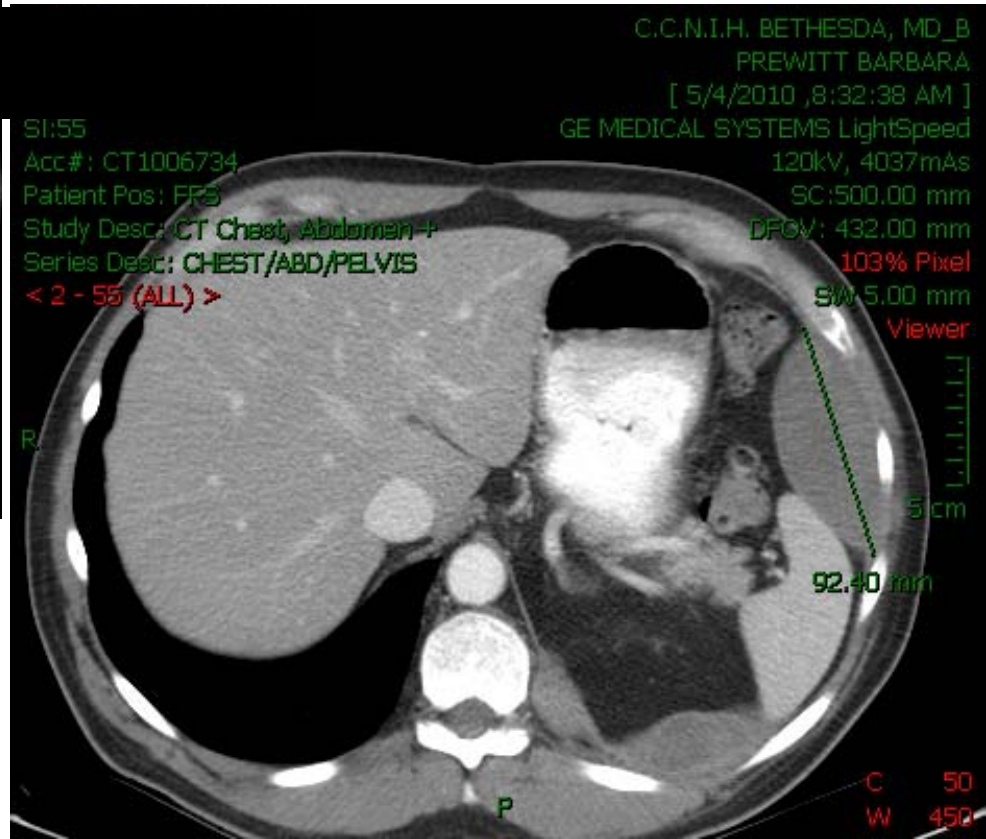
09-C-

CT scans demonstrating a Partial Response in a patient with thymoma



Baseline – Oct 2009

May 2010



09-C-0212

- Common Toxicities:
  - Pain at the site of tumor(s)
  - Hyperglycemia
  - Hyperuricemia
  - Asymptomatic elevation of creatinine

- Uncommon but potentially serious toxicity
  - High frequency sensori-neural hearing loss (1 out of 18)

Genomic aberrations of TETs

- Karyotype studies
  - 13 patients evaluated
  - Several events of genomic imbalance reported
  - Only t(15;19) and Del chr6p25 were recurrent
  - t(15;19) was recurrent, resulting in the NUT-BRD4 fusion-gene

Herens C. et al. Cancer Genetics and Cytogenetics 146:66–69, 2003

- CGH studies
  - TET histotypes present peculiar copy number CN imbalance
  - Type A: Rare chromosomal abnormalities
  - Type B3: chr1q CN gain chr6 CN loss and chr13 CN loss
  - Thymic carcinoma: chr1q CN gain, chr6, chr13, chr16q and chr 17p CN loss

Zettl A et al Am J Path 157(1):257, 2000

Expression profiling

Girard et al. Clin Cancer Res 15, 6790, 2009

- 23 tumors

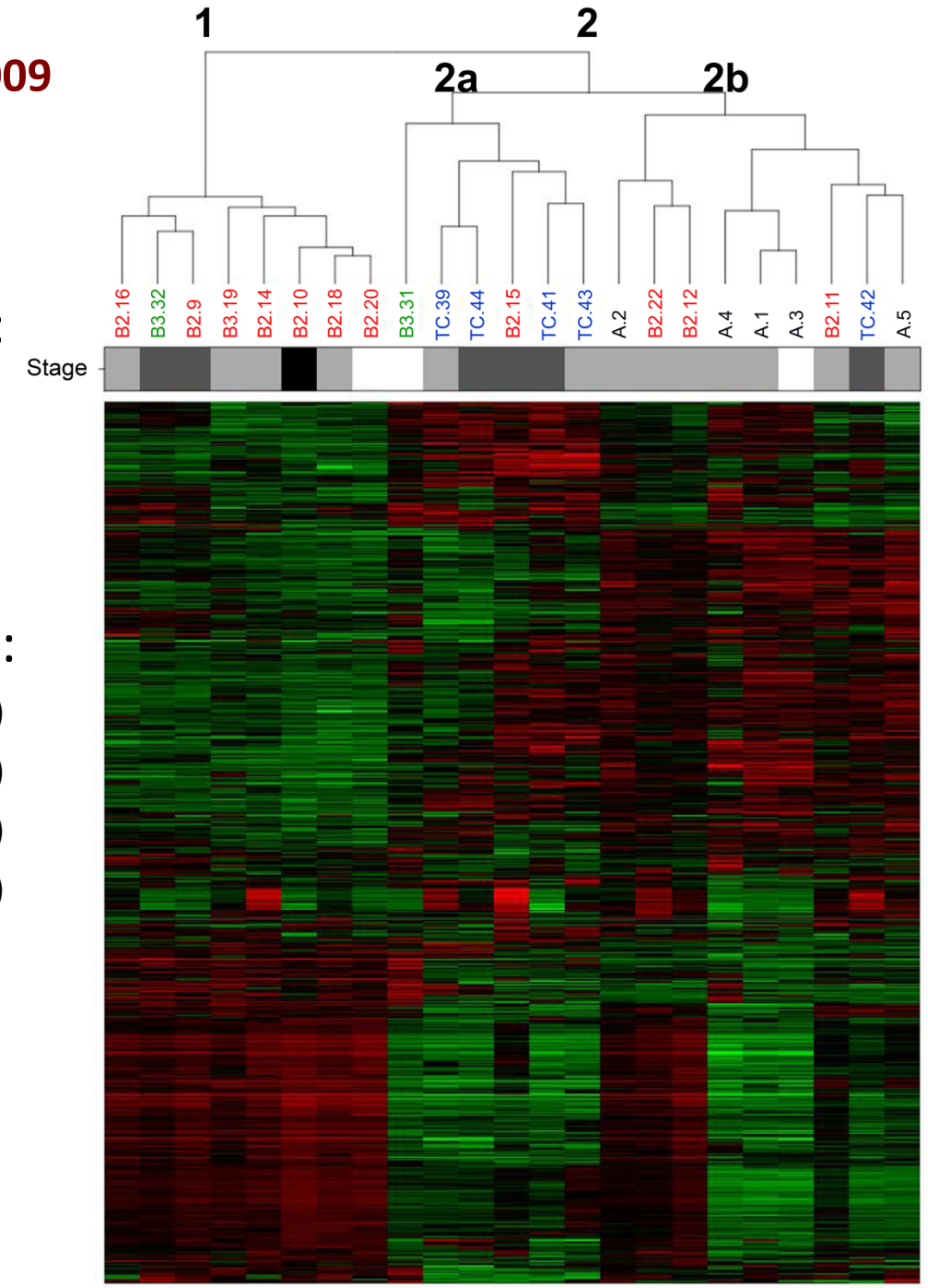
- Unsupervised clustering analysis:
  - cluster 1 (n=8): type B2 thymomas
  - cluster 2 (n=15): others

  (p=0.023)

- Genes overexpressed in cluster 1:
  - immune system process (p=5.3E-19)
  - immune response (p=2.0E-15)
  - T cell activation (p=6.5E-11)
  - lymphocyte activation (p=6.5E-11)

- Cluster 2 was subdivided in:
  - cluster 2a (n=6): thymic carcinoma
  - cluster 2b (n=9): type A thymomas

  (p=0.023)



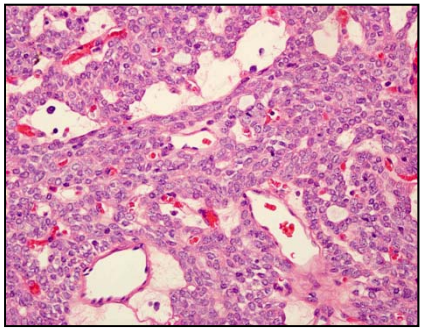
EGFR and RAS

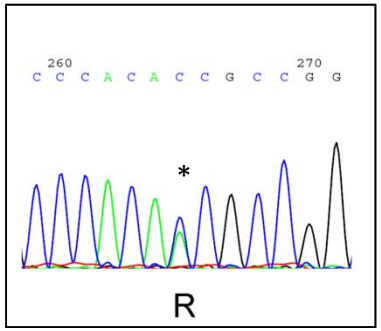
- 45 cases
- No *EGFR* mutation, but 3 (7%) *RAS* mutations:

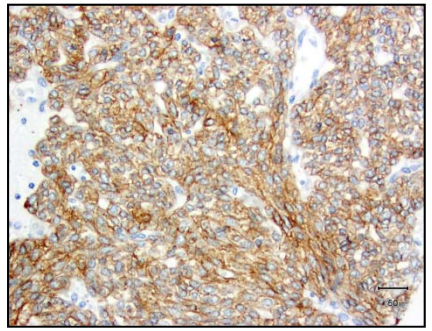
EGFR expression

Type A thymoma

HRAS ^{G13V} **mutation**

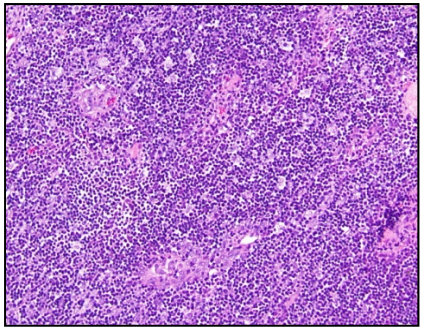


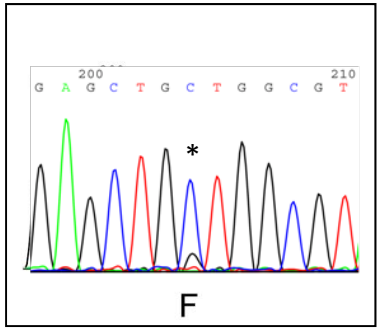


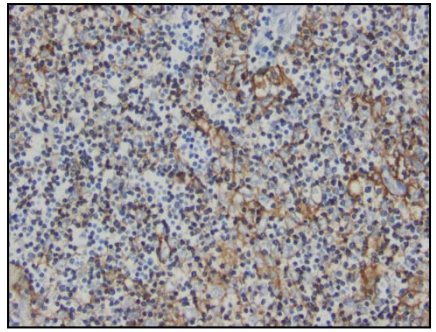


Type B2 thymoma

KRAS ^{G12A} **mutation**

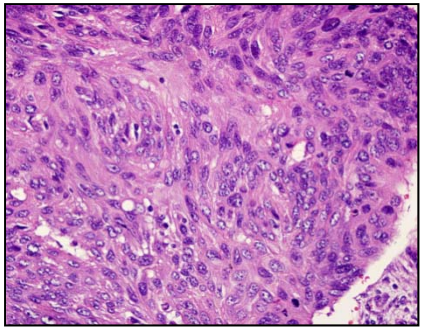


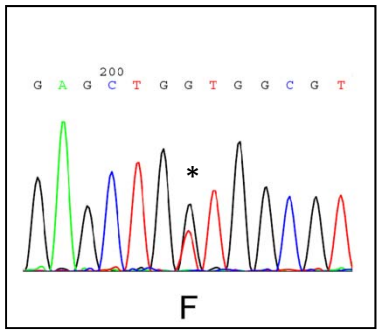


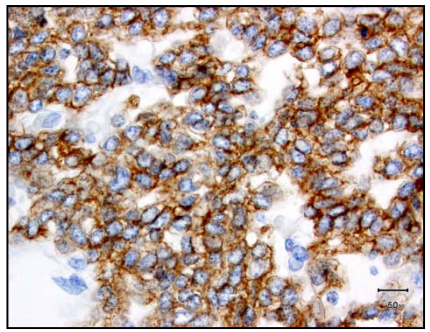


Thymic carcinoma

KRAS ^{G12V} **mutation**







KIT

- 45 cases
- 2 *KIT* mutations, both in thymic carcinomas:
  - The *KIT* ^{V560del} mutation was previously reported in a case of thymic carcinoma sensitive to imatinib.

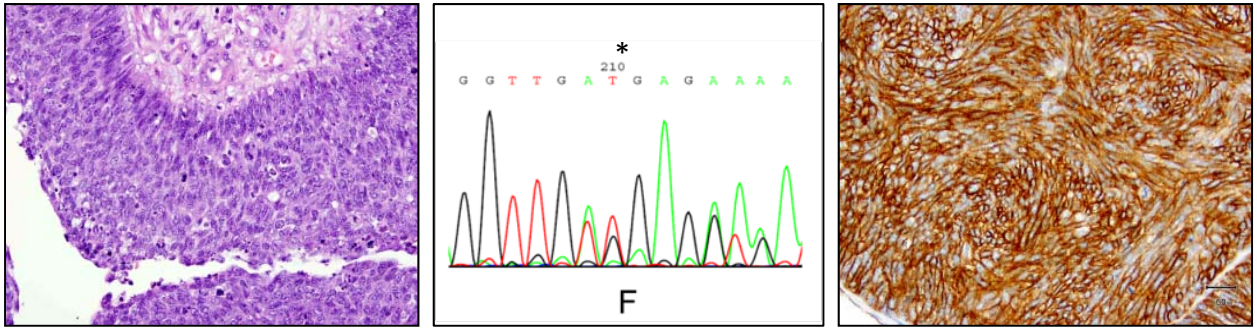
Strobel et al. NEJM 2004;350;2625

  - No correlation with KIT expression at IHC

KIT expression

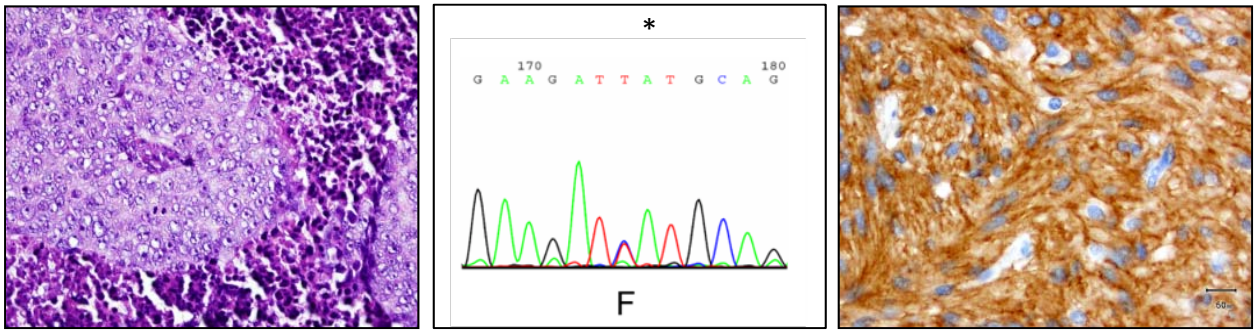
Thymic carcinoma

KIT ^{V560del} **mutation**



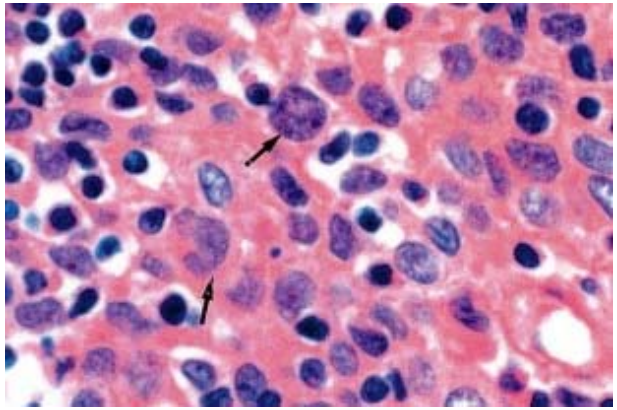
Thymic carcinoma

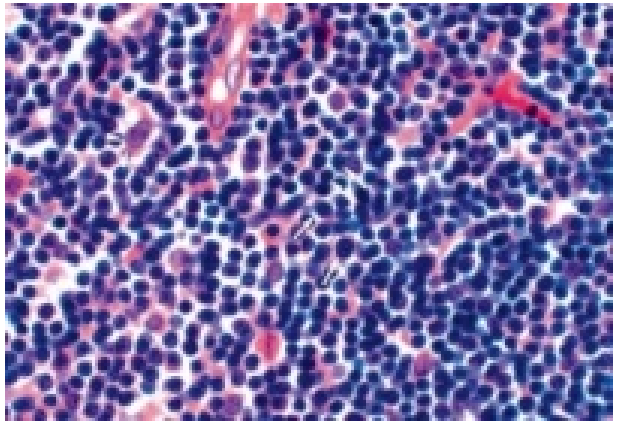
KIT ^{H697Y} **mutation**



Array CGH study

- Premise: obscure biology
- FFPE blocks from a series of 134 resected thymoma patients
- 59 samples with > 80% epithelial cancer cells were analyzed



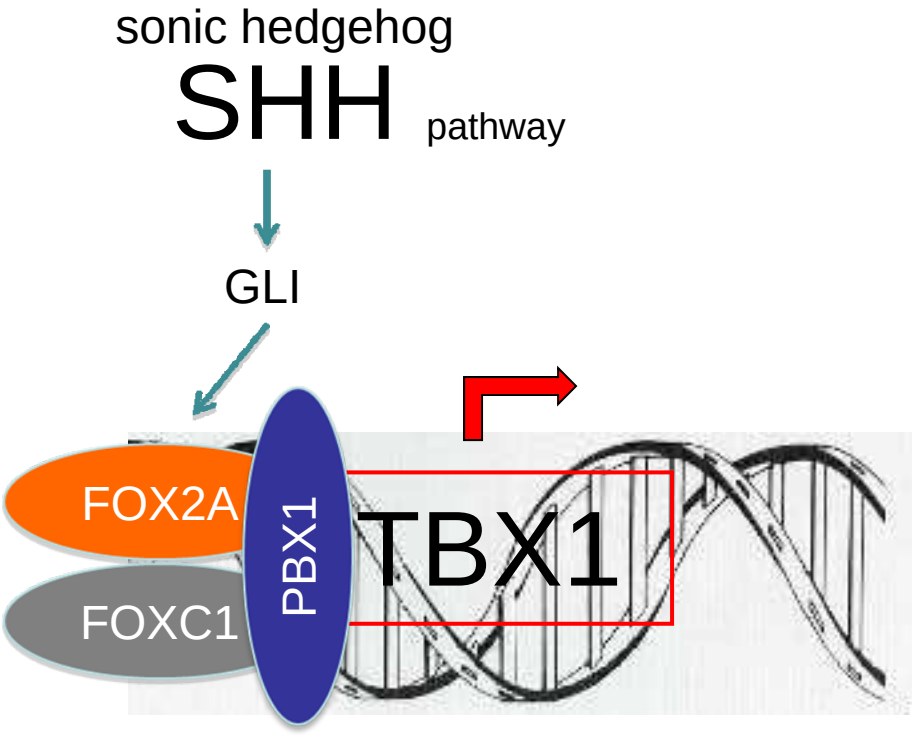


Petrini, unpublished

Copy number variation (n=59)

Progression by histological type

Genes involved in development of thymus with frequent copy number imbalance
Regulation of TBX1



PBX1(1q23.3), oncogene
CN gain 42% Chr1q23.3

FOXC1(6p25.3), putative TSG
CN loss 42% Chr6q25.3

NTRK1 gain 45.8% Chr1q23.1

Hypothesis:
PBX1 and/or FOXC1 and/or NTRK1 are involved in development of thymomas

Goals:
Confirm results with alternative methods
Establish function in cells lines
Develop therapeutic strategies

FISH for NTRK1 and SNIP1 in T1889 cells

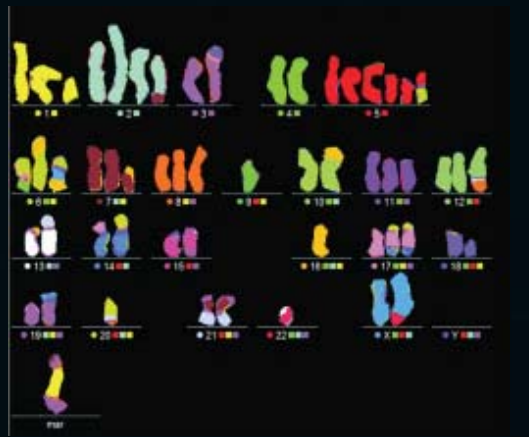
Chr1q with NTRK1 amplification

Normal Chr 1

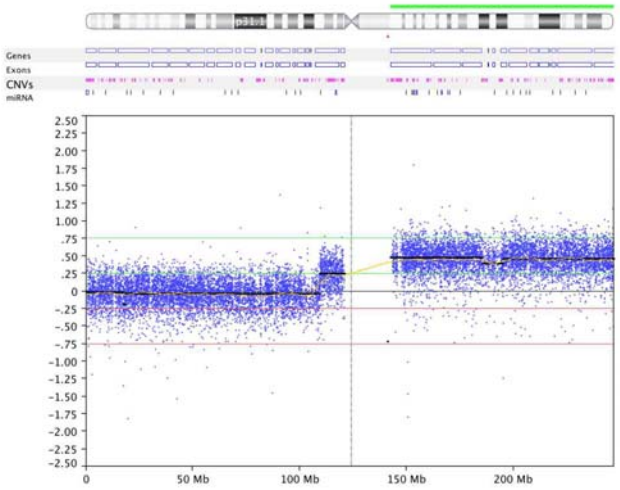
Chr 1p

Chr1q with NTRK1 amplification

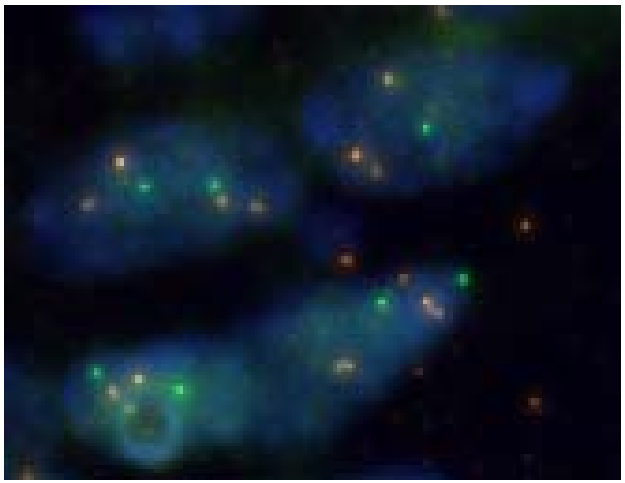
Chr 1p

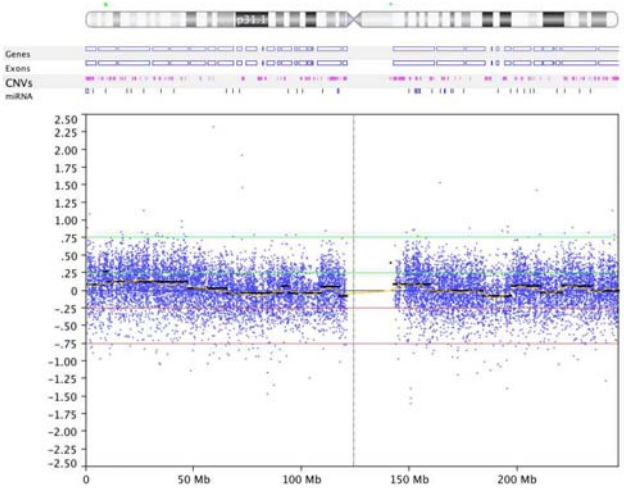


Thymic epithelial tumors FFPE

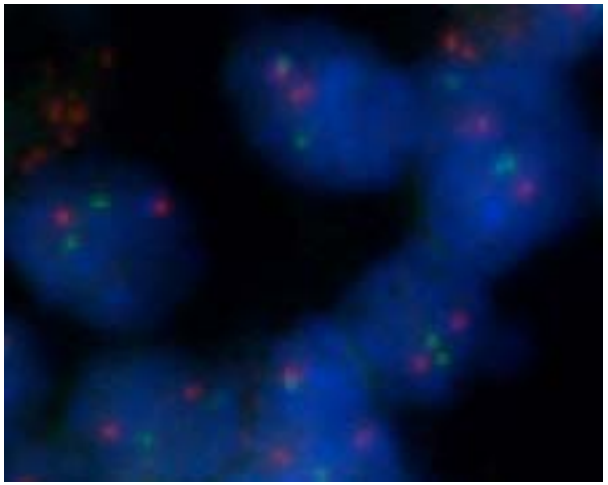


I-Thy 016B: Chromosome 1





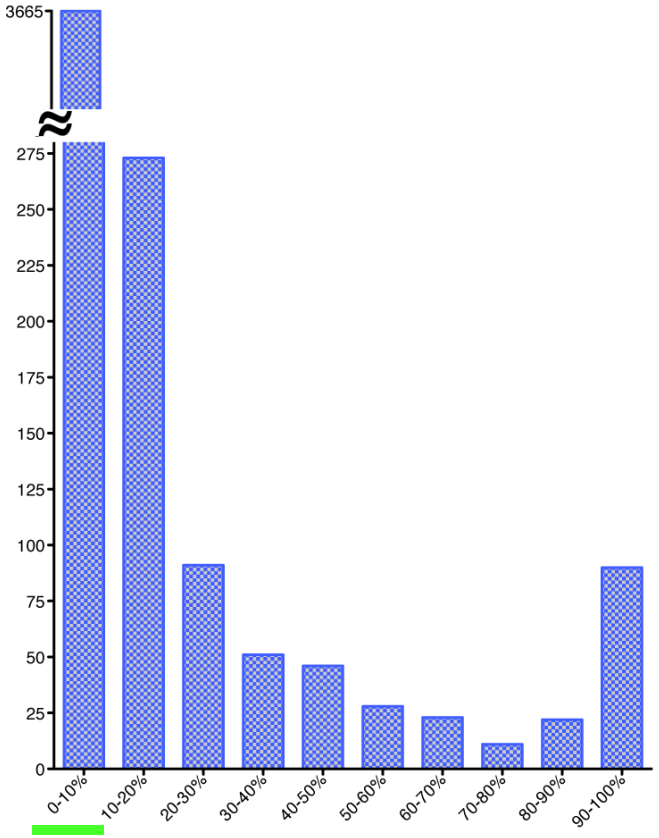
I-Thy 120: Chromosome 1

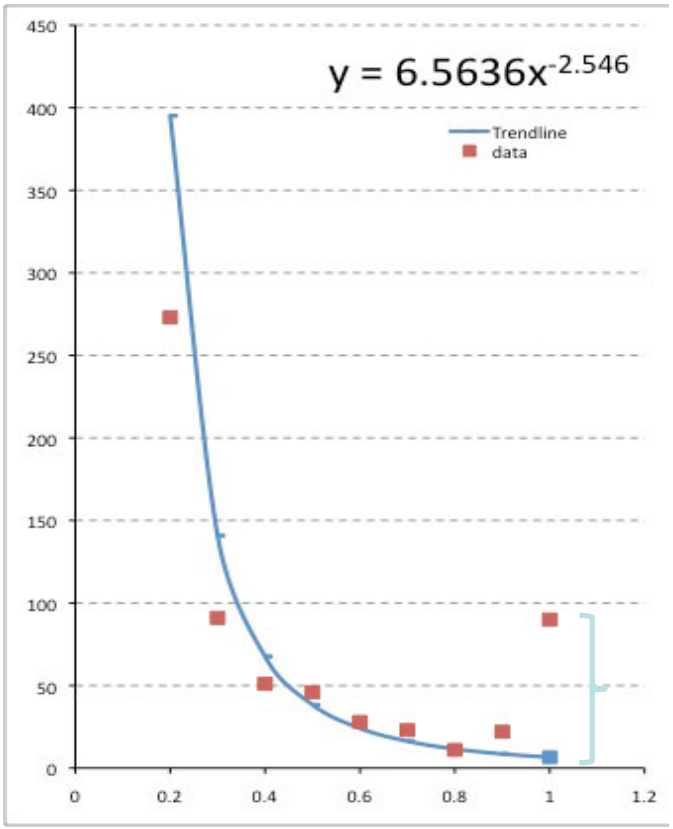


Phase II studies of oral PHA-848125AC in patients with Thymic Carcinoma

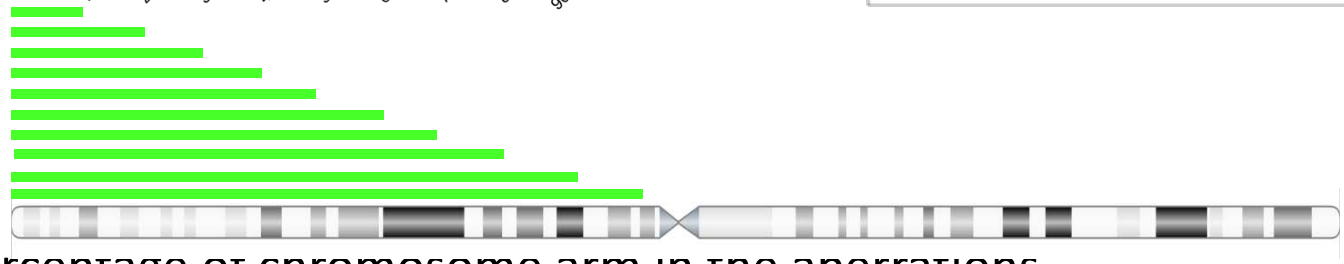
- PHA-848125AC – inhibits the kinase activity of the CDK2/Cyclin A complex, CDK1, CDK4, CDK5 and TRKA.
- Currently being evaluated in two phase II studies in patients with thymic carcinoma
  - Multicenter study in patients with WHO subtype C disease who have received only one prior line of systemic therapy:
    - Number of patients screened (as of 2/22/2011) – 13
    - Number of patients enrolled (as of 2/22/2011) – 11
  - Single institution study (NCI) in patients with WHO subtype B3 and C disease who have received more than one prior line of systemic therapy:
    - Number of patients screened and enrolled (as of 3/7/2011) – 1

Distribution of CN aberrations



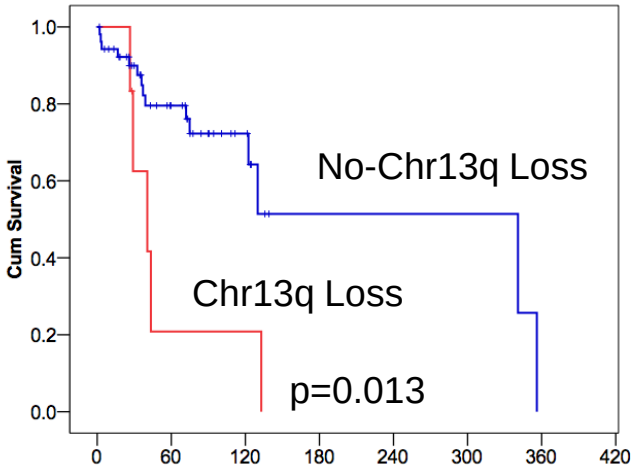


p<0.001

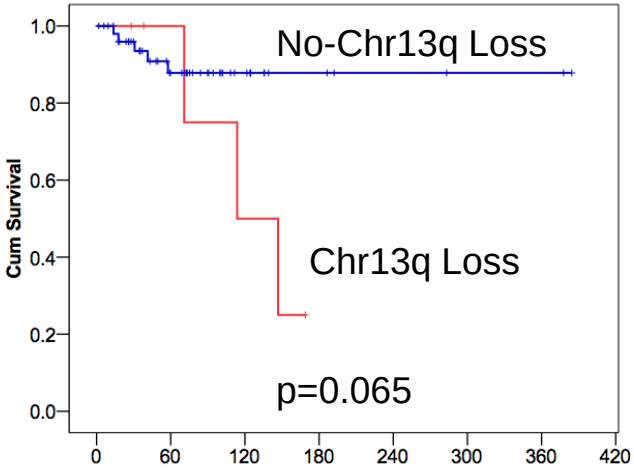


Percentage of chromosome arm in the aberrations

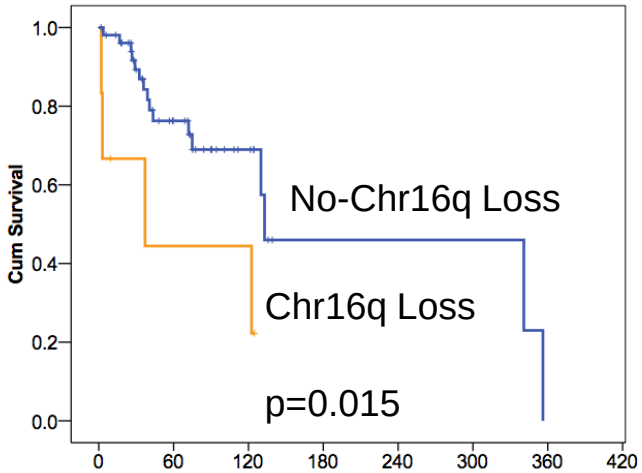
Survival implications



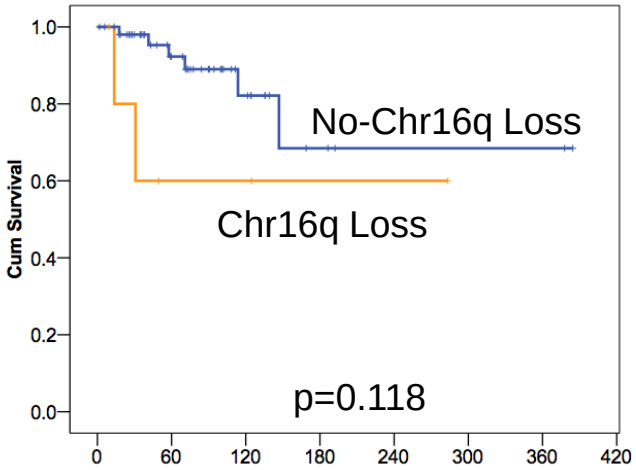
Time to progression (months)



Disease related survival (months)



Time to progression (months)

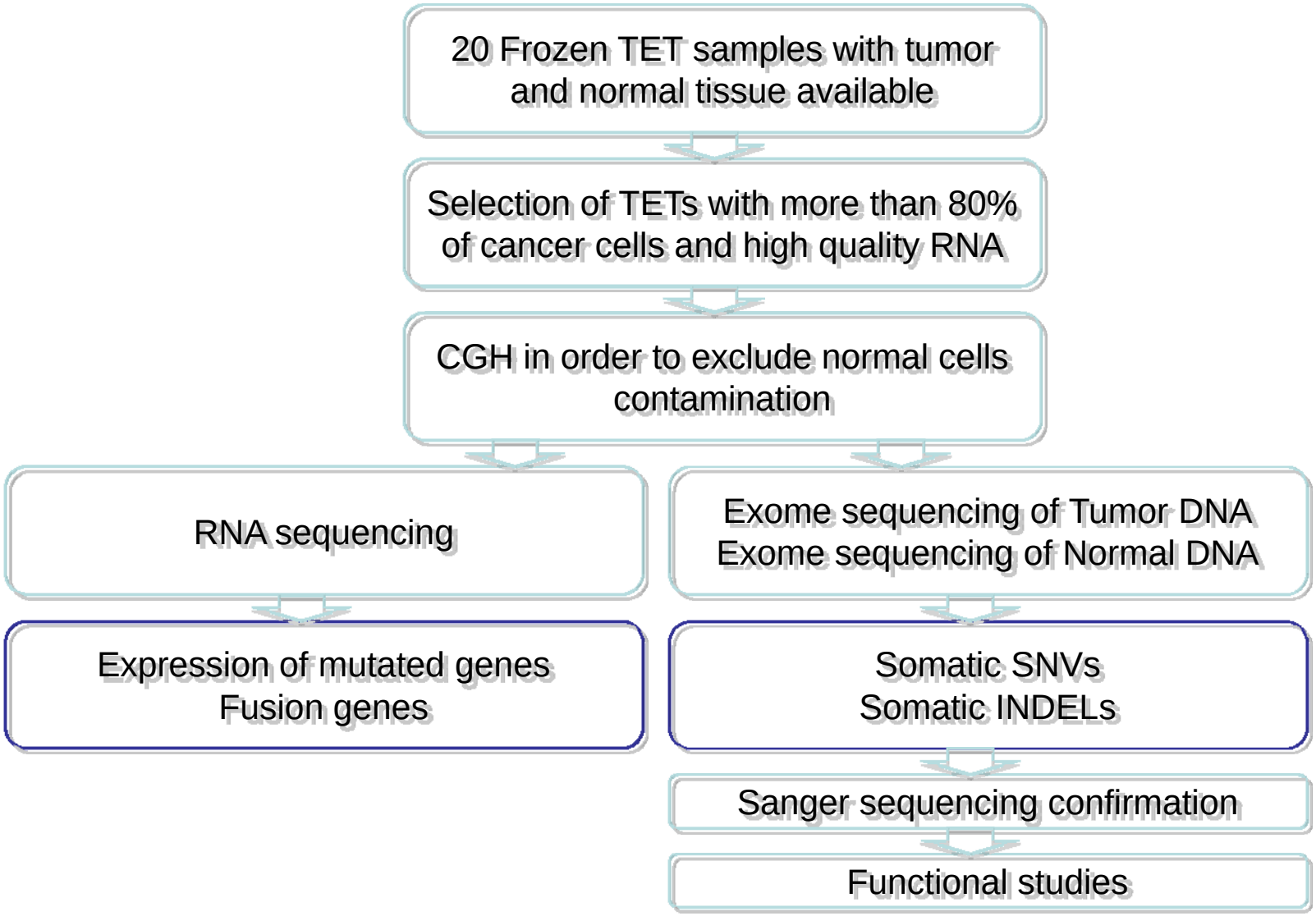


Disease related survival (months)

Transcriptome/exome sequencing Objectives

- To identify genomic imbalances in TETs
- To characterize genes or gene regions potentially important for tumor development, prognosis or potential targets for systemic therapies

Study design

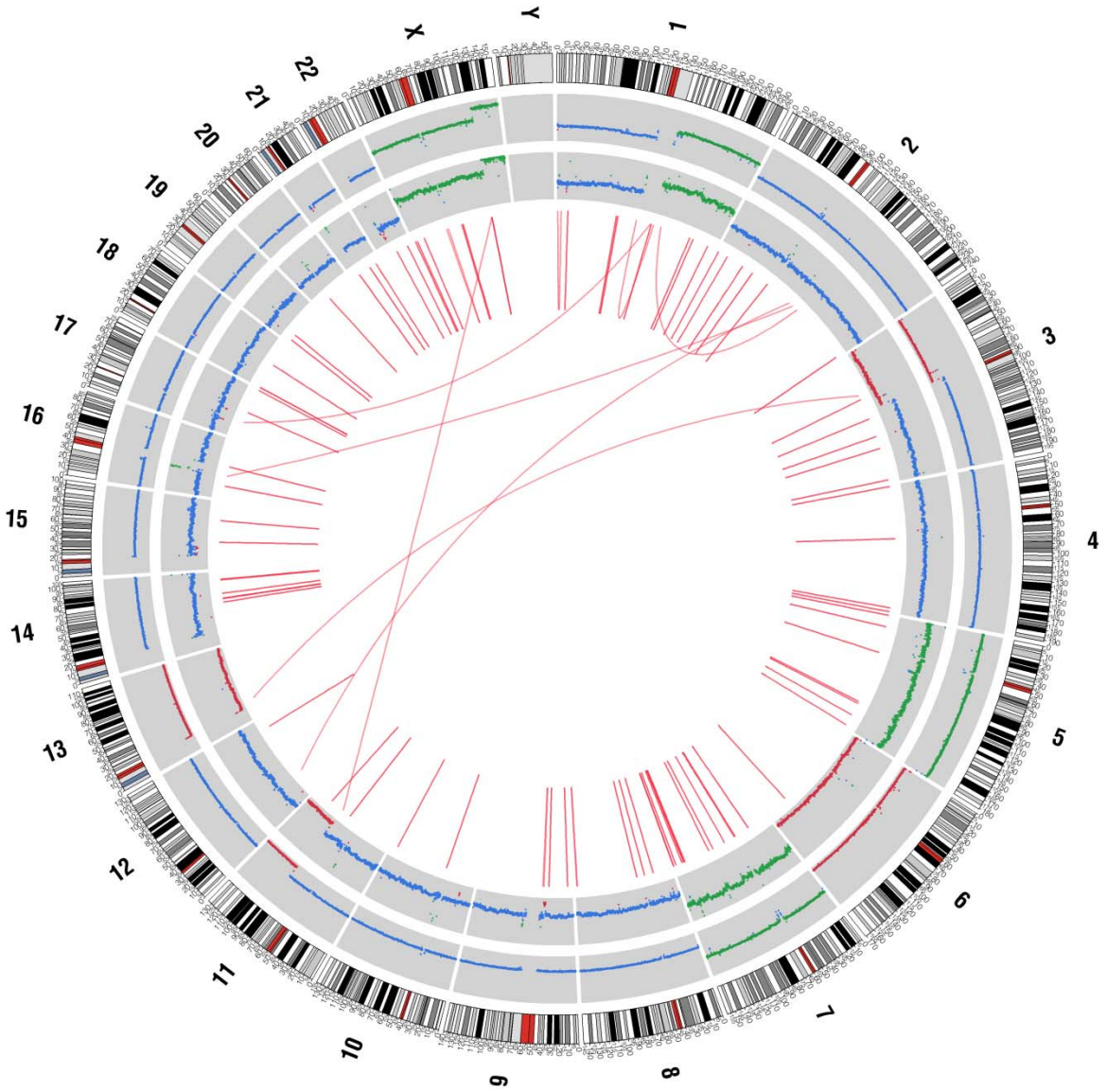


Sequencing technologies

- cDNA libraries were created from RNA using Illumina kit poly-A tail enrichment was use to select mRNA
- Enon libraries were built using SureSelect Human All Exon Kits (Agilent)
- Libraries were sequenced using Hiseq2000 (Illumina)
- Complete genome sequencing become an available tool and we integrated the analysis with this technique

Complete Genomics Inc technology

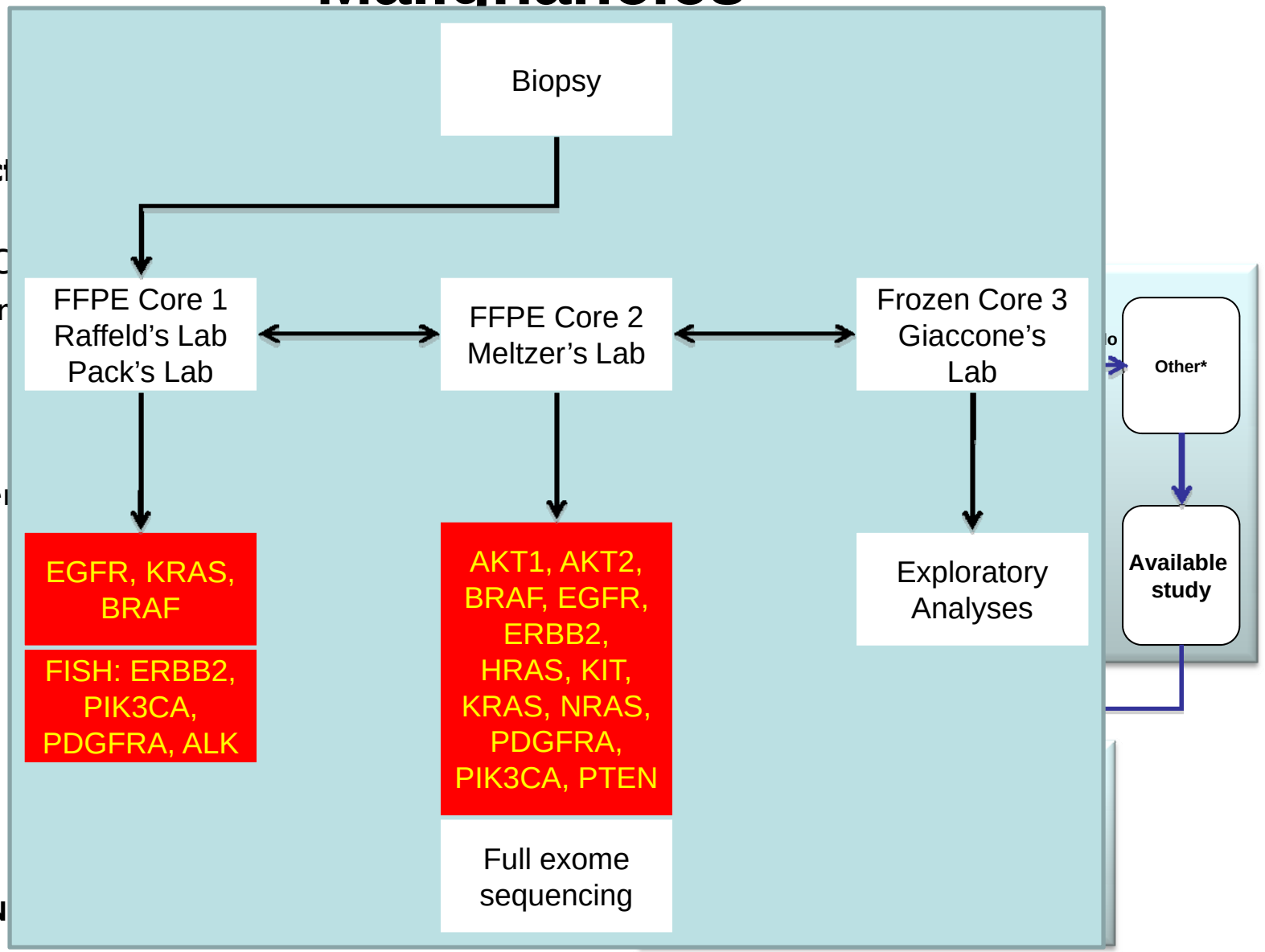
Complete Genome sequencing of a B3 thymoma



Molecularly Targeted Treatment of Advanced Thoracic Malignancies

Patient selec
Molecular +
NSCLC, SCLC
thymic malign

Treatment:
Targeted ther



N

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