GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

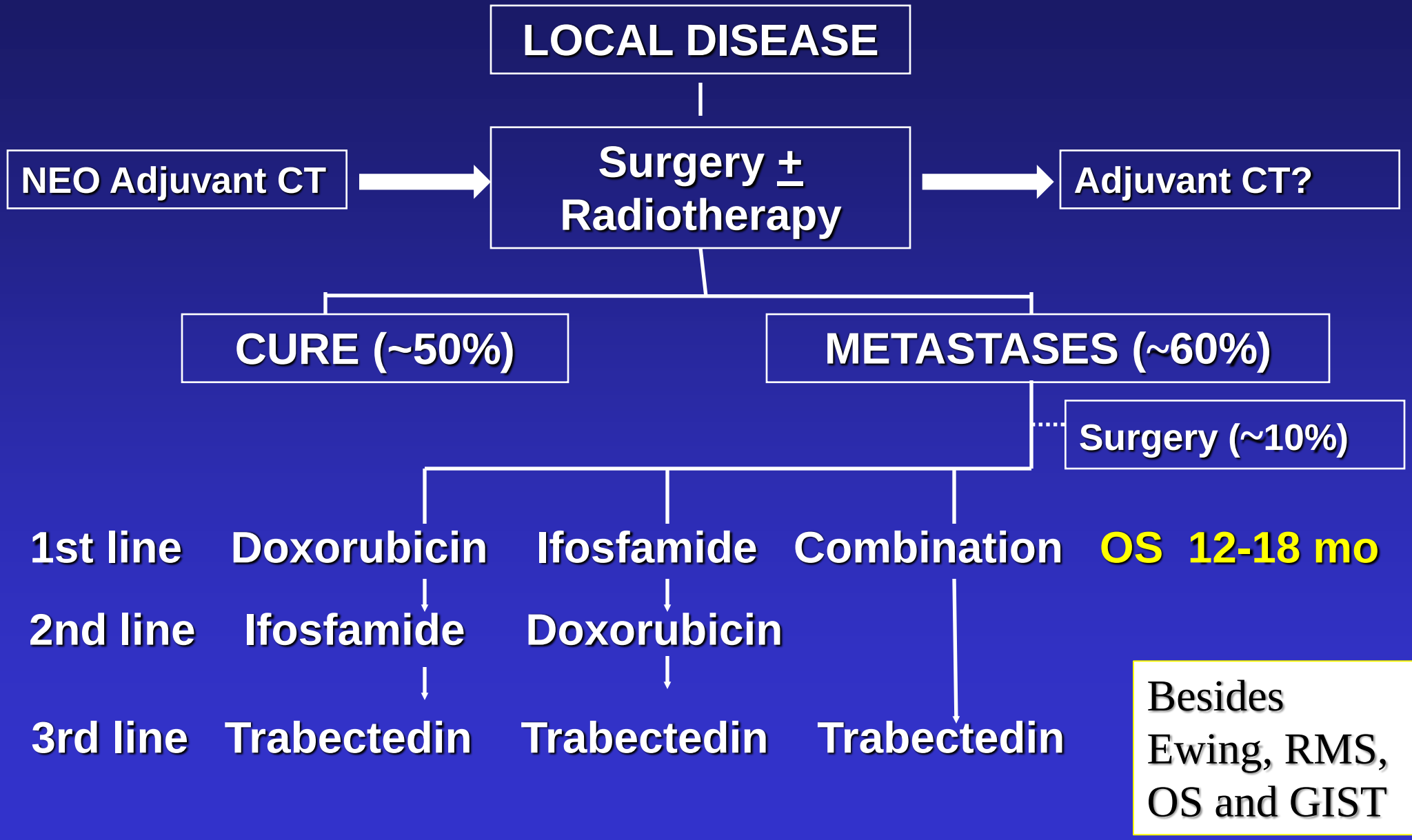
www.esmo.org

Treating sarcoma subtypes based on molecular characteristics

JY Blay
Lyon, France
FSG, EORTC

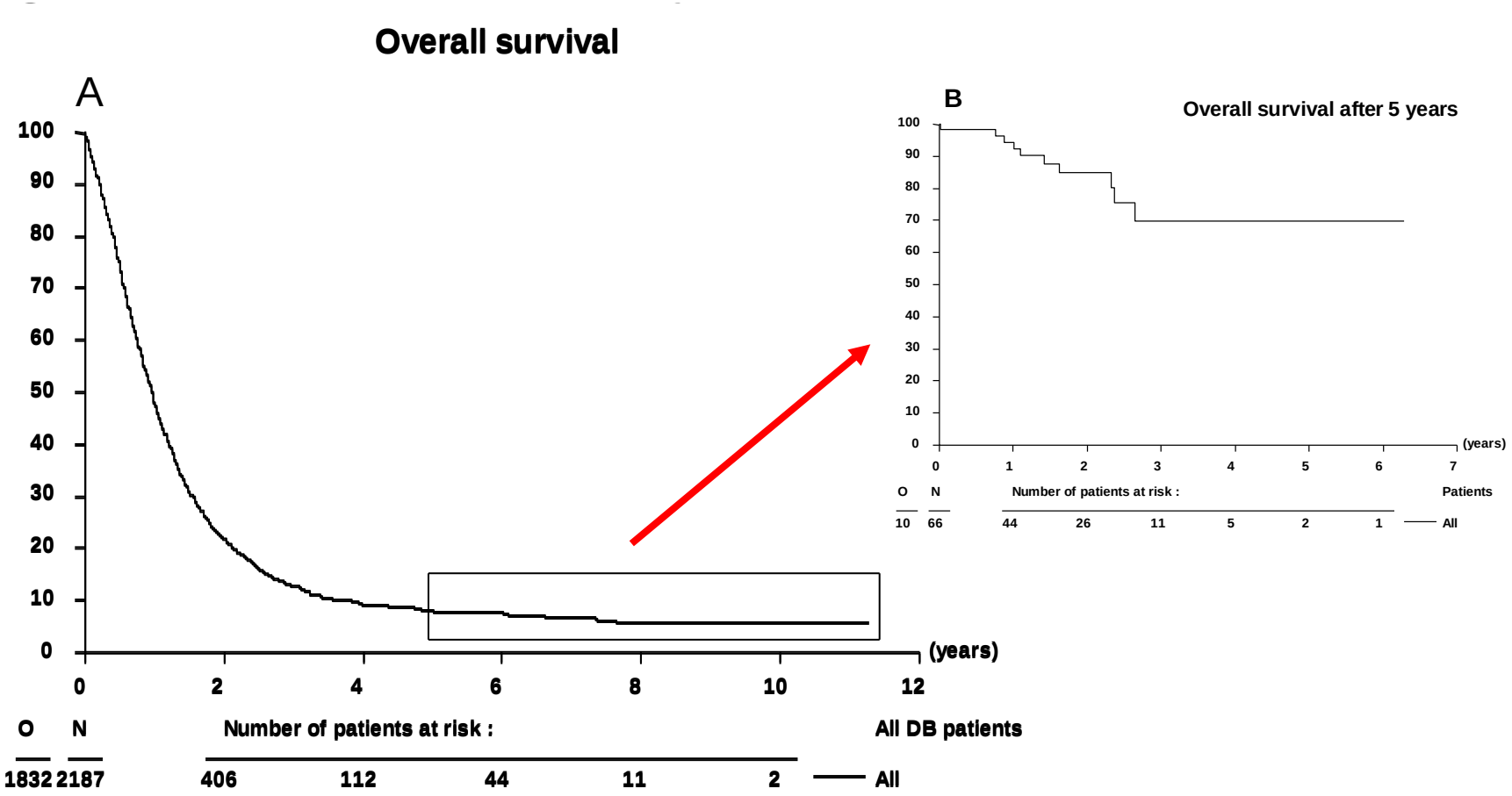
A simple algorithm?

ESMO 2012



Besides Ewing, RMS, OS and GIST

After local or metastatic relapse



Long term survivors

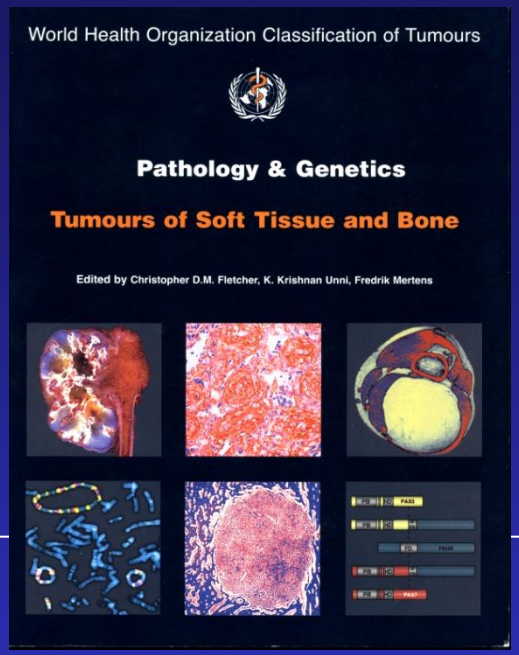
Response to first line doxorubicin-containing regimens.

Response to 1st line ¶	5-year survivor (n=66) N (%)	Others* (n=1822) N (%)	p	% of 5-year survivors among response subgroup
CR	17 (31%)	64 (4%)		17/81 (21%)
PR	17 (31%)	306 (19%)		17/323 (5%)
SD	17 (31%)	641 (39%)		17/658 (3%)
PD	3 (6%)	627 (38%)	0.00001	3/630 (0.5%)

*: patients with a minimum follow-up of 5 years after inclusion who died within the 5 years of inclusion.

¶: Response was not documented in 196 (10%) patients

Blay et al EJC 2003



Fragmentation

>50 different histotypes
AND molecular subtypes
2013 classification

Adipocytic tumours
- Well deifferentiated / dedifferentiated liposarcoma
- Myxoid / round cell liposarcoma
- Pleomorphic liposarcoma
- …..

Fibroblastic / myofibroblastic tumours
- Fibromatosis (desmoid)
- Solitary fibrous tumour / haemangiopericytoma
- Low grade myofibroblastic tumour
- Infantile fibrosarcoma
- Adult fibrosarcoma
- Mixofibrosarcoma
- …..

So-called fibrohistiocytic tumours
- Pleomorphic MFH / Undifferentiated pleomorphic sarcoma
- …..

Smooth muscle tumours
- Leiomyosarcoma
- …..

Skeletal muscle tumours
- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma

Vascular tumours
- Epithelioid haemangioendothelioma
- Angiosarcoma of soft tissue
- …..

Chondro-osseous tumours
- Mesenchymal chondrosarcoma
- Extraskeletal osteosarcoma

Tumours of uncertain differentiation
- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Extraskeletal Ewing tumour
- Desmoplastic small round cell tumour
- Extra-renal rhabdoid tumour
- Malignant mesenchymoma
- Neoplasms with perivascular epithelioid cell differentiation (PEComa)
- Intimal sarcoma

Connective tissue tumours

- Sarcoma with translocations ~15%
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- Sarcomas with complex genetic alterations ~50%
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- Low grade or locally agressive
  - Desmoid tumors beta catenin or APC mutation
  - Giant cell tumor of the bone ? (RANK involved)
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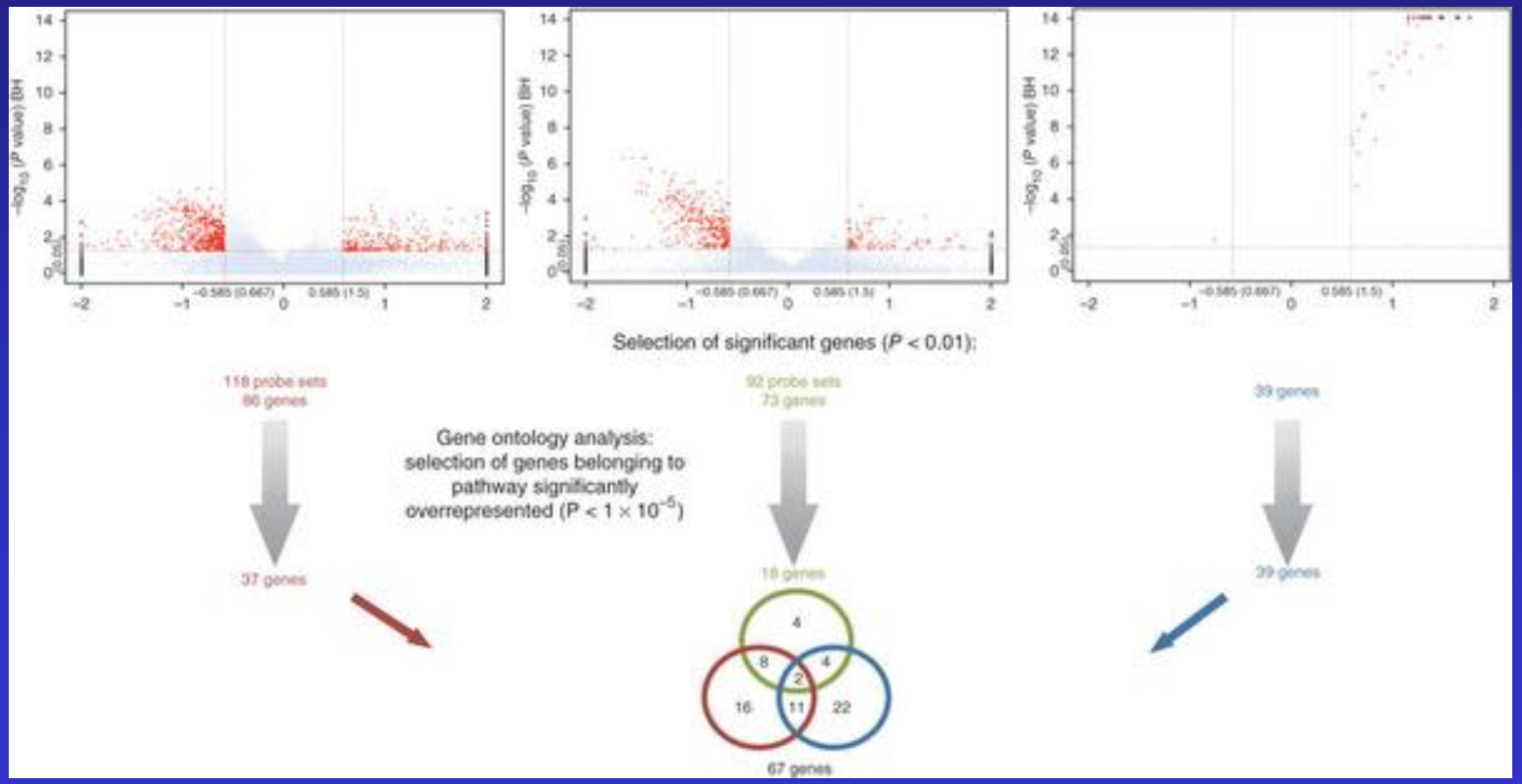
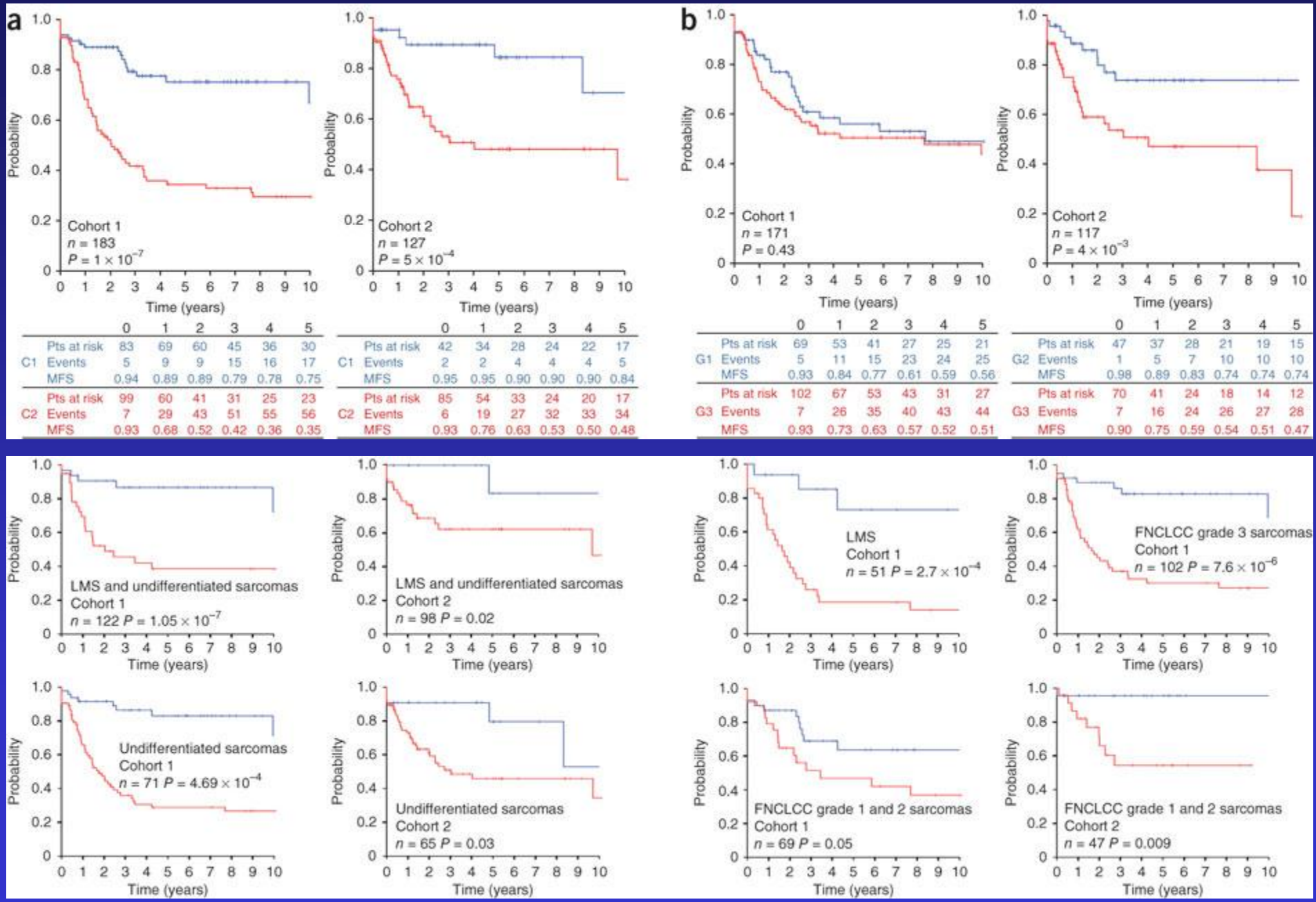
Sarcomas with complex genomics

- Molecular signature for sarcoma
- Beyond FNCLCC grading?



Chibon et al. Nat Med, 2010



		0	1	2	3	4	5
C1	Pts at risk	83	69	60	45	36	30
	Events	5	9	9	15	16	17
	MFS	0.94	0.89	0.89	0.79	0.78	0.75
C2	Pts at risk	99	60	41	31	25	23
	Events	7	29	43	51	55	56
	MFS	0.93	0.68	0.52	0.42	0.36	0.35

		0	1	2	3	4	5
C1	Pts at risk	42	34	28	24	22	17
	Events	2	2	4	4	4	5
	MFS	0.95	0.95	0.90	0.90	0.90	0.84
C2	Pts at risk	85	54	33	24	20	17
	Events	6	19	27	32	33	34
	MFS	0.93	0.76	0.63	0.53	0.50	0.48

		0	1	2	3	4	5
G1	Pts at risk	69	53	41	27	25	21
	Events	5	11	15	23	24	25
	MFS	0.93	0.84	0.77	0.61	0.59	0.56
G3	Pts at risk	102	67	53	43	31	27
	Events	7	26	35	40	43	44
	MFS	0.93	0.73	0.63	0.57	0.52	0.51

		0	1	2	3	4	5
G2	Pts at risk	47	37	28	21	19	15
	Events	1	5	7	10	10	10
	MFS	0.98	0.89	0.83	0.74	0.74	0.74
G3	Pts at risk	70	41	24	18	14	12
	Events	7	16	24	26	27	28
	MFS	0.90	0.75	0.59	0.54	0.51	0.47

Systemic treatment of sarcomas 2000-2012

ESMO 2012

2000:

- All sarcomas
  - Doxorubicin
  - Ifosfamide
  - DTIC
- Ewing , RMS, OS
  - Dactinomycin
  - CDDP
  - Vincaalcaloids
  - Cyclophosphamide
  - HDMTX

2012

- All subtypes : Trabectedin
- GIST: Imatinib, sunitinib,
- DFSP : Imatinib
- Osteosarcomas: MTPPE

- LMS: Gemcitabine (+/- DTIC or Tax)
- EWS: TopoI inh., IGF1R
- A/E RMS: Topo inh
- Angio: Dox, Paclitaxel, GemTax
- ESS : Aromatase inh.
- All but LPS: pazopanib
- PVNS :Imatinib
- Desmoid Tumors : HT, imatinib

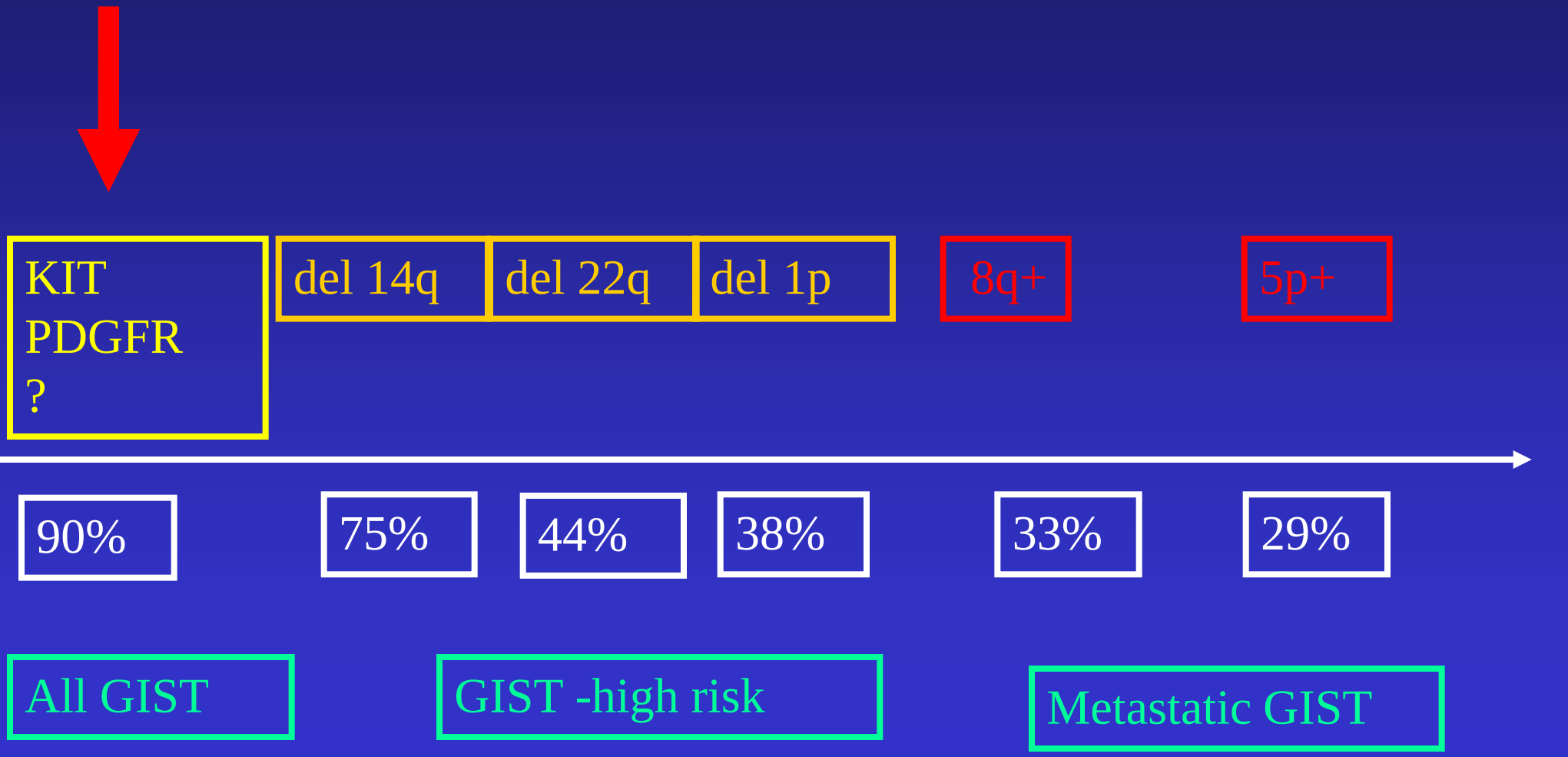
- GCTB : denosumab
- PECOMAs: mTOR
- WD/DD: LPS:CDK4, MDM2
- GIST: regorafenib
- ASPS: cediranib


Clinical research
Translational research
Basic research

Three situations

- Initial molecular event
  - KIT in GIST
  - Loss NF1, TSC
  - Translocations
  - Mdm2 amplification
  - …
- Secondary event
  - VEGF production
  - Activation of mTOR pathway
  - ER expression in ESS
- Simple bystander
  - PDGFR expression in normal (and malignant) cells of connective tissue

1.Targeting an initial event



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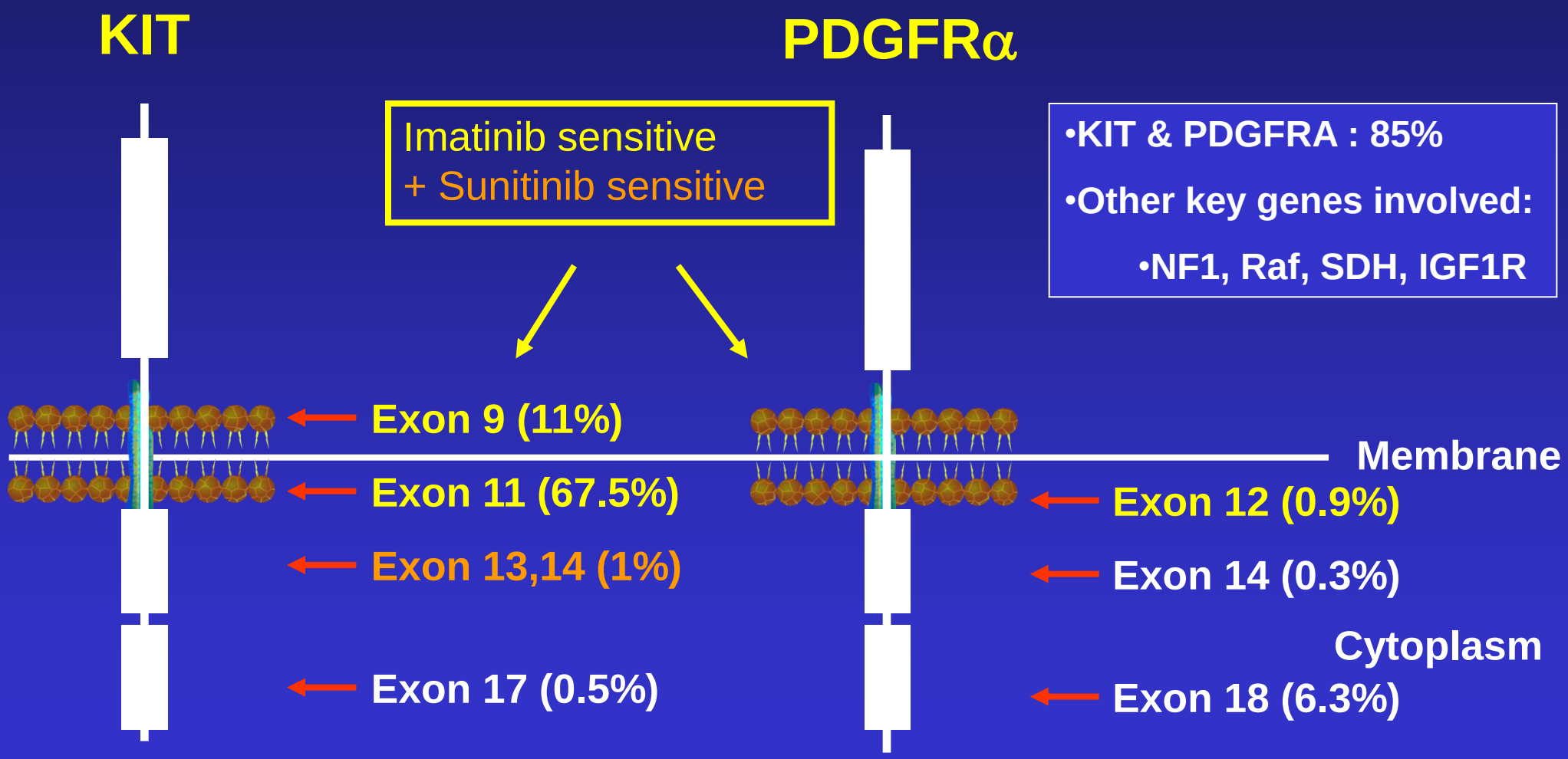
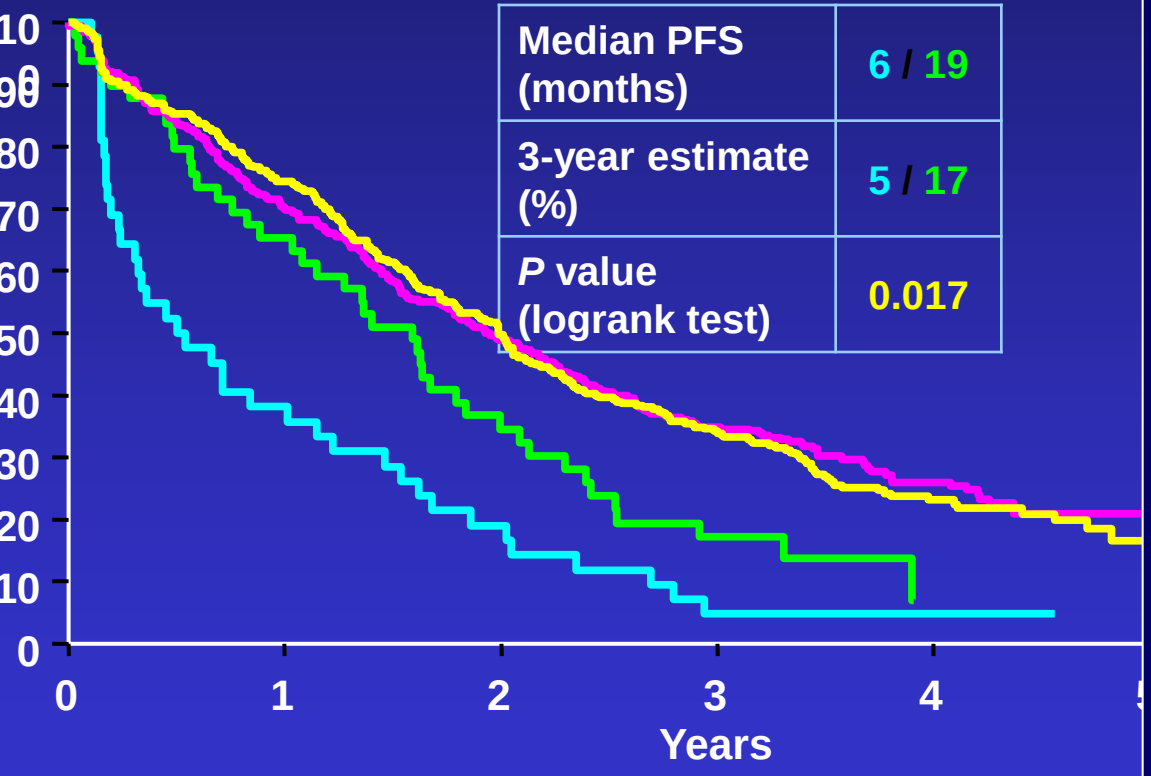
KIT and PDGFRα mutations in GIST



Heinrich et al. *Hum Pathol.* 2002;33:484; Science 2003,
Corless et al. *Proc AACR.* 2003

GIST are at least 10 diseases

***KIT* exon 9 mutants (10% of patients)**



Median PFS (months)	6 / 19
3-year estimate (%)	5 / 17
P value (logrank test)	0.017

***KIT* exon 9 mutants: 400 mg / 800 mg**
Other patients: 400 mg / 800 mg

	Dose	Adjuvant
KIT Exon 11	Im 400	+
KIT exon 9	Im 800	+
PDGFRA		
Non D842V	Im 400	+
D842V:	0	0
KIT/PDGFR WT	Im 400	+/?
NF1	?/Im 400	+/?
SDHB	?/Im 400	+/?
Raf	?	?
Pediatric	?	?

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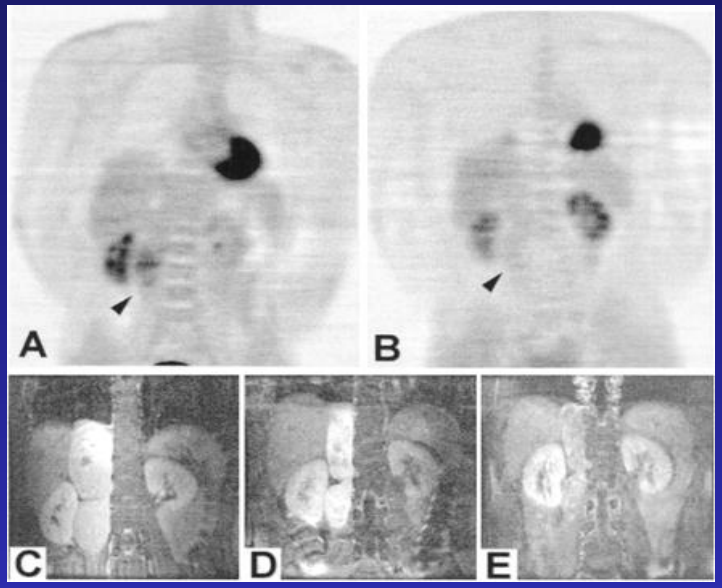
DFSP and imatinib

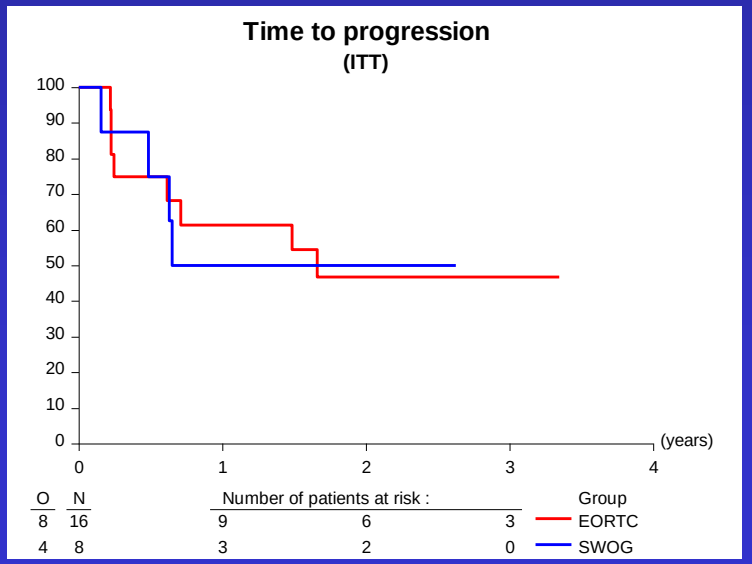
DFSP /giant cell fibroblastoma

- t(17,22) :17q22 and 22q13 (*COL1A1* et *PDGFB*)

- Autocrine loop with PDGFβ

Maki et al 2002
Mc Arthur et al 2005
Rutkowski et al 2010





ESMO 2012

Imatinib mesylate (IM) for the treatment of locally advanced and/or metastatic pigmented villonodullar synovitis/tenosynovial giant cell tumor (PVNS/TGCT).

Philippe A. Cassier, Silvia Stacchiotti, Hans Gelderblom, David Thomas, Winette van der Graaf, Beatrice Seddon, Julien Domont, Andrew J. Wagner, Jean-Yves Blay.

ESMO 2012

Original Article

Efficacy of Imatinib Mesylate for the Treatment of Locally Advanced and/or Metastatic Tenosynovial Giant Cell Tumor/ Pigmented Villonodular Synovitis

Philippe A. Cassier, MD[1]; Hans Gelderblom, MD[2]; Silvia Stacchiotti, MD[3]; David Thomas, MD[4]; Robert G. Maki, MD[5]; Judith R. Kroep, MD[2]; Winette T. van der Graaf, MD[6]; Antoine Italiano, MD[7]; Beatrice Seddon, MD[8]; Julien Dômont, MD[9]; Emanuelle Bompas, MD[10]; Andrew J. Wagner, MD[11]; and Jean-Yves Blay, MD[1,12]

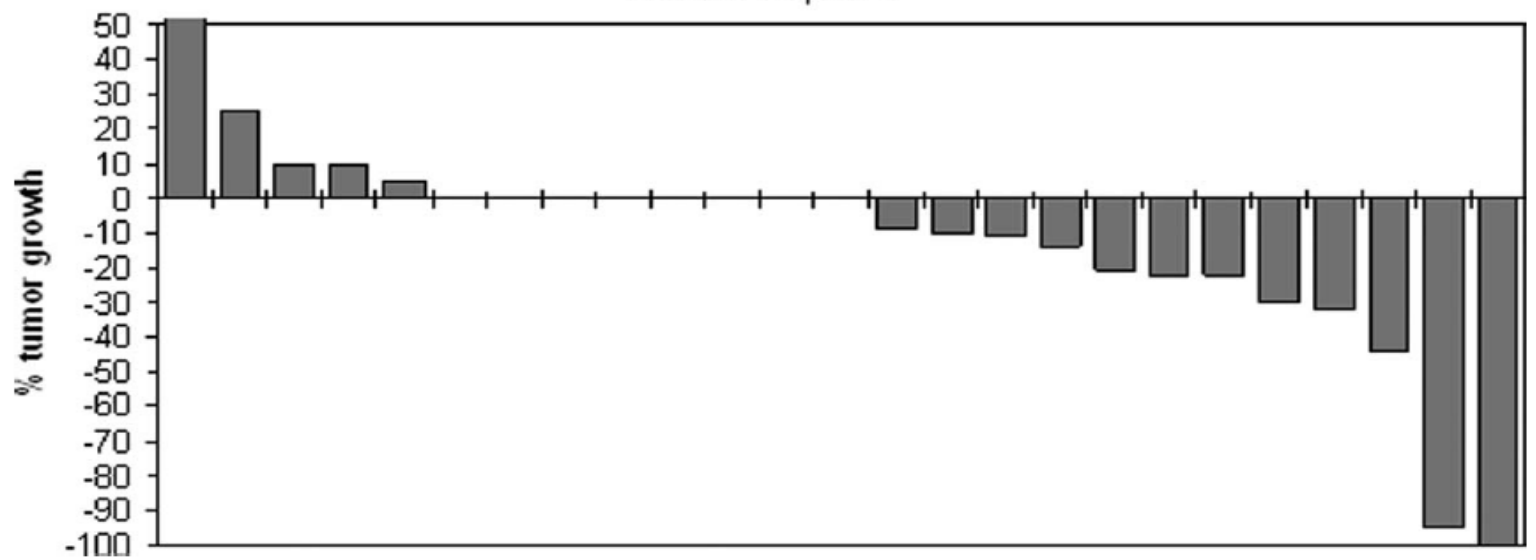


Figure 1. The best tumor shrinkage is illustrated according to Response Evaluation Criteria in Solid Tumors (RECIST).

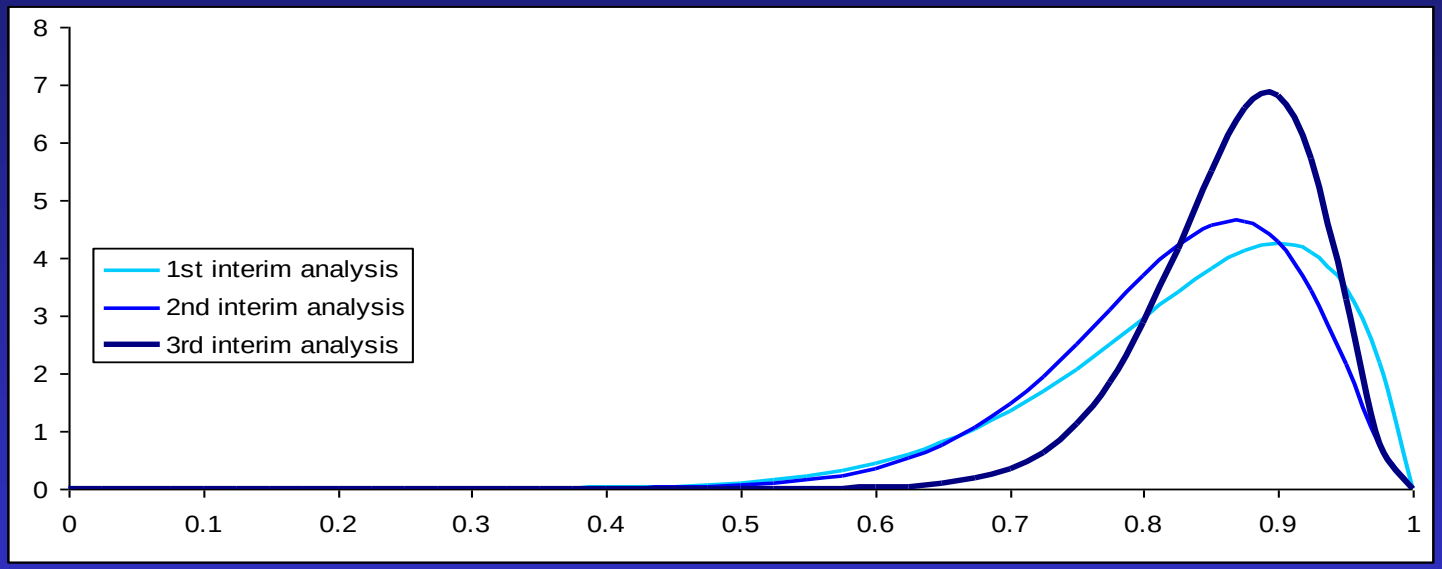
PVNS study: An open-label international multicentric phase II study of nilotinib in progressive pigmented villonodular synovitis not amenable to a conservative surgical treatment

Isabelle RAY-COQUARD, Hans GELDERBLOM, Christine CHEVREAU, Judith R. KROEP, Antoine ITALIANO, Silvia STACCHIOTTI, Axel LE CESNE, Sophie PIPERNO-NEUMANN, Virginia FERRARESI, Florence DUFFAUD, Nicolas PENEL, Philippe A. CASSIER, Martin TATTERSALL, Andrew Bassim HASSAN, Binh BUI NGUYEN, Valérie BOURNE-BRANCHU, Séverine GUILLEMAUT, Claire CROPET, David PEROL, Jean-Yves BLAY

for the World Sarcoma Network

Phase II nilotinib in PVNS

- Non progression rate at 12 weeks: **88.9% (95% CI: 70.8-97.6)**
- Updated distributions of the NPR (Bayesian estimation)



➔ Based on the updated distribution (3rd interim analysis):

Pr.(NPR≤30%)=3.34x10^{-11} : **the study has not to be stopped at this stage**

Crizotinib in *ALK*-Rearranged Inflammatory Myofibroblastic Tumor

James E. Butrynski, M.D., David R. D'Adamo, M.D., Ph.D., Jason L. Hornick, M.D., Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, M.D., Suresh C. Jhanwar, Ph.D., Marc Ladanyi, M.D., Marzia Capelletti, Ph.D., Scott J. Rodig, M.D., Ph.D., Nikhil Ramaiya, M.D., Eunice L. Kwak, M.D., Jeffrey W. Clark, M.D., Keith D. Wilner, Ph.D., James G. Christensen, Ph.D., Pasi A. Jänne, M.D., Ph.D., Robert G. Maki, M.D., Ph.D., George D. Demetri, M.D., and Geoffrey I. Shapiro, M.D., Ph.D.

SUMMARY

Inflammatory myofibroblastic tumor (IMT) is a distinctive mesenchymal neoplasm characterized by a spindle-cell proliferation with an inflammatory infiltrate. Approximately half of IMTs carry rearrangements of the anaplastic lymphoma kinase (*ALK*) locus on chromosome 2p23, causing aberrant ALK expression. We report a sustained partial response to the ALK inhibitor crizotinib (PF-02341066, Pfizer) in a patient with *ALK*-translocated IMT, as compared with no observed activity in another patient without the *ALK* translocation. These results support the dependence of *ALK*-rearranged tumors on ALK-mediated signaling and suggest a therapeutic strategy for genomically identified patients with the aggressive form of this soft-tissue tumor. (Funded by Pfizer and others; ClinicalTrials.gov number, NCT00585195.)

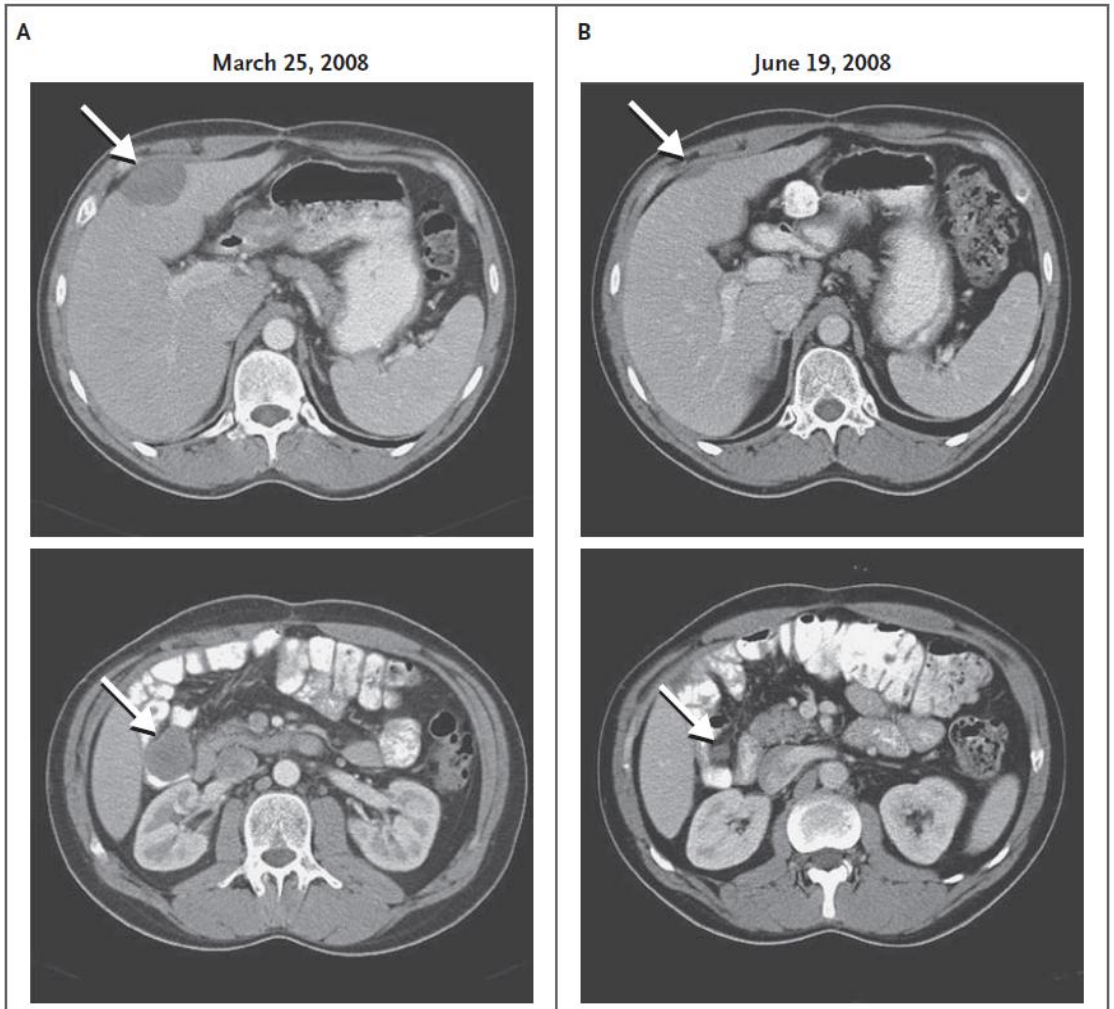
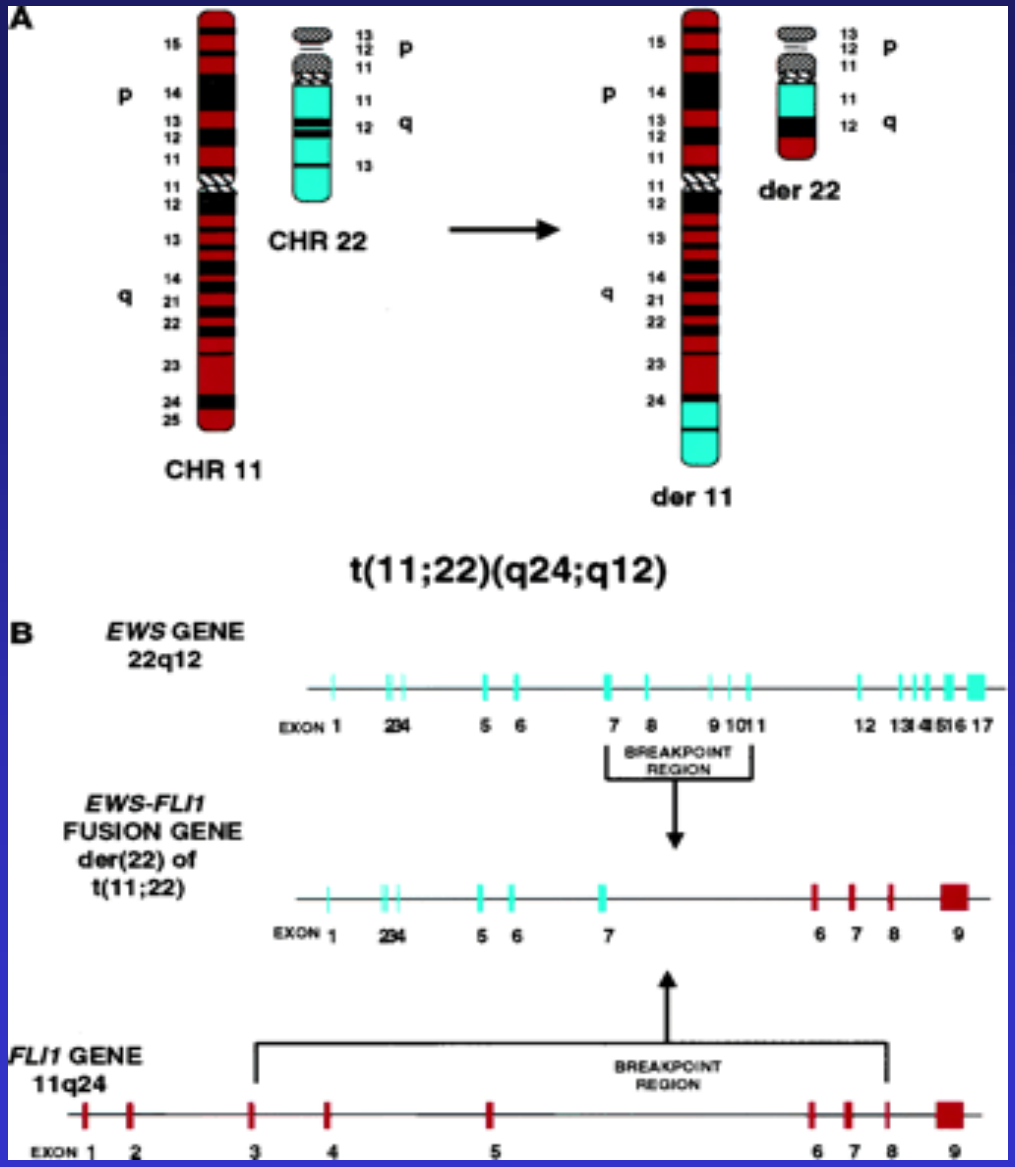
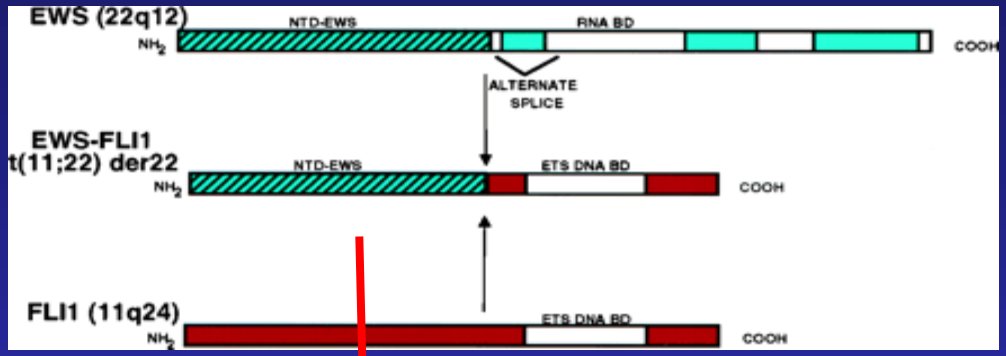


Figure 2. CT Scans Showing the Response to Crizotinib in Patient 1.

The baseline abdominal CT scan shows a hepatic mass measuring 4.8 by 3.3 cm (top) and one of several mesenteric masses measuring 3.8 by 3.3 cm (bottom) (Panel A, arrows). After 13 weeks of treatment with crizotinib, the hepatic and mesenteric masses measured 2.3 by 0.8 cm and 1.3 by 1.2 cm, respectively (Panel B, arrows). In October 2008, these masses measured 3.6 by 2.2 cm and 0.5 by 0.5 cm, respectively (not shown), indicating that the hepatic mass had regrown, despite a continued response, according to the Response Evaluation Criteria in Solid Tumors.





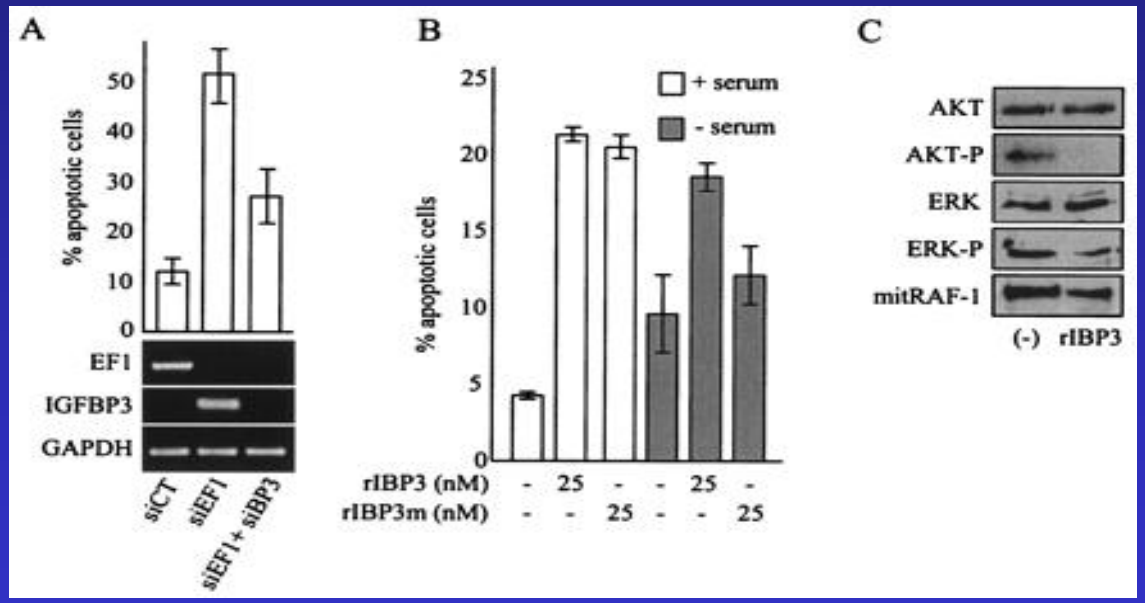
Abnormal gene transcription

Transformation

Target genes: include kinases and ligands (PDGF, IGFBP3…)

Delattre et al 2003

IGFBP3 induces Ewing tumor cells apoptosis

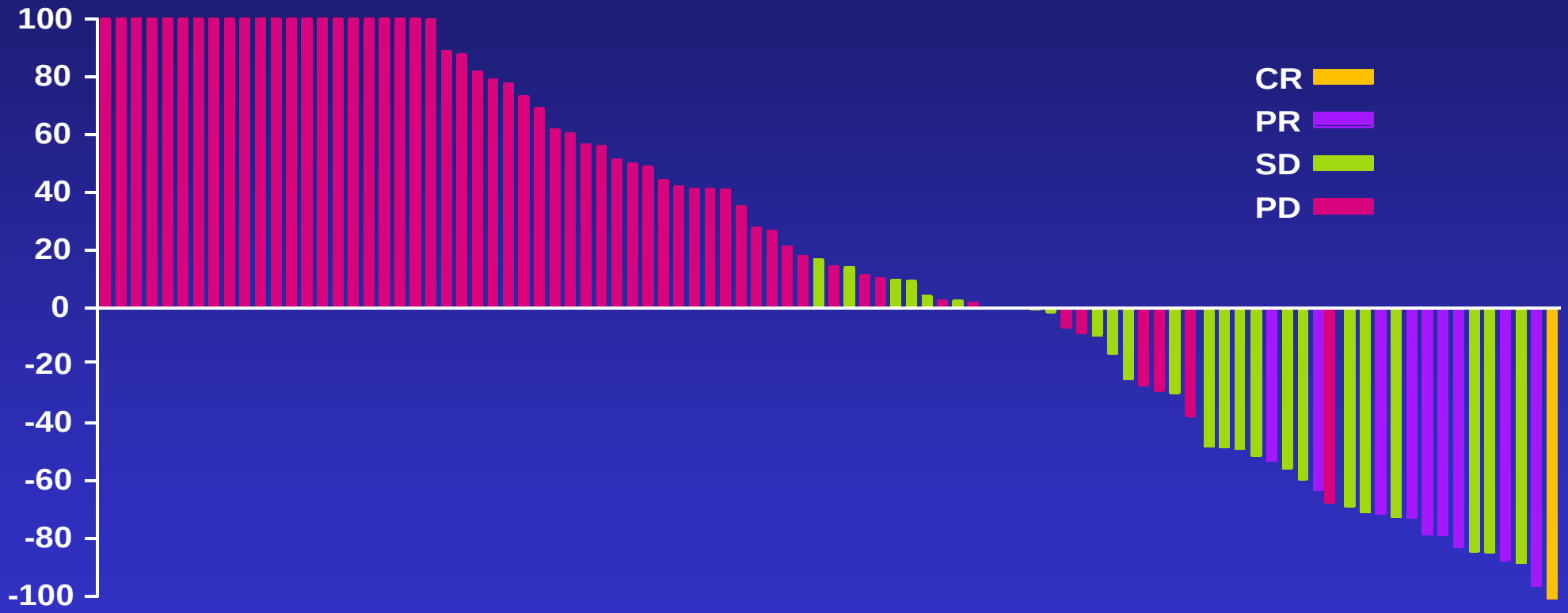


IGF1 inhibitors as potential targeted therapy in ES ?

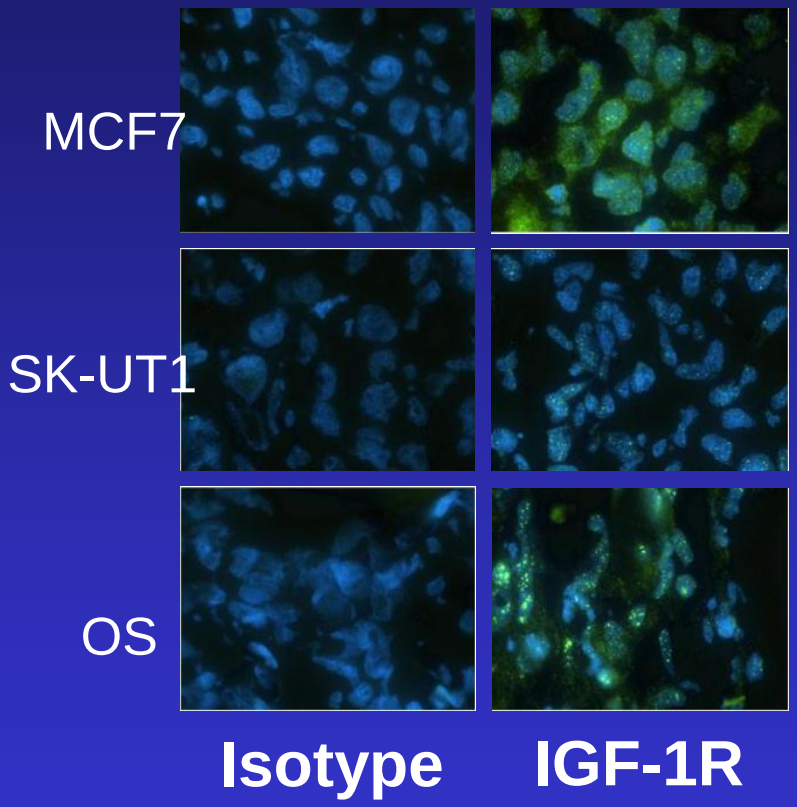
Prieur 2004

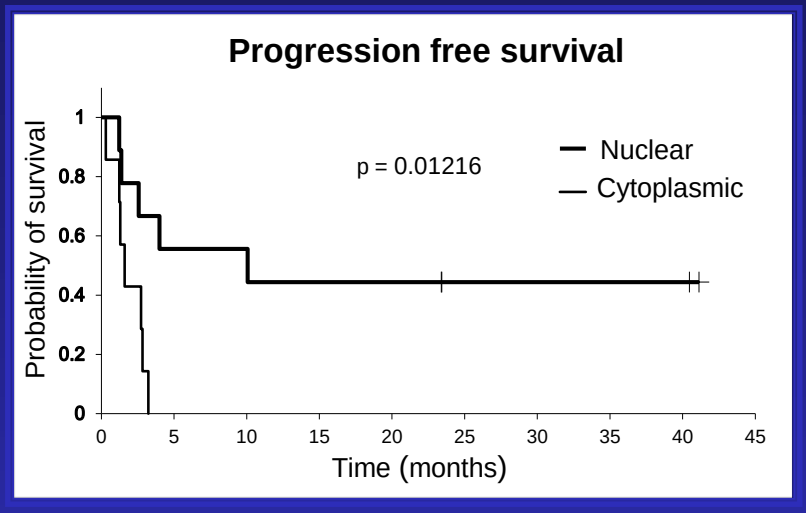
ESMO 2012

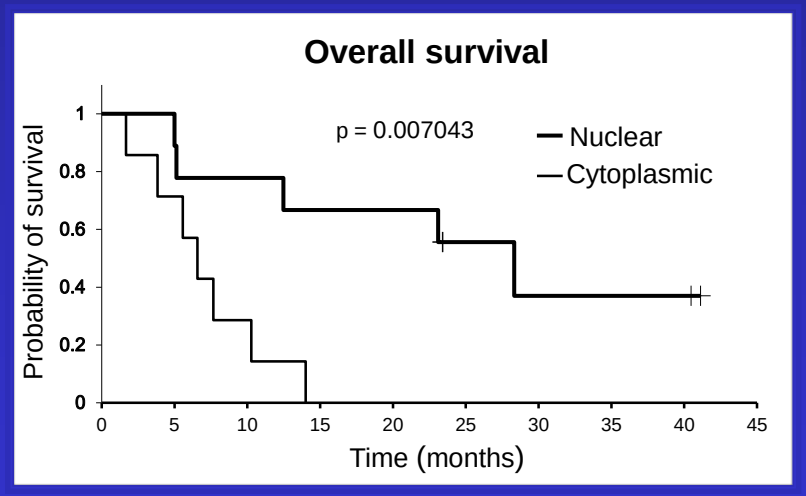
Best Recorded Variation in Tumor Size: Ewing's Cohorts



Nuclear staining for IGF1R: a biomarker for response in sarcoma?







Asmane I, Blay JY, AACR 2012

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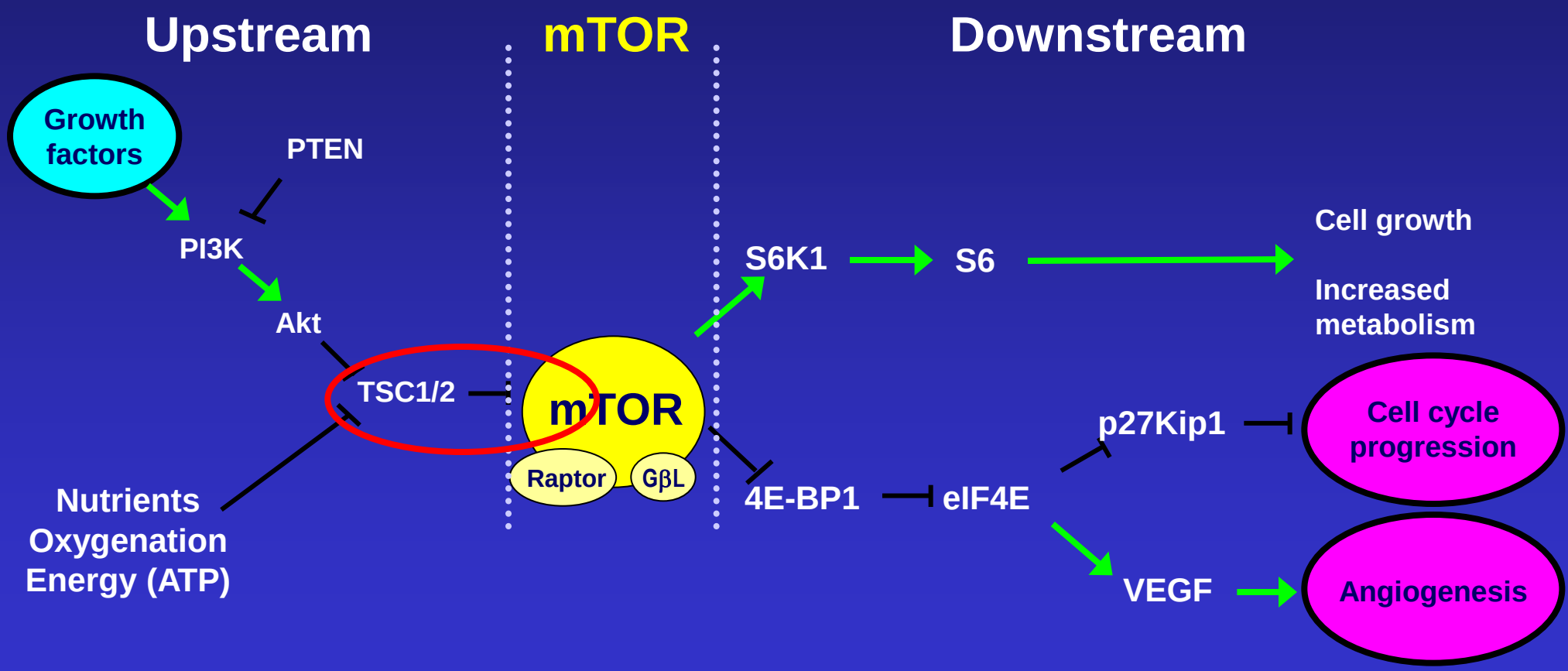
mTOR signalling pathway



ORIGINAL ARTICLE

Sirolimus for Angiomyolipoma in Tuberous Sclerosis Complex or Lymphangioleiomyomatosis

John J. Bissler, M.D., Francis X. McCormack, M.D., Lisa R. Young, M.D., Jean M. Elwing, M.D., Gail Chuck, L.M.T., Jennifer M. Leonard, R.N., Vincent J. Schmithorst, Ph.D., Tal Laor, M.D., Alan S. Brody, M.D., Judy Bean, Ph.D., Shelia Salisbury, M.S., and David N. Franz, M.D.

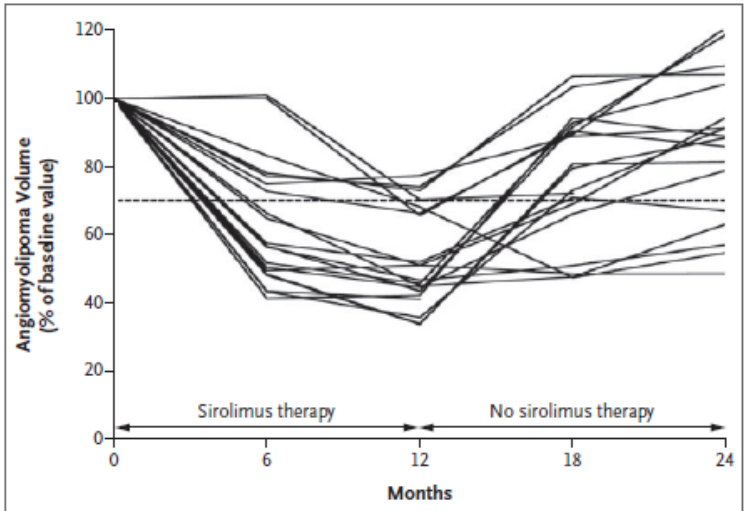


Figure 2. Angiomyolipoma Volume in the Patients with the Tuberous Sclerosis Complex or Sporadic Lymphangioleiomyomatosis during the Study.

Angiomyolipomas were visualized with the use of abdominal magnetic resonance imaging, and volumetric analysis was performed at baseline and at 2, 4, 6, 12, 18, and 24 months. The angiomyolipoma volume at each visit is expressed as a percentage of the baseline size. The dashed line represents 70% of the baseline value; data below the line indicate that the mean angiomyolipoma volume was reduced by 30% or more.

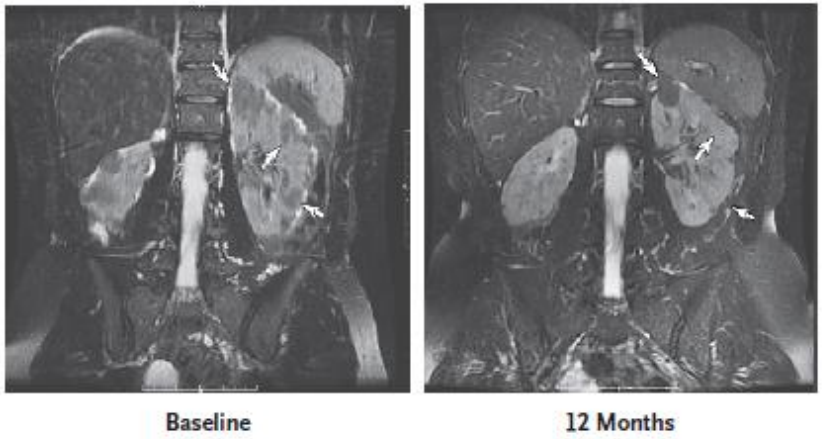


Figure 3. Renal Angiomyolipomas in the Abdomen of a Patient with the Tuberous Sclerosis Complex.

Bilateral angiomyolipomas are shown at baseline and after 12 months of sirolimus therapy. Three lesions in the left kidney are identified by arrows; at 12 months, the top lesion had become reduced in size and the bottom two had become imperceptible. The images were obtained with the use of fast spin–echo T_2-weighted magnetic resonance imaging with fat suppression.

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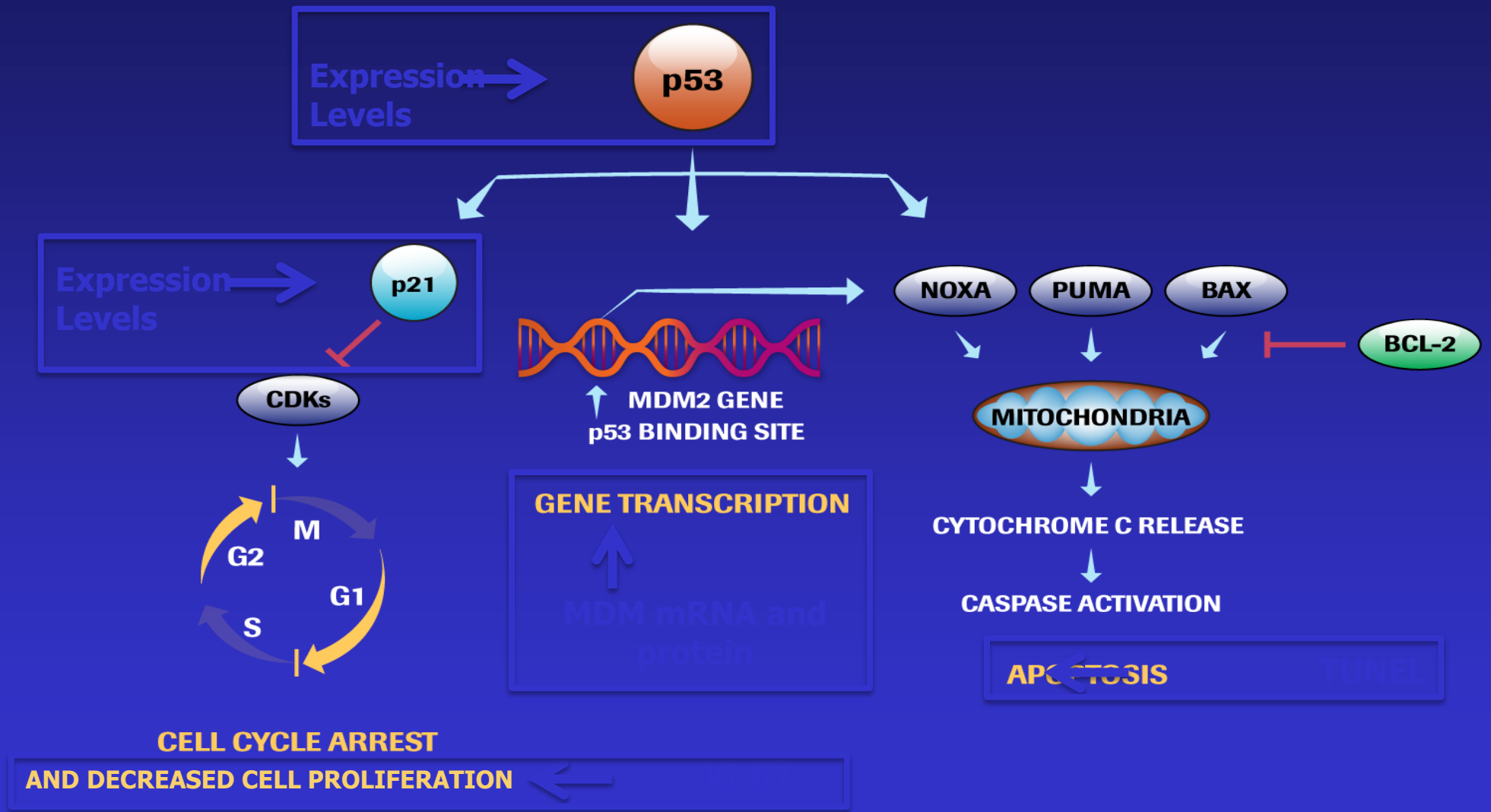
Neoadjuvant MDM2 Antagonist RG7112 for Well-Differentiated and Dedifferentiated Liposarcomas (WD/DD LPS): A Pharmacodynamic (PD) Biomarker Study. (Abstract 10007b)

I. Ray-Coquard[1], J. Y. Blay[1], A. Italiano[2], A. Le Cesne[3], N. Penel[4], J. Zhi[5], A. Beryozkina[5], F. Heil[6], R. Rueger[6], G. L. Nichols[5], B. Bui Nguyen[2]

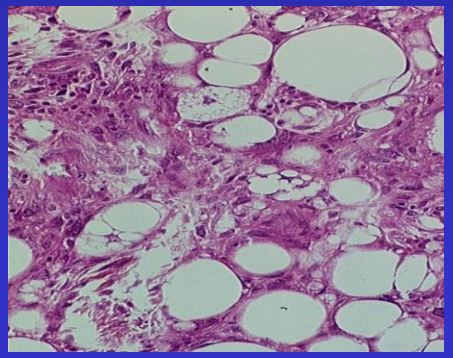
Centre Leon Bérard, Lyon, France[1]; Institut Bergonie, Bordeaux, France[2]; Institut Gustave-Roussy, Villejuif, France[3]; Centre Oscar Lambret, Lille, France[4]; Hoffmann-La Roche, Nutley, NJ[5]; Roche Diagnostics GmbH, Penzberg, Germany[6]

Activated p53 Pathway Biomarkers

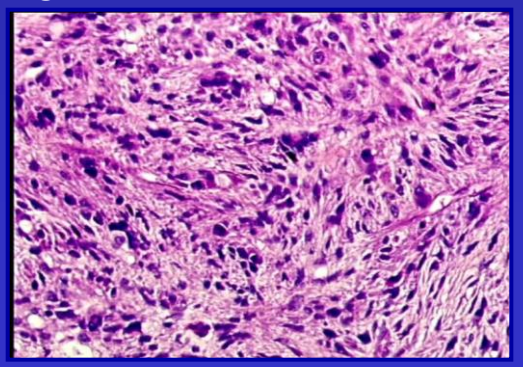


Liposarcoma: a Tumor Type Enriched for *mdm2* Amplification

- Well differentiated (WD) and de-differentiated (DD) morphologies are most common types of liposarcoma (LPS) (~80% of cases)
- Surgery is the main therapy for WD/DD LPS
  - WD LPS: low grade with low rate of recurrence and good prognosis after complete surgical resection
  - DD LPS: high grade, aggressive with higher rates of recurrence after surgery
- *mdm2* gene amplification common in LPS
  - *mdm2* gene resides on chromosome 12q13-15



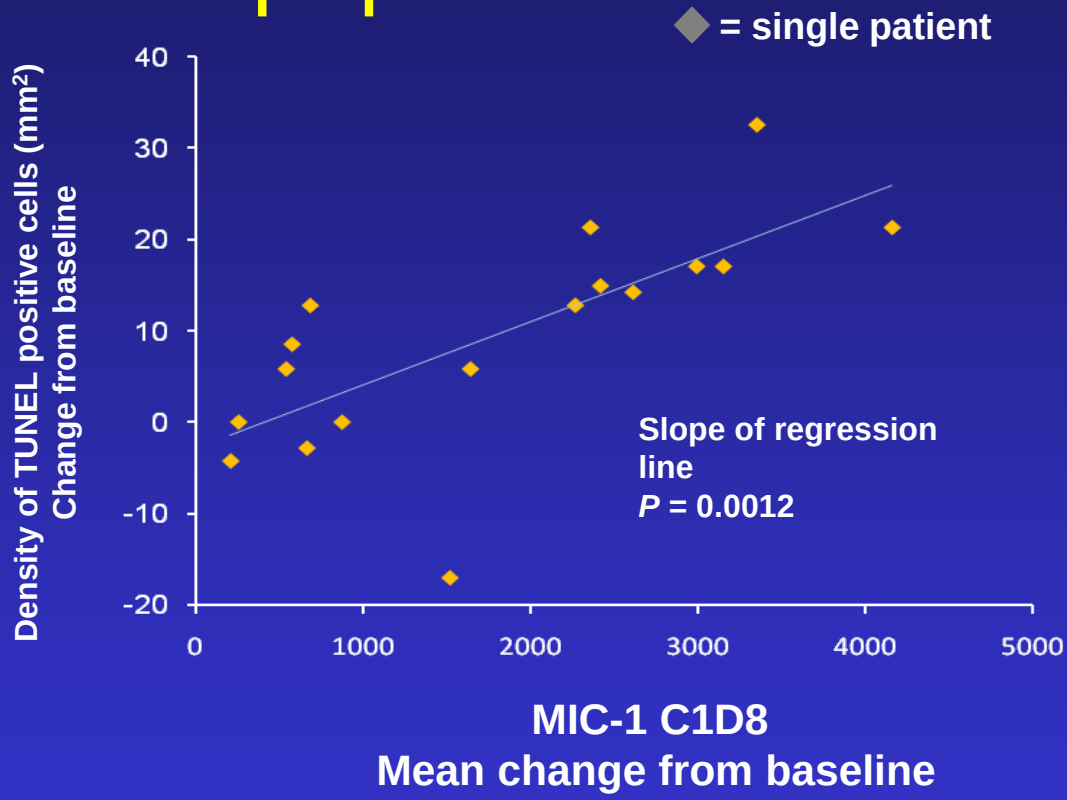
Well Differentiated



De-Differentiated

Increased MIC-1 Significantly Correlated With Increased Apoptosis

- Both MIC-1 and TUNEL are significantly positively correlated with drug exposure in this study
- In addition, MIC-1 blood levels and TUNEL changes in tumor biopsies were also well correlated
- Future studies will further evaluate MIC-1 blood levels as a quantitative PD marker



RG7112 in Liposarcoma

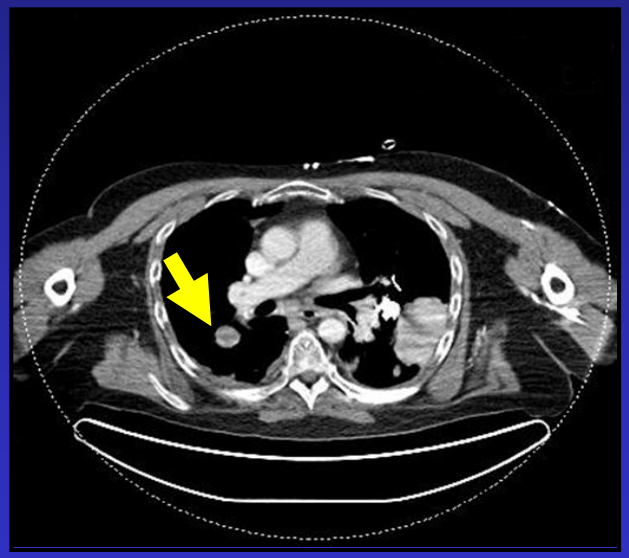
- MDM2 inhibition in human tumors activates p53, arrests cell proliferation, and induces apoptosis
- This proof of mechanism study in patients with LPS demonstrates:
  - Pharmacological p53 activation by an inhibitor of the p53-mdm2 interaction
  - Post-treatment Increases in p53, p21, and mdm2 levels
  - Exposure-related increases in MIC-1 levels
  - Post-treatment decreases proliferation as measured by change in Ki-67
  - Exposure-related induction of apoptotic signals
  - While not designed as an efficacy study, early signs of clinical activity included:
    - 1 PR after a single cycle
    - 13 SD
- This study also supports the feasibility of multiple biopsies in patients with liposarcomas eligible for surgery

Denosumab Treatment of Giant Cell Tumor of Bone: Interim Analysis of an Open-Label Phase 2 Study

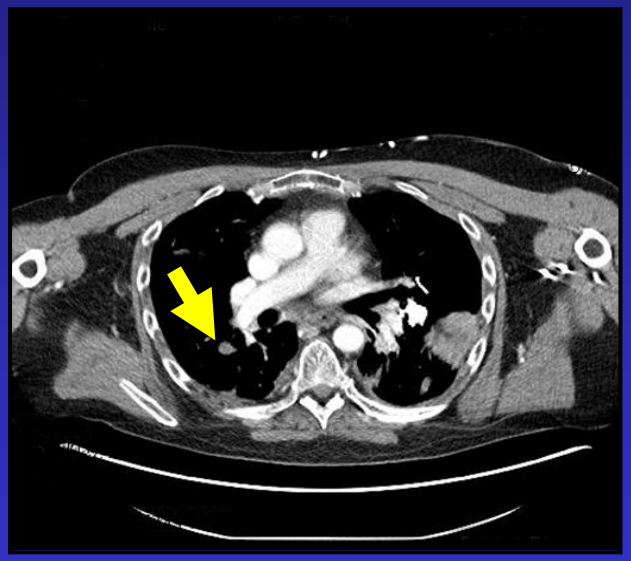
David Thomas,[1] Sant Chawla,[2] Keith Skubitz,[3] Arthur Staddon,[4] Robert Henshaw,[5] Armelle Dufresne[6], Jean-Yves Blay,[6] Judy Smith,[7] Zhishen Ye,[7] Winnie Sohn,[7] Martine Roudier,[8] Susie Jun[7]

[1]Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia;
[2]Sarcoma Oncology Center, Los Angeles, CA, USA;
[3]University of Minnesota, Minneapolis, MN, USA;
[4]Pennsylvania Hematology/Oncology Associates, Philadelphia, PA, USA;
[5]Washington Cancer Institute, Georgetown University School of Medicine, Washington DC, USA;
[6]Hôpital Edouard Heriot, Lyon, France;
[7]Amgen Inc., Thousand Oaks, CA, USA;
[8]Amgen Inc., Seattle, WA, USA

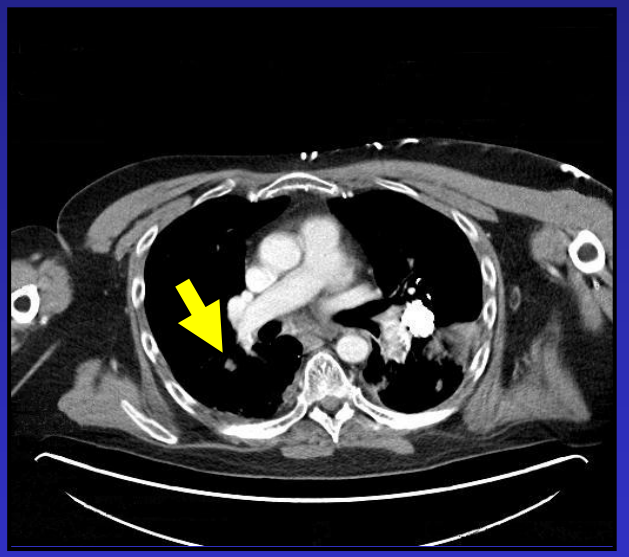
Radiologic Response to Denosumab



Baseline



Week 5



Week 37

Targeted treatments of sarcomas and connective tissue tumors

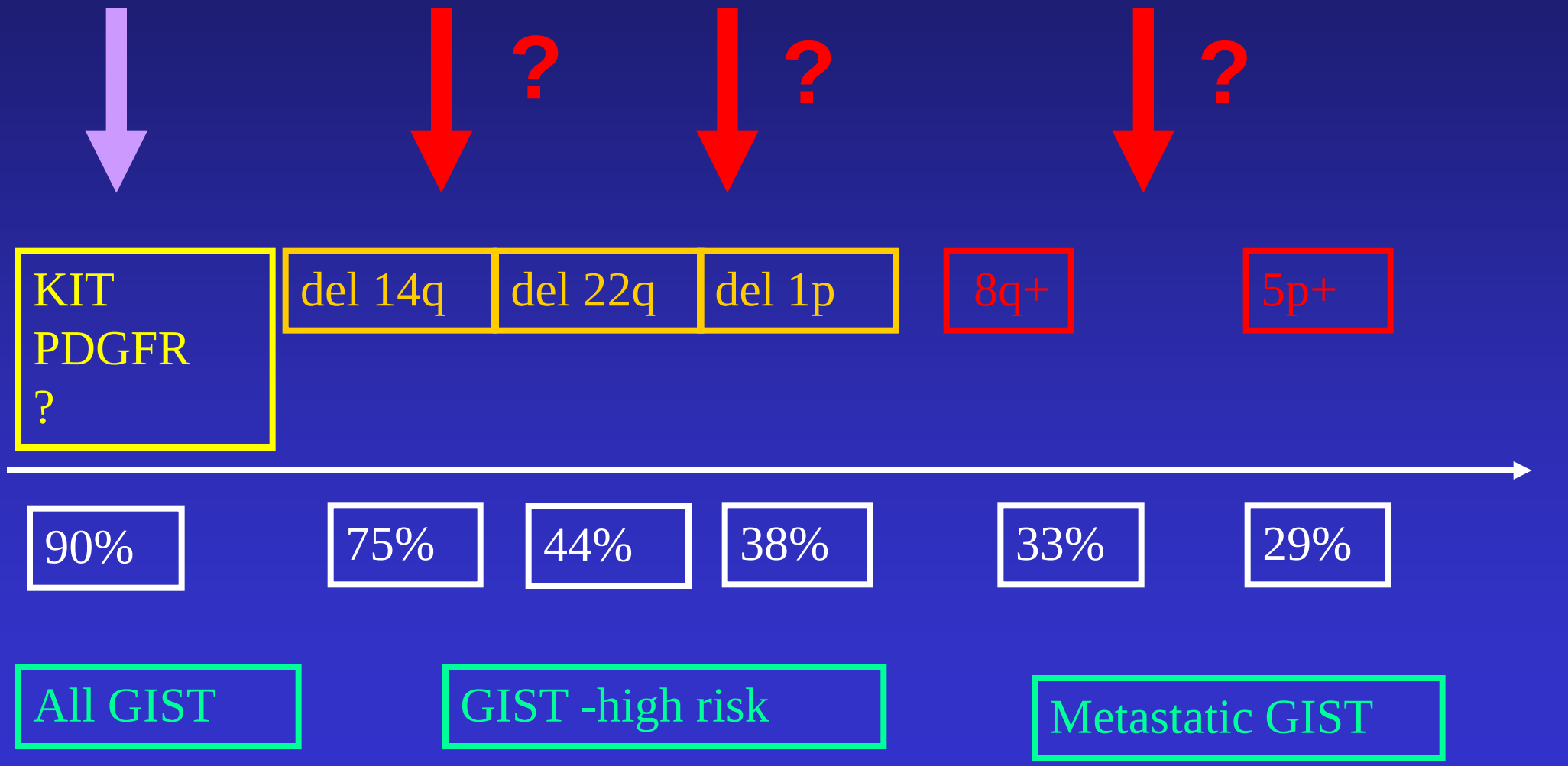
ESMO 2012

• GIST	Imatinib 400
• GIST KIT exon 9	Imatinib 800
• GIST PDGFR D842V	crenolanib?
• Other GIST	Imatinib 400
• GIST2nd line	Sunitinib
• GIST3rd line	Regorafenib
• DFSP	Imatinib
• GCT of the bone	Denosumab
• PEComas	mTOR inh.
• PVNS	CSF1R antagonists
• ASPS	Cediranib/VEGFR2 inhibitors
• Ewing/OS/RMS subsets	IGF1R Ab
• MLPS	trabectedine

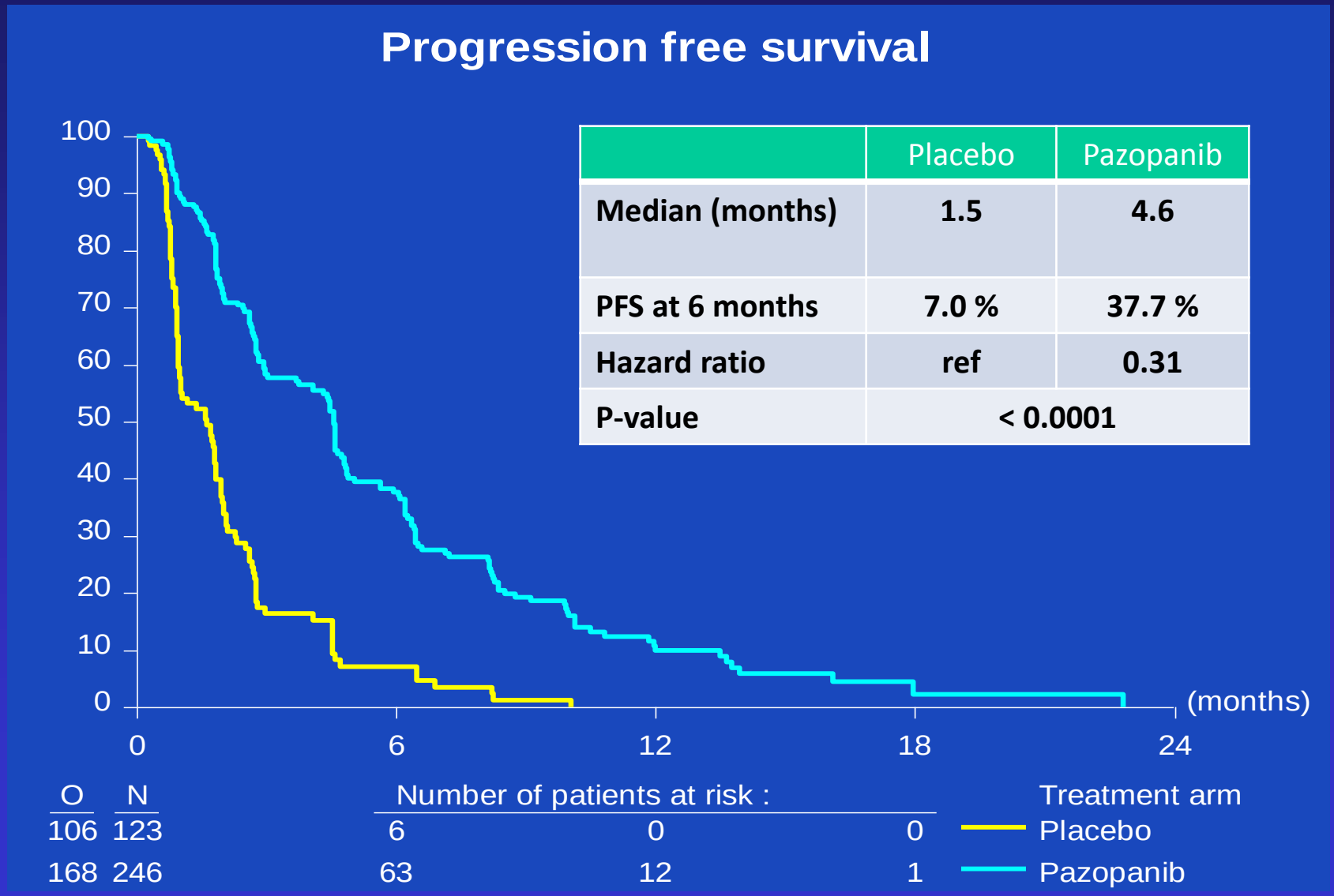
Three situations

- Initial molecular event
  - KIT in GIST
  - Loss NF1, TSC
  - Translocations
  - Mdm2 amplification
  - …
- Secondary event
  - VEGF production
  - Activation of mTOR pathway
  - ER expression in ESS
- Simple bystander
  - PDGFR expression in normal (and malignant) cells of connective tissue

2.Targeting a « latter » event

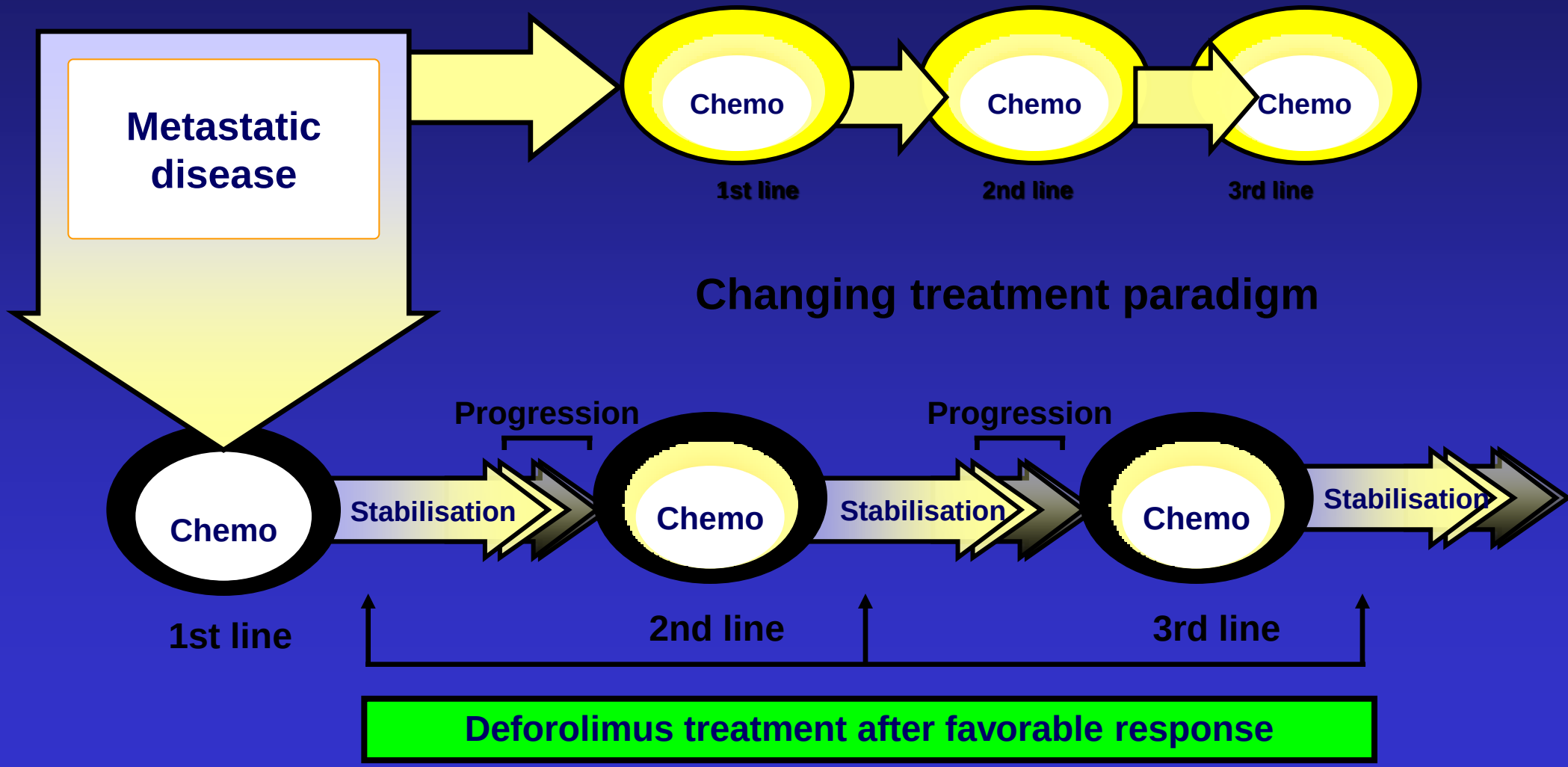


Palette: primary efficacy end-point

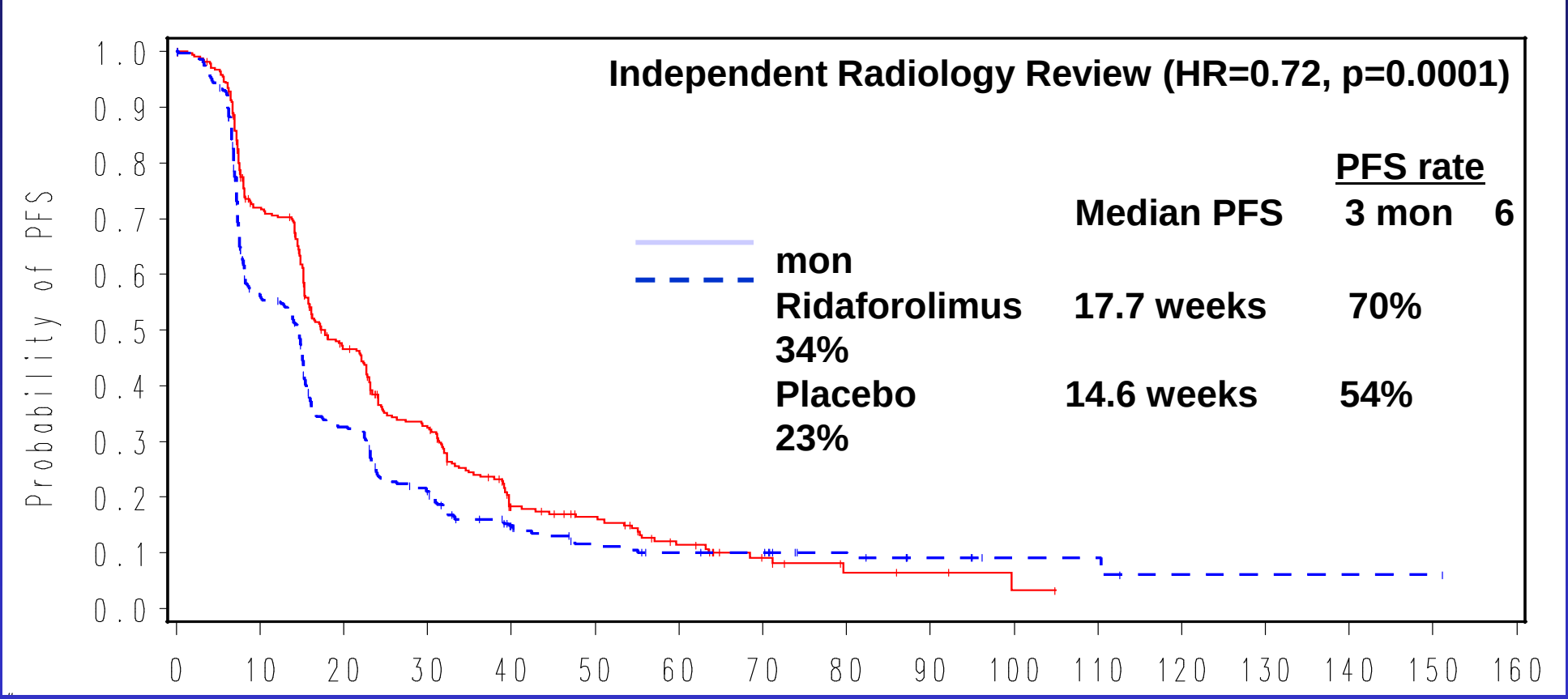


	Placebo	Pazopanib
Median (months)	**1.5**	**4.6**
PFS at 6 months	**7.0 %**	**37.7 %**
Hazard ratio	**ref**	**0.31**
P-value	**< 0.0001**	

SUCCEED : Ridaforolimus in maintenance



SUCCEED: PFS



Chawla SP et al; ASCO 2011; # 10005

Ridaforolimus : a need for biomarkers?

Table 4: Summary of Potential Biomarkers Examined in Archival Tissue

Protein	Staining Index				p-value[b]
	CBR		Non-CBR		
	n[a]	Median	n[a]	Median	
Upstream of mTOR					
PTEN	28	70	33	90	0.96
p-AKT	30	75	31	90	0.73
FKBP12	15	200	12	230	0.52
IGF-1R	15	0	12	0	0.26
Downstream of mTOR					
p-S6	19	165	48	97.5	0.47
4E-BP1	18	180	46	200	0.30
eIF4E	19	135	47	130	0.52
p27kip1	26	25	58	12.5	0.48

CBR = Clinical benefit response

a: Number of patient samples analyzed

b: p-value for the difference in staining index between CBR and non-CBR; Kruskal-Wallis test

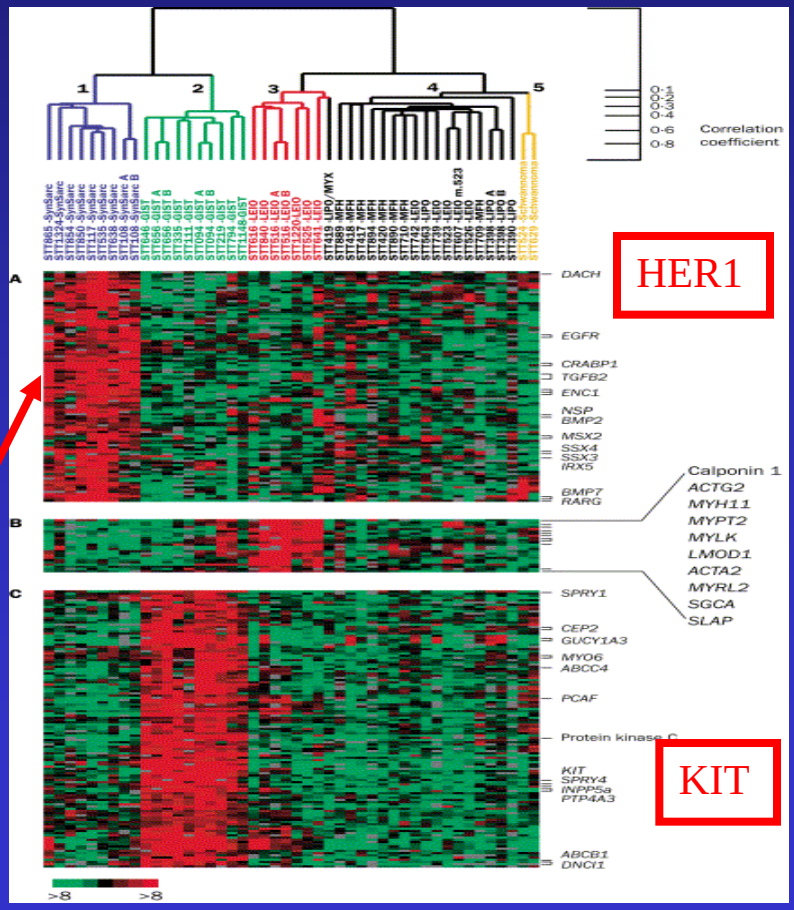
Three situations

- Initial molecular event
  - KIT in GIST
  - Loss NF1, TSC
  - Translocations
  - Mdm2 amplification
  - …
- Secondary event
  - VEGF production
  - Activation of mTOR pathway
  - ER expression in ESS
- Simple bystander
  - PDGFR expression in normal (and malignant) cells of connective tissue

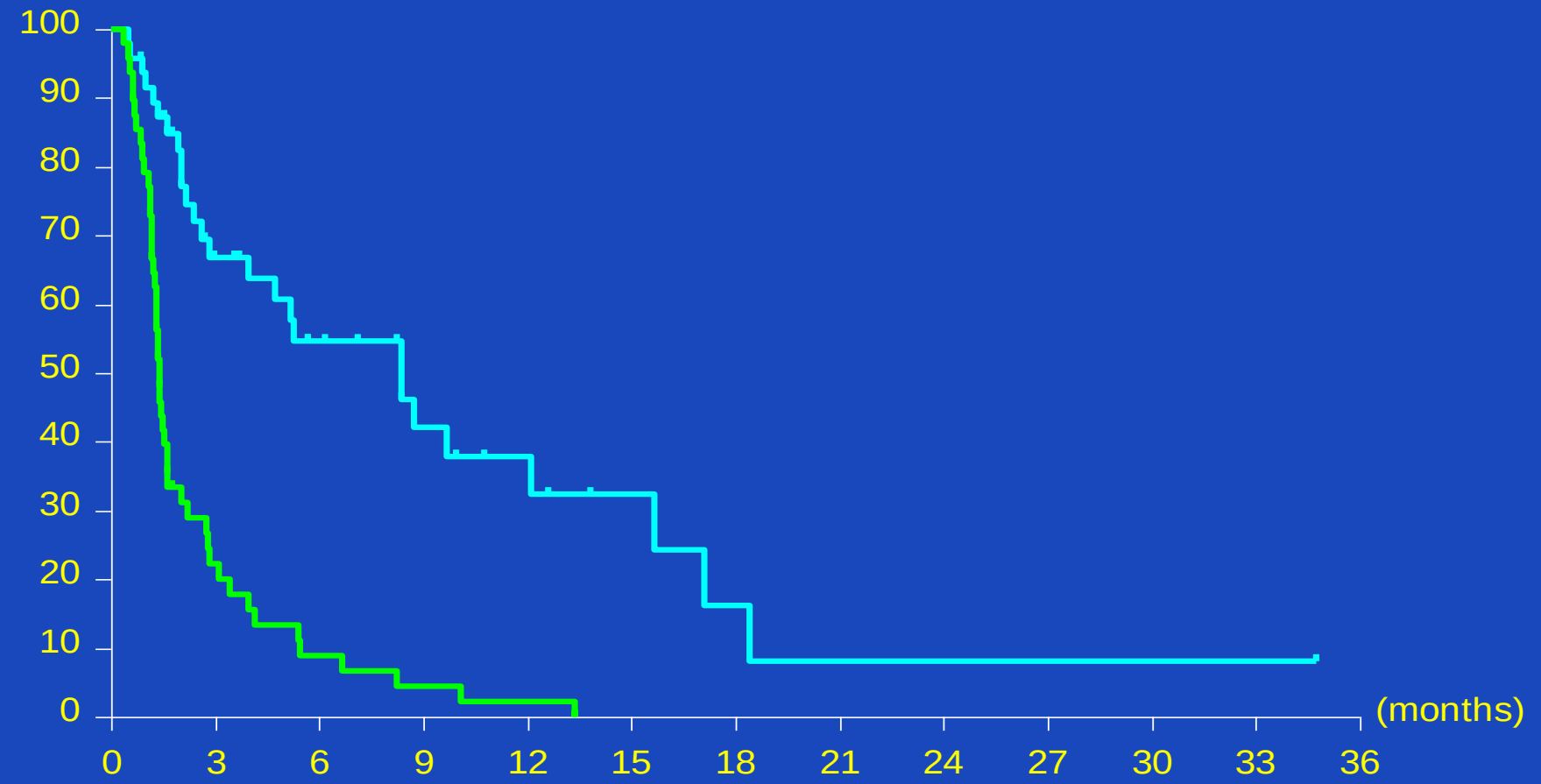
Find a target using expression microarrays ?

- Synovial sarcoma
  - t(X,18)
  - Over expression of HER1
  - gefitinib single agent
- Clinical trial:
  - 62022 EORTC STBSG
  - Single agent in HER1+ SynS
  - Patients with advanced disease failing AI
  - N=47- Completed sept 05
  - **ASCO 2006**

(Nielsen Lancet 2002)



Overall and progression free survival



O	N	Number of patients at risk :											event
26	48	24	16	10	7	4	2	1	1	1	1	1	OS
47	48	10	4	2	1	0	0	0	0	0	0	0	PFS

Systemic treatment of sarcomas 2000-2012

ESMO 2012

2000:

- All sarcomas
  - Doxorubicin
  - Ifosfamide
  - DTIC
- Ewing , RMS, OS
  - Dactinomycin
  - CDDP
  - Vincaalcaloids
  - Cyclophosphamide
  - HDMTX

2012

- All subtypes : Trabectedin
- GIST: Imatinib, sunitinib,
- DFSP : Imatinib
- Osteosarcomas: MTPPE

- LMS: Gemcitabine (+/- DTIC or Tax)
- EWS: TopoI inh., IGF1R
- A/E RMS: Topo inh
- Angio: Dox, Paclitaxel, GemTax
- ESS : Aromatase inh.
- All but LPS: pazopanib
- PVNS :Imatinib
- Desmoid Tumors : HT, imatinib

- GCTB : denosumab
- PECOMAs: mTOR
- WD/DD: LPS:CDK4, MDM2
- GIST: regorafenib
- ASPS: cediranib

nature genetics

Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy

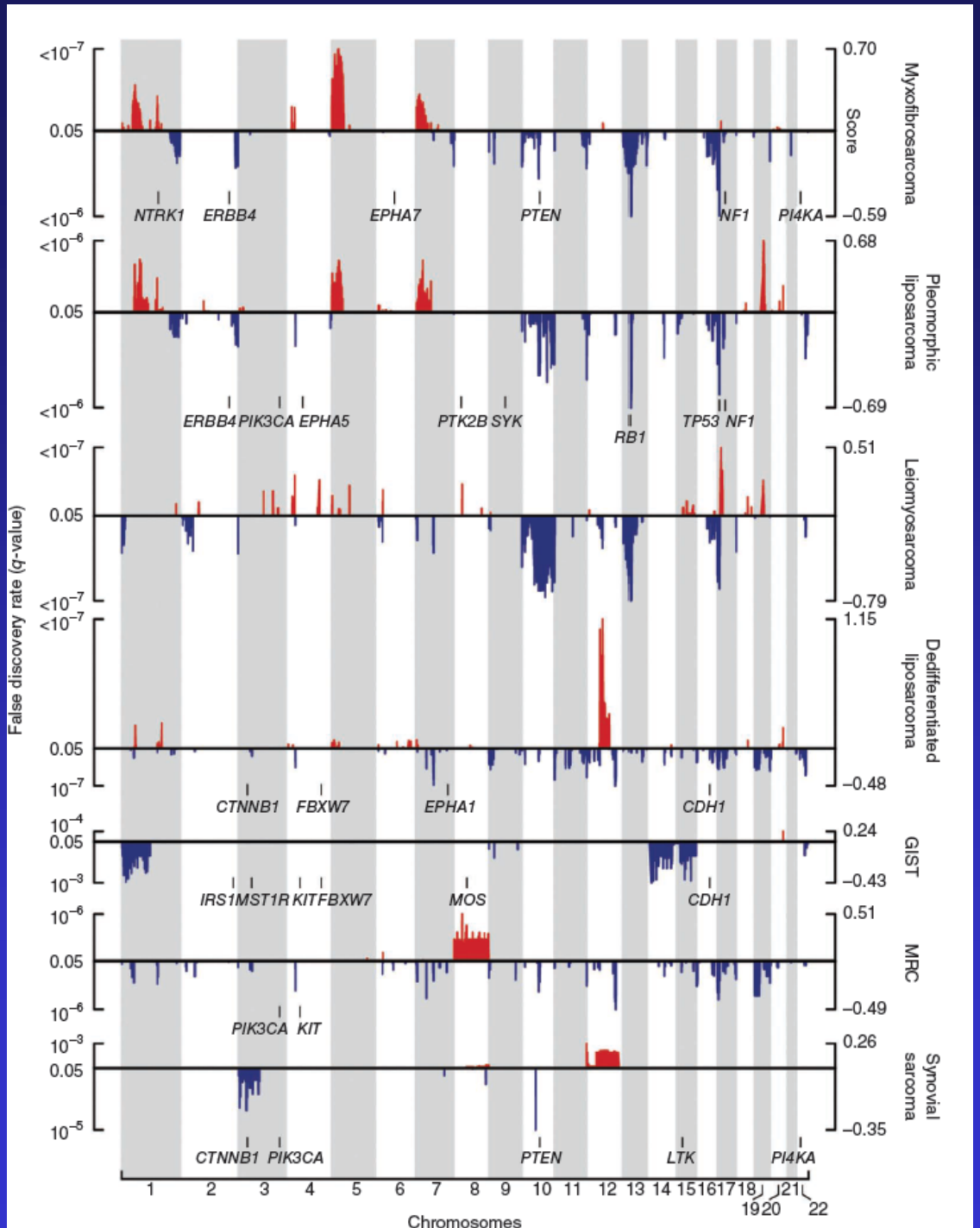
Jordi Barretina[1–3,15], Barry S Taylor[4,5,15], Shantanu Banerji[1–3], Alexis H Ramos[1–3], Mariana Lagos-Quintana[6], Penelope L DeCarolis[6], Kinjal Shah[1,3], Nicholas D Socci[4], Barbara A Weir[1–3], Alan Ho[7], Derek Y Chiang[1–3], Boris Reva[4], Craig H Mermel[1–3], Gad Getz[3], Yevgenyi Antipin[4], Rameen Beroukhim[1–3], John E Major[4], Charles Hatton[1,2], Richard Nicoletti[1,2], Megan Hanna[1,2], Ted Sharpe[3], Tim J Fennell[3], Kristian Cibulskis[3], Robert C Onofrio[3], Tsuyoshi Saito[8,9], Neerav Shukla[8,9], Christopher Lau[8,9], Sven Nelander[4], Serena J Silver[3], Carrie Sougnez[3], Agnes Viale[10], Wendy Winckler[1–3], Robert G Maki[11], Levi A Garraway[1–3], Alex Lash[4], Heidi Greulich[1–3], David E Root[3], William R Sellers[12], Gary K Schwartz[7], Cristina R Antonescu[8], Eric S Lander[3], Harold E Varmus[13], Marc Ladanyi[8,9], Chris Sander[4], Matthew Meyerson[1–3,14,16] & Samuel Singer[6,16]

Table 2 Mutations identified in soft-tissue sarcoma

Gene	No. of mut.[a]	Subtype	Tumor ID	Cases affected (%)[b]	mRNA	Protein
CDH1	2	DDLPS	PT7DD	2.0	712A>AG	N238D
		GIST	PT61GT	4.5	1849G>AG	A617T[c]
CTNNB1	2	DDLPS	PT18DD	2.0	122C>CT	T41I[d]
		Synovial	PT195SYN	4.0	95A>AT	D32V[d]
EPHA1	1	DDLPS	PT10DD	2.0	634G>GA	A212T
EPHA5	1	Pleomorphic	PT182PL	4.2	2386A>AG	Y796H
EPHA7	1	MYXF	PT106MF	2.6	1649C>CT	S550N
ERBB4	2	MYXF	PT130MF	2.6	3437A>AT	D1146V
		Pleomorphic	PT167PL	4.2	1558A>AT	C520S
FBXW7	2	DDLPS	PT38DD	2.0	338_342delTCATC>TC	E113fs
		GIST	PT58GT	4.5	563G>GT	C188F
IRS1	1	GIST	PT61GT	4.5	3406C>CT	E1136K
KIT	6	GIST	PT57GT	23.0	1727T>CT	L576P[d]
		GIST	PT63GT		1961T>CT	V654A[d]
		GIST	PT61GT		1667_1674delAGTGGAAG>AG	Q556fs
		GIST	PT60GT		1667_1687del[e]	Q556_I563>Q
		GIST	PT59GT		1670_1675delGGAAGG	W557_V559>F[c]
		MRC	PT149MRC	4.8	2334G>CG	K778N
LTK	1	Synovial	PT190SYN	4.0	2243_2244delTT>T	C748fs
MOS	1	GIST	PT61GT	4.5	898A>AG	S300P
MST1R	1	GIST	PT60GT	4.5	1229G>AG	P410L
NF1	7	MYXF	PT104MF	10.5	7972C>CT	H2658Y
		MYXF	PT104MF		7790C>CT	S2597L
		MYXF	PT127MF		910C>T	R304*[d]
		MYXF	PT134MF		910C>T	R304*[d]
		MYXF	PT102MF		7010T>TG	L2337R
		Pleomorphic	PT176PL	8.3	1105C>CT	Q369*[d]
		Pleomorphic	PT179PL		4006C>CT	Q1336*
NTRK1	1	MYXF	PT101MF	2.6	2338C>CT	R780W
PI4KA	2	MYXF	PT137MF	2.6	4081_4088delTCTTATCT>TCT	1361fs
		Synovial	PT203SYN	4.0	4081_4088delTCTTATCT>TCT	1361fs
PIK3CA	6	MRC	PT143MRC	18.0	1633G>AG	E545K[e]
		MRC	PT149MRC		1633G>AG	E545K[e]
		MRC	PT138MRC		3140A>AG	H1047R[e]
		MRC	PT158MRC		3140A>AG	H1047R[e]
		Pleomorphic	PT173PL	4.2	1660delC	H554fs
		Synovial	PT195SYN	4.0	1659delT	S553fs
PTEN	2	MYXF	PT100MF	2.6	G>CG	Splice site
		Synovial	PT206SYN	4.0	106G>AA	G36R[c]
PTK2B	1	Pleomorphic	PT163PL	4.2	G>AG	Splice site
RB1	1	Pleomorphic	PT167PL	4.2	1818T>TA	Y606*[c]
SYK	1	Pleomorphic	PT163PL	4.2	52G>AA	G18S
TP53	4	Pleomorphic	PT163PL	16.7	404C>AA	C135F[c]
		Pleomorphic	PT169PL		464G>AA	T155I
		Pleomorphic	PT173PL		C>CT	Splice site
		Pleomorphic	PT164PL		C>TT	Splice site

DDLPS, dedifferentiated liposarcoma; MYXF, myxofibrosarcoma.
[a]Number of nonsynonymous or splice-site mutations detected in either primary sequencing or extended genotyping. [b]Percentage of cases by subtype. [c]Mutations previously identified in any cancer type, as indicated in the Catalogue of Somatic Mutations in Cancer. [d]Mutations previously identified in soft-tissue sarcoma. [e]Reference allele: GTGGAAGGTTGTTGAGGAGAT. Asterisks indicate nonsense mutations.

ESMO 2012



Barretina et al Nat Gen 2010

Vol 463|18 February 2010|doi:10.1038/nature08822 nature

ESMO 2012

ARTICLES

The landscape of somatic copy-number alteration across human cancers

Rameen Beroukhim[1,3,4,5]*, Craig H. Mermel[1,3]*, Dale Porter[8], Guo Wei[1], Soumya Raychaudhuri[1,4], Jerry Donovan[8], Jordi Barretina[1,3], Jesse S. Boehm[1], Jennifer Dobson[1,3], Mitsuyoshi Urashima[9], Kevin T. Mc Henry[8], Reid M. Pinchback[1], Azra H. Ligon[4], Yoon-Jae Cho[6], Leila Haery[1,3], Heidi Greulich[1,3,4,5], Michael Reich[1], Wendy Winckler[1], Michael S. Lawrence[1], Barbara A. Weir[1,3], Kumiko E. Tanaka[1,3], Derek Y. Chiang[1,3,13], Adam J. Bass[1,3,4], Alice Loo[8], Carter Hoffman[1,3], John Prensner[1,3], Ted Liefeld[1], Qing Gao[1], Derek Yecies[3], Sabina Signoretti[3,4], Elizabeth Maher[10], Frederic J. Kaye[11], Hidefumi Sasaki[12], Joel E. Tepper[13], Jonathan A. Fletcher[4], Josep Tabernero[14], José Baselga[14], Ming-Sound Tsao[15], Francesca Demichelis[16], Mark A. Rubin[16], Pasi A. Janne[3,4], Mark J. Daly[1,17], Carmelo Nucera[7], Ross L. Levine[18], Benjamin L. Ebert[1,4,5], Stacey Gabriel[1], Anil K. Rustgi[19], Cristina R. Antonescu[18], Marc Ladanyi[18], Anthony Letai[3], Levi A. Garraway[1,3], Massimo Loda[3,4], David G. Beer[20], Lawrence D. True[21], Aikou Okamoto[22], Scott L. Pomeroy[6], Samuel Singer[18], Todd R. Golub[1,3,23], Eric S. Lander[1,2,5], Gad Getz[1], William R. Sellers[8] & Matthew Meyerson[1,3,5]

Sarcomas, as many rare tumors, are valuable models for « frequent » tumors on their way to fragmentation

LETTER

doi:10.1038/nature11003

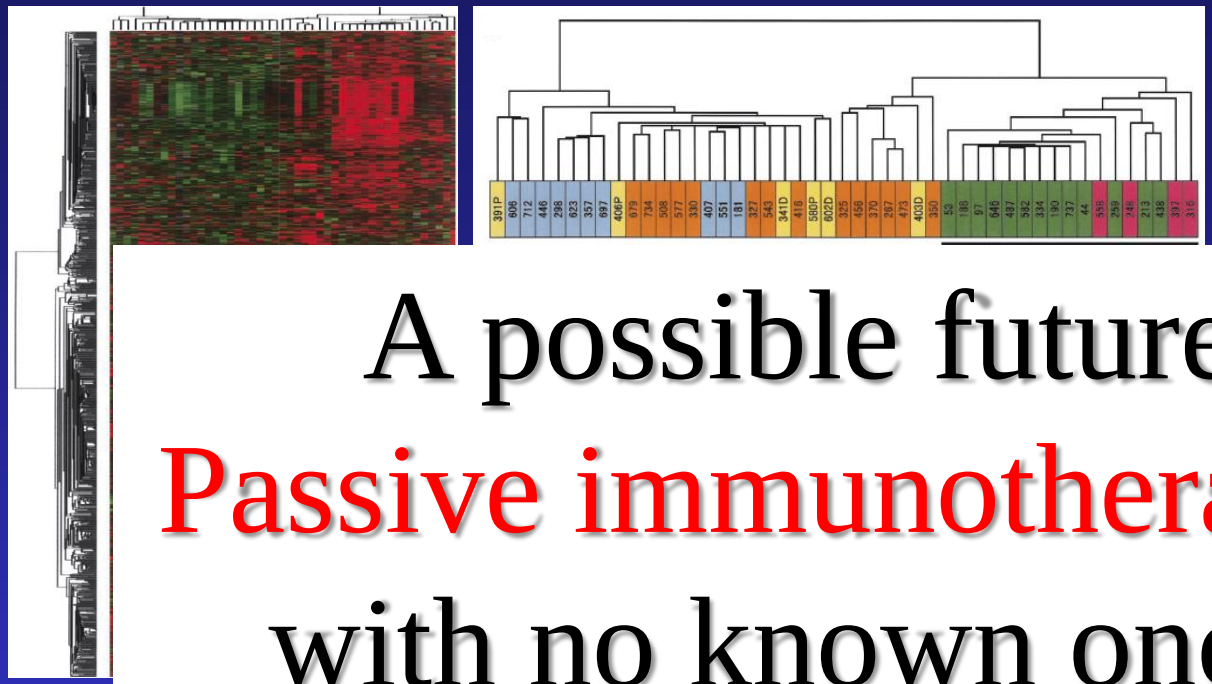
The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity

Jordi Barretina[1,2,3]†*, Giordano Caponigro[4]*, Nicolas Stransky[1]*, Kavitha Venkatesan[4]*, Adam A. Margolin[1]†*, Sungjoon Kim[5], Christopher J. Wilson[4], Joseph Lehár[4], Gregory V. Kryukov[1], Dmitriy Sonkin[4], Anupama Reddy[4], Manway Liu[4], Lauren Murray[1], Michael F. Berger[1]†, John E. Monahan[4], Paula Morais[1], Jodi Meltzer[4], Adam Korejwa[1], Judit Jané-Valbuena[1,2], Felipa A. Mapa[4], Joseph Thibault[5], Eva Bric-Furlong[4], Pichai Raman[4], Aaron Shipway[5], Ingo H. Engels[5], Jill Cheng[6], Guoying K. Yu[6], Jianjun Yu[6], Peter Aspesi Jr[4], Melanie de Silva[4], Kalpana Jagtap[4], Michael D. Jones[4], Li Wang[4], Charles Hatton[3], Emanuele Palescandolo[3], Supriya Gupta[1], Scott Mahan[1], Carrie Sougnez[1], Robert C. Onofrio[1], Ted Liefeld[1], Laura MacConaill[3], Wendy Winckler[1], Michael Reich[1], Nanxin Li[5], Jill P. Mesirov[1], Stacey B. Gabriel[1], Gad Getz[1], Kristin Ardlie[1], Vivien Chan[6], Vic E. Myer[4], Barbara L. Weber[4], Jeff Porter[4], Markus Warmuth[4], Peter Finan[4], Jennifer L. Harris[5], Matthew Meyerson[1,2,3], Todd R. Golub[1,3,7,8], Michael P. Morrissey[4]*, William R. Sellers[4]*, Robert Schlegel[4]* & Levi A. Garraway[1,2,3]*

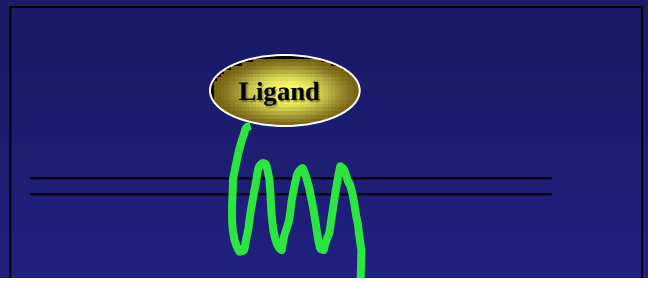
FZD10 is specifically up-regulated in synovial sarcoma

ESMO 2012

Genome-wide cDNA microarray of soft tissue sarcoma



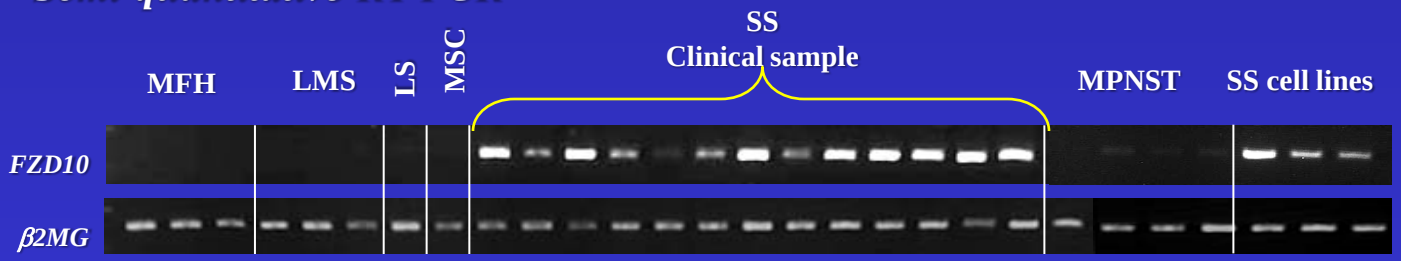
Frizzled Homologue 10 (FZD10)



A possible future strategy?

Passive immunotherapy for targets with no known oncogenic role

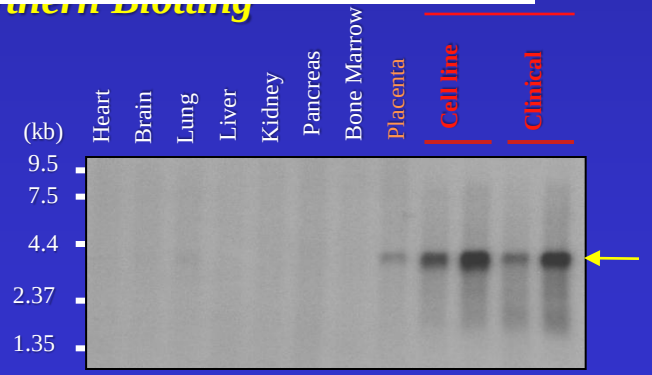
Semi-quantitative RT-PCR



MFH , Malignant fibrous histiocytoma ; LMS , Leiomyosarcoma ; LS, Liposarcoma ; MSC , Mesenchymal stem cell ; SS , Synovial Sarcoma ; MPNST , Malignant peripheral nerve sheath tumor

Nagayama et al., Cancer Research 62, 5859-66 (2002)

Northern Blotting

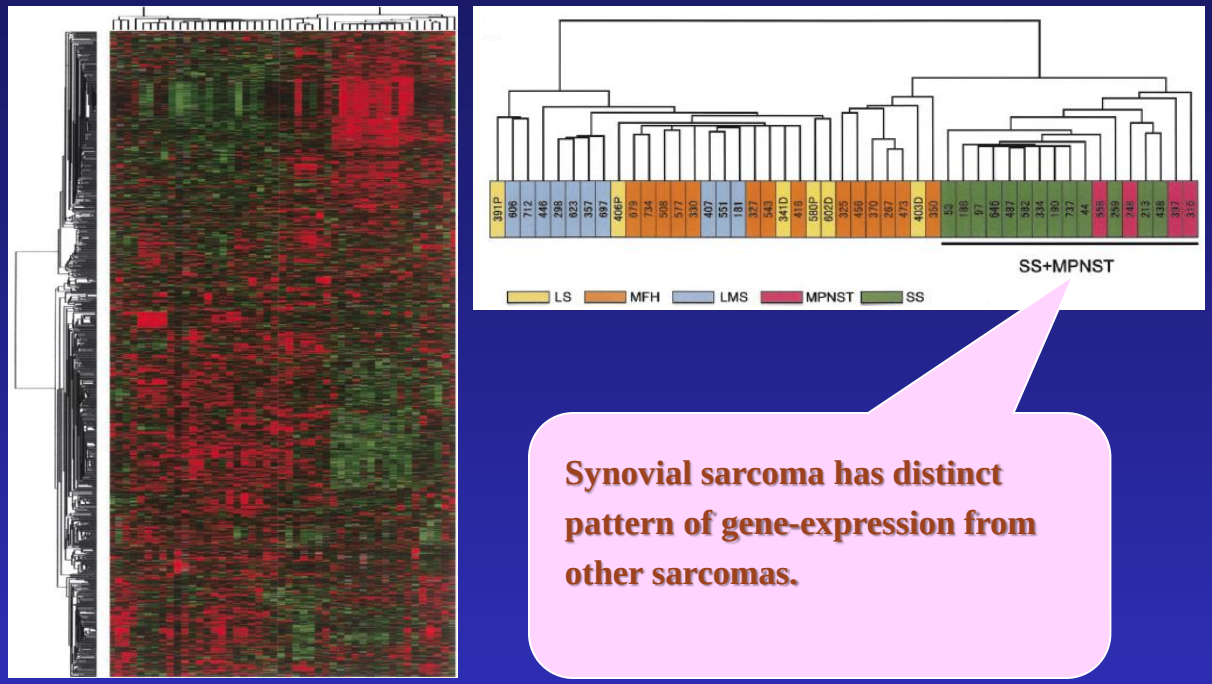


Nagayama et al., Oncogene 24, 6201-12 (2005)

FZD10 is specifically up-regulated in synovial sarcoma

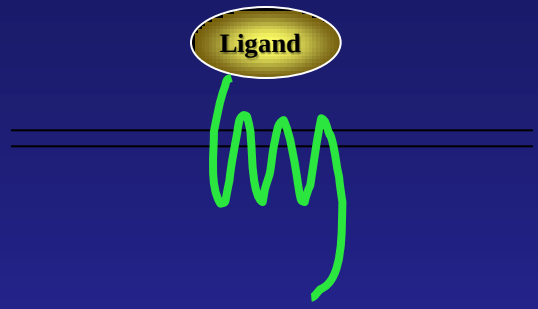
ESMO 2012

Genome-wide cDNA microarray of soft tissue sarcoma



Synovial sarcoma has distinct pattern of gene-expression from other sarcomas.

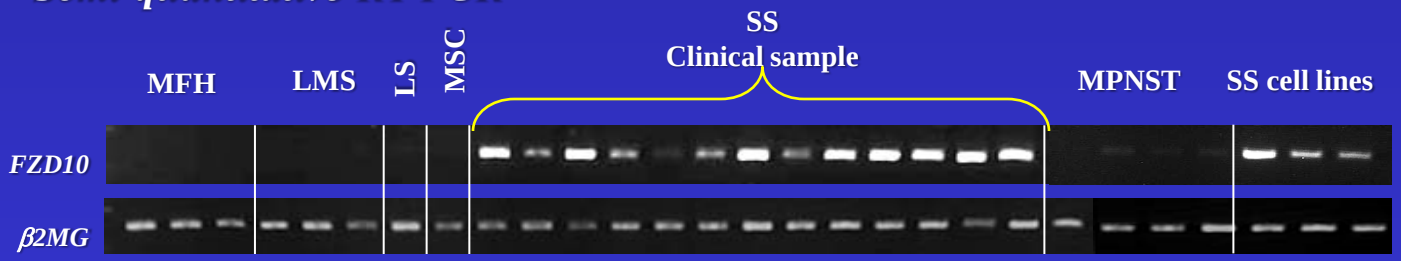
Frizzled Homologue 10 (FZD10)



Criteria for gene selection

- No detection in normal organs
- Frequent and high expression in synovial sarcoma
- Related in cell-growth / survival

Semi-quantitative RT-PCR



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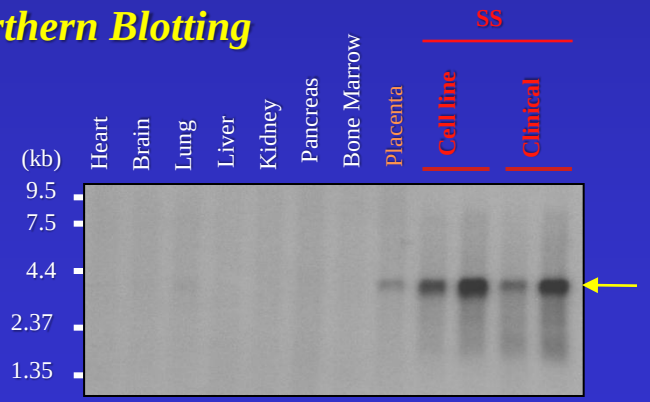
Nagayama et al., Cancer Research 62, 5859-66 (2002)

Northern Blotting

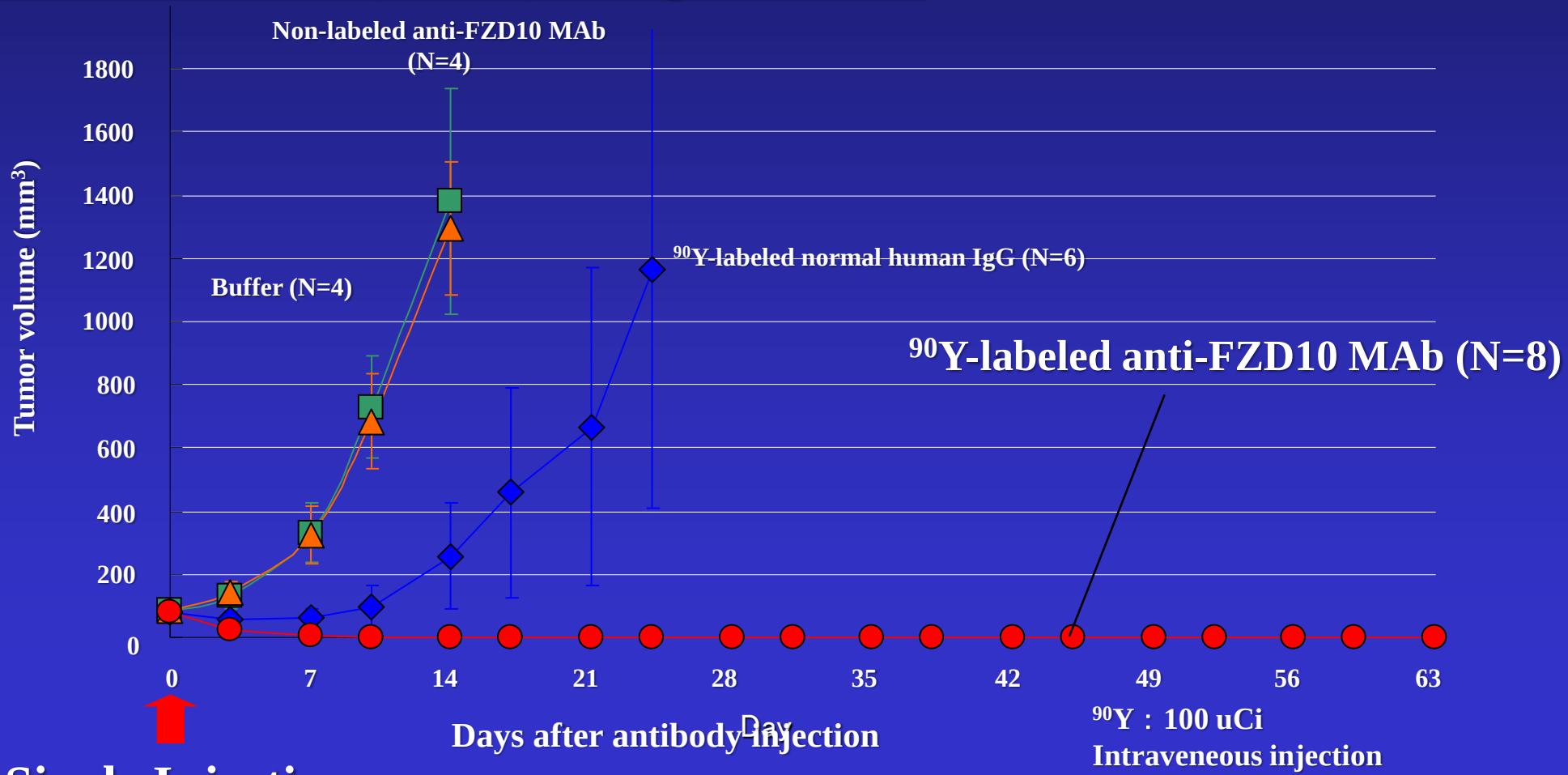


Nagayama et al., Oncogene 24, 6201-12 (2005)

Antitumor activity of ^{90}Y-labeled anti-FZD10 MAb

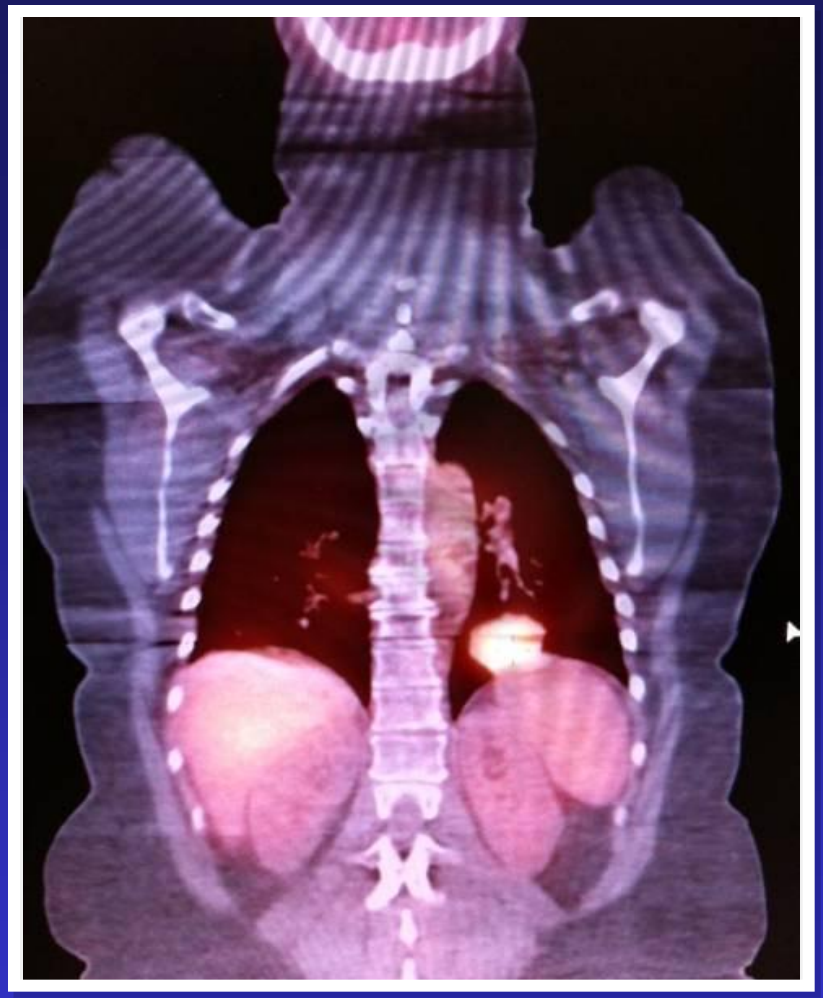
Potent antitumor effect was shown in all xenograft mice by just single injection of ^{90}Y-labeled anti-FZD10 MAb.

Synovial sarcoma (SYO-1) xenograft mouse

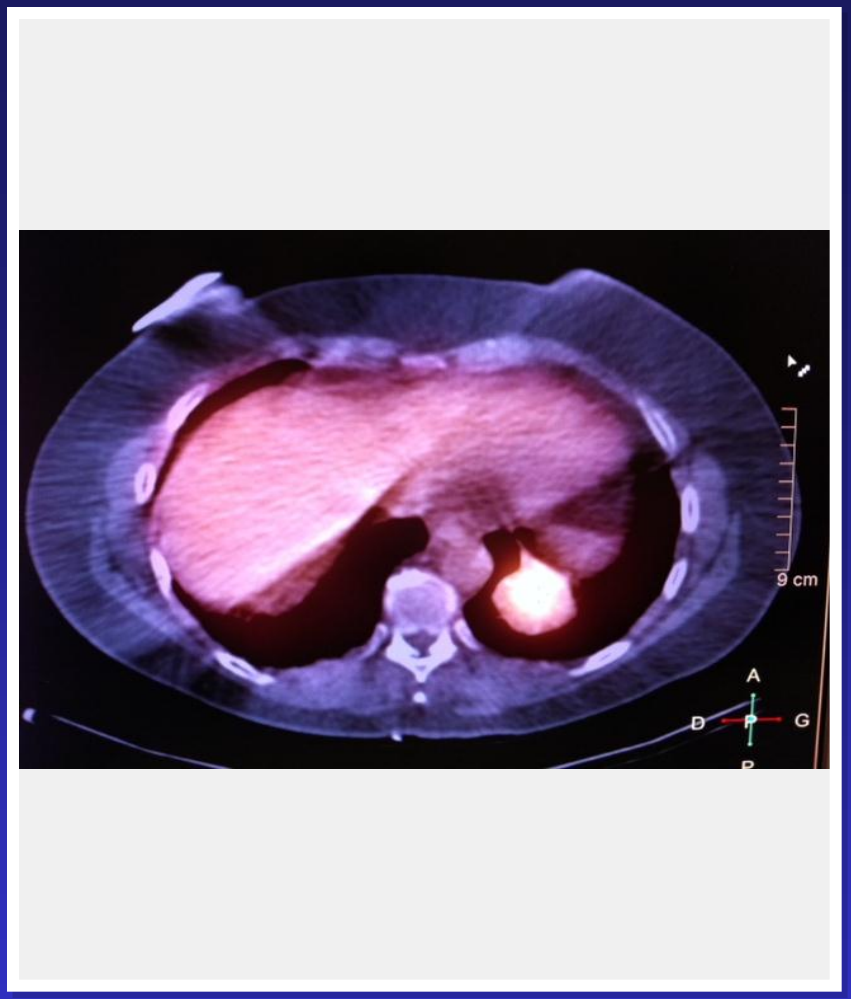


Single Injection

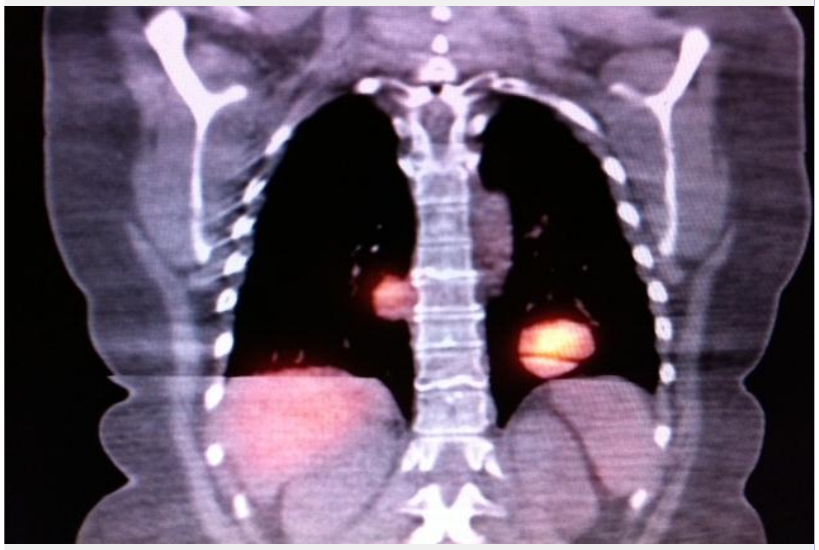
SYNFRIZZ Clinical Trial



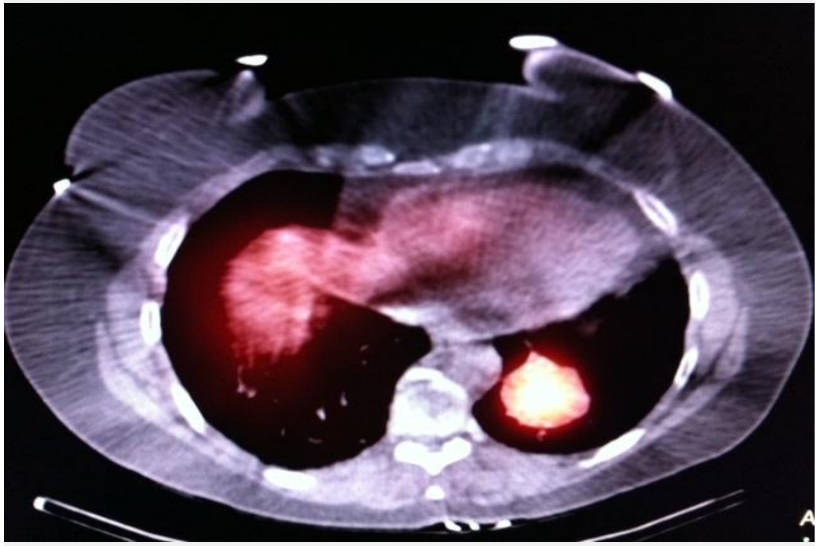
Transversal image
24H uptake
Met1 has very good uptake



Distal image
24h uptake



144H
Met1 & Met 2



Distal image
144h uptake

Conclusions

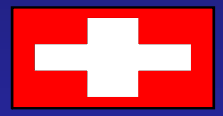
- Rare and multiple heterogenous subtypes and molecular subtypes
- Models for oncogenesis and clinical research
- Treatment adapted to driving molecular alterations
- Translational research to identify further driver mutations
- The challenge of resistance

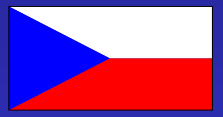












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and all investigators

A World Sarcoma Network is needed

Conticanet AUSTRALASIAN SARCOMA STUDY GROUP GSF GETO EORTC European Organisation for Research and Treatment of Cancer SARC Sarcoma Alliance for Research through Collaboration Collaborating for a Cure. GISG German Interdisciplinary Sarcoma Group EuroBoNeT