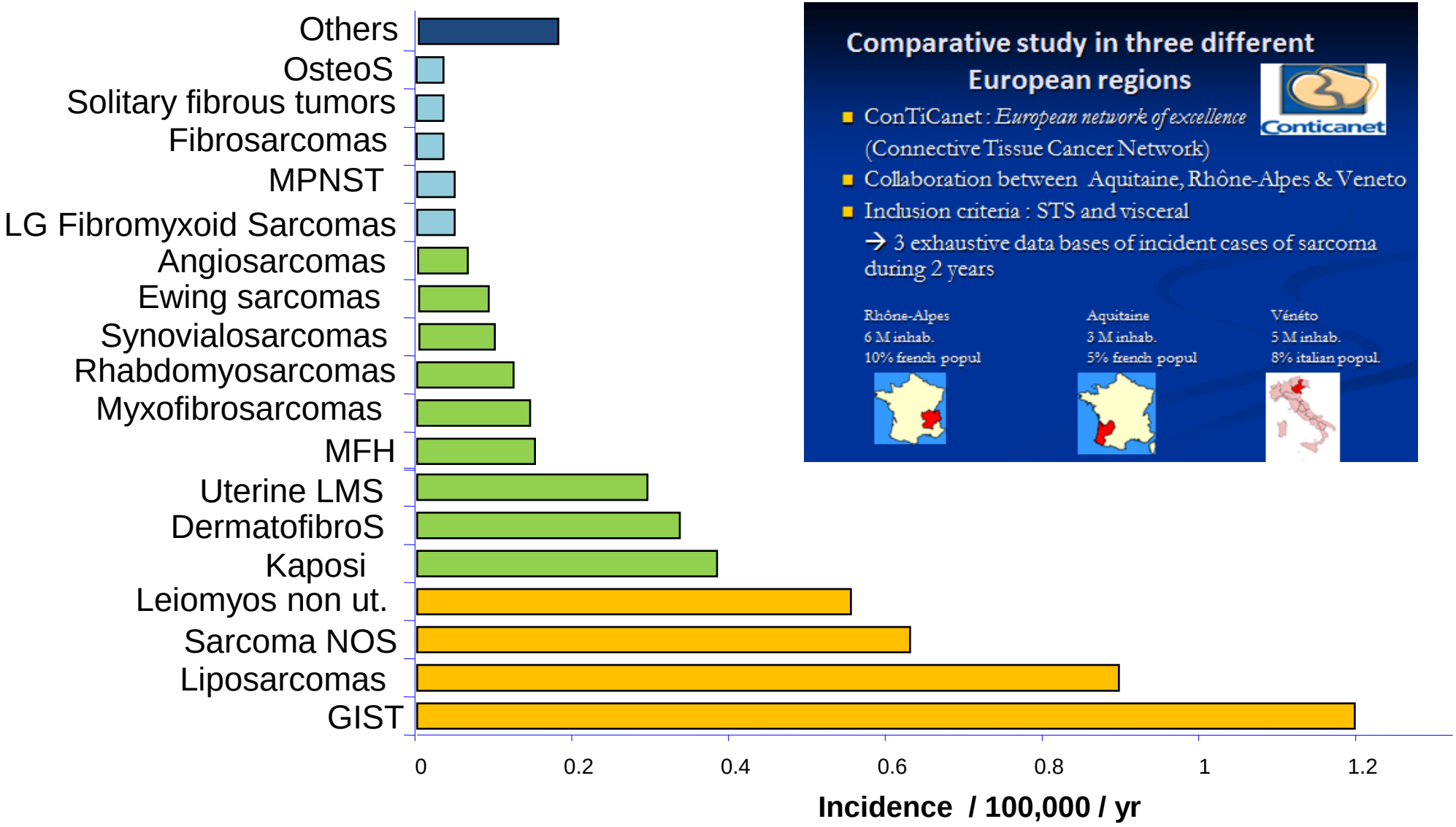
Evolving biology of sarcomas

JY Blay

Medical Oncology, Lyon

UCBL1- CLB

Incidence of sarcoma in three European regions

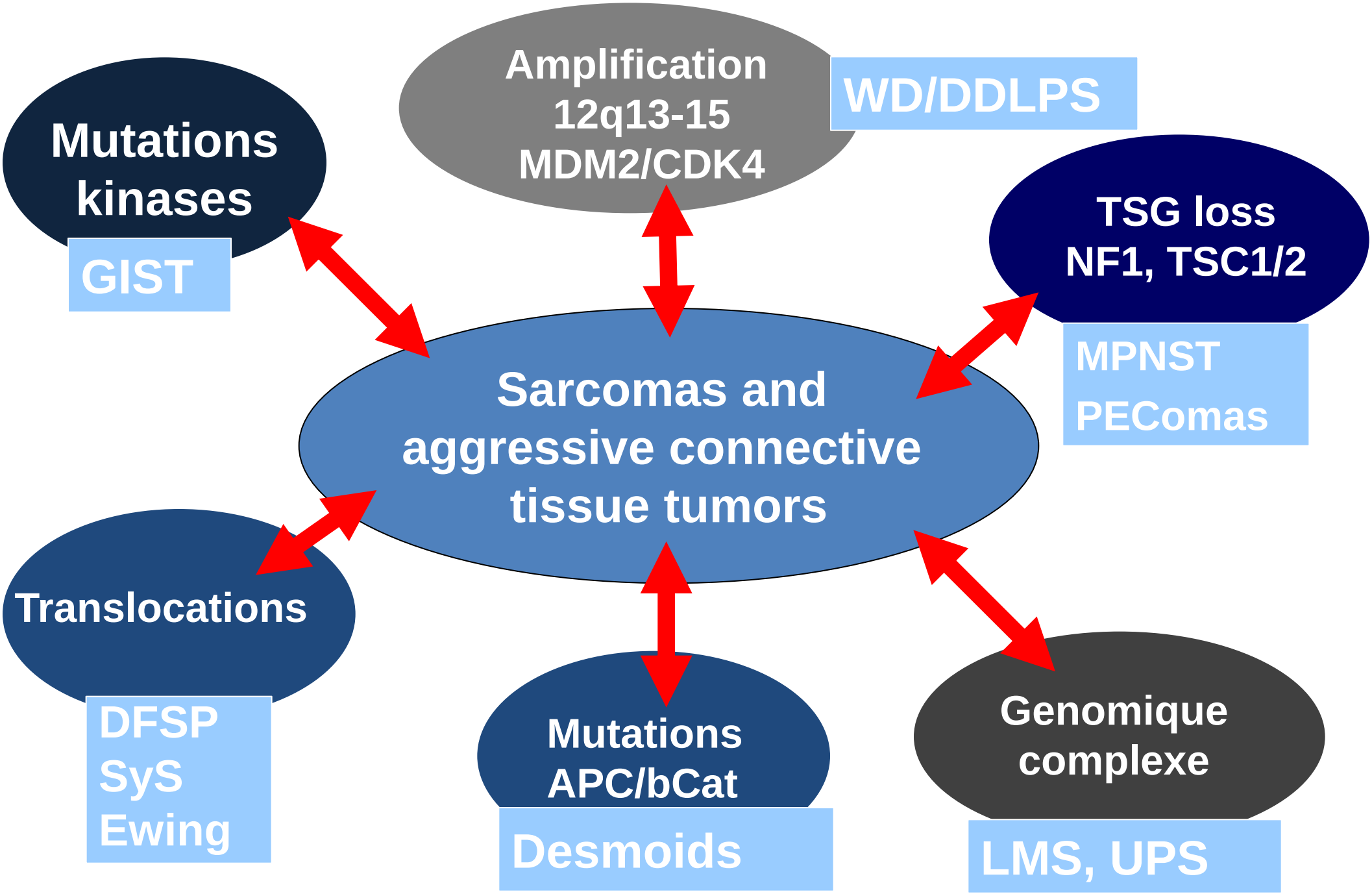


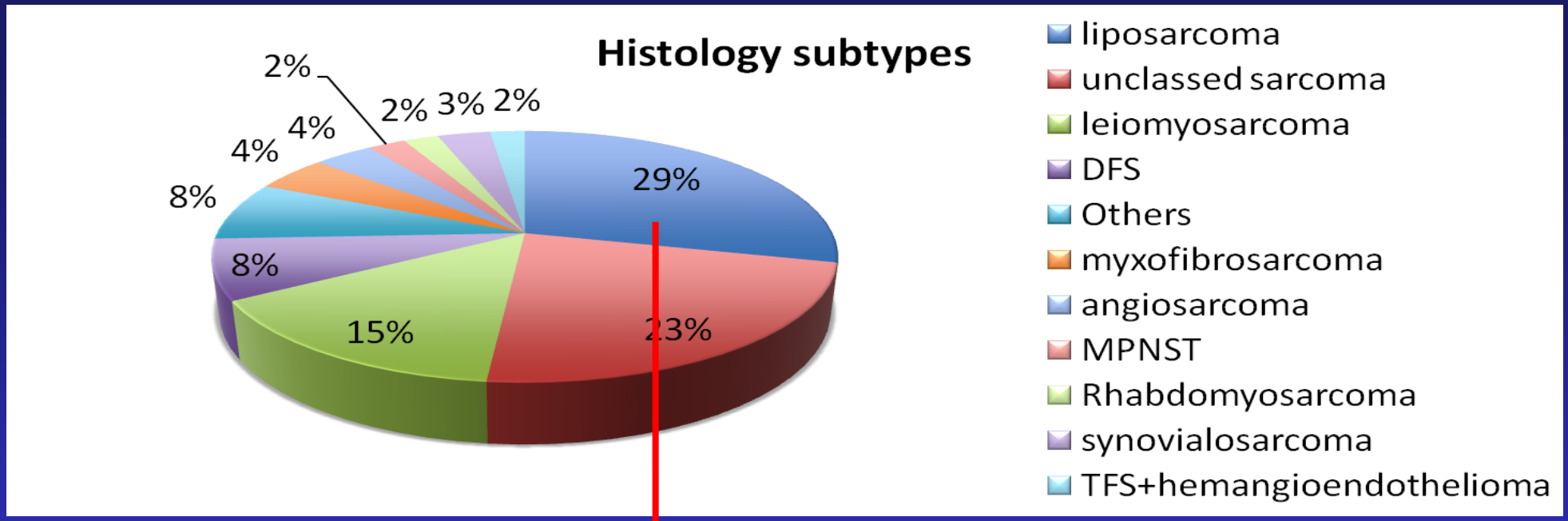
Comparative study in three different European regions

- ConTiCanet : *European network of excellence* (Connective Tissue Cancer Network)
- Collaboration between Aquitaine, Rhône-Alpes & Veneto
- Inclusion criteria : STS and visceral

→ 3 exhaustive data bases of incident cases of sarcoma during 2 years

Rhône-Alpes	Aquitaine	Vénéto
6 M inhab.	3 M inhab.	5 M inhab.
10% french popul	5% french popul	8% italian popul.

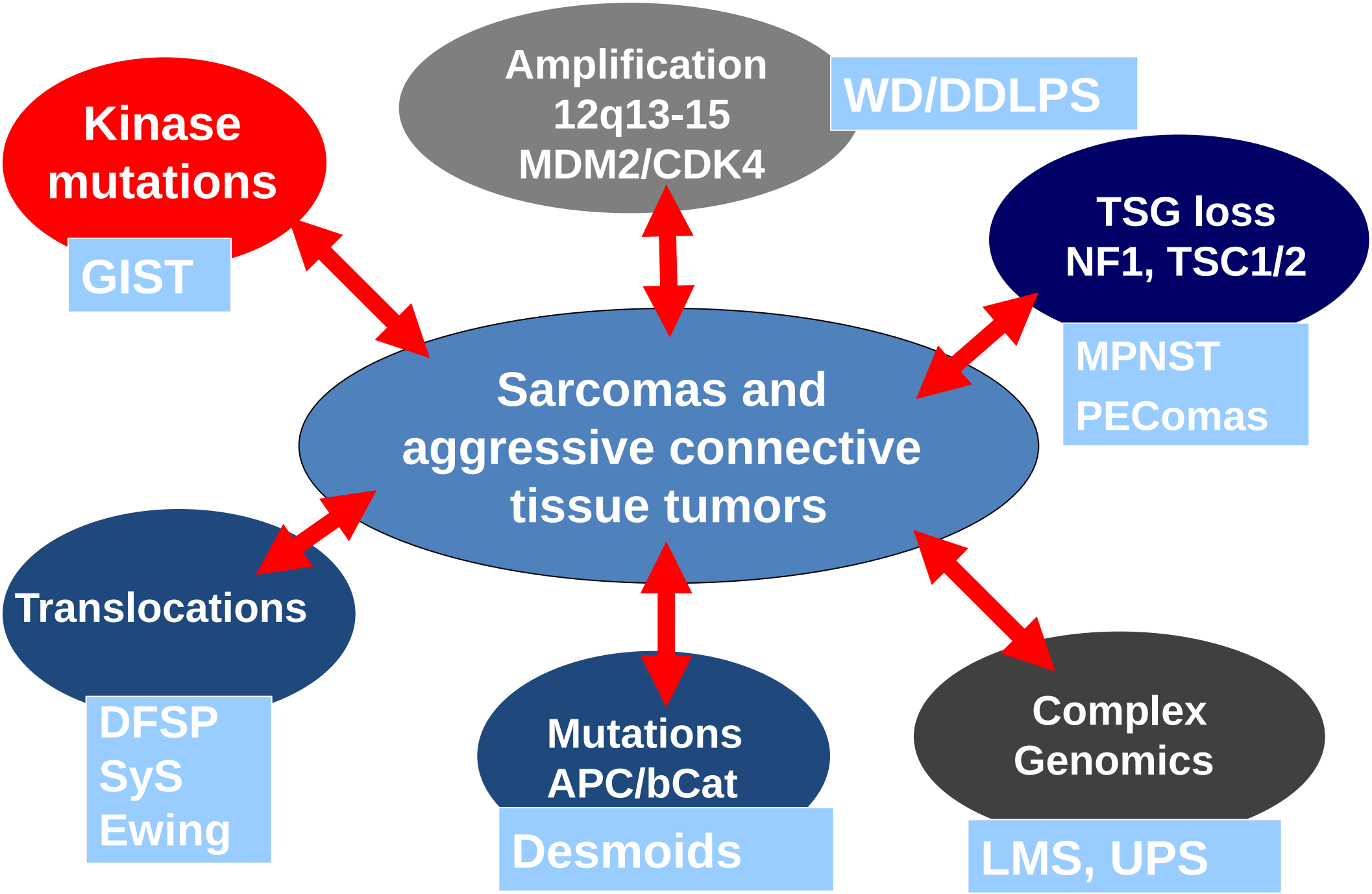

Amplification
12q13-15
MDM2/CDK4
WD/DDLPS
Mutations
kinases
GIST
TSG loss
NF1, TSC1/2
MPNST
PEComas
Sarcomas and
aggressive connective
tissue tumors
Translocations
DFSP
SyS
Ewing
Mutations
APC/bCat
Desmoids
Genomique
complexe
LMS, UPS



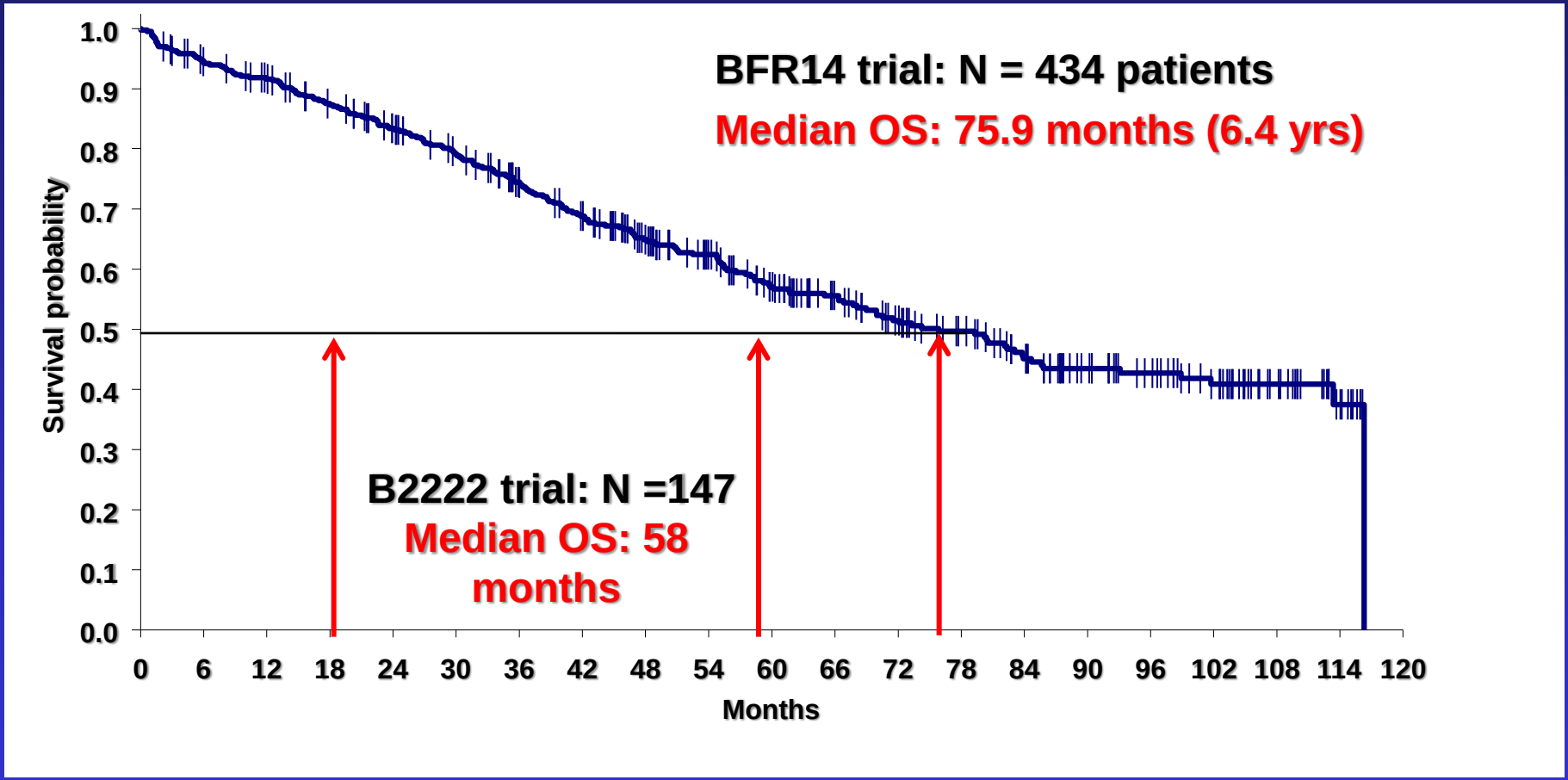
• Specific translocations generating fusion genes (Myx LPS)	15%
• Kinase mutations (KIT…)	?
• Gene inactivation (NF1…)	?
• Amplifications chromosome 12 (MDM2+CDK4)	75-80%
• Complex genetic alterations (Pleo LPS, ...)	5-10%

Ducimetière F *et al*. *PLoS One* 2011; **6**: e20294.

Drivers

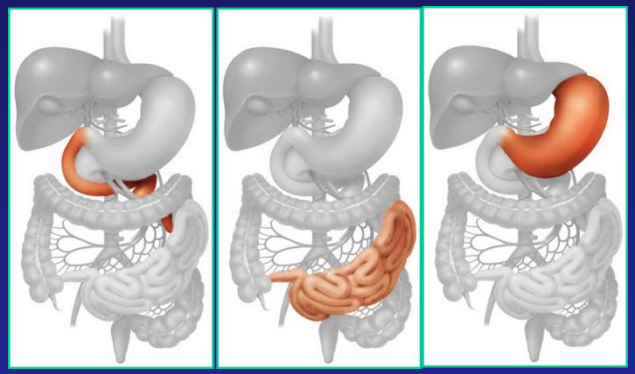

Kinase mutations
GIST
Amplification 12q13-15 MDM2/CDK4
WD/DDLPS
TSG loss NF1, TSC1/2
MPNST
PEComas
Sarcomas and aggressive connective tissue tumors
Translocations
DFSP
SyS
Ewing
Mutations APC/bCat
Desmoids
Complex Genomics
LMS, UPS

Long term OS of GIST patients in the BFR14 trial



Perol M *et al.*, *J Clin Oncol.*, 2012; 30: 2516-24; Blanke CD *et al.*, *J Clin Oncol.*, 2008; 26:620-25.

GISTS Are different diseases



	Dose	Adjuvant
***KIT* exon 11**	**Im 400**	**+**
***KIT* exon 9**	**Im 400**	**+**
PDGFRA		
Non-*D842V*	**Im 400**	**+**
***D842V*:**	**0**	**0**
KIT/PDGFR WT	**Im 400**	**+/?**
NF1	**?/Im 400**	**+/?**
SDH	**?/Im 400**	**+/?**
BRAF	**?**	**?**
Pediatric	**?**	**?**

Blay JY, et al. *Discov Med*. 2012;13:357-367.

Deletions Affecting Codons 557-558 of the *c-KIT* Gene Indicate a Poor Prognosis in Patients With Completely Resected Gastrointestinal Stromal Tumors: A Study by the Spanish Group for Sarcoma Research (GEIS)

Javier Martín, Andrés Poveda, Antonio Llombart-Bosch, Rafael Ramos, José A. López-Guerrero, Javier García del Muro, Joan Maurel, Silvia Calabuig, Antonio Gutierrez, José L. González de Sande, Javier Martínez, Ana De Juan, Nuria Laínez, Ferrán Losa, Valentín Alija, Pilar Escudero, Antonio Casado, Pilar García, Remei Blanco, and José M. Buesa

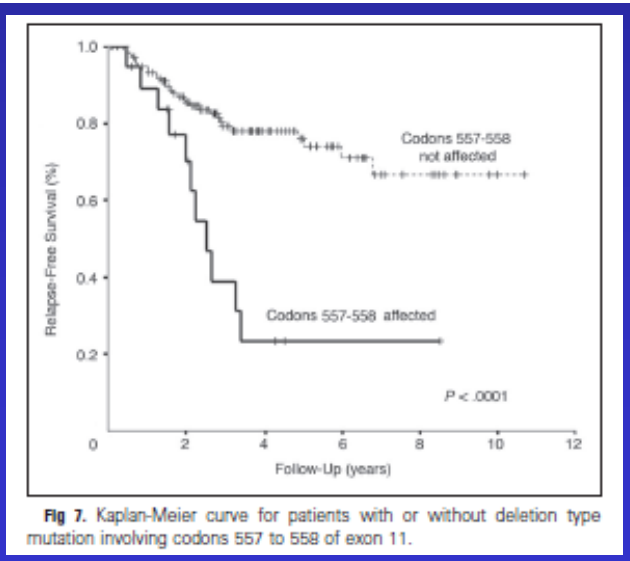
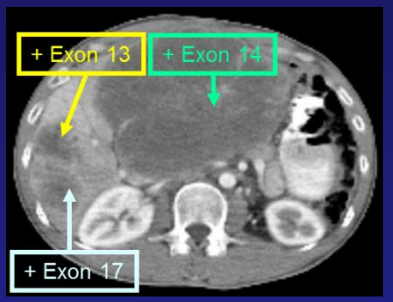


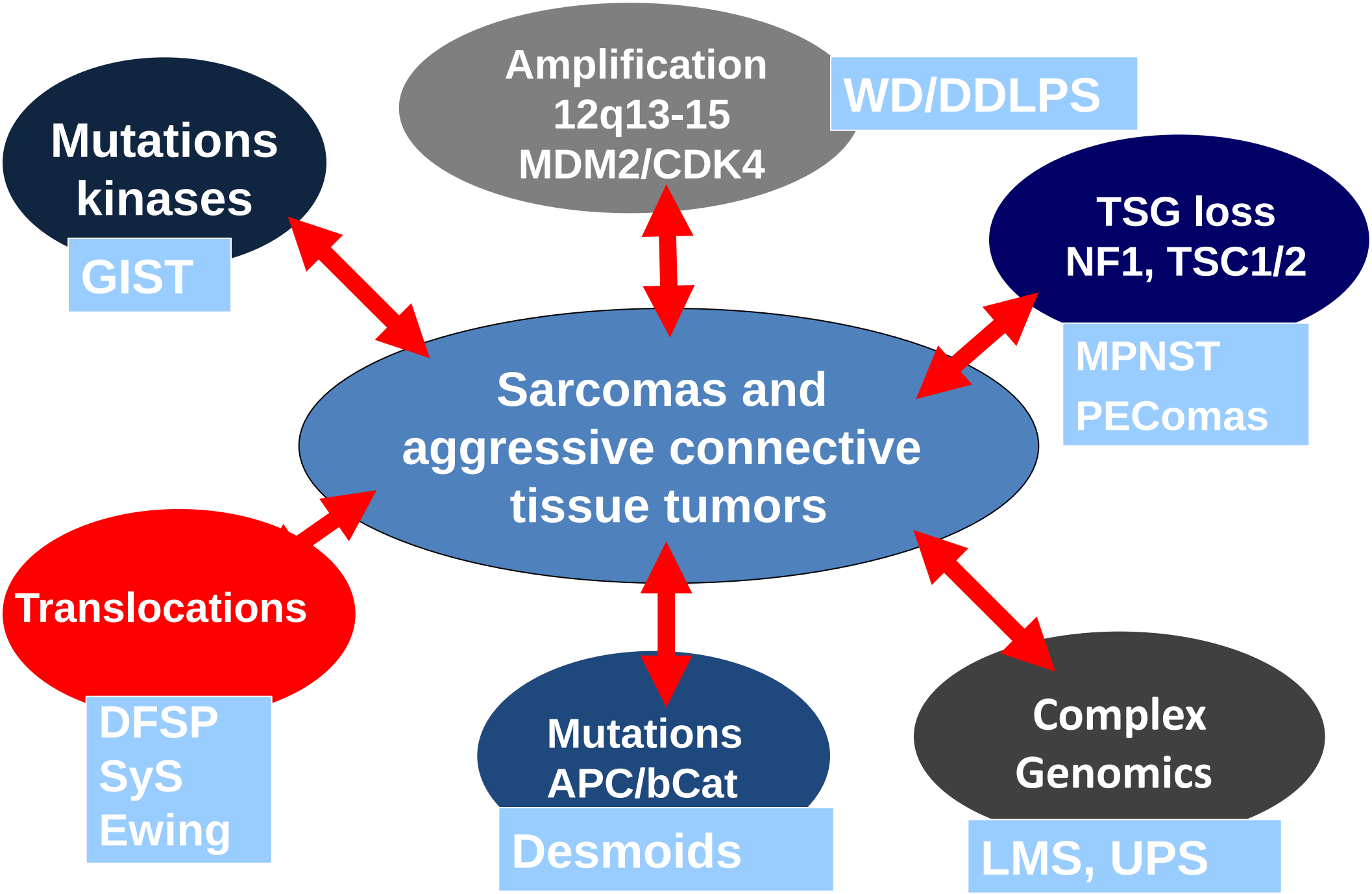
Fig 7. Kaplan-Meier curve for patients with or without deletion type mutation involving codons 557 to 558 of exon 11.



GRID Study: Plasma or tumor detection of *KIT* exon 9 or other mutations

Patient no.	*KIT* mutation detected	
	Plasma BEAMing	*Tissue sequencing*
1	Exon 9 INS	Exon 9 INS
2	Exon 9 INS	Exon 9 INS
3	Exon 9 INS + exon 17 MUT	Exon 9 INS + exon 17 MUT
4	Exon 9 INS	Exon 9 INS
5	Exon 9 INS + exon 17 MUT	None (local test: exon 9 MUT)
6	Exon 9 INS + exon 17 MUT	Exon 9 INS
7	Exon 9 INS + exon 17 MUT	Exon 9 INS
8	Exon 9 INS	Exon 9 INS
9	Exon 9 INS	Exon 9 INS
10	Exon 9 INS	Exon 9 INS
11	Exon 9 INS + exon 17 MUT	None (local test: exon 9 MUT)
12	Exon 9 INS	Exon 9 INS
13	Exon 9 INS	Exon 9 INS
14	Exon 9 INS + exons 17 & 18 MUT	Exon 9 INS
15	Exon 9 INS	Exon 9 INS
16	Exon 9 INS + exon 17 MUT	Exon 9 INS
17	Exon 9 INS + exon 17 MUT	Exon 9 INS
18	Exon 9 INS + exon 17 MUT	Exon 9 INS

Demetri GD, et al. *J Clin Oncol*. 2013;31(suppl). Abstract 10503.


Mutations
kinases
GIST
Amplification
12q13-15
MDM2/CDK4
WD/DDLPS
TSG loss
NF1, TSC1/2
MPNST
PEComas
Sarcomas and
aggressive connective
tissue tumors
Translocations
DFSP
SyS
Ewing
Mutations
APC/bCat
Desmoids
Complex
Genomics
LMS, UPS

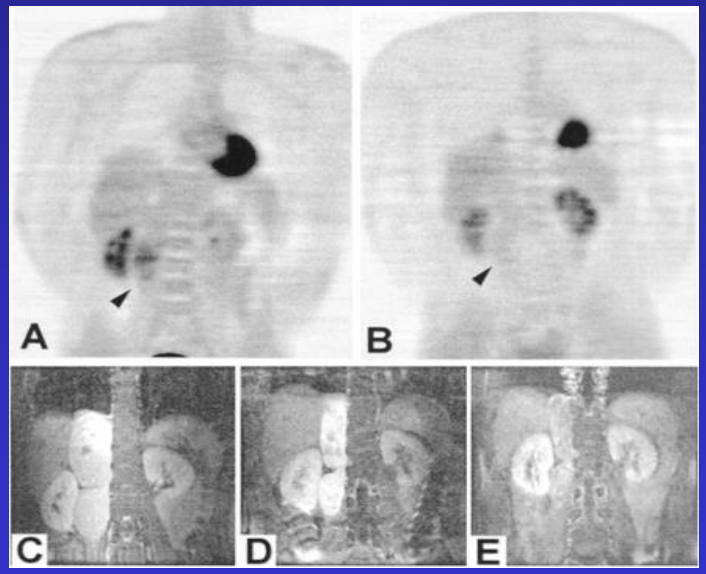
Imatinib mesylate in advanced dermatofibrosarcoma protuberans (DFSP) - pooled analysis of two phase II clinical trials

ESMO 2014

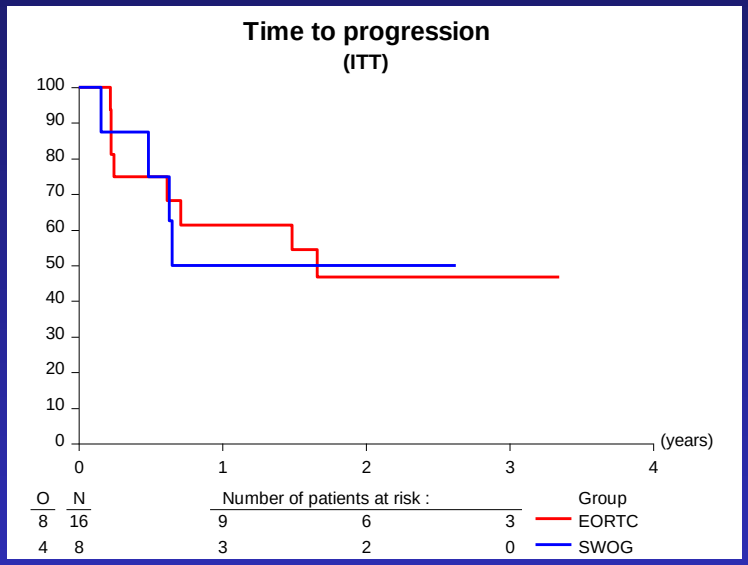
P. Rutkowski, S. Schuetze, M. M. Van Glabbeke, C. Rankin, W. Ruka, B. P. Rubin, M. Debiec-Rychter, A. Lazar, H. Gelderblom, J-Y Blay, R. Sciot, P. Hohenberger, A. T. van Oosterom;
for the EORTC Soft Tissue/Bone Sarcoma Group and South-West Oncology Group

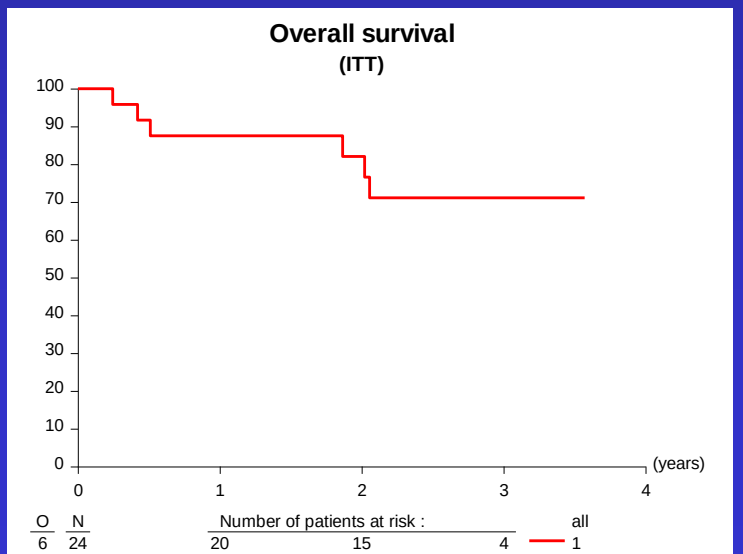
DFSP /giant cell fibroblastoma

- t(17,22) :17q22 and 22q13 (*COL1A1* et *PDGFB*)
- Autocrine loop with PDGFβ



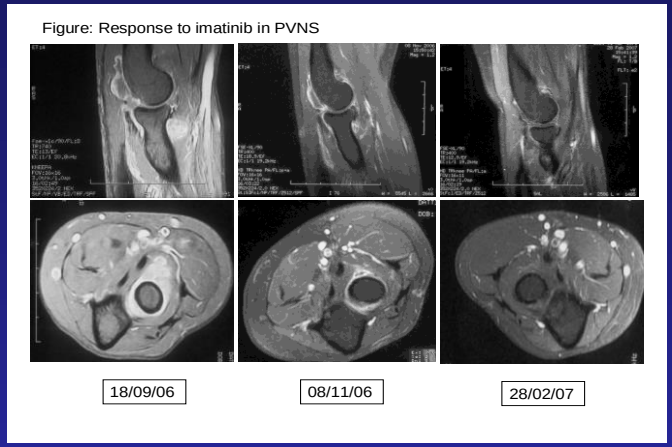
Maki et al IJC,
Rubin et al JCO
Mc Arthur et al JCO



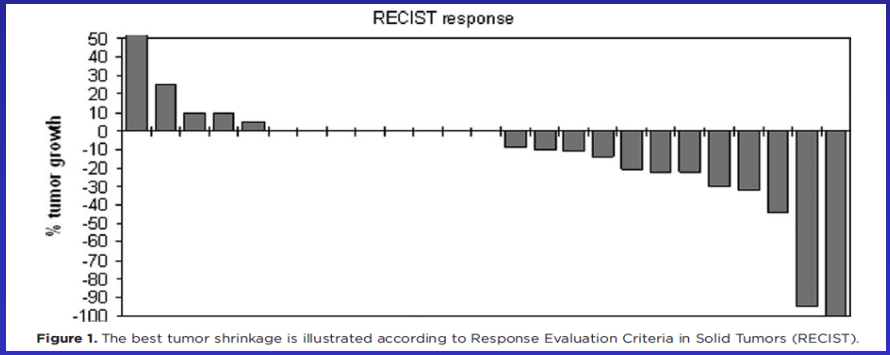


MCSFR inhibitors in PVNS with t(1,2)- col6a3-CSF1

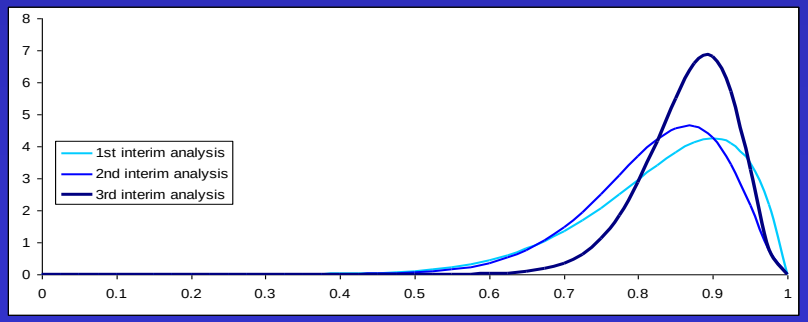
- Case report in 2008
  - (Ann Oncol 2008)



- Retrospective study 2011
  - (Cancer 2011)



- Prospective study 2012
  - (Proc ASCO 2012)



Phase 1 study of RG7155, a novel anti-CSF1R antibody, in patients with locally advanced pigmented villonodular synovitis (PVNS)

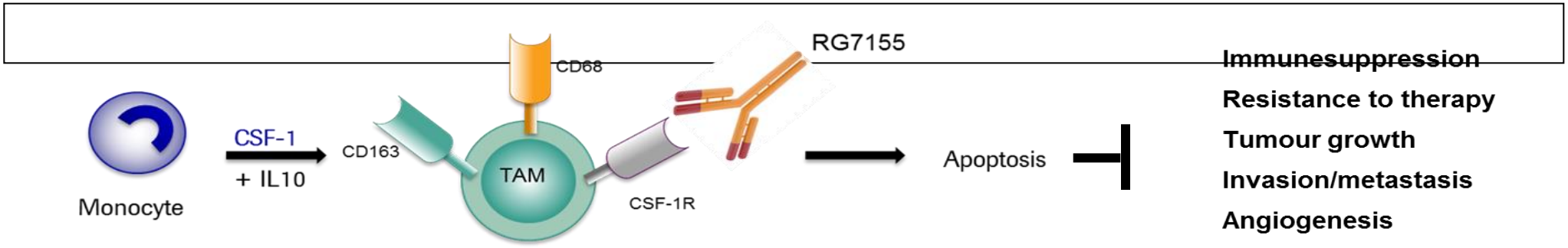
P.A. Cassier, C.A. Gomez-Roca, A. Italiano, M. Cannarile, C. Ries, A. Brillouet, C. Mueller, G. Meneses-Lorente, M. Baehner, J. Ratnayake, R. Harding, K. Abiraj, N. Gass, K. Noh, R.D. Christen, M. Campone,

C. Le Tourneau, J. Delord, D. Rüttinger, J.-Y. Blay

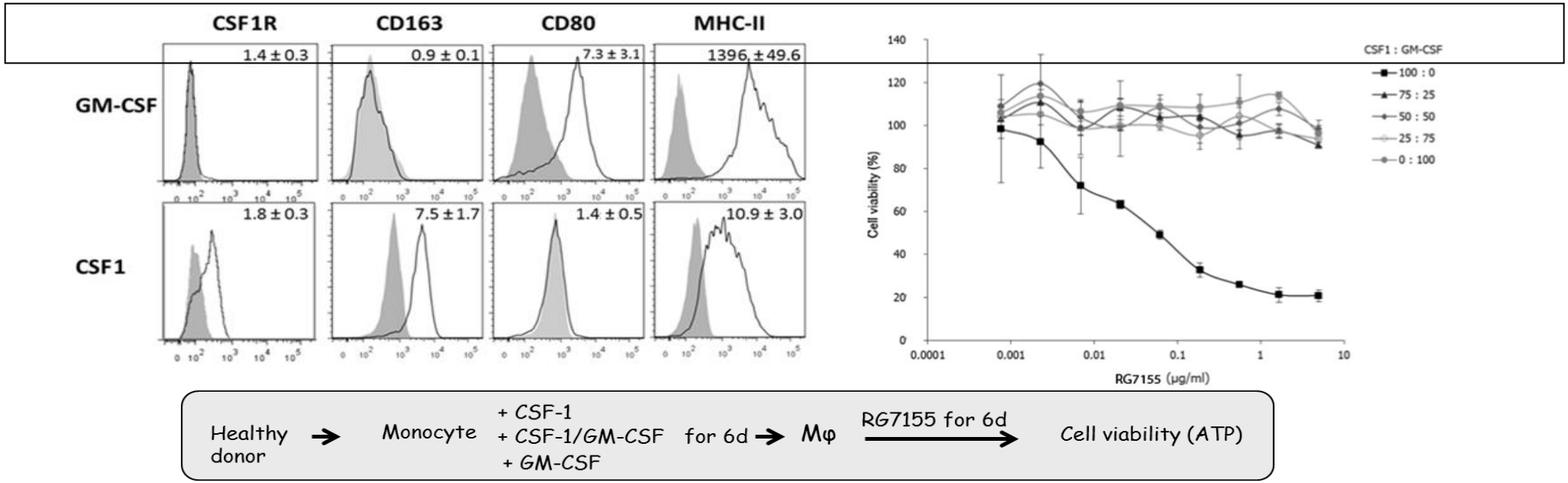
Study fully sponsored by **F. HOFFMANN-LA ROCHE**

RG7155 targets the tumor microenviroment

PVNS as "proof-of-principle" for inhibition of CSF1R



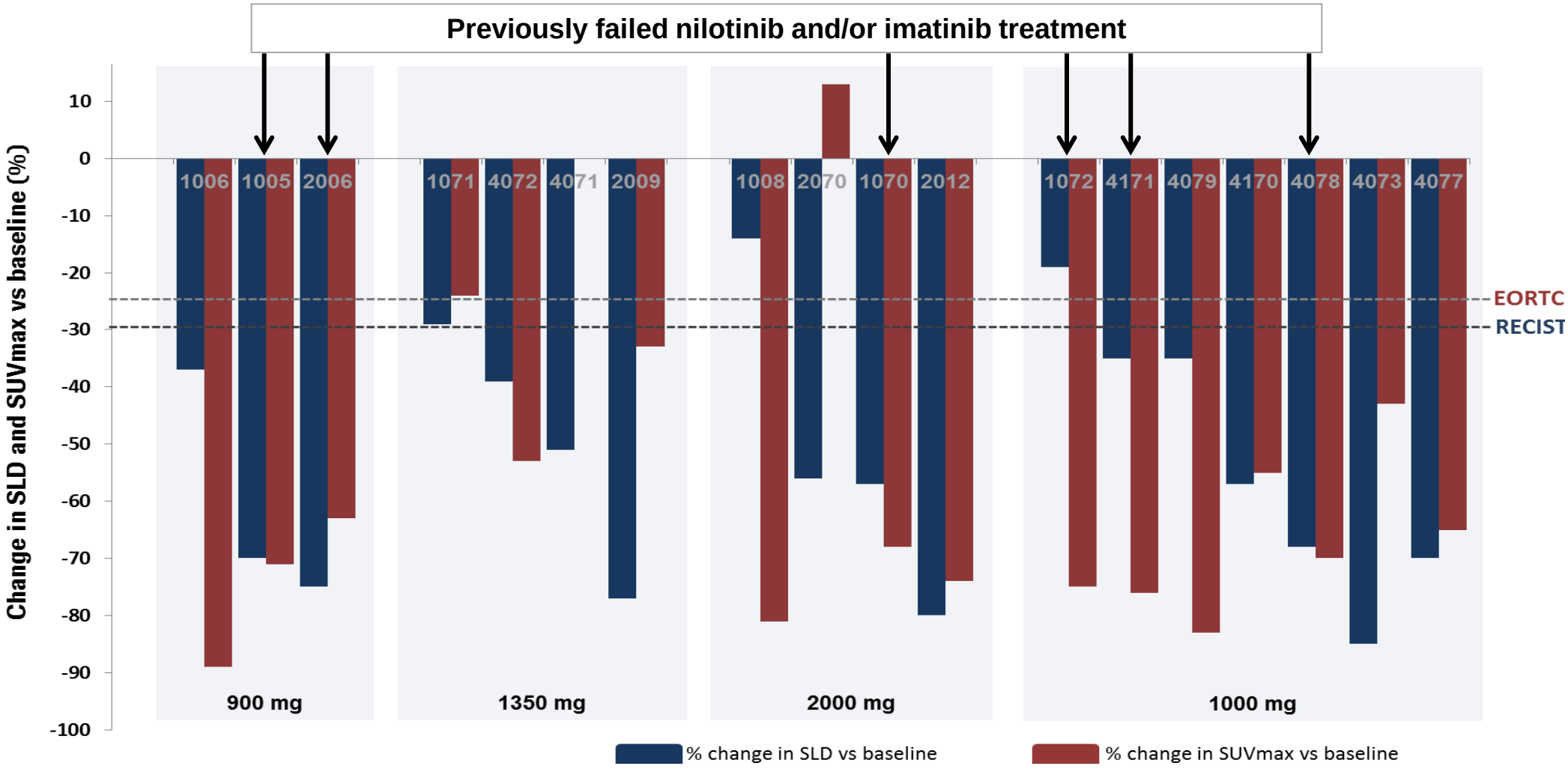
RG7155 targets CSF1R+CD163+ tumor associated macrophages (TAM)



RG7155 selectively depletes CSF1-differentiated CSF1R+CD163+ macrophages *in vitro*

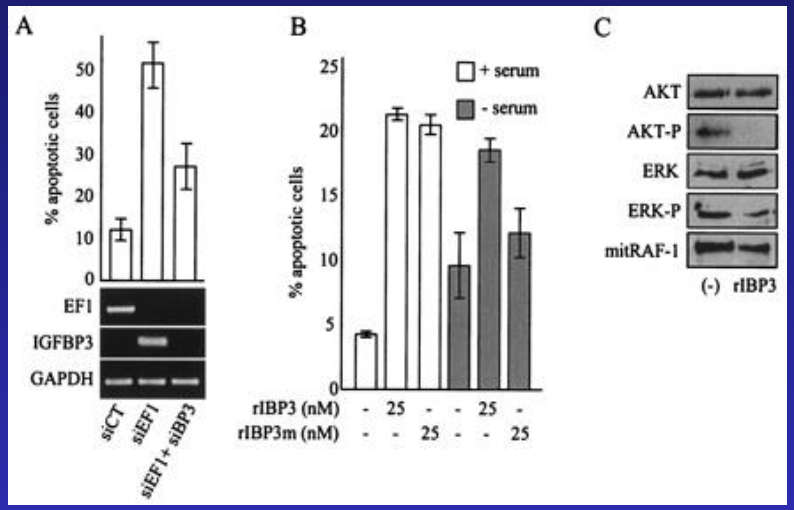
RG7155 induces high ORR in PVNS

Time Point Responses (RECIST 1.1)



Ries et al. *Cancer Cell* 2014 (in press)

The missed opportunity of IGF1R Ab treatment in sarcomas



IGF1 inhibitors as potential targeted therapy in ES ?

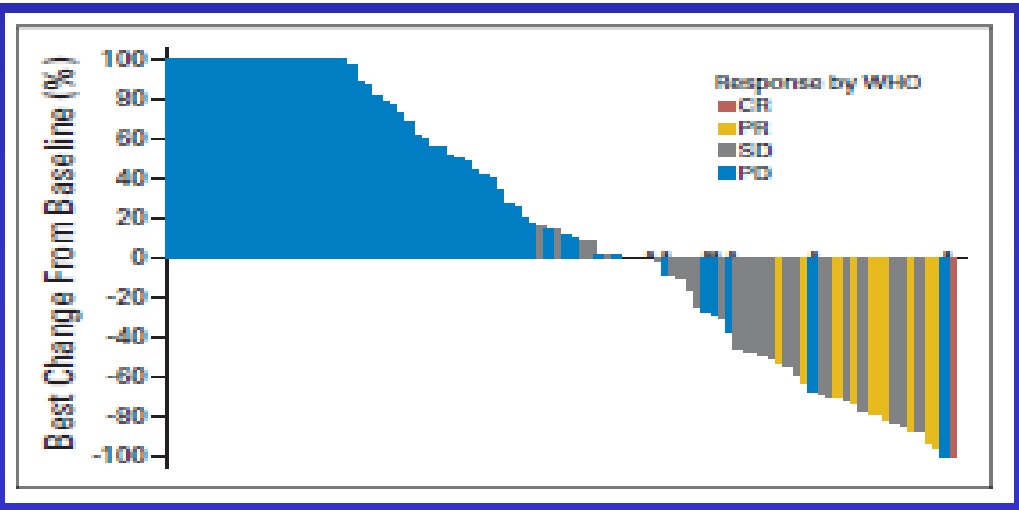
Prieur 2004, Olmos 2009, Pappo 2011

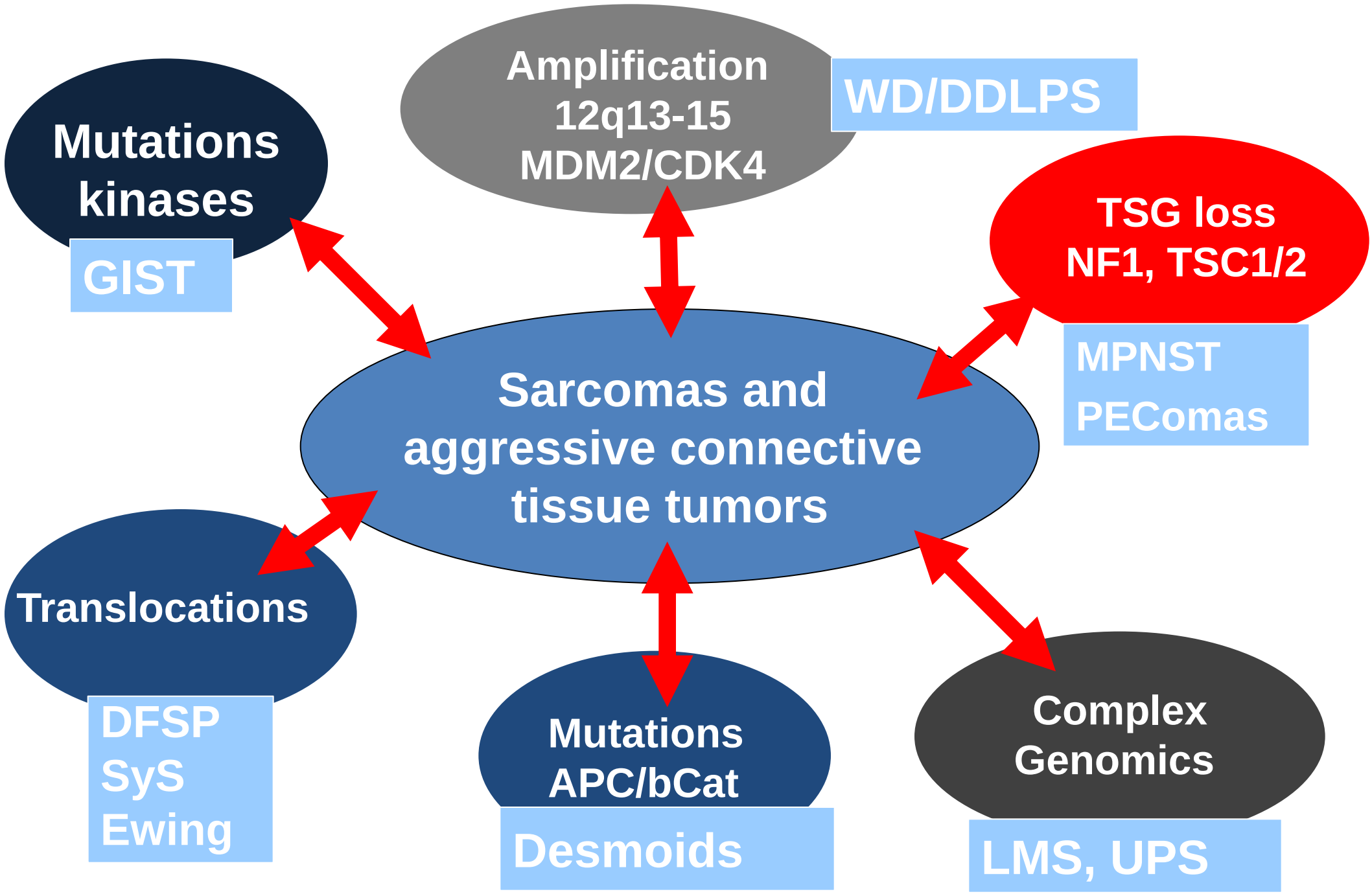
Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study

David Olmos, Sophie Postel-Vinay, L Rhoda Molife, Scott H Okuno, Scott M Schuetze, M Luisa Paccagnella, Gretchen N Batzel, Donghua Yin, Kathryn Pritchard-Jones, Ian Judson, Francis P Worden, Antonio Gualberto, Michelle Scurr, Johann S de Bono, Paul Haluska

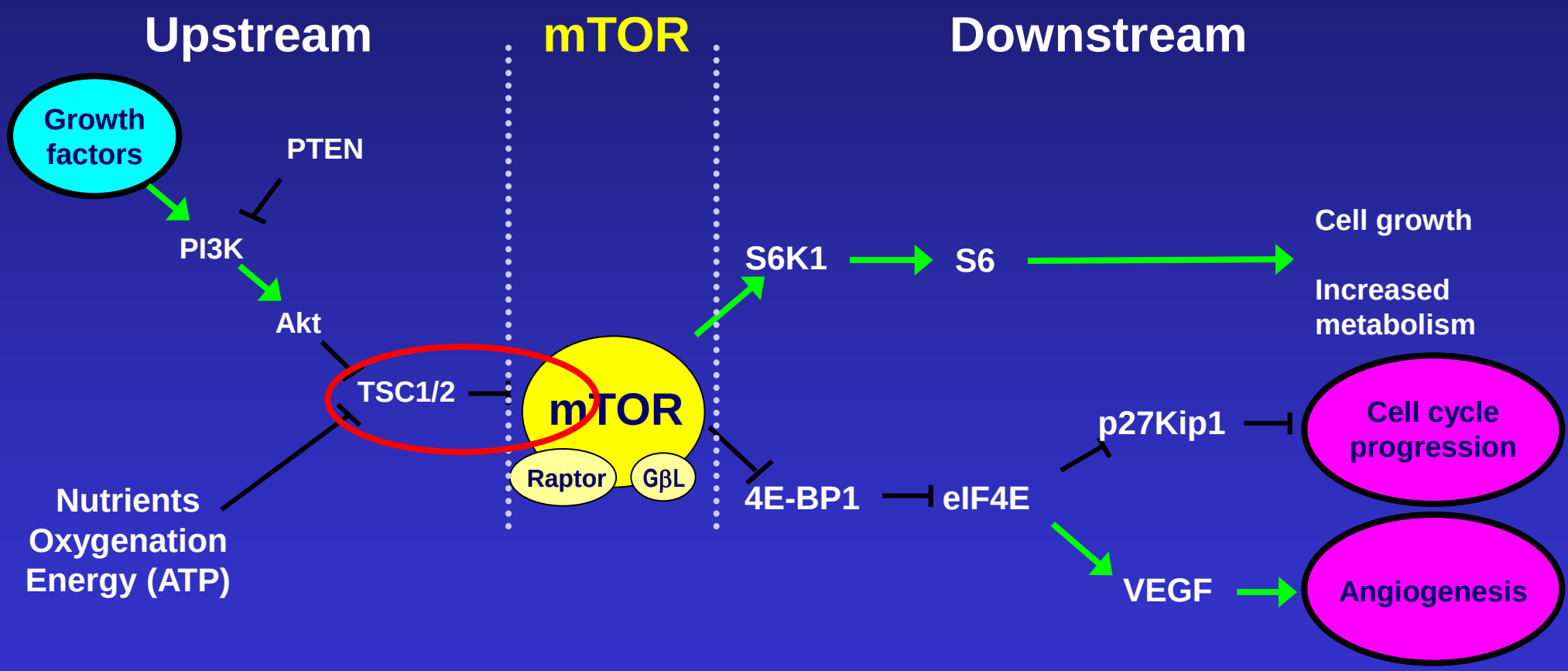
R1507, a Monoclonal Antibody to the Insulin-Like Growth Factor 1 Receptor, in Patients With Recurrent or Refractory Ewing Sarcoma Family of Tumors: Results of a Phase II Sarcoma Alliance for Research Through Collaboration Study

Alberto S. Pappo, Shreyaskumar R. Patel, John Crowley, Denise K. Reinke, Klaus-Peter Kuenkele, Sant P. Chawla, Guy C. Toner, Robert G. Maki, Paul A. Meyers, Rashmi Chugh, Kristen N. Ganjoo, Scott M. Schuetze, Heribert Juergens, Michael G. Leahy, Birgit Geoerger, Robert S. Benjamin, Lee J. Helman, and Laurence H. Baker




Amplification
12q13-15
MDM2/CDK4
WD/DDLPS
Mutations
kinases
GIST
TSG loss
NF1, TSC1/2
MPNST
PEComas
Sarcomas and
aggressive connective
tissue tumors
Translocations
DFSP
SyS
Ewing
Mutations
APC/bCat
Desmoids
Complex
Genomics
LMS, UPS

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.

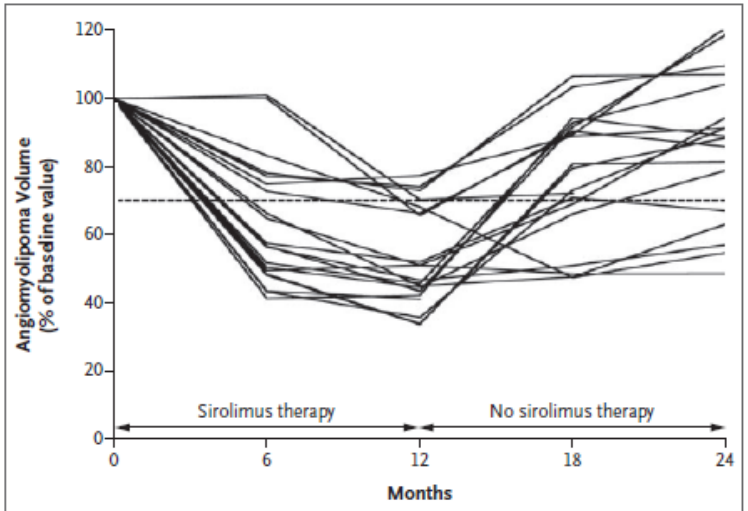


Figure 2. Angiomyolipoma Volume in the Patients with the Tuberous Sclerosis Complex or Sporadic Lymphangioleiomyomatosis during the Study.

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.

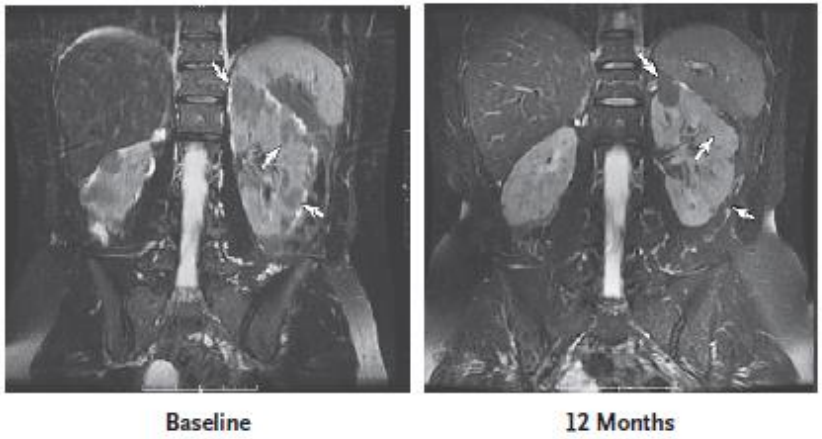


Figure 3. Renal Angiomyolipomas in the Abdomen of a Patient with the Tuberous Sclerosis Complex.

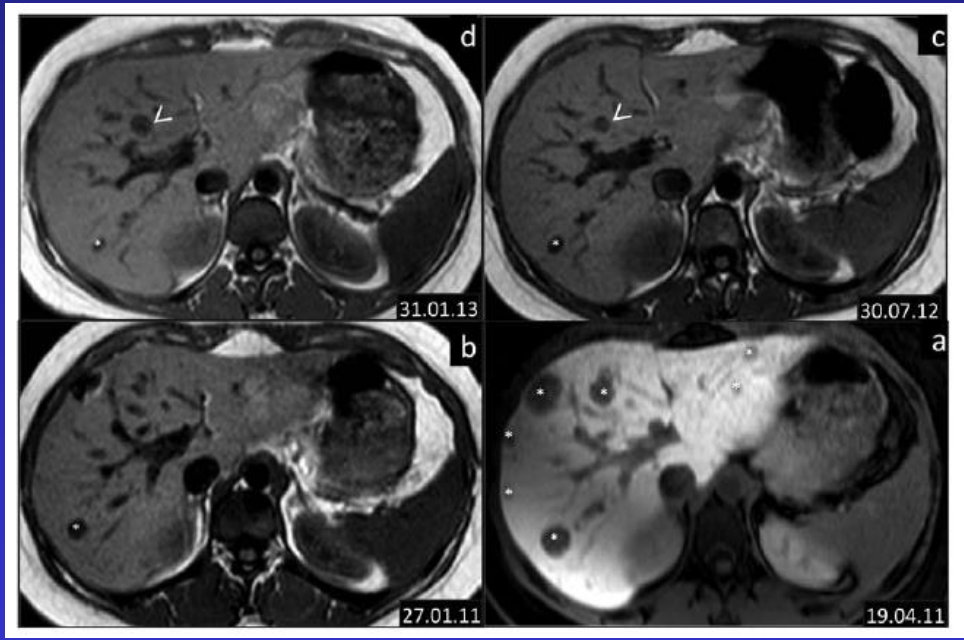
Bilateral angiomyolipomas are shown at baseline and after 12 months of sirolimus therapy. Three lesions in the left kidney are identified by arrows; at 12 months, the top lesion had become reduced in size and the bottom two had become imperceptible. The images were obtained with the use of fast spin–echo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

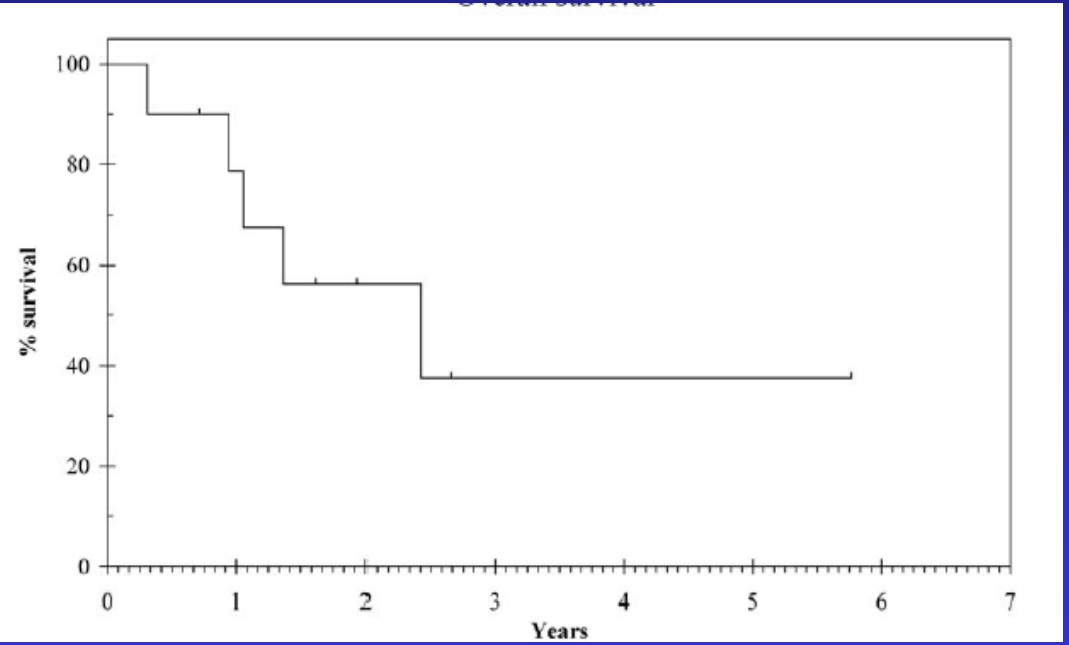
ESMO 2014

A Retrospective Study of Patients with Malignant PEComa Receiving Treatment with Sirolimus or Temsirolimus: The Royal Marsden Hospital Experience

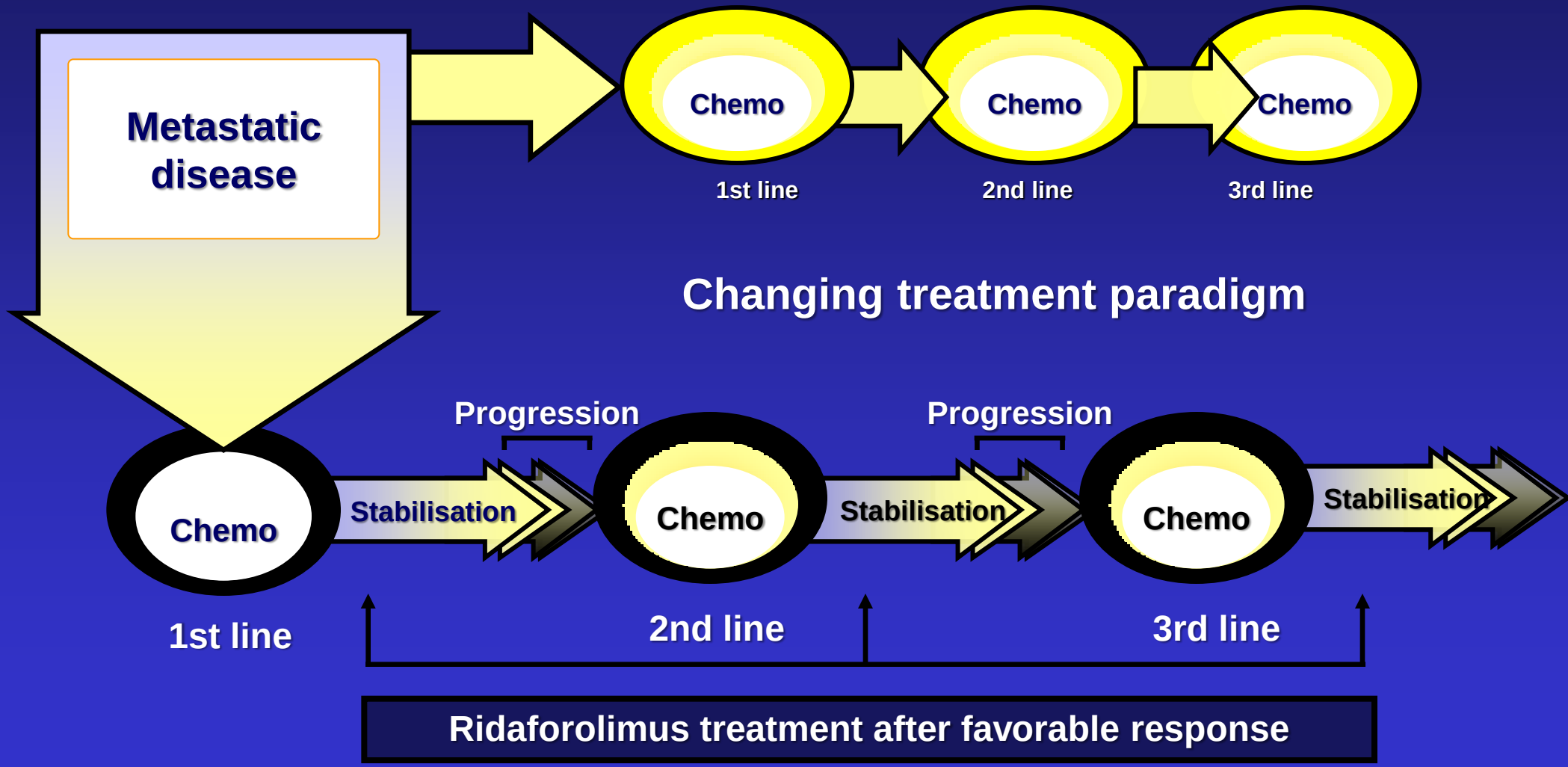
CHARLOTTE BENSON[1], JOANNA VITFELL-RASMUSSEN[2], MARCO MARUZZO[1], CYRIL FISHER[3], NINA TUNARIU[4], SCOTT MITCHELL[1], OMAR AL-MUDERIS[1], KHIN THWAY[3], JAMES LARKIN[5] and IAN JUDSON[1]

[1]Sarcoma Unit, [3]Pathology Department, [4]Radiology Department, and [5]Renal and Melanoma Unit, The Royal Marsden NHS Foundation Trust, London, UK; [2]Oncology Department, Herlev Hospital, Herlev, Denmark

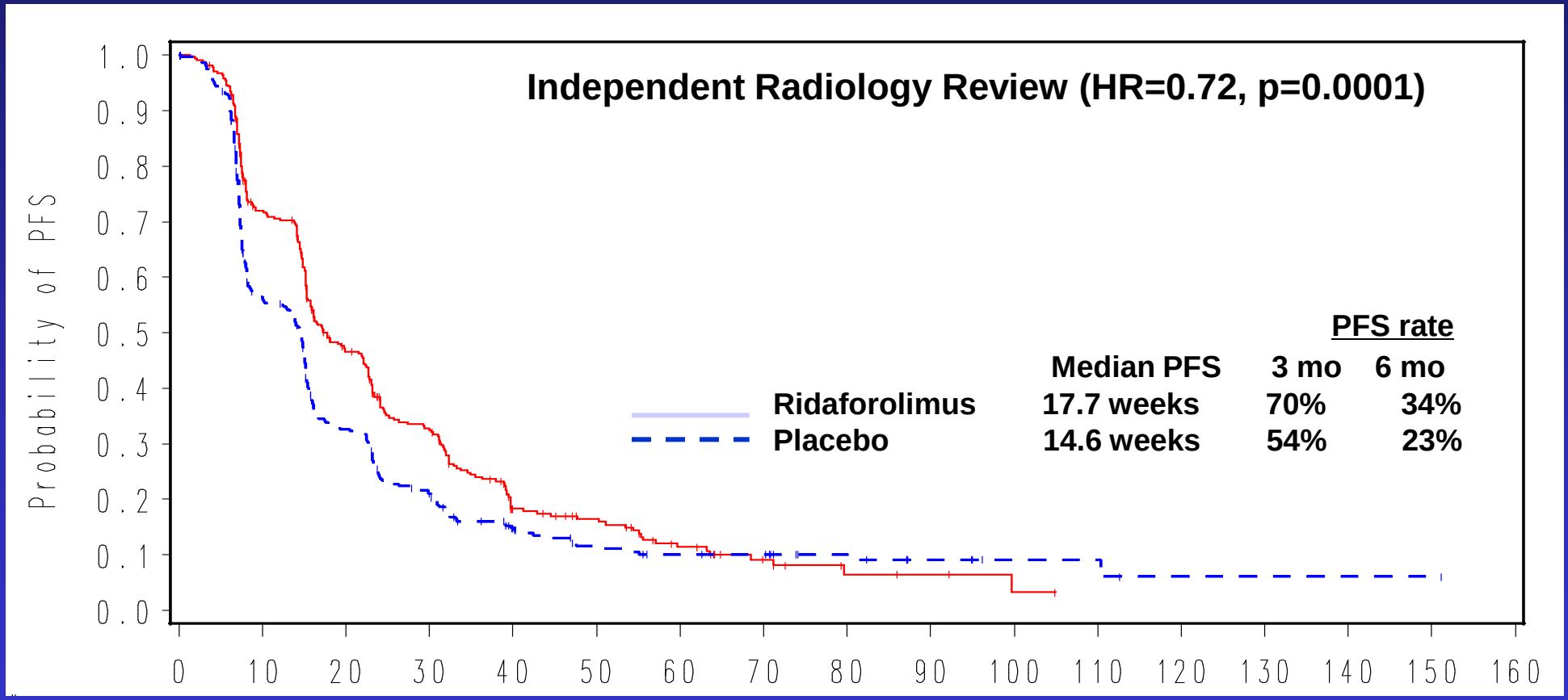




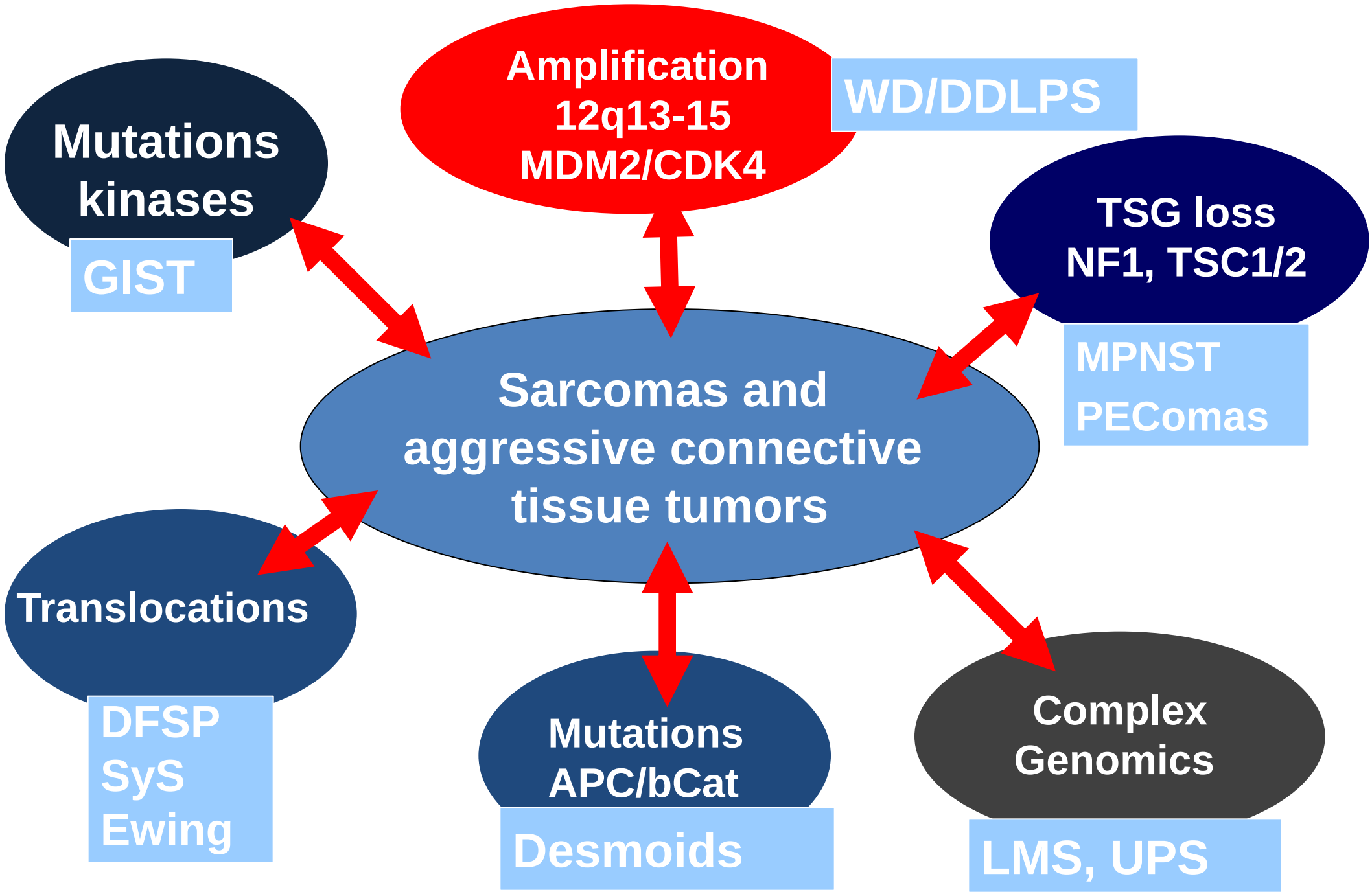
Maintenance treatment
SUCCEED : Ridaforolimus in maintenance



Ridaforolimus as maintenance in advanced soft tissue sarcomas



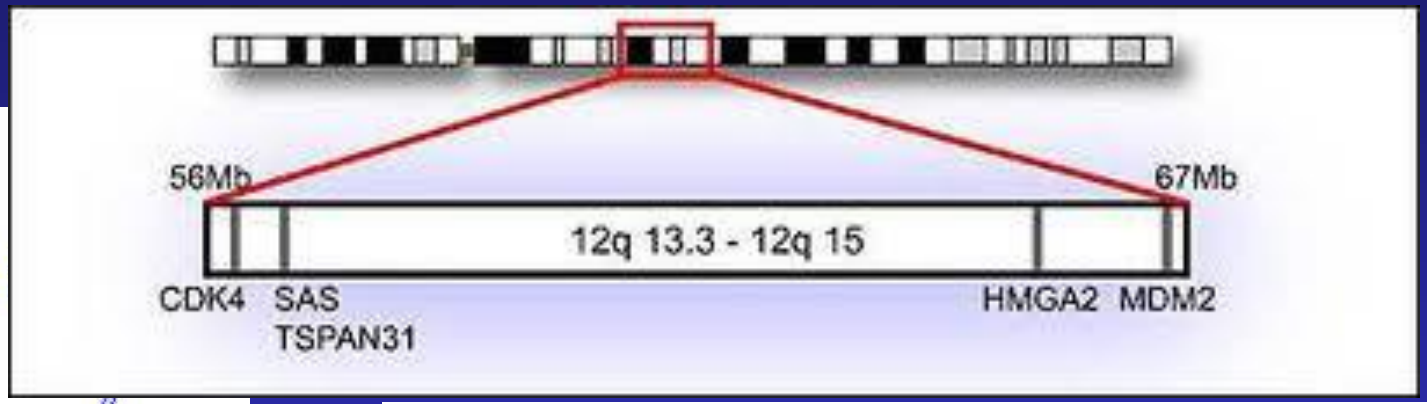
Demetri et al; JCO 2013

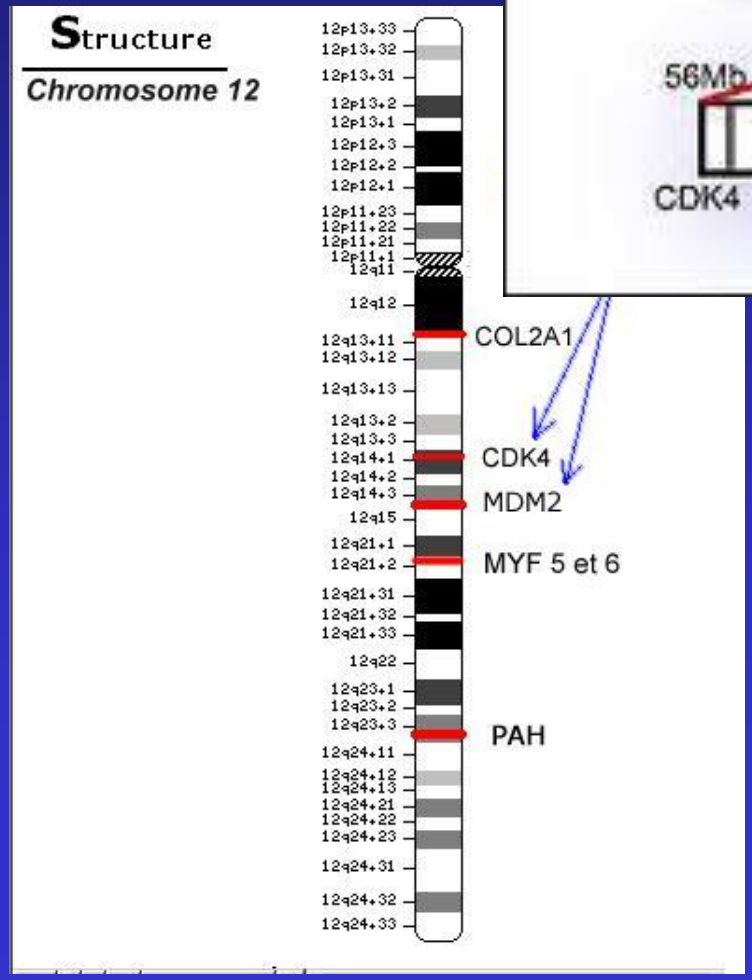

Amplification
12q13-15
MDM2/CDK4
WD/DDLPS
Mutations
kinases
GIST
TSG loss
NF1, TSC1/2
MPNST
PEComas
Sarcomas and
aggressive connective
tissue tumors
Translocations
DFSP
SyS
Ewing
Mutations
APC/bCat
Desmoids
Complex
Genomics
LMS, UPS

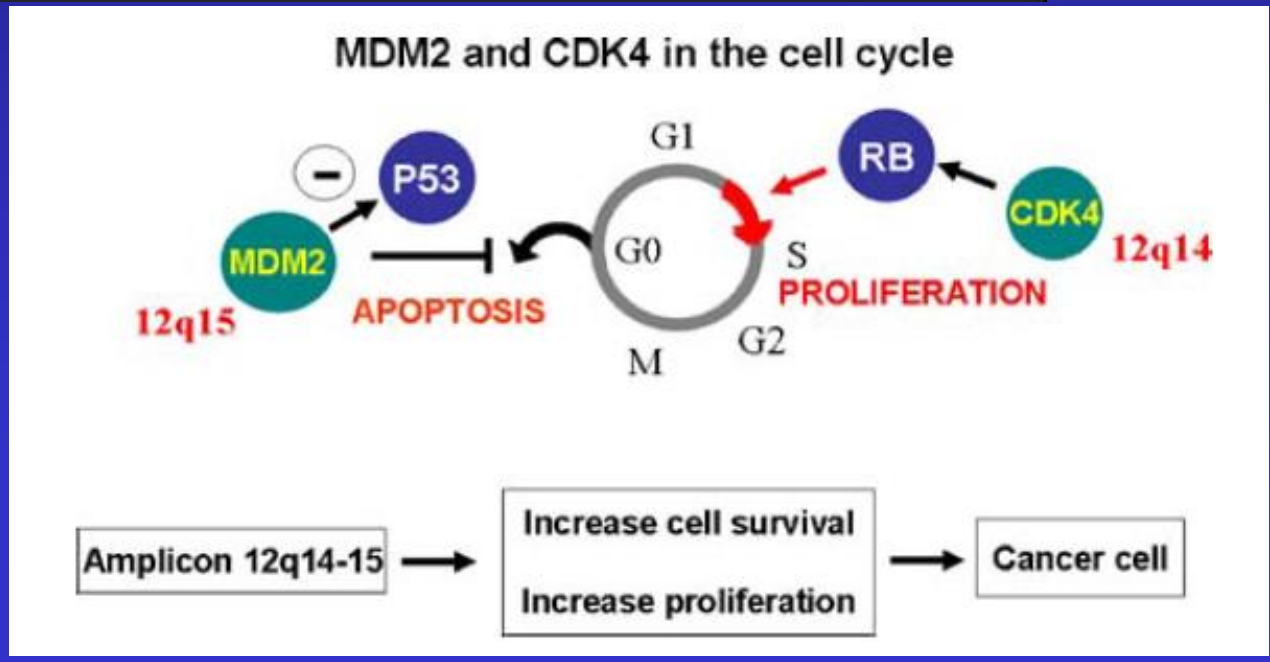
ESMO 2014

Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with *MDM2*-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study

Isabelle Ray-Coquard, Jean-Yves Blay, Antoine Italiano, Axel Le Cesne, Nicolas Penel, Jianguo Zhi, Florian Heil, Ruediger Rueger, Bradford Graves, Meichun Ding, David Geho, Steven A Middleton, Lyubomir T Vassilev, Gwen L Nichols, Binh Nguyen Bui







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],

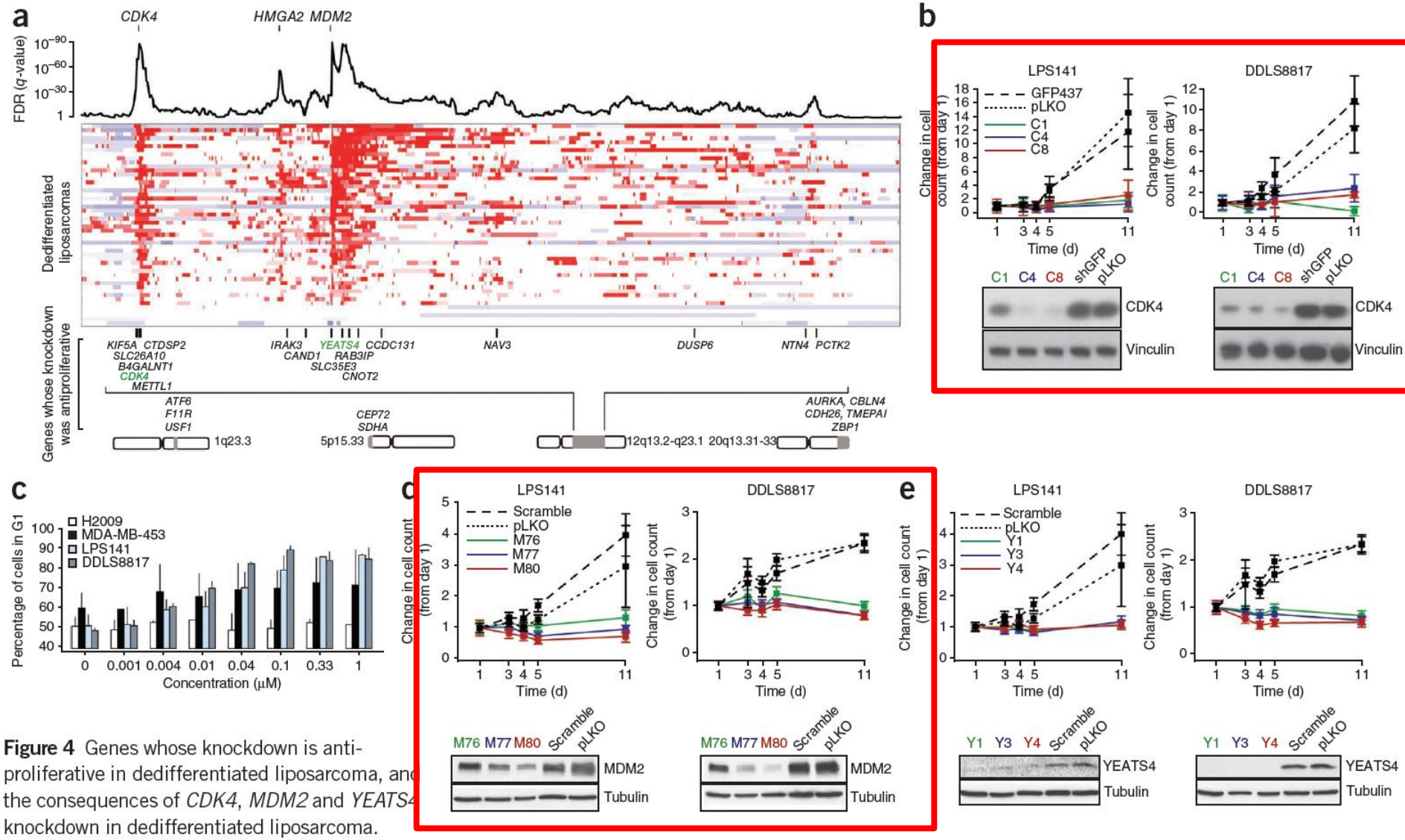


Figure 4 Genes whose knockdown is anti-proliferative in dedifferentiated liposarcoma, and the consequences of *CDK4*, *MDM2* and *YEATS4* knockdown in dedifferentiated liposarcoma.

Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with *MDM2*-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study

Lancet Oncol 2012; 13: 1133–40

Isabelle Ray-Coquard, Jean-Yves Blay, Antoine Italiano, Axel Le Cesne, Nicolas Penel, Jianguo Zhi, Florian Heil, Ruediger Rueger, Bradford Graves, Meichun Ding, David Geho, Steven A Middleton, Lyubomir T Vassilev, Gwen L Nichols, Binh Nguyen Bui

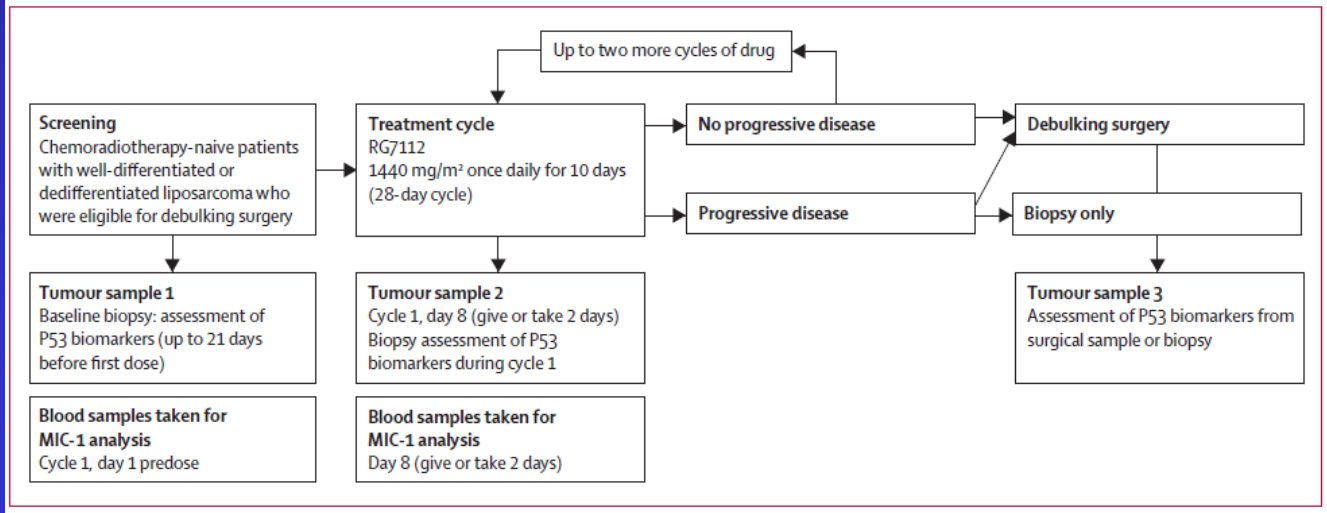


Figure 1: Study design

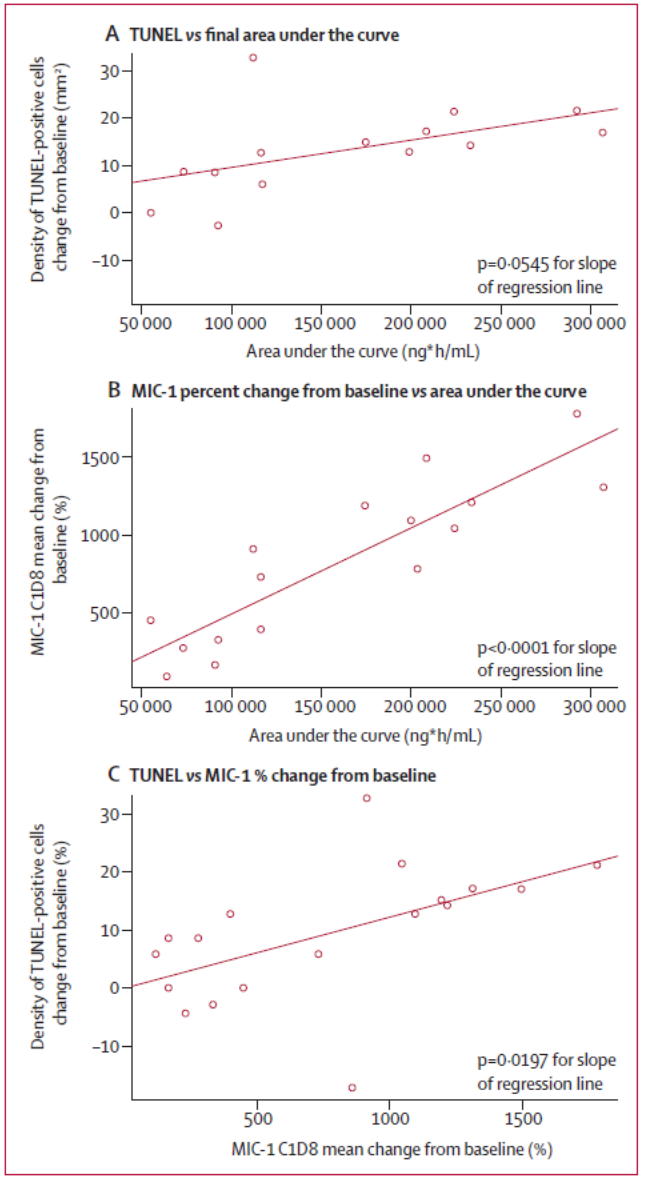
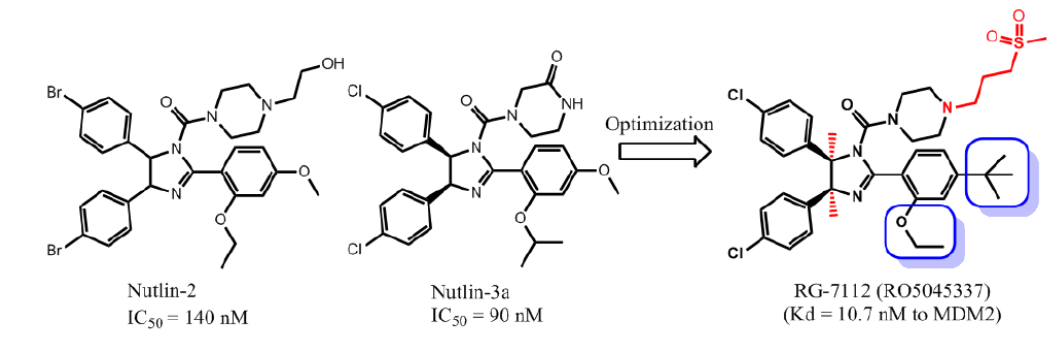


Figure 3: Phamacokinetic and pharmacodynamic data

MDM2/p53 inhibitors

- RG7112 & RO5503781 (Roche)
- CGM097 (Novartis)
- MI-888 & SAR405838 (Sanofi)
- MK-8242 (Merck)
- DS-3032b (Daichii)
- AMG232 (Amgen)



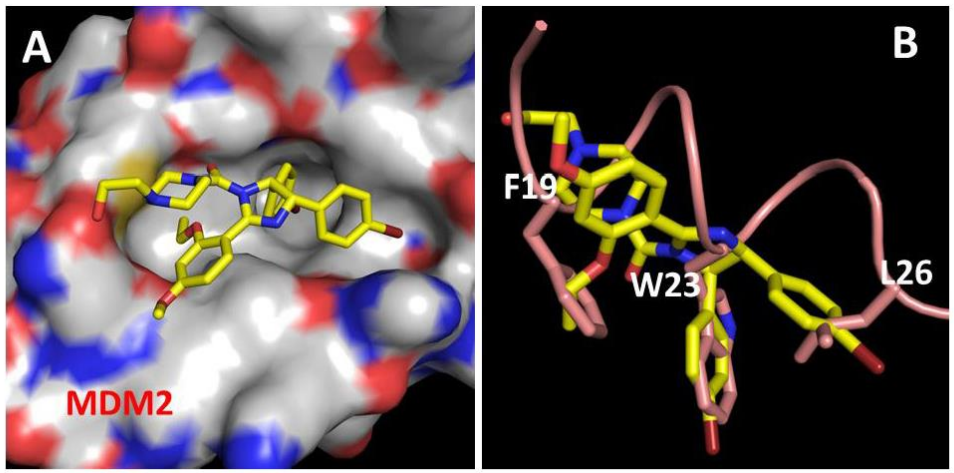


Figure 3. A) Crystal structure of nutlin-2 (shown as sticks) and MDM2 (PDB: 1RV1). B) Aligned orientation of p53 and Nutlin-3a. p53 residues essential for interaction are shown as sticks.

CDK4 and WD/DD liposarcomas

- 90% amplification
- >10x overexpression of the proteins
- Detectable by IHC : diagnostic tool
- shRNA block LPS proliferation
- PD-0332991
  - Activity in xenograft models
  - Long term PFS in phase I for LPS patients

Phase II Trial of the CDK4 Inhibitor PD0332991 in Patients With Advanced *CDK4*-Amplified Well-Differentiated or Dedifferentiated Liposarcoma

Mark A. Dickson, William D. Tap, Mary Louise Keohan, Sandra P. D'Angelo, Mrinal M. Gounder, Cristina R. Antonescu, Jonathan Landa, Li-Xuan Qin, Dustin D. Rathbone, Mercedes M. Condy, Yelena Ustoyev, Aimee M. Crago, Samuel Singer, and Gary K. Schwartz

ESMO 2014

VOLUME 31 · NUMBER 16 · JUNE 1 2013

JOURNAL OF CLINICAL ONCOLOGY

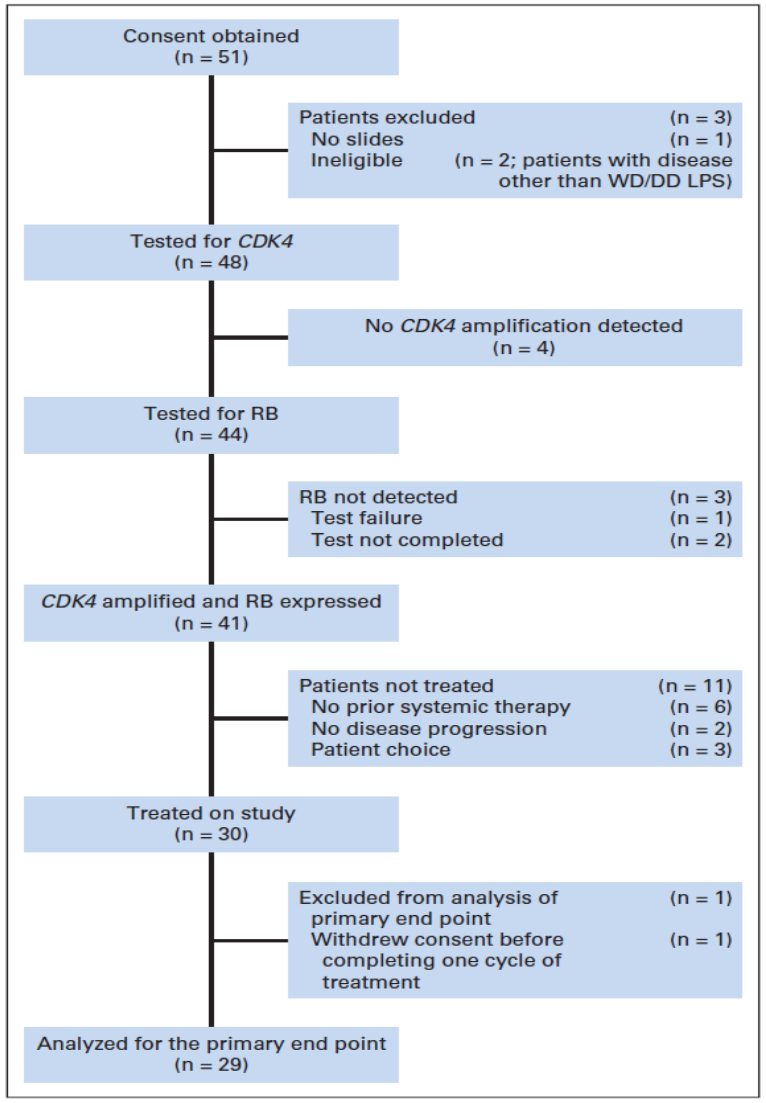


Fig 1. Diagram showing flow of patients and testing for *CDK4* and retinoblastoma protein (RB). DD, dedifferentiated; LPS, liposarcoma; WD, well differentiated.

Table 1. Demographic and Clinical Characteristics of Patients Treated With PD0332991 (n = 30)

Characteristic	No.	%
Sex		
Male	16	52
Female	14	48
Age, years		
Median	65	
Range	37-83	
ECOG PS		
0	20	67
1	10	33
Primary site		
Retroperitoneum	29	97
Extremity	1	3
Histology		
Well differentiated	5	17
Dedifferentiated	25	83
No. of prior systemic treatments		
Median	1	
Range	1-5	
Prior systemic treatments		
Doxorubicin or liposomal doxorubicin	19	
Gemcitabine	4	
Gemcitabine and docetaxel	4	
Ifosfamide	5	
Trabectedin	3	
Other cytotoxics (dacarbazine, cyclophosphamide, irinotecan)	3	
Other targeted agents (imatinib, sunitinib, brivanib, flavopiridol, and inhibitors of notch, hedgehog, MDM2)	18	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MDM2, mouse double minute 2 homolog.

Phase II Trial of the CDK4 Inhibitor PD0332991 in Patients With Advanced *CDK4*-Amplified Well-Differentiated or Dedifferentiated Liposarcoma

Mark A. Dickson, William D. Tap, Mary Louise Keohan, Sandra P. D'Angelo, Mrinal M. Gounder, Cristina R. Antonescu, Jonathan Landa, Li-Xuan Qin, Dustin D. Rathbone, Mercedes M. Condy, Yelena Ustoyev, Aimee M. Crago, Samuel Singer, and Gary K. Schwartz

ESMO 2014

VOLUME 31 · NUMBER 16 · JUNE 1 2013

JOURNAL OF CLINICAL ONCOLOGY

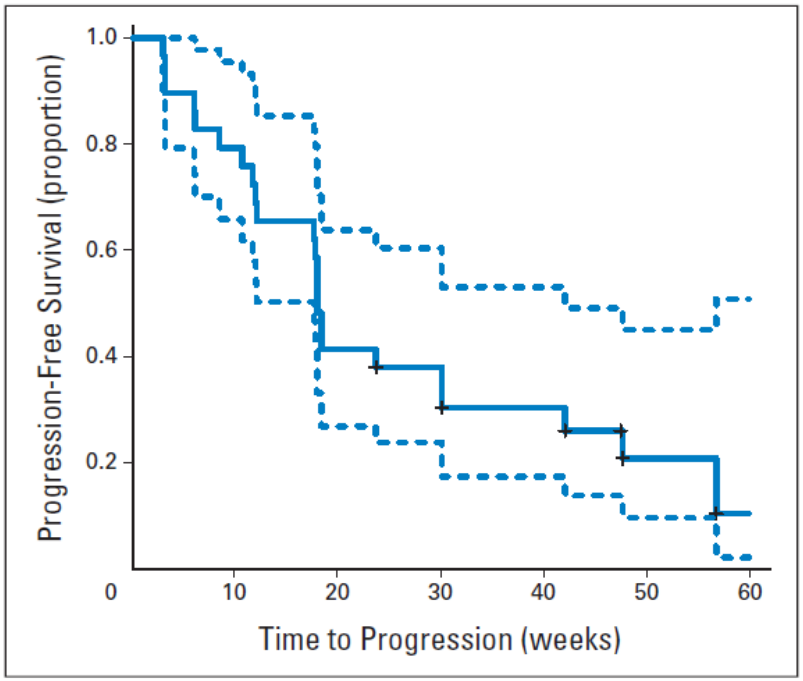


Fig 2. Kaplan-Meier curve of progression-free survival. Dashed lines indicate 95% CI.

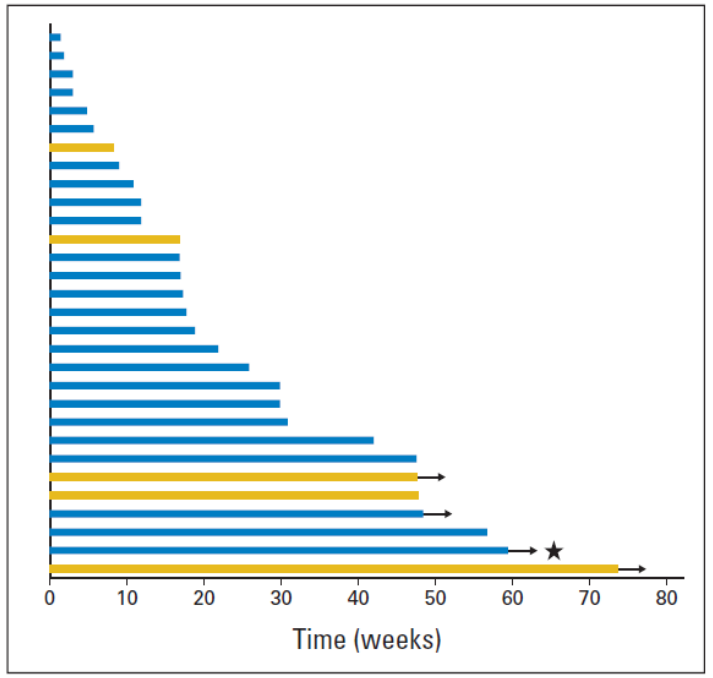


Fig 3. Time in study for all evaluable patients. Gold bars represent patients with purely well-differentiated liposarcoma; blue bars represent dedifferentiated tumors. Arrows indicate patients who remained in study at the data cutoff. Star indicates patient with partial response.

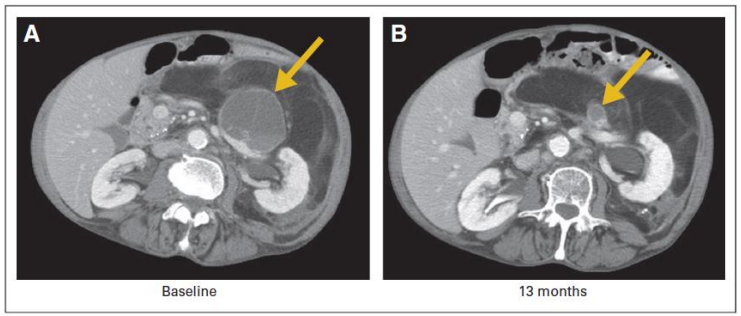
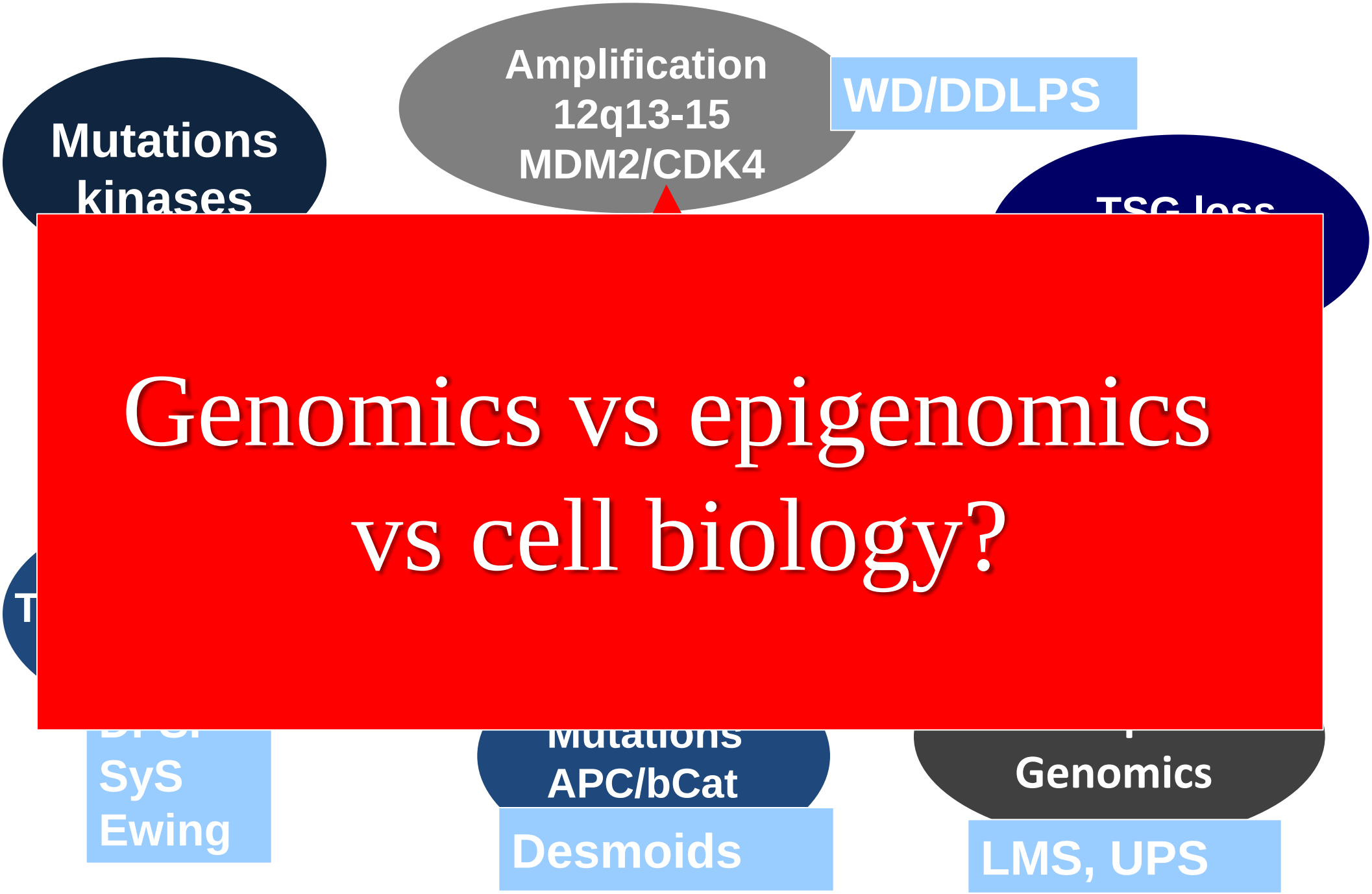


Fig 4. Computed tomography scans at (A) baseline and (B) after 13 months of treatment with PD0332991, demonstrating favorable tumor response (arrows) in dedifferentiated liposarcoma surrounded by well-differentiated liposarcoma.


Amplification
12q13-15
MDM2/CDK4
WD/DDLPS
Mutations
kinases
TSG loss
Genomics vs epigenomics
vs cell biology?
SyS
Ewing
Mutations
APC/bCat
Desmoids
Genomics
LMS, UPS

Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study

David Thomas, Robert Henshaw, Keith Skubitz, Sant Chawla, Arthur Staddon, Jean-Yves Blay, Martine Roudier, Judy Smith, Zhishen Ye, Winnie Sohn, Roger Dansey, Susie Jun

www.thelancet.com/oncology **Published online February 10, 2010** DOI:10.1016/S1470-2045(10)70010-3

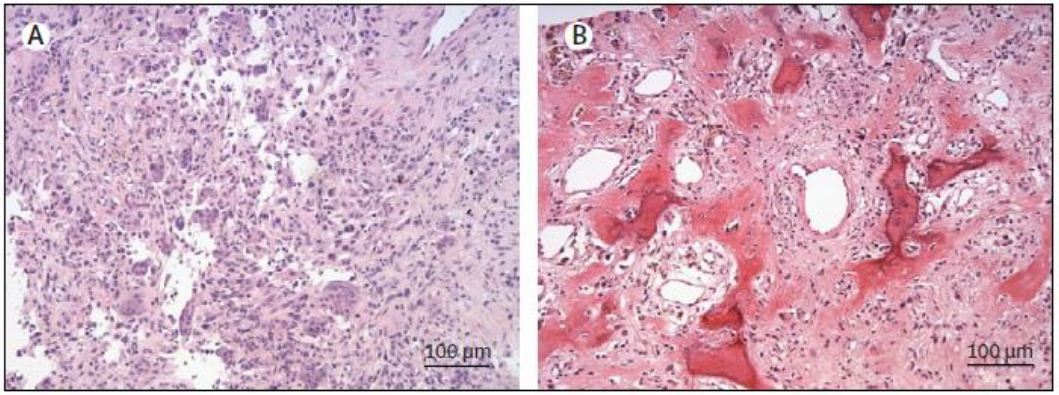


Figure 1: **Pretreatment (A) and week 13 post-treatment biopsy (B)**
Cells stained with haematoxylin and eosin.

Among the 31 patients with baseline and post-dose investigator assessments of clinical response (made at various stages of treatment), investigators reported that 26 patients (84%; 66–95) experienced clinical benefit (ie, reduced pain or improvement in functional status) and nine patients (29%; 14–48) had bone repair.

…followed by a phase II trial with >500 patients

Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study

Sant Chawla, Robert Henshaw, Leanne Seeger, Edwin Choy, Jean-Yves Blay, Stefano Ferrari, Judith Kroep, Robert Grimer, Peter Reichardt, Piotr Rutkowski, Scott Schuetze, Keith Skubitz, Arthur Staddon, David Thomas, Yi Qian, Ira Jacobs

Published Online
July 16, 2013
http://dx.doi.org/10.1016/S1470-2045(13)70277-8
See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(13)70291-2

ESMO 2014

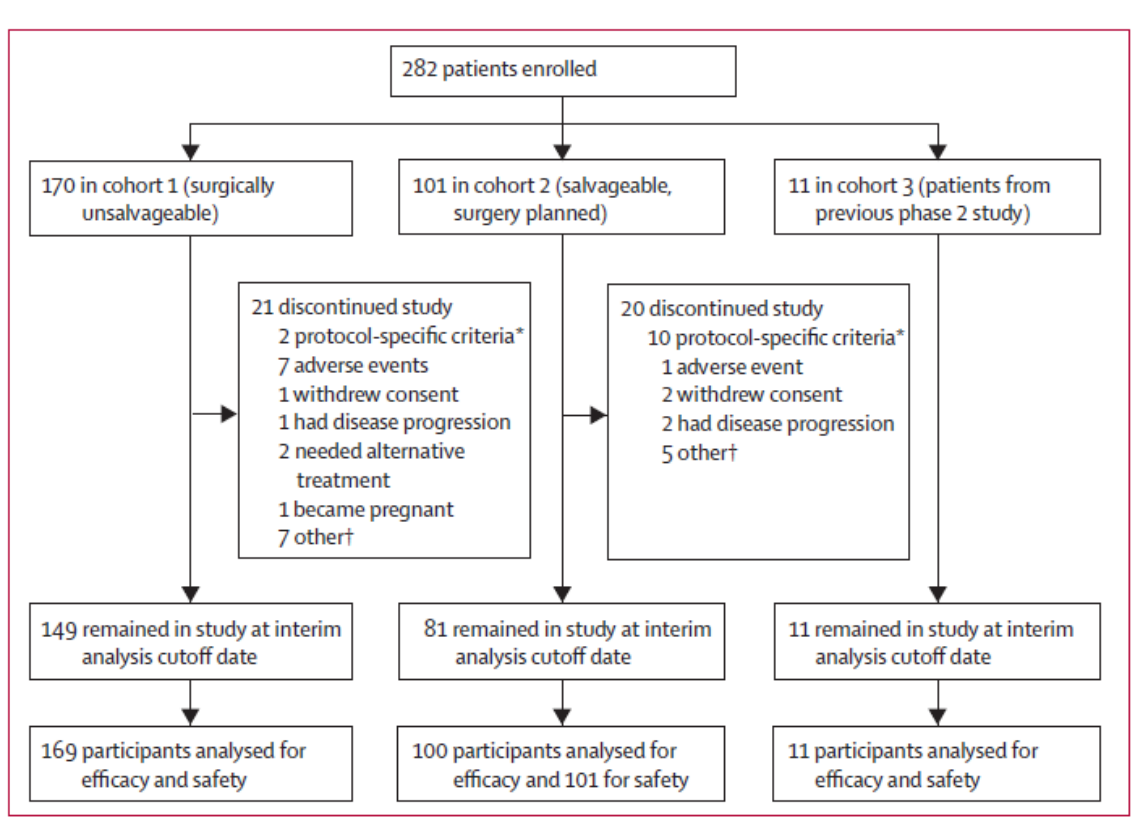


Figure 1: Trial profile

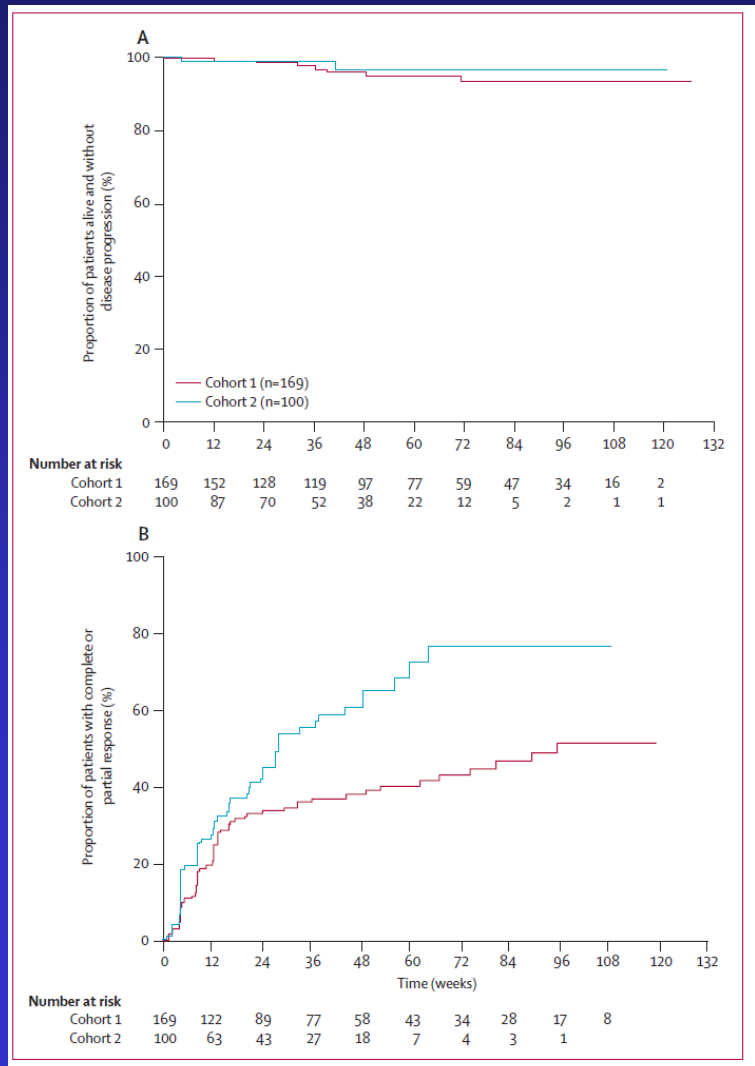


Figure 2: Kaplan-Meier graphs of investigator-determined progression-free survival (A) and time to complete or partial response (B) in patients with surgically unsalvageable disease (cohort 1) and salvageable

Distinct *H3F3A* and *H3F3B* driver mutations define chondroblastoma and giant cell tumor of bone

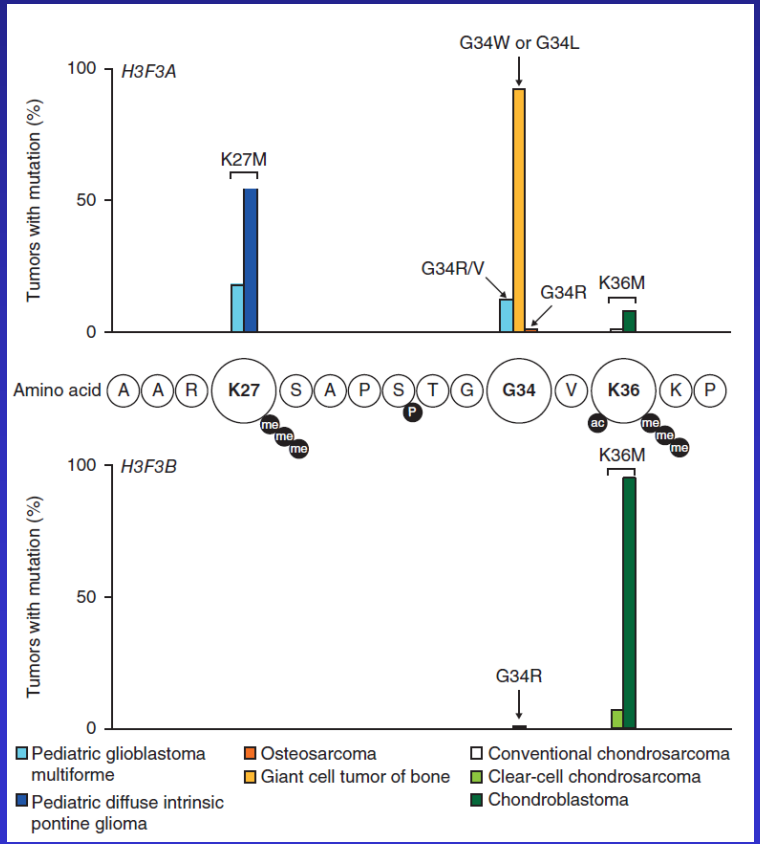
Sam Behjati[1,2,12], Patrick S Tarpey[1,12], Nadège Presneau[3,4], Susanne Scheipl[3,5], Nischalan Pillay[3,6], Peter Van Loo[1,7], David C Wedge[1], Susanna L Cooke[1], Gunes Gundem[1], Helen Davies[1], Serena Nik-Zainal[1], Sancha Martin[1], Stuart McLaren[1], Victoria Goodie[1], Ben Robinson[1], Adam Butler[1], Jon W Teague[1], Dina Halai[6], Bhavisha Khatri[6], Ola Myklebost[8], Daniel Baumhoer[9], Gernot Jundt[9], Rifat Hamoudi[3,4], Roberto Tirabosco[6], M Fernanda Amary[6], P Andrew Futreal[1], Michael R Stratton[1], Peter J Campbell[1,10,11] & Adrienne M Flanagan[3,4,6]

nature genetics

Table 2 Histone H3.3 somatic alterations in bone and cartilage tumors

			H3F3A					*H3F3B*	
Tumor type	Number screened	Number mutated	Gly34Leu	Gly34Arg	Gly34Val	Gly34Trp	Lys36Met	Gly34Arg	Lys36Met
Chondroblastoma	77	73 (95%)					5		68
Giant cell tumor of bone	53	49 (92%)	1			48			
Clear-cell chondrosarcoma	15	1 (7%)							1
Osteosarcoma	103	2 (2%)		1				1	
Conventional chondrosarcoma	75	1 (1%)					1		
Chondromyxoid fibroma	43	0							
Chordoma	25	0							
Chondroma	7	0							

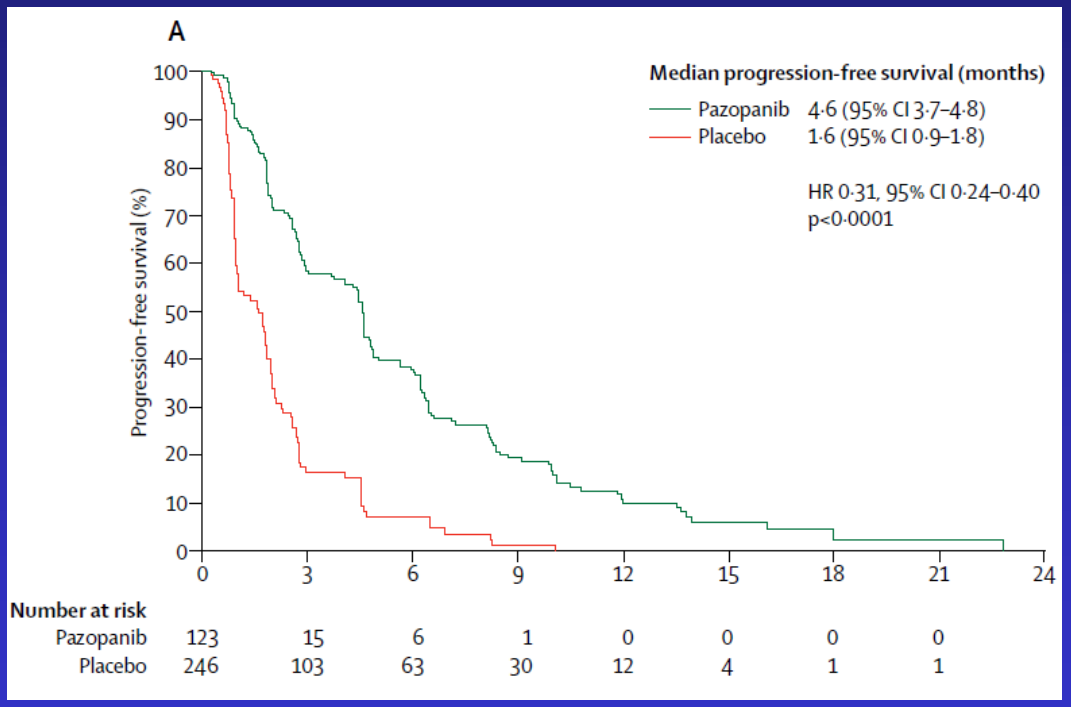
Prevalence of histone H3.3 alterations in eight different tumor types. p.Lys36Met and p.Gly34Trp alterations are mutually exclusive in chondroblastoma and giant cell tumor of bone ($P < 1 \times 10^{-15}$)

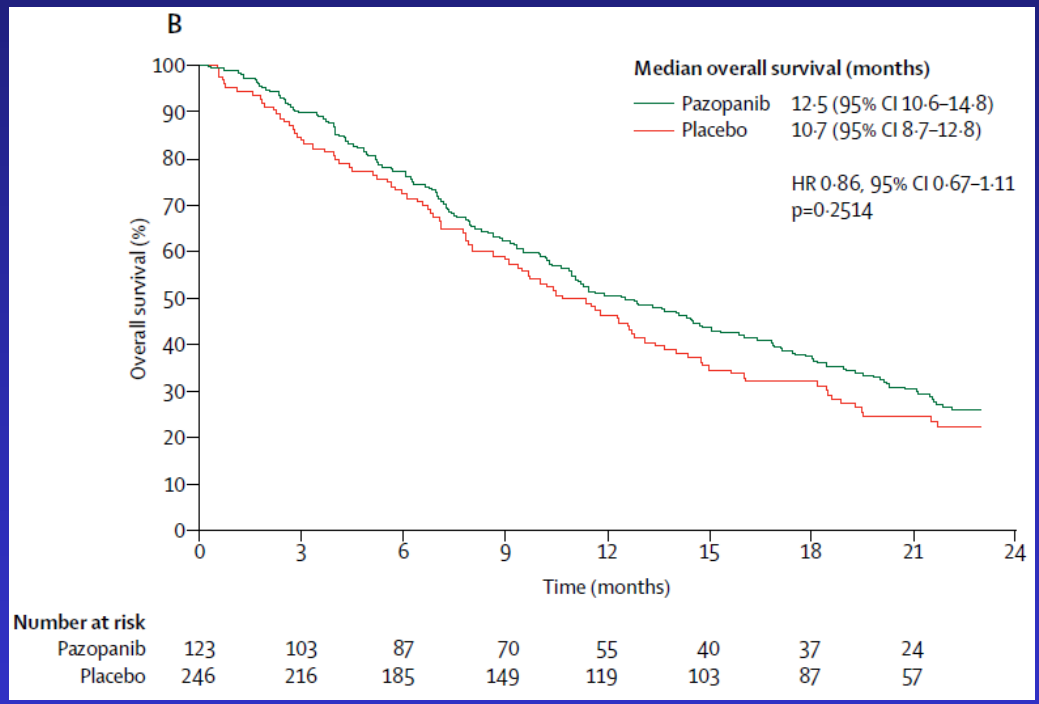


Passengers or weak drivers

Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

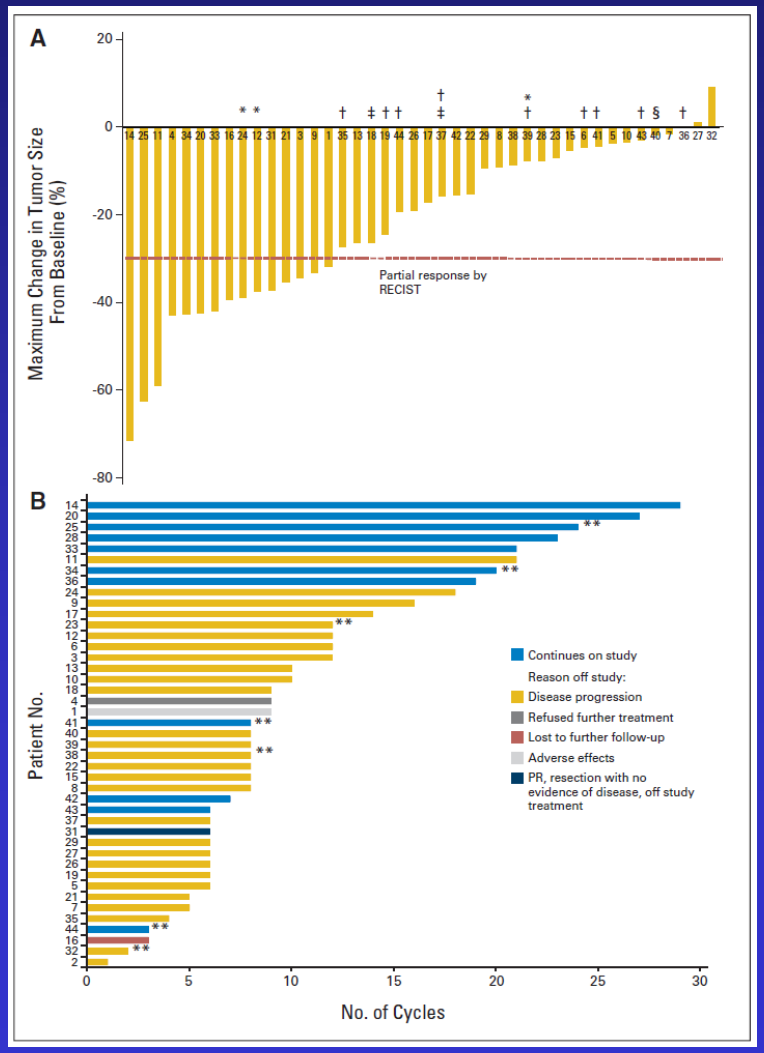
Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Corneel Coens, George D Demetri, Christopher D Fletcher, Angelo P Dei Tos, Peter Hohenberger, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group and the PALETTE study group





Cediranib for Metastatic Alveolar Soft Part Sarcoma

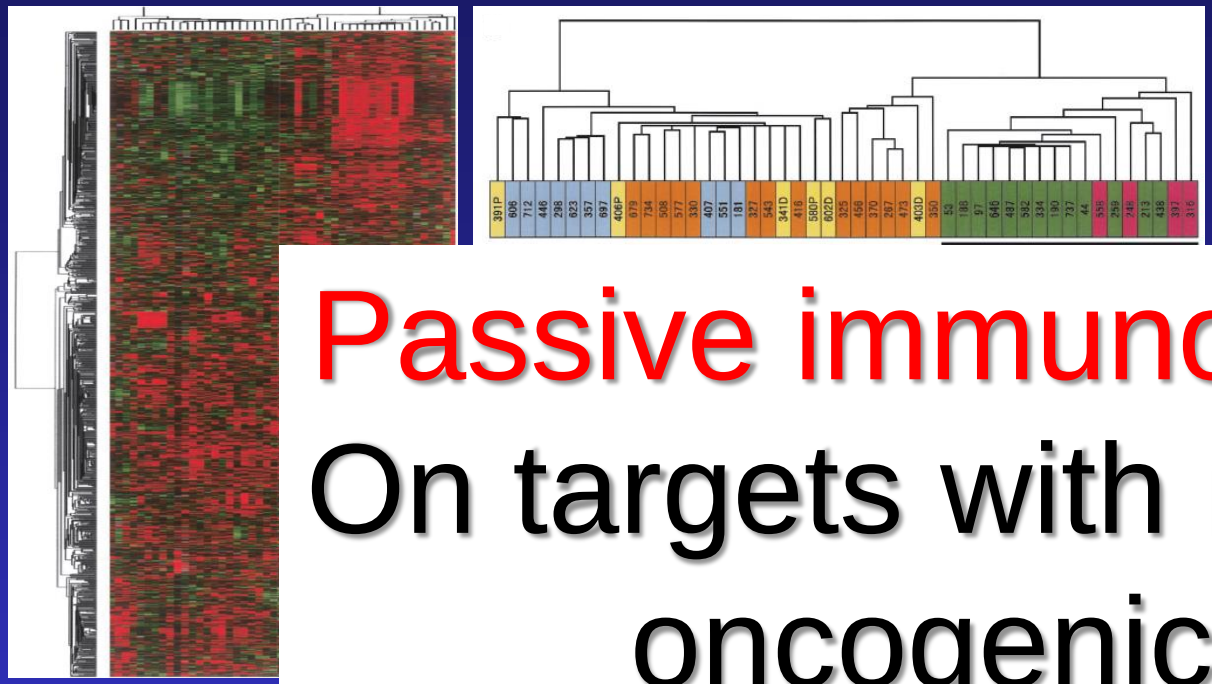
Shivaani Kummar, Deborah Allen, Anne Monks, Eric C. Polley, Curtis D. Hose, S. Percy Ivy, Ismail B. Turkbey, Scott Lawrence, Robert J. Kinders, Peter Choyke, Richard Simon, Seth M. Steinberg, James H. Doroshow, and Lee Helman



FZD10 is specifically up-regulated in synovial sarcoma

ESMO 2014

Genome-wide cDNA microarray of soft tissue sarcoma

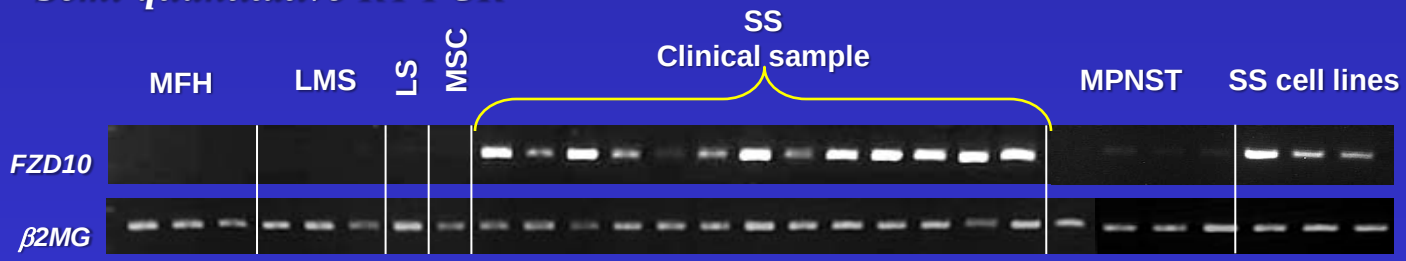


Frizzled Homologue 10 (FZD10)

Passive immunotherapy?

On targets with no known oncogenic role

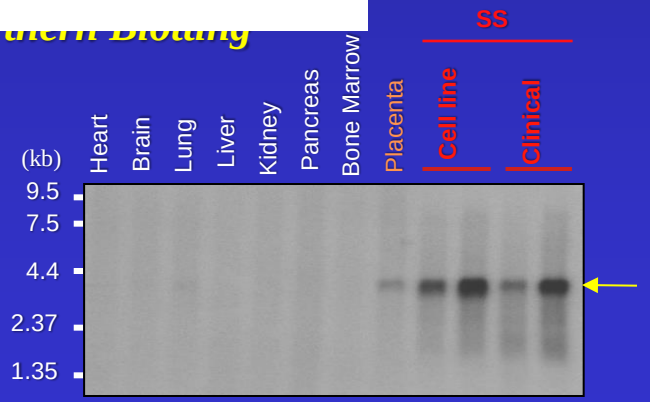
Semi-quantitative RT-PCR



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

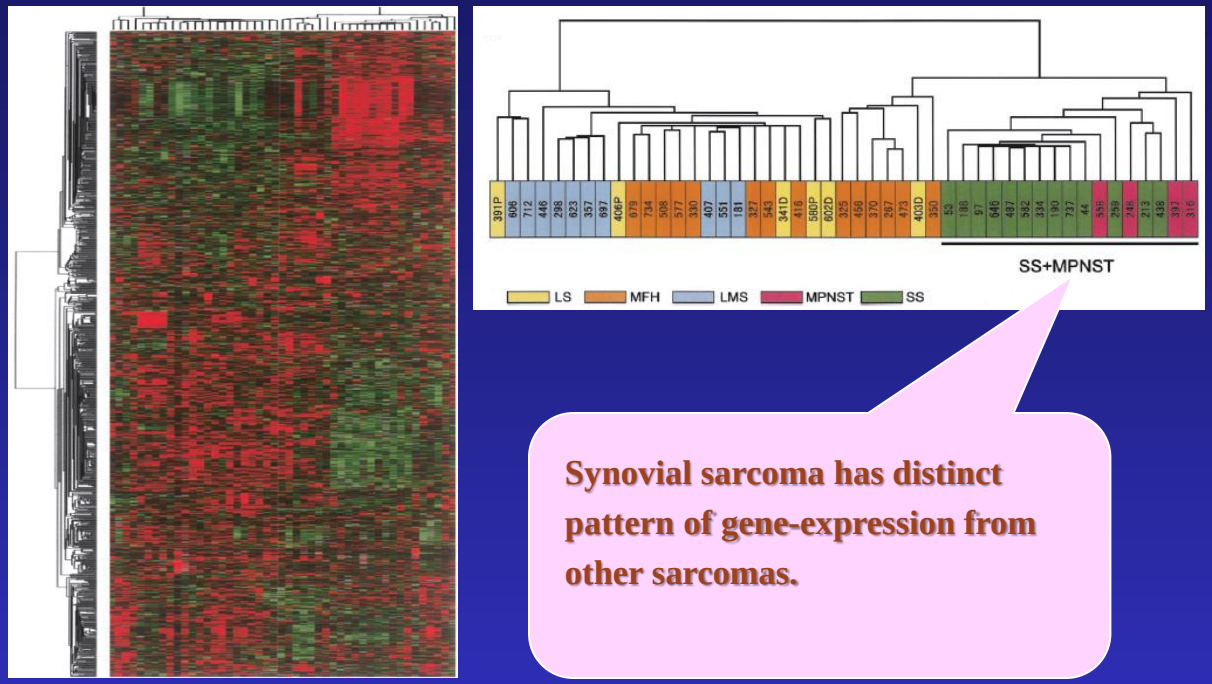


Nagayama et al., Oncogene 24, 6201-12 (2005)

FZD10 is specifically up-regulated in synovial sarcoma

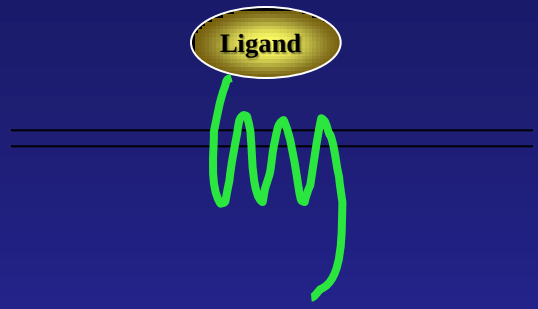
ESMO 2014

Genome-wide cDNA microarray of soft tissue sarcoma



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

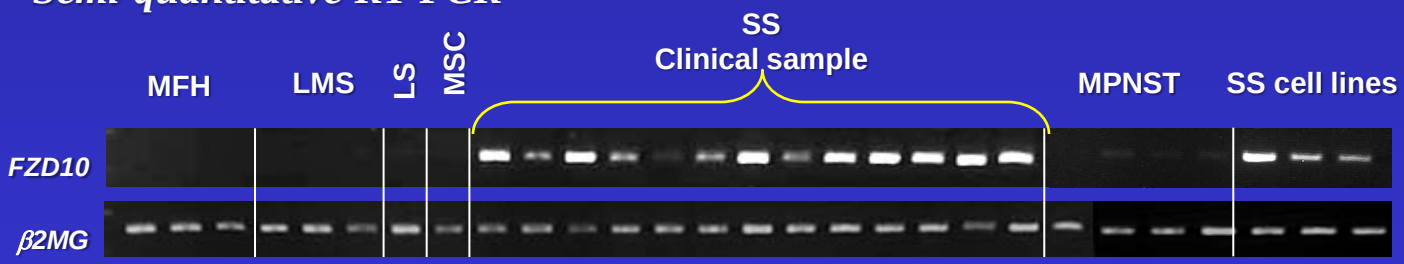
Frizzled Homologue 10 (FZD10)



Criteria for gene selection

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

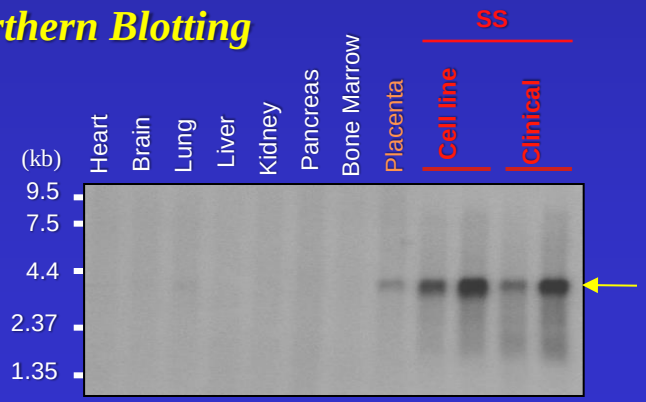
Semi-quantitative RT-PCR



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

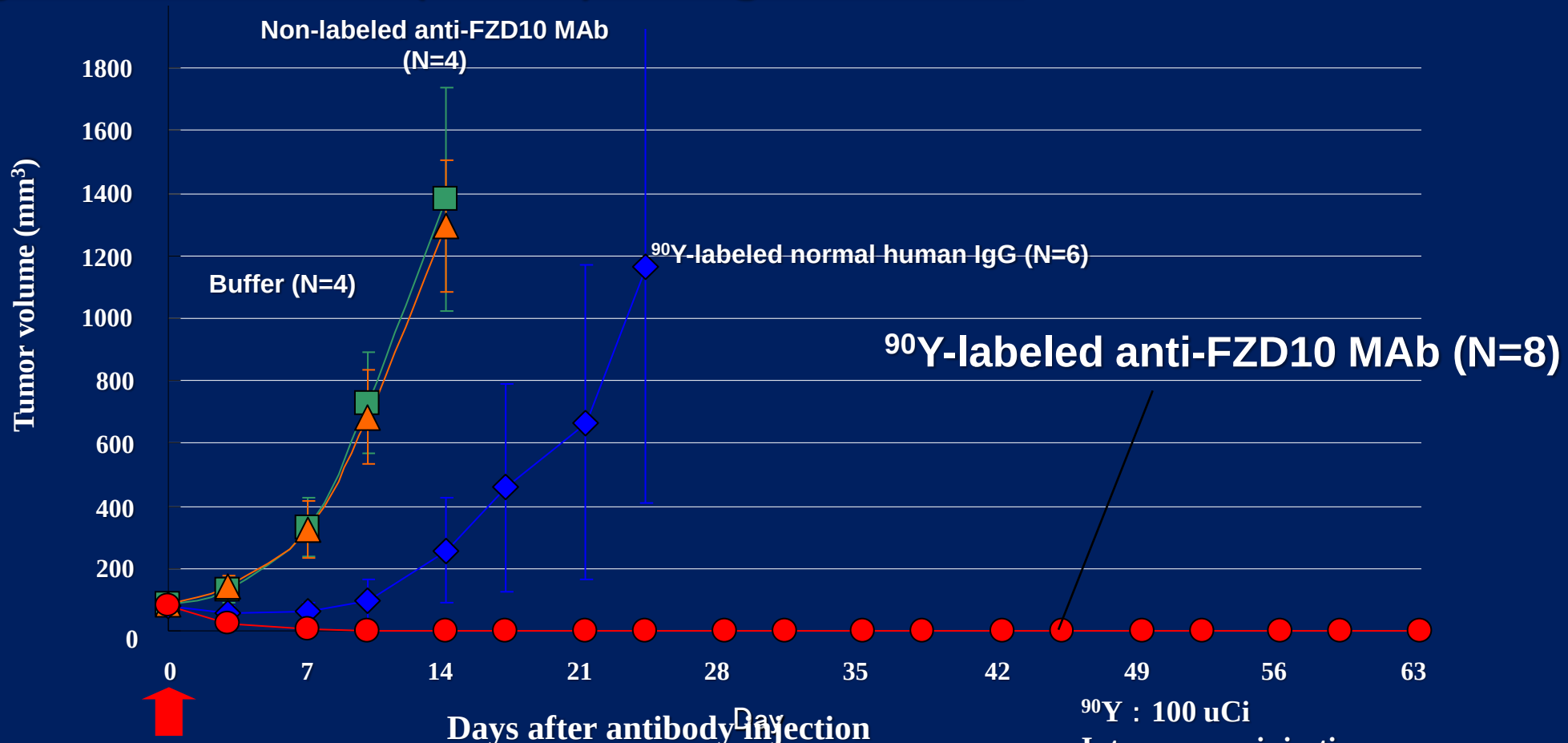


Nagayama et al., Oncogene 24, 6201-12 (2005)

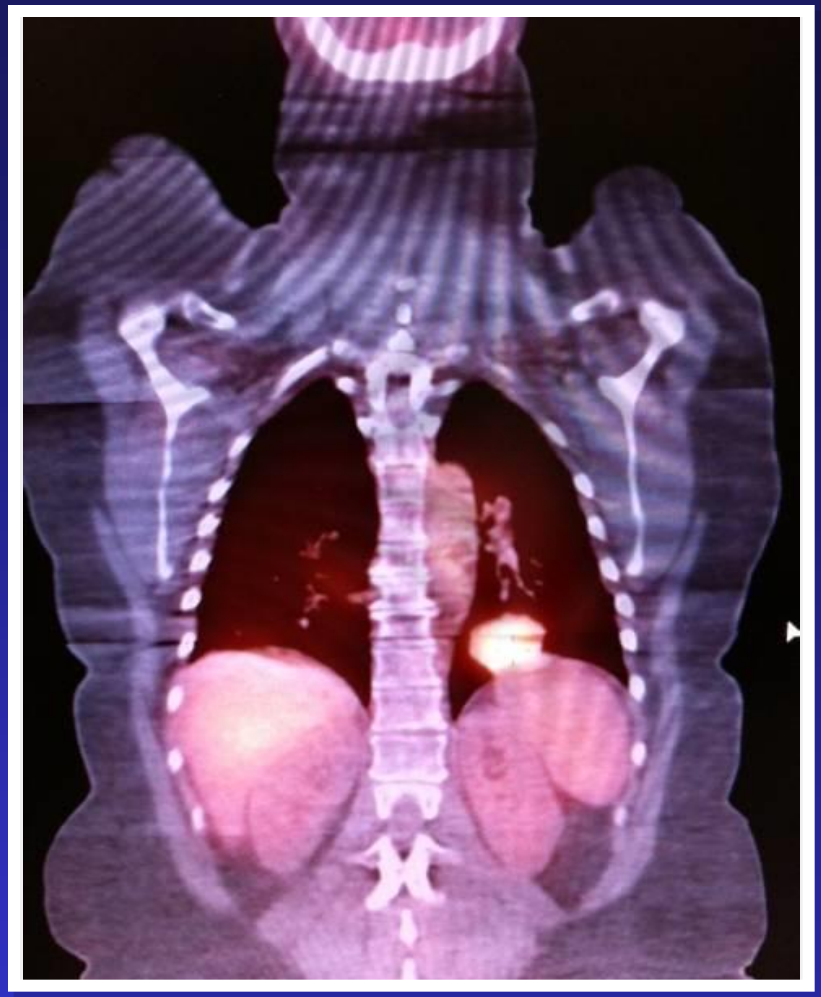
Antitumor activity of ^{90}Y-labeled anti-FZD10 MAb

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

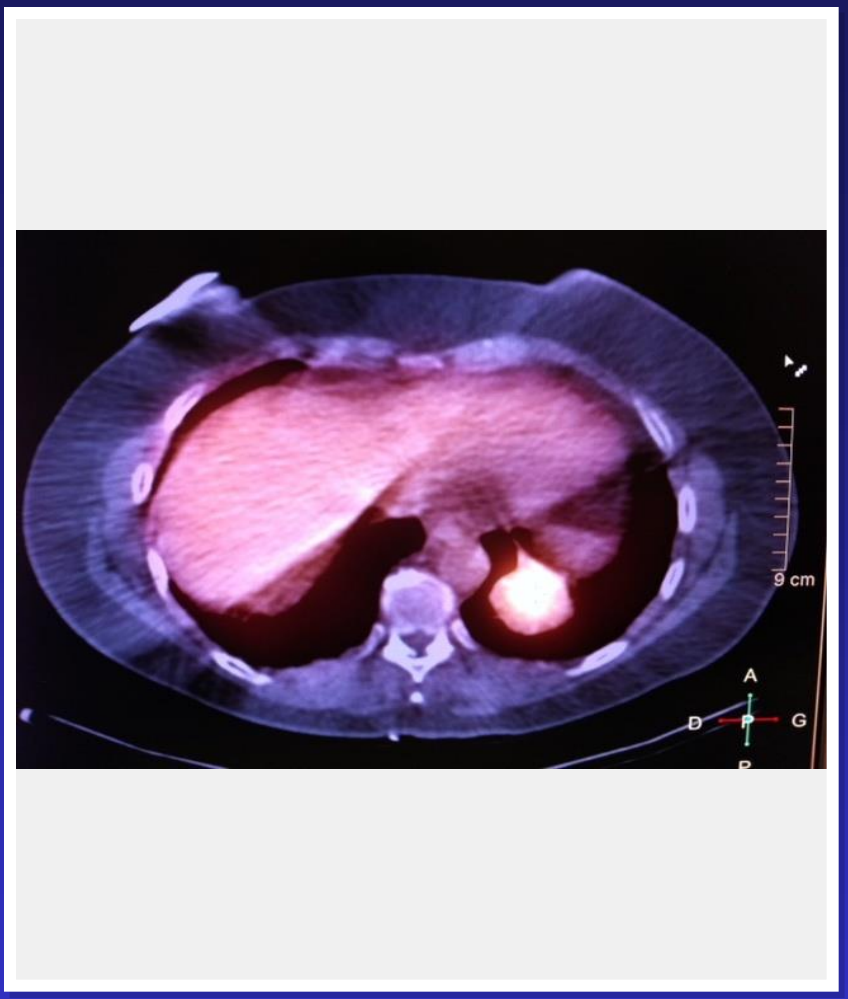
Synovial sarcoma (SYO-1) xenograft mouse



SYNFRIZZ Clinical Trial



Transversal image
24H uptake
Met1 has very good uptake



Distal image
24h uptake

Rapidly growing genomic informations

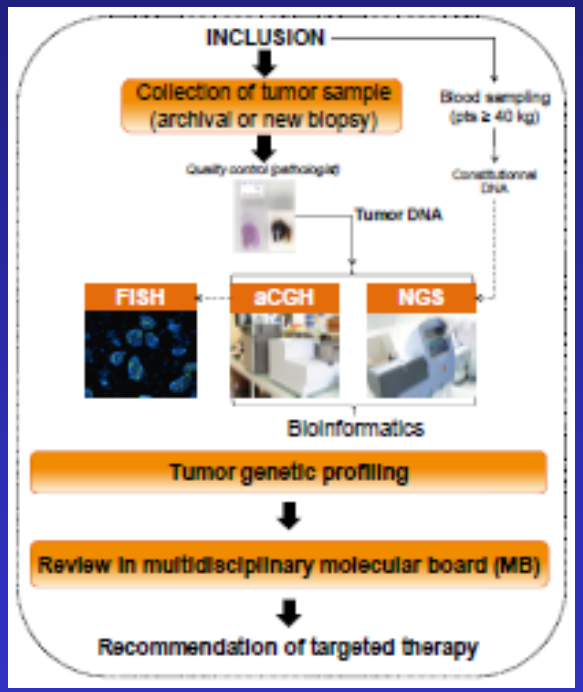
Identifying actionable targets in advanced cancer patients: Preliminary results from the ProfiLER program.

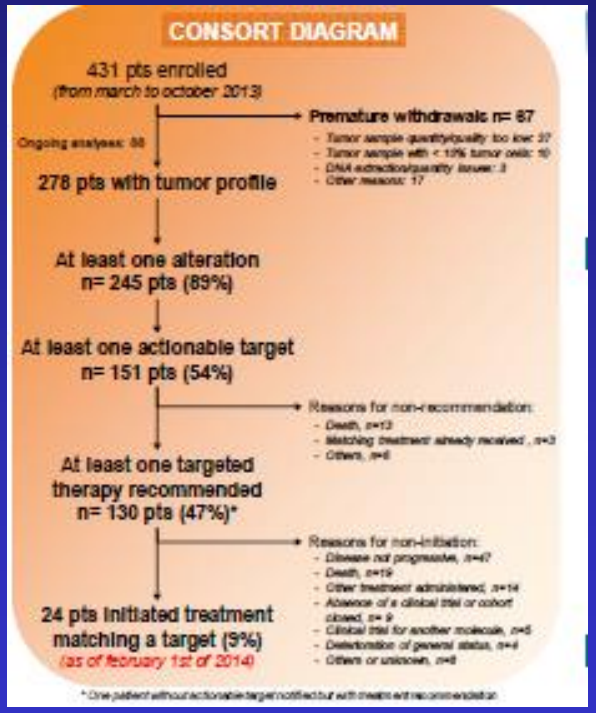
P. Cassier, O.Trédan, C. Seigne, E. Lavergne, J. Fayette, F. Desseigne, P. Biron, C. de la Fouchardière, I. Ray-Coquard, M. Pérol, D. Frappaz, M. Bernardin, Q. Wang, V. Attignon, D. Pissaloux, V. Combaret, V. Agrapart, M.E. Fondrevelle, D. Pérol, J.Y. Blay, Centre Léon Bérard, 28 rue Laennec, Lyon, France

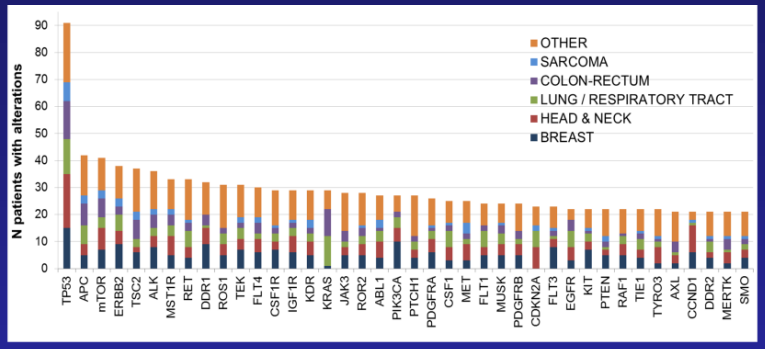
Funding: Grant INCa-4664 / CANOPEE program (Ligue contre le cancer de L'Ain)

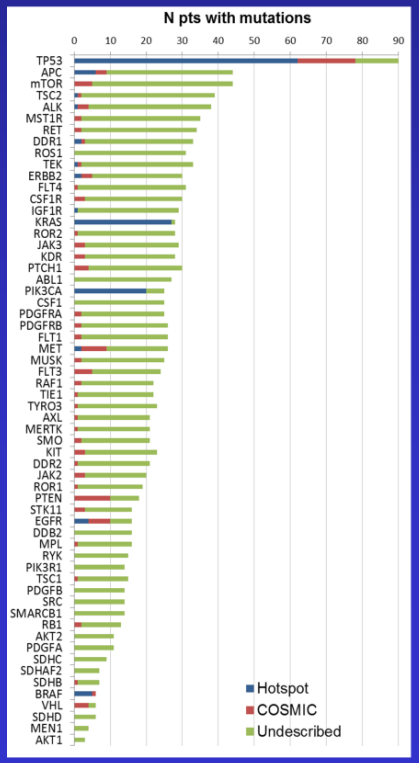
Acknowledgments to all investigators not cited in the authors, to Centre Léon Bérard's pathologists and technical staff (Biopathology department, Biological Ressources Center, molecular plateforms), to all public or private pathology structures sending tumor samples and to CRAs who collected clinical data.

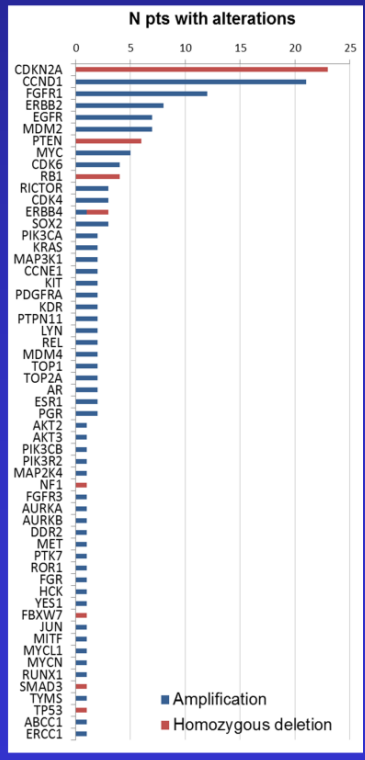
1. COSMIC database: http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/







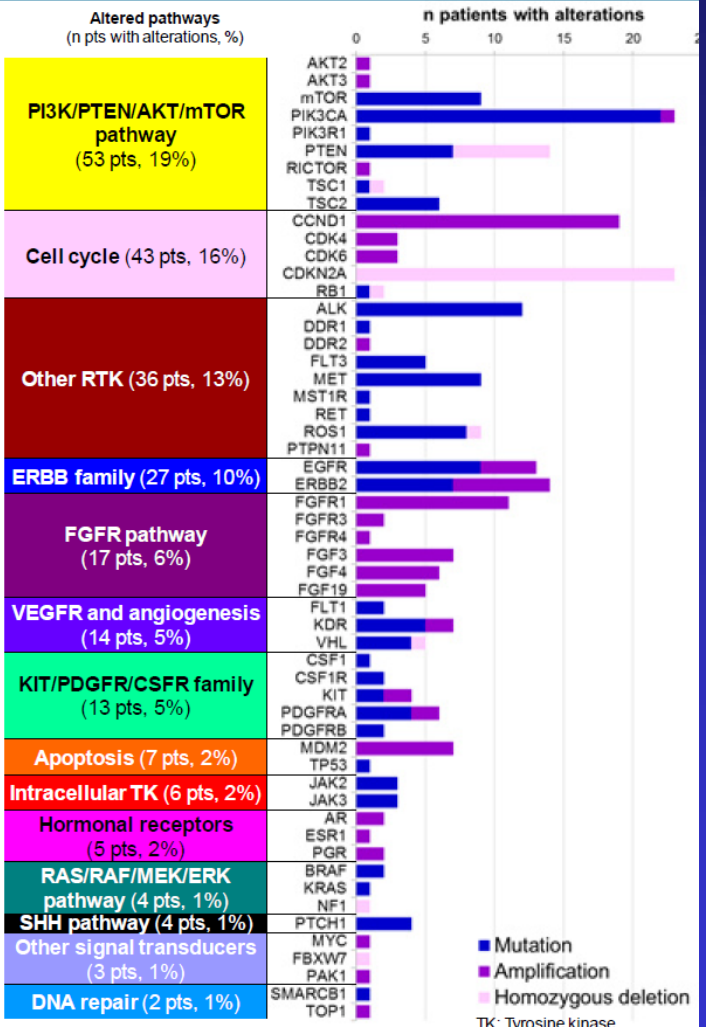




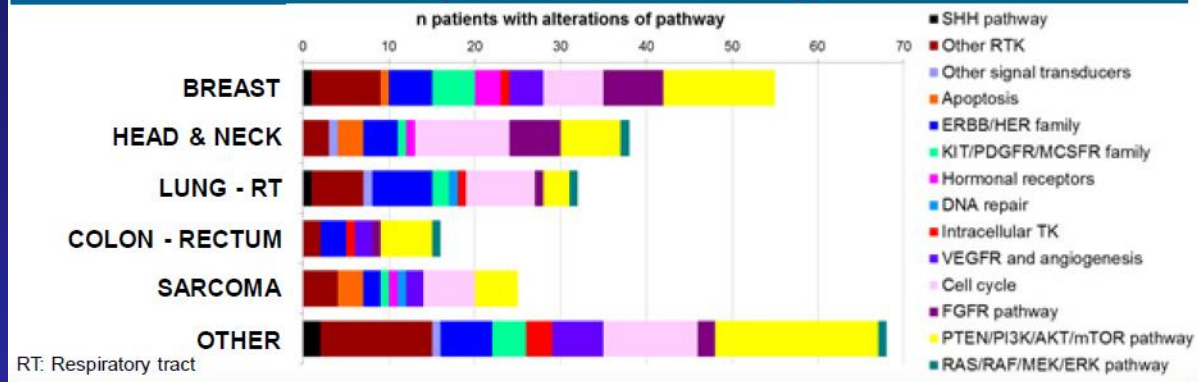
N=1053 patients as of Sept 2014 (single center)

Identifying actionable targets in advanced cancer patients: Preliminary results from the ProfiLER program.

Actionable genes/pathways and their alterations



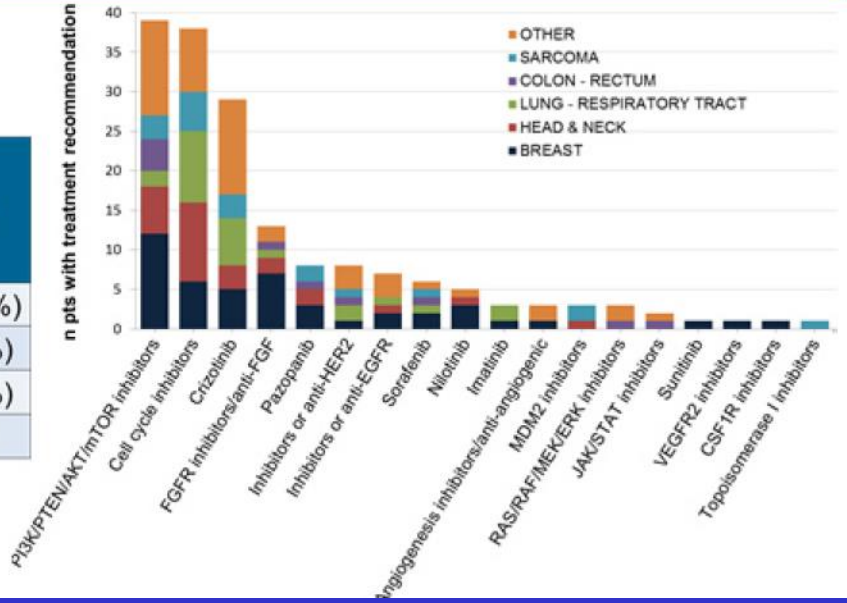
Pathways altered across tumor types



RT: Respiratory tract

Classes of targeted therapies recommended and tumor types

Nb of recommended targeted therapies/pt	n (%)
0	148 (53%)
1	94 (34%)
2	29 (10%)
3	7 (3%)



EORTC
European Organisation for Research and Treatment of Cancer

EORTC
Avenue E. Mounierlaan 83 / 11
Brussel 1200 Bruxelles
België - Belgique
Tel : +32 2 774 16 11
Fax : +32 2 772 35 45
E-mail : eortc@eortc.be
Web : http://www.eortc.be

EORTC Network of Core Institutions (NOCI)

Cross-tumoral phase 2 clinical trial exploring crizotinib (PF-02341066) in patients with advanced tumors induced by causal alterations of ALK and/or MET ("CREATE")

EORTC protocol 90101

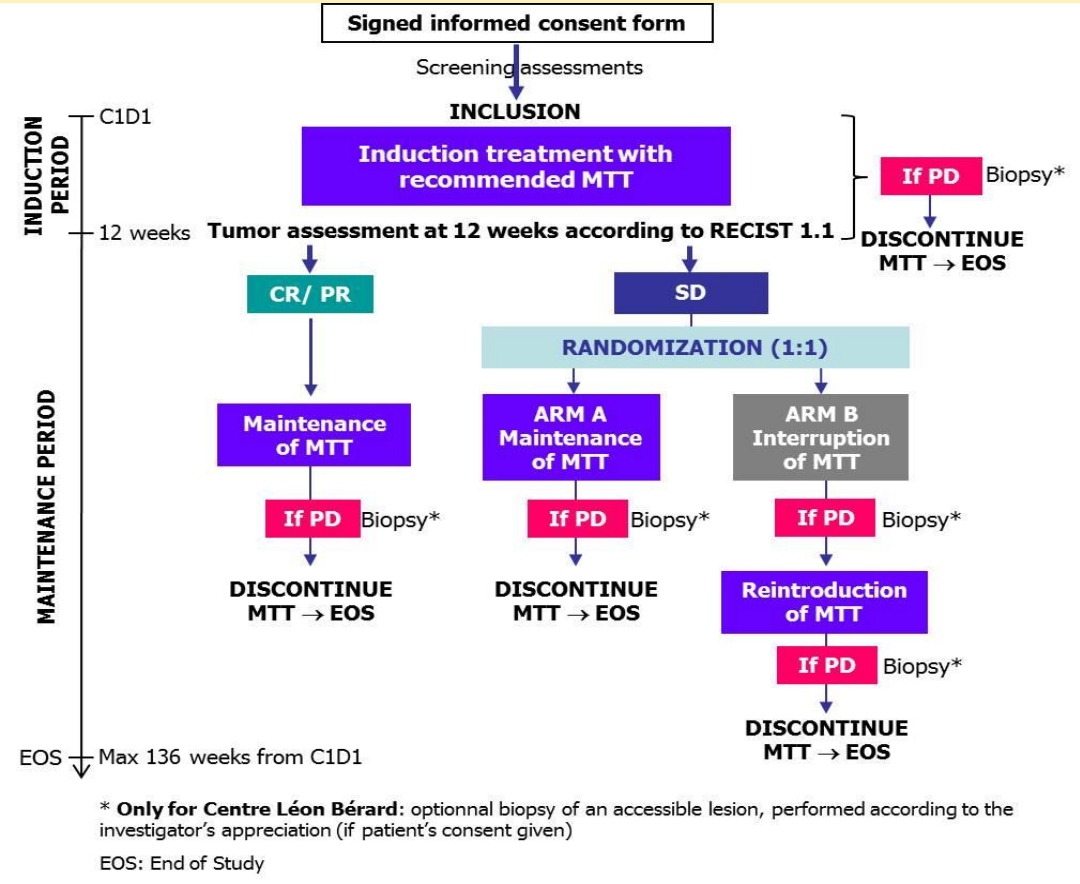
(EudraCT number 2011-001988-52)
(NCT01524926)

Study Coordinator: Patrick Schöffski
Phone: +32 16 346900
Fax: +32 16 346901
E-mail: patrick.schoffski@uzleuven.be

My Own Specific Treatment (MOST)

(NCT02029001)

- **Design:** two-period, national, multicentre, randomised, open-label, phase II study using a randomised discontinuation design
- **Aim:** to evaluate, in patients with advanced solid tumours after at least 1 prior systemic treatment regimen, the clinical benefit of a maintenance treatment in patients with stable disease after a 12-week induction treatment with a therapy targeting the molecular alterations identified in the patient's tumour
- **Start date:** July 2013/ March 2014!
- Sorafenib, pazopanib, everolimus, nilotinib, lapatinib
- Centre Leon Berard, Institut Curie, Institut Bergonié, soon Hospices Civils de Lyon, Institut Claudius Regaud,



Mutations

Amplification
12q13-15
MDM2/CDK4

WD/DDLPS

If it was so simple we would have Glivec for all sarcomas!

Translocations

DFSP
SyS
Ewing

Mutations
APC/bCat

Desmoids

Complex
Genomics

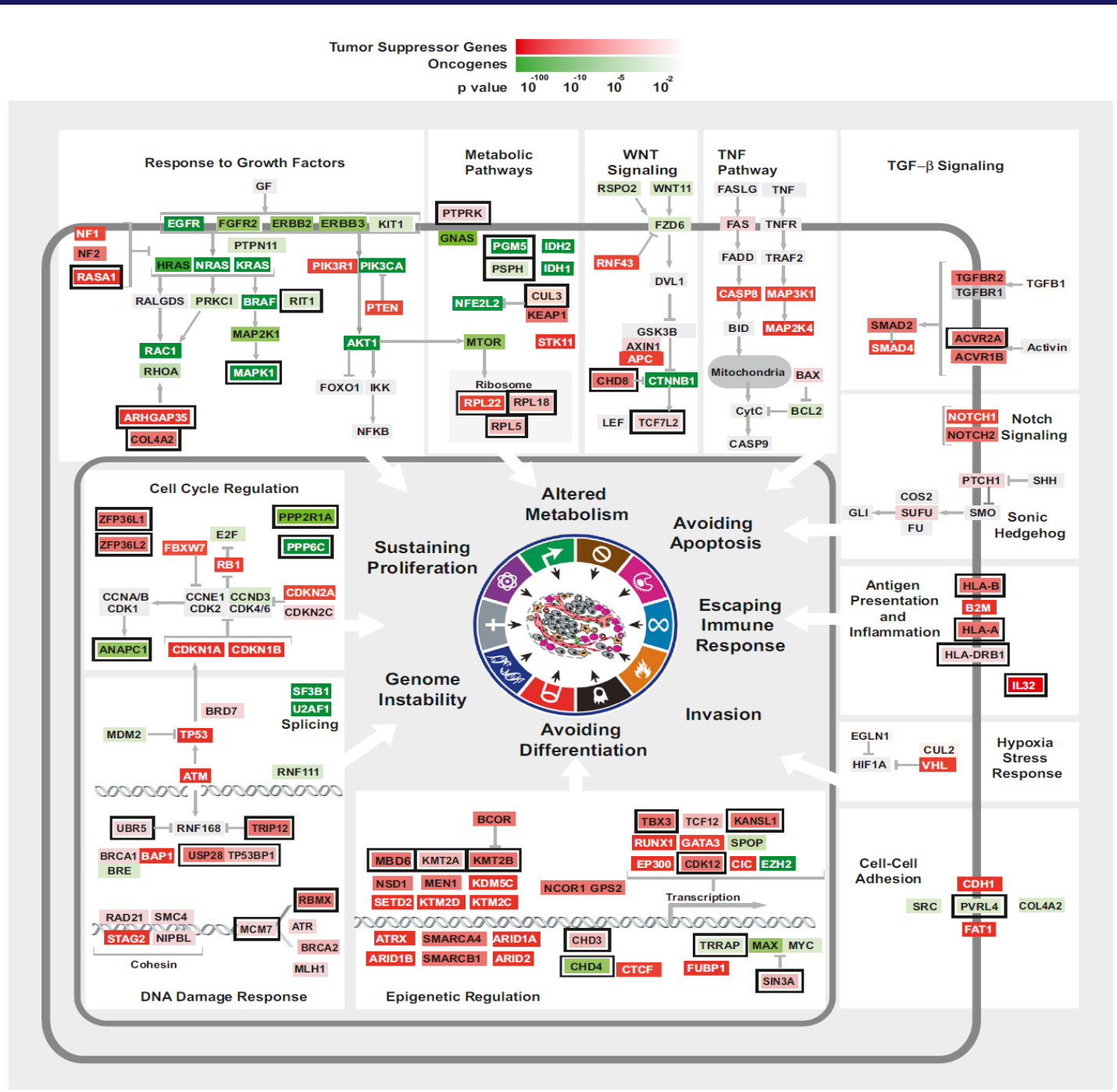
LMS, UPS

Cumulative Haploinsufficiency and Triplosensitivity Drive Aneuploidy Patterns and Shape the Cancer Genome

Teresa Davoli,[1,2,5] Andrew Wei Xu,[2,4,5] Kristen E. Mengwasser,[1,2] Laura M. Sack,[1,2] John C. Yoon,[2,3] Peter J. Park,[2,4] and Stephen J. Elledge[1,2,*]

[1]Howard Hughes Medical Institute, Department of Genetics, Harvard Medical School, Boston, MA 02115, USA
[2]Division of Genetics, Brigham and Women's Hospital, Boston, MA 02115, USA
[3]Department of Medicine, Massachusetts General Hospital, Boston, MA 02114, USA
[4]Center for Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA
[5]These authors contributed equally to this work
*Correspondence: selledge@genetics.med.harvard.edu
http://dx.doi.org/10.1016/j.cell.2013.10.011

Please cite this article in press as: Davoli et al., Cumulative Haploinsufficiency and Triplosensitivity Drive Aneuploidy Patterns and Shape the Cancer Genome, Cell (2013), http://dx.doi.org/10.1016/j.cell.2013.10.011


Tumor Suppressor Genes
Oncogenes
p value 10^-100 10^-10 10^-5 10^-2
Response to Growth Factors
GF
EGFR FGFR2 ERBB2 ERBB3 KIT1
NF1
NF2
RASA1
PTPN11
HRAS NRAS KRAS
PIK3R1 PIK3CA
RALGDS PRKCI BRAF RIT1
PTEN
MAP2K1
RAC1
RHOA
MAPK1
AKT1
FOXO1 IKK
NFKB
ARHGAP35
COL4A2
Metabolic Pathways
PTPRK
GNAS
PGM5 IDH2
PSPH IDH1
NFE2L2 CUL3
KEAP1
MTOR
STK11
Ribosome
RPL22 RPL18
RPL5
WNT Signaling
RSPO2 WNT11
FZD6
RNF43
DVL1
GSK3B
AXIN1
APC
CHD8 CTNNB1
LEF TCF7L2
TNF Pathway
FASLG TNF
FAS TNFR
FADD TRAF2
CASP8 MAP3K1
BID MAP2K4
Mitochondria BAX
CytC BCL2
CASP9
TGF–β Signaling
TGFBR2
TGFBR1
TGFB1
SMAD2
SMAD4
ACVR2A
ACVR1B
Activin
NOTCH1
NOTCH2
Notch Signaling
PTCH1 SHH
COS2
GLI SUFU SMO
FU
Sonic Hedgehog
Antigen Presentation and Inflammation
HLA-B
B2M
HLA-A
HLA-DRB1
IL32
EGLN1
HIF1A
CUL2
VHL
Hypoxia Stress Response
Cell-Cell Adhesion
CDH1
SRC
PVRL4
COL4A2
FAT1
Cell Cycle Regulation
ZFP36L1
ZFP36L2
FBXW7
E2F
RB1
PPP2R1A
PPP6C
CCNA/B CDK1
CCNE1 CDK2
CCND3 CDK4/6
CDKN2A
CDKN2C
ANAPC1
CDKN1A CDKN1B
SF3B1
U2AF1
Splicing
BRD7
MDM2
TP53
ATM
RNF111
UBR5
RNF168
TRIP12
BRCA1 BAP1
USP28 TP53BP1
BRE
RBMX
RAD21 SMC4
STAG2 NIPBL
MCM7
ATR
BRCA2
MLH1
Cohesin
DNA Damage Response
Altered Metabolism
Avoiding Apoptosis
Sustaining Proliferation
Escaping Immune Response
Genome Instability
Invasion
Avoiding Differentiation
BCOR
MBD6 KMT2A KMT2B
NSD1 MEN1 KDM5C
SETD2 KTM2D KTM2C
TBX3 TCF12 KANSL1
RUNX1 GATA3 SPOP
EP300 CDK12 CIC EZH2
NCOR1 GPS2
Transcription
ATRX SMARCA4 ARID1A
ARID1B SMARCB1 ARID2
CHD3
CHD4 CTCF
TRRAP MAX MYC
FUBP1
SIN3A
Epigenetic Regulation

The challenge of multiple levels of heterogeneity

- Across similar tumors in different patients
- At the molecular level of invididual cells of the primary tumor
- Across metastatic sites
- Upon therapeutic pressure

Conclusions
Evolving biology of sarcoma

- Well characterized histological & molecular subtypes
- More to be identified (NGS, CGH,…)
- Treatment adapted to driving molecular alterations
- How to identify a driver mutation?
- Novel approaches or clinical research
- Novel paradigms needed!