unicancer

Sarcomas: why does progress take time to emerge ?

J-Y Blay

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Université Claude Bernard Lyon 1

Disclosures

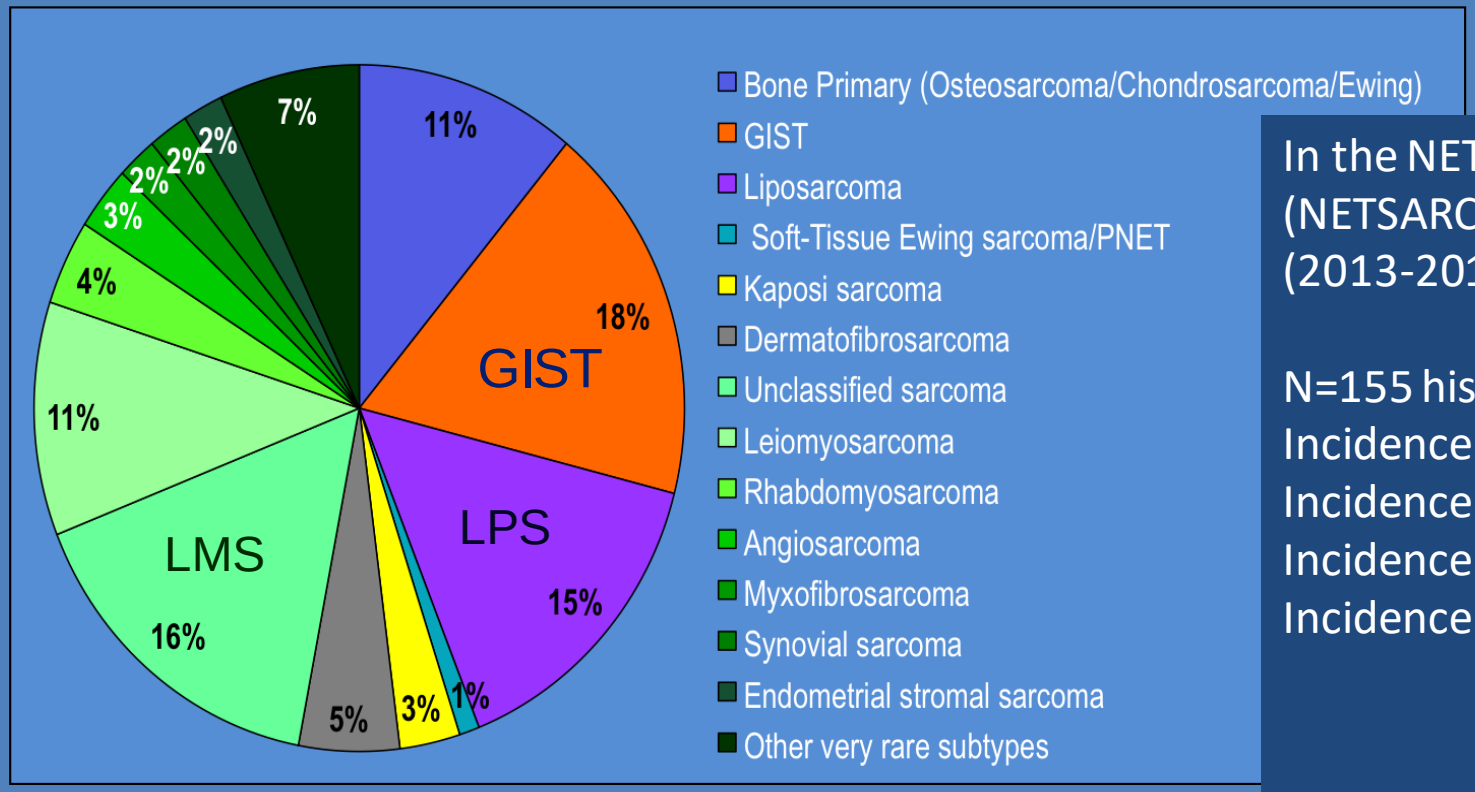
(presenter orange, institution grey)

Company	Scientific advice	Research support	Symposia & oral communications
Abbvie	X	X	
Amgen	X	X	X
ARIAD	X	X	
AstraZeneca		X	X
Bayer	X	X	X
BMS	X	X	X
DDB	X	X	
EISAI	X	X	X
Genomic Health		X	X
Gilead		X	X
GSK		X	X
Innate-Pharma	X	X	
Jansen		X	X
LILLY		X	X
Merck Serono		X	X
MSD		X	X
Nanobiotix	X	X	
Novartis	X	X	X
Novex		X	X
Onxeo	X		
Pfizer		X	X
Pharmamar	X	X	
PRA		X	
Roche	X	X	X
Sanofi Aventis		X	X
Swedish Orphan		X	X
Takeda		X	
Toray	X	X	

Why slow progresses?

- Difficult to diagnose
- Complex to organize optimal management
- A highly fragmented group of disease for novel treatments

Sarcomas represent a very heterogeneous set of diseases



In the NETSARC Database (NETSARC.org, N=25203 (2013-2016)

N=155 histotypes
Incidence >10^e5:n=1 (GIST)
Incidence 10^e5-10^e6, n=23
Incidence 10^e6-10^e7, n=64
Incidence <10^e7, n=68

Ducimetiere et al. PLoS ONE 6(8): e20294. doi:10.1371/journal.pone.0020294.

Histological discordances

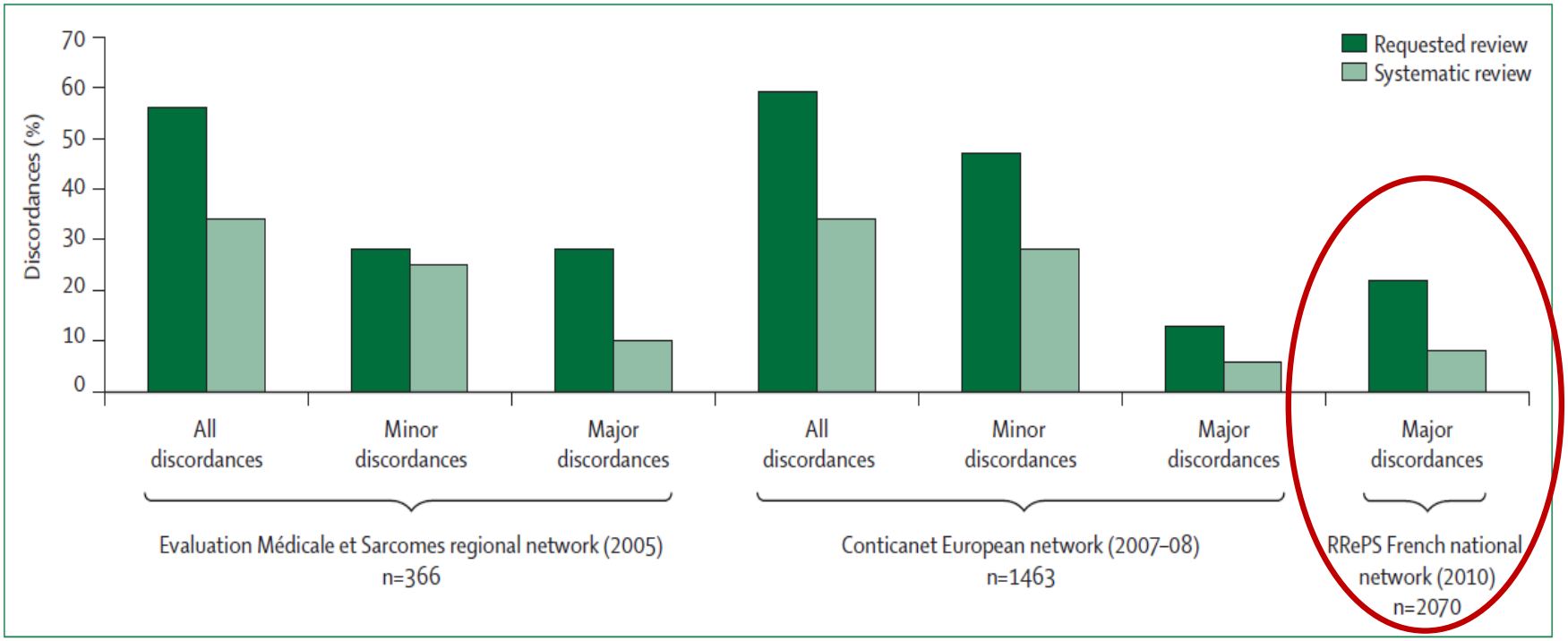


Figure 1: **Proportion of diagnostic discordances in three sarcoma networks**
In the Evaluation Médicale et Sarcomes study, major discordances were defined as changes between two different histological types, and minor discordances as changes between two different grades. In the Conticanet and RRePPS studies, major discordances were defined as changes between benign and malignant sarcoma or between sarcoma and non-mesenchymal diagnosis (ie, carcinoma). Minor discordances were defined as changes between two different histological types.
RRePS=Réseau de Référence en Pathologie des Sarcomes.

Cancer. 2012 Nov 1;118(21):5339-48

Histological reviews registered in 2010: 14% of major discordances (341 cases)

Cost of the treatments assessed for the initial diagnosis: €2,186,816 vs. final diagnosis: €1,060,174

Histological reviews/molecular biology result in a cost saving of more than €1,000,000

Diagnosis of genomic alterations

Table 3 Detectable alterations in clinical practice

Tumour type	Diagnostic tool (method)	Prognostic and/or predictive tool (method)	Oncogenetic test (method)
GIST	*KIT* overexpression (IHC)	*KIT* and/or *PDGFRA* mutation (sequencing)	NA
	Loss of *SDHB* expression (IHC)	NA	*SDH* mutation (sequencing)
Epithelioid sarcoma	Loss of *SMARCB1* expression (IHC) ± LOH (CGH)	NA	NA
Rhabdoid tumours	loss of *SMARCB1* and/or *SMARCA4* expression (IHC)	NA	*SMARCB1* and/or *SMARCA4* mutation (sequencing)
SMARCA4-deficient sarcoma	Loss of *SMARCA4* and/or *SMARCA2* expression (IHC)	NA	NA
Giant cell tumours	$H3F3A^{G34W}$ expression (IHC) ± *H3F3A* mutation (sequencing)	NA	NA
Langerhans cell histiocytosis	NA	$BRAF^{V600E}$ mutation (sequencing)	NA
Translocation involving a growth factor or kinase	Sarcoma defined by the presence of the fusion transcript (FISH, RT-PCR, or RNA-seq)	*ALK/ROS1/NTRK/PDGFB* rearrangement (FISH/PCR/RNA-seq)	NA
Translocation involving transcription factors	Sarcoma defined by the presence of the fusion transcript (FISH, RT-PCR, or RNA-seq)	NA	NA
Well-differentiated and/or dedifferentiated liposarcoma	*MDM2* amplification (FISH ± CGH)	NA	NA
Low-grade osteosarcoma	*MDM2* amplification (FISH ± CGH or quantitative PCR)	NA	NA
Secondary angiosarcoma	*MYC* amplification (IHC ± FISH)	NA	NA

CGH, comparative genomic hybridization; FISH, fluorescence in situ hybridization; GIST, gastrointestinal stromal tumour; IHC, immunohistochemistry; LOH, loss of heterozygosity; NA, not available; RNA-seq, RNA sequencing; RT-PCR, reverse transcription PCR, SMARCA4, transcription activator BRG1.

Dufresne A, et al. *Nat Rev Clin Oncol* 2018;15:443–58.

Ordered incidences of sarcomas and connective tissue tumors in NETSARC & published clinical trials

Histotypes	Total (2013-2016)	Incidence /10e6/year	Ph III	RPh II	Ph II
	25172	95,104			
Incidence >10/10e6/year					
Fibroblastic and myofibroblastic tumours	5274	19,977			
Gastrointestinal stromal tumors (GIST).	3272	12,394			
Adipocytic tumours	3247	12,299			
ALL Undifferentiated sarcoma	2717	10,292			
ALL smooth muscle tumours	2679	10,148			
Incidence <10/10e6/year					
Undifferentiated pleomorphic sarcoma	1556	5,894			
All vascular tumor	1520	5,758			
Liposarcoma – dedifferentiated	1345	5,095			
Desmoid fibromatosis	1339	5,072			
Atypical lipomatous tumour/WDLPS	1266	4,795			
Uterine sarcoma	1138	4,311			
Leiomyosarcoma	1094	4,144			
Dermatofibrosarcoma Protuberans	1040	3,939			
Leiomyosarcoma -differentiated	945	3,580			
Solitary fibrous tumour (all)	925	3,504			
Undifferentiated sarcoma NOS	853	3,231			
Sarcoma NOS	844	3,197			
Solitary fibrous tumor	751	2,845			
Angiosarcoma	728	2,758			
Kaposi sarcoma	663	2,511			
Conventional osteosarcoma	661	2,504			
Myxofibrosarcoma	630	2,386			
Ewing sarcoma	614	2,326			
ALL Rhabdomyosarcoma	608	2,303			
Chondrosarcoma NOS	572	2,167			
Uterine leiomyosarcoma	545	2,064			
Leiomyosarcoma – poorly differentiated	516	1,955			
ALL Synovial sarcoma	442	1,674			
Atypical fibroxanthoma	429	1,625			
Myxoid or round cell liposarcoma	409	1,549			
Liposarcoma - myxoid	355	1,345			
All GCTB	330	1,250			
Giant cell tumour of bone	324	1,227			
Undifferentiated spindle cell sarcoma	308	1,167			
ALL Peripheral nerve sheath tumours	286	1,083			

Histotypes	Total (2013-2016)	Incidence /10e6/year	Ph III	RPh II	Ph II
		95,104			
Incidence <1/10e6/year					
Synovial sarcoma - monophasic	244	0,924			
Endometrial stromal sarcoma, low grade	238	0,902			
Embryonal RMS	179	0,678			
High risk SFT	174	0,659			
Malignant peripheral nerve sheath tumour	173	0,655			
Other histological subtypes of bone sarcoma	171	0,648			
Osteosarcoma NOS	168	0,636			
Conventional chordoma	164	0,621			
Adenosarcoma	156	0,591			
All undifferentiated sarcoma of bone	152	0,576			
Inflammatory myofibroblastic Tumour	145	0,549			
Pleomorphic RMS	144	0,545			
Undifferentiated uterine sarcoma	141	0,534			
Liposarcoma - pleomorphic	139	0,527			
Phyllode sarcoma	138	0,523			
Embryonal rhabdomyosarcoma usual type	137	0,519			
Low grade fibromyxoid sarcoma	136	0,515			
Alveolar RMS	123	0,466			
Smooth muscle tumour of undetermined ma	122	0,462			
Epithelioid sarcoma	120	0,455			
Central chondrosarcoma, grades 2 and 3	117	0,443			
So-called fibrohistiocytic tumours	106	0,402			
EpithelioidhemangioEndothelioma	100	0,379			
Epithelioid sarcoma	98	0,371			
Extraskeletal osteosarcoma	96	0,364			
Myoepithelioma, myoepithelial carcinoma,	96	0,364			
Dedifferentiated chondrosarcoma	93	0,352			
RMS NOS	88	0,333			
Myoepithelioma	85	0,322			
Central atypical cartilaginous tumour / chon	76	0,288			
Clear cell sarcoma of soft tissue	71	0,269			
Giant cell tumour of soft tissue	70	0,265			
Synovial sarcoma - biphasic	70	0,265			
Undifferentiated pleomorphic sarcoma of bo	69	0,261			
PECOMA - NOS	67	0,254			
Extraskeletal myxoid chondrosarcoma	58	0,220			
Round cell sarcoma with EWSR1-non-ETS fus	56	0,212			
Liposarcoma - round cell	54	0,205			
Aneurysmal bone cyst	53	0,201			
Desmoplastic small round cell tumour	52	0,197			
Tumors of intermediate malignancy NOS ALL	52	0,197			
Chondroblastoma	52	0,197			
Extrarenal rhabdoid tumour	51	0,193			
Intimal sarcoma	46	0,174			
Angiomatoid fibrous histiocytoma	43	0,163			
Sclerosing epithelioid fibrosarcoma	41	0,155			
Endometrial stromal sarcoma - high-grade	41	0,155			
All parosteal osteosarcoma	40	0,152			
Leiomyosarcoma of bone	40	0,152			
Spindle cell RMS	39	0,148			
Peripheral chondrosarcoma	39	0,148			
Synovial sarcoma - poorly Differentiated	37	0,140			
Malignant rhabdoid tumor	36	0,136			
Ossifying fibromyxoid Tumour	32	0,121			
Alveolar soft part sarcoma	31	0,117			
Mesenchymal chondrosarcoma	31	0,117			
Osteoblastoma	31	0,117			
Plexiform fibrohistiocytic tumors	29	0,110			
Embryonal rhabdomyosarcoma spindle cell	29	0,110			
Angiosarcoma of bone	29	0,110			
Adult fibrosarcoma	28	0,106			
Parosteal osteosarcoma	27	0,102			

Histotypes	Total (2013-2016)	Incidence /10e6/year	Ph III	RPh II	Ph II
Incidence <0.1/10e6/year					
Osteoblastoma-like osteosarcoma					
Chondromyxoid fibroma	26	0,098			
Undifferentiated spindle cell sarcoma	26	0,098			
Periosteal chondrosarcoma	25	0,095			
High-grade surface osteosarcoma	25	0,095			
Myxoinflammatory Fibroblastic Sarcoma	23	0,087			
Embryonal RMS sarcoma - botryoid type	23	0,087			
Undifferentiated epithelioid sarcoma	22	0,083			
Langerhans cell histiocytosis	20	0,076			
Malignant PECOMA	19	0,072			
Low grade central osteosarcoma (ALL)	19	0,072			
Adamantinoma	19	0,072			
UTROSC	17	0,064			
Endometrial stromal nodule	16	0,061			
Telangiectasic osteosarcoma	16	0,061			
SMARCA4-deficient thoracic sarcoma	15	0,057			
Clear cell chondrosarcoma	14	0,053			
Low grade Myofibroblastic Sarcoma	13	0,049			
Dedifferentiated parosteal osteosarcoma	13	0,049			
Dedifferentiated low grade central osteosar	12	0,045			
Giant cell Fibroblastoma	11	0,042			
Sclerosing RMS	11	0,042			
CIC-rearranged sarcoma	11	0,042			
Infantile fibrosarcoma	10	0,038			
Pericytic (perivascular) tumours	10	0,038			
Malignant Triton tumour	10	0,038			
Retiform hemangio-endothelioma	9	0,034			
Ectomesenchymoma : Malignant mesenchym	9	0,034			
Malignant granular cell Tumour	9	0,034			
Haemosiderotic fibrolipomatous tumour	9	0,034			
Synovial sarcoma of bone	9	0,034			
RMS of bone	9	0,034			
Lipofibromatosis	8	0,030			
Sarcoma with BCOR genetic alterations	7	0,027			
Low-grade central osteosarcoma	7	0,027			
Pseudomyogenic hemangioendothelioma	6	0,023			
Intermediate vascular tumours	6	0,023			
MPNST - epithelioid type	6	0,023			
Mixed tumour	6	0,023			
Desmoplastic fibroma of bone	6	0,023			
Malignant/dedifferentiated GCTB	6	0,023			
BCOR Sarcoma of bone	6	0,023			
Intermediate fibrohistiocytic tumors	5	0,019			
Adult spindle cell RMS	5	0,019			
Phosphaturic mesenchymal tumour	5	0,019			
Low grade sinonasal sarcoma	5	0,019			
Periosteal osteosarcoma	5	0,019			
Kaposiform hemangioendothelioma	4	0,015			
Small cell osteosarcoma	4	0,015			
Myoepithelioma of bone	4	0,015			
Liposarcoma of bone	4	0,015			
Composite hemangioendothelioma	3	0,011			
Malignant perineurioma	3	0,011			
Adult fibrosarcoma of bone	3	0,011			
Liposarcoma - mixed type	2	0,008			
Malignant tenosynovial giant cell tumors	2	0,008			
Metastatic leiomyoma	2	0,008			
Malignant myoepithelial Tumour	2	0,008			
Osteoblastoma-like osteosarcoma	2	0,008			
Dedifferentiated chordoma	2	0,008			
Lipomatous spindle cell/pleomorphic tum	1	0,004			
Papillary intralymphatic angioendotheliom	1	0,004			
Melanotic neuroectodermal tumour of infan	1	0,004			
Osteogenic tumor of uncertain prognosis	1	0,004			
Fibro-osseous tumour of bone NOS	1	0,004			
Undifferentiated epithelioid sarcoma	1	0,004			

Why slow progresses?

- Difficult to diagnose
- Complex to organize optimal management
- A highly fragmented group of disease for novel treatments

Soft tissue and visceral sarcomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†

- **Biopsy** first
  - Assessment by an experienced team
- Appropriate **imaging** of the tumor: MRI andd/or CT scan
- **Staging** : CT scan (adapted to histology)
- **En bloc surgical resection by a trained surgeon**
  - Planning R0; If R1, consider re resection
- Post operative **radiotherapy** (or preoperative)
  - (G2-3 and/or deep seated, and/or >5cm)
- (Neoaduvant/adjuvant **chemotherapy**)

NetSARC: a network of 26 sarcoma reference centers in France
35784 pts with follow-up presented in MDT since 2010

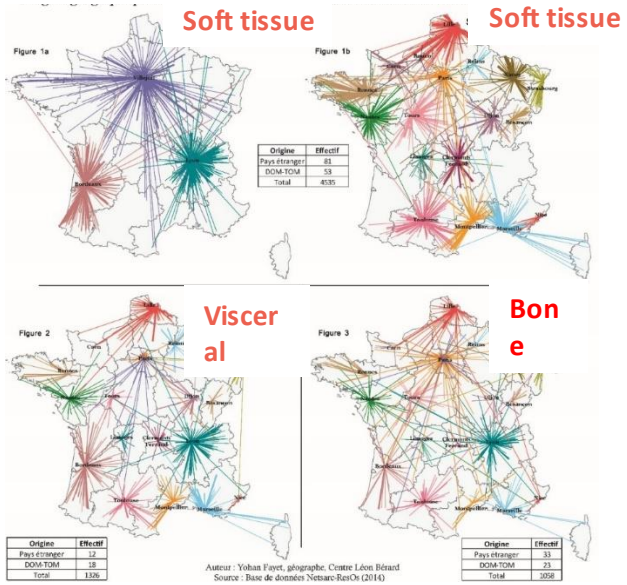
- 26 centers of reference in **Netsarc**
- Linked with Pathology network (**RREPS**)
- Linked with Bone Network **RESOS** (2014)

- 3 networks to be merged (2019)

- Single website

- Entry in the site by CRAs
- Not a clinical trial, a registry

- **Aims:**
  - Guidelines
  - Guiding best practices/patient pathways
  - Measuring
  - Research

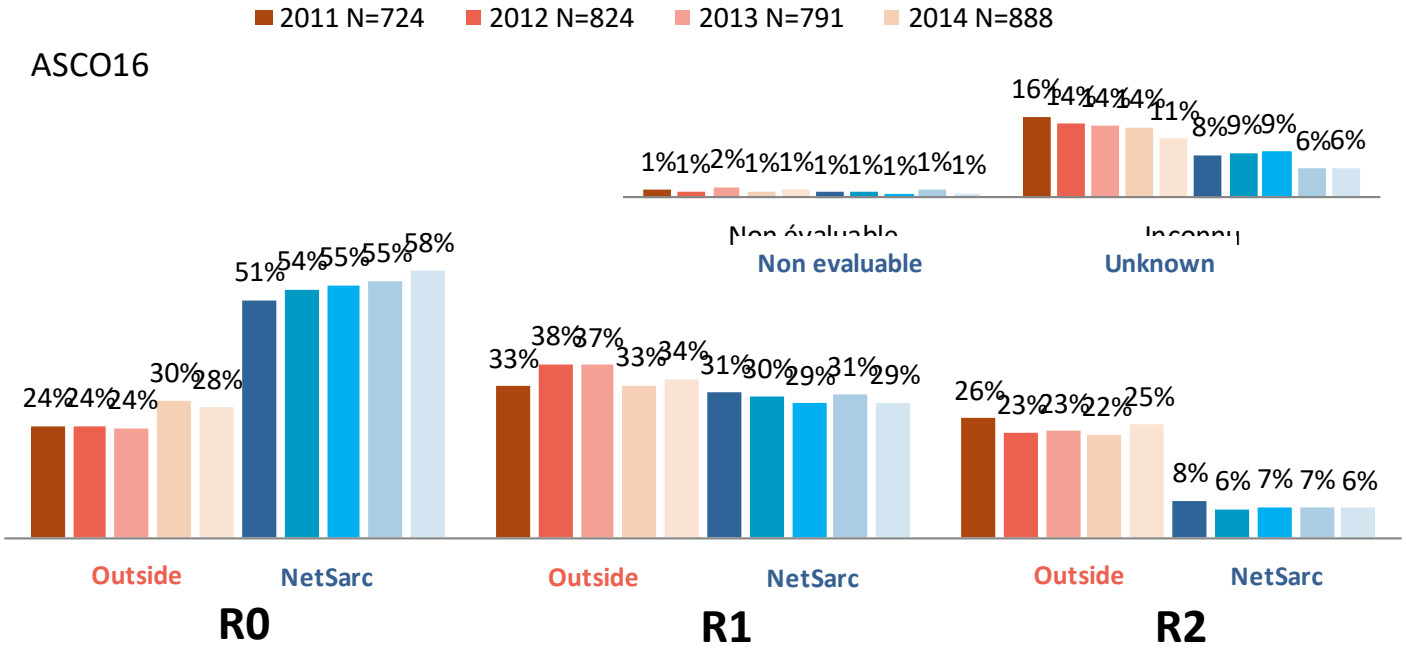


Websites

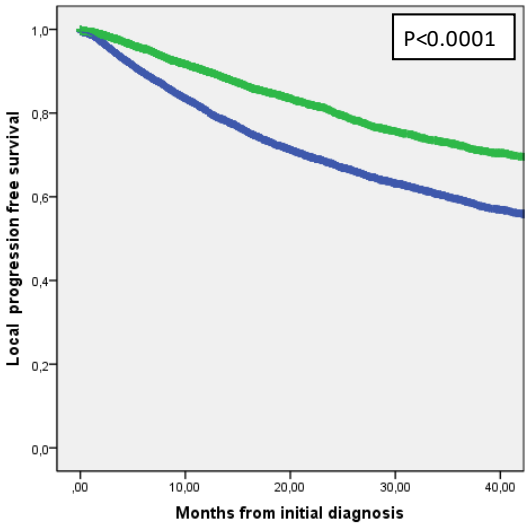
- netsarc.org
- rreps.org
- resos.org

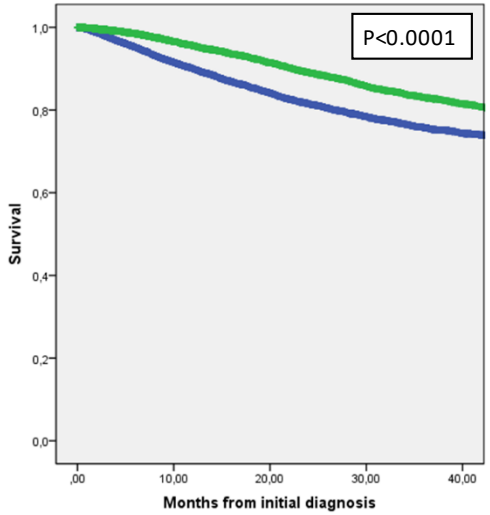
MUNICH 2018 ESMO congress

Quality of initial surgery, incident patients (STS & visceral sarcomas operated)



LRFS & OS : incident patient population





Operated
- In NETSARC, N=9910 (33.9%)
- Outside NETSARC or
  no data, N=19307 (66.1%)

Ann Surg Oncol
https://doi.org/10.1245/s10434-019-07421-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – SARCOMA

Survival Benefit of the Surgical Management of Retroperitoneal Sarcoma in a Reference Center: A Nationwide Study of the French Sarcoma Group from the NetSarc Database

S. Bonvalot, MD, PhD[1], E. Gaignard, MD[1], E. Stoeckle, MD[2], P. Meeus, MD[3], G. Decanter, MD[4], S. Carrere, MD[5], C. Honore, MD, PhD[6], J. B. Delhorme, MD[7], M. Fau, MD[8], D. Tzanis, MD[1], S. Causeret, MD[9], P. Gimbergues, MD[10], J. M. Guillois, MD[11], B. Meunier, MD[12], A. Le Cesne, MD[13], F. Ducimetiere, PhD[14], M. Toulmonde, MD, PhD[15], and J. Y. Blay, MD, PhD[16]

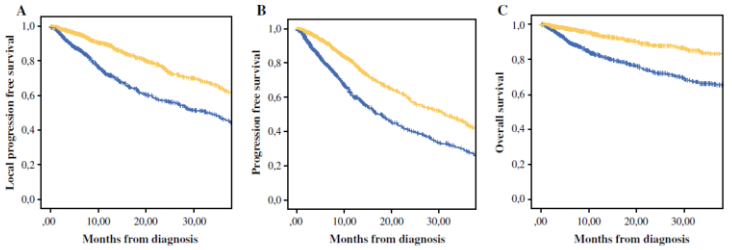


FIG. 1 Local progression-free survival (**a**), progression-free survival (**b**), and overall survival (**c**) of the retroperitoneal sarcoma patients in the NetSarc database. In blue: patients operated on outside of the NetSarc network. In yellow: patients operated on at a NetSarc center. Log-rank $p < 0.0001$ for LRFS, PFS, and OS

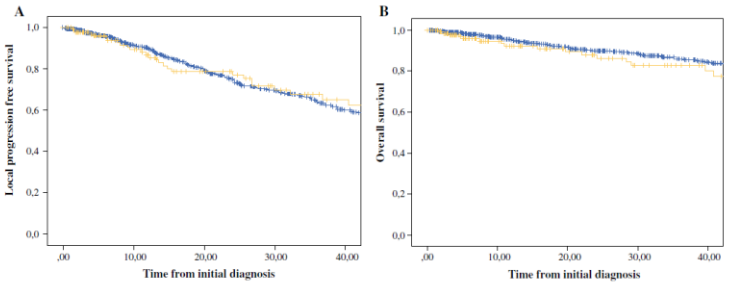


FIG. 2 Local progression-free survival (**a**) and overall survival (**b**) of patients operated on at NetSarc centers. In blue: patients operated on at the 13 NetSarc centers with the largest accrual of RPS patients. In yellow: patients operated on at the 13 NetSarc centers with the smallest accrual of RPS patients. Log-rank $p > 0.05$

Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial

Alessandro Gronchi, Stefano Ferrari, Vittorio Quagliuolo, Javier Martin Broto, Antonio Lopez Pousa, Giovanni Grignani, Umberto Basso, Jean-Yves Blay, Oscar Tendero, Robert Diaz Beveridge, Virginia Ferraresi, Iwona Lugowska, Domenico Franco Merlo, Valeria Fontana, Emanuela Marchesi, Davide Maria Donati, Elena Palassini, Emanuela Palmerini, Rita De Sanctis, Carlo Morosi, Silvia Stacchiotti, Silvia Bagué, Jean Michelle Coindre, Angelo Paolo Dei Tos, Piero Picci, Paolo Bruzzi, Paolo Giovanni Casali

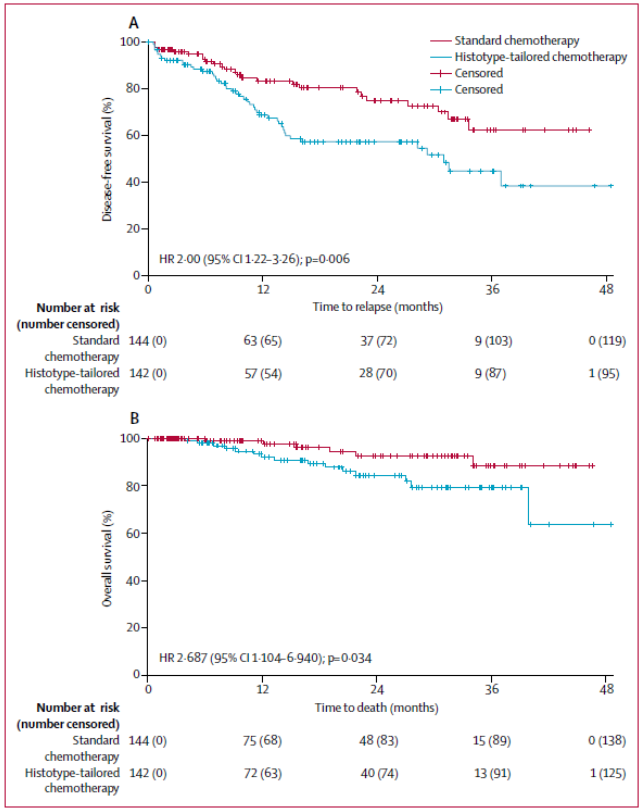


Figure 2: **Disease-free survival and overall survival at 46 months from randomisation**
(A) Disease-free survival. (B) Overall survival. HR=hazard ratio.

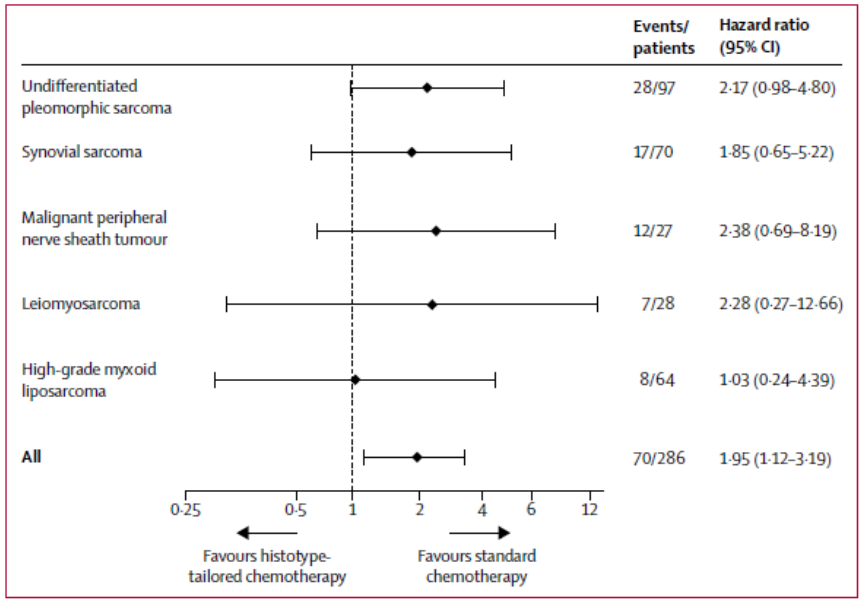
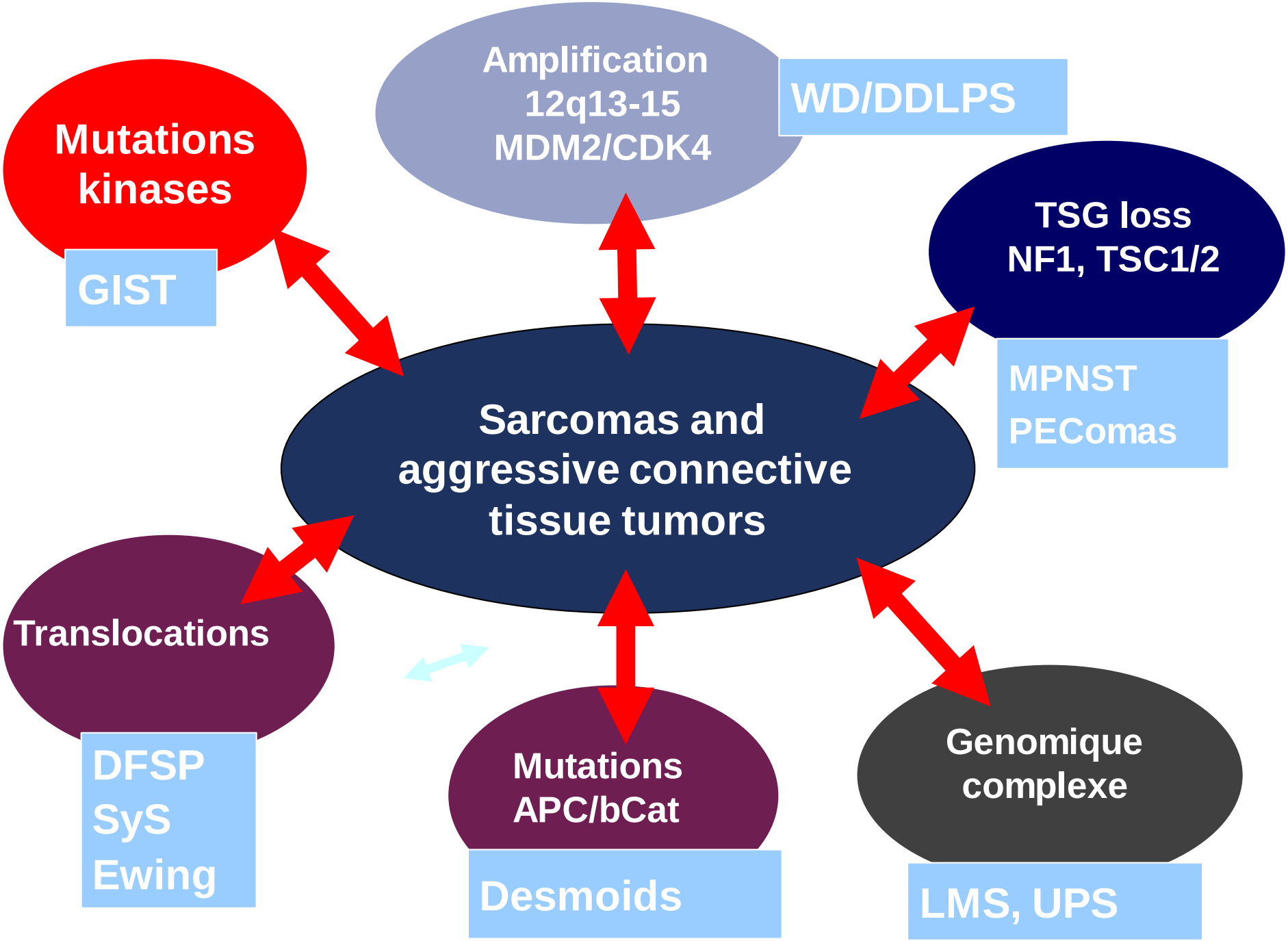


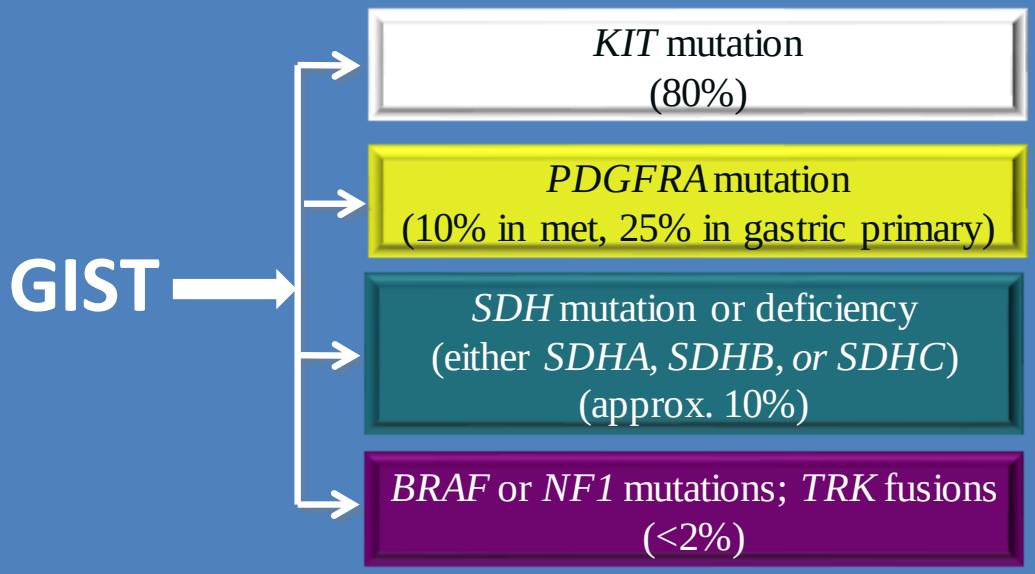
Figure 4: **Standard versus histotype-tailored chemotherapy in the five different histology subtypes**
Hazard ratios of disease-free survival were estimated with binary logistic models.

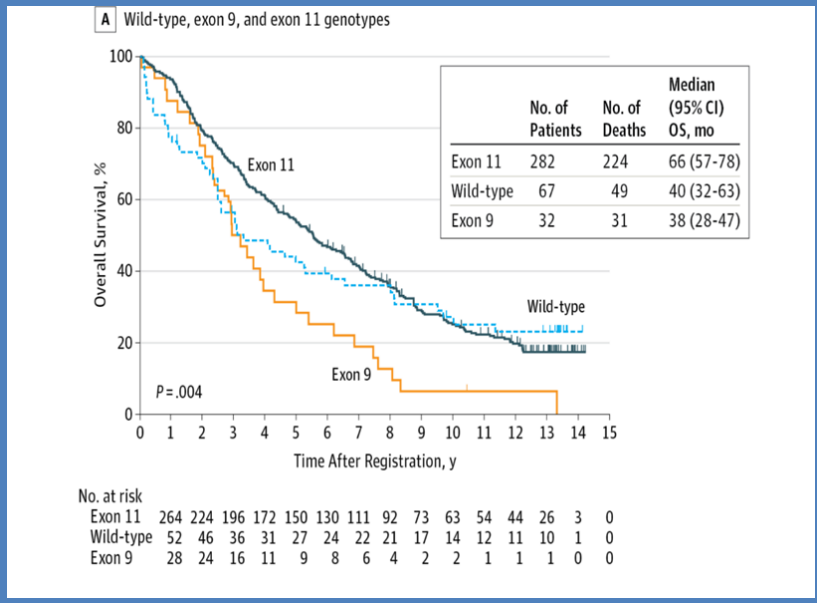
Why slow progresses?

- Difficult to diagnose
- Complex to organize optimal management
- A highly fragmented group of disease for novel treatments


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

>10 molecular subtypes of GISTs

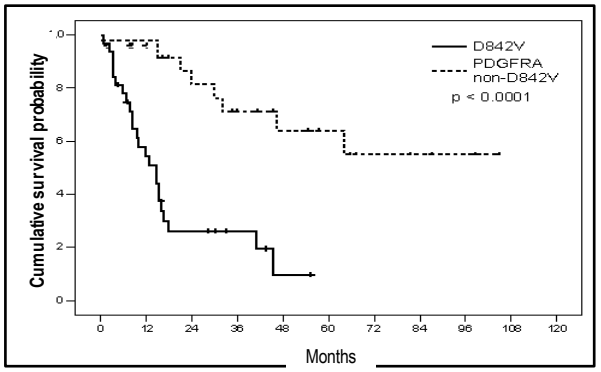


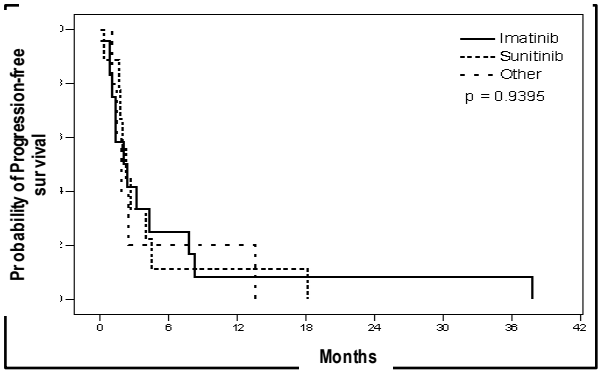


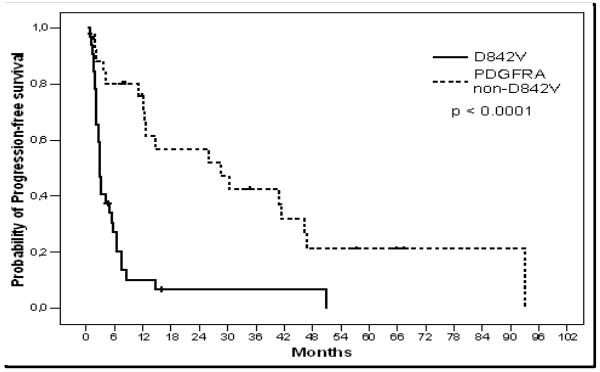
Corless CL, et al. *Nat Rev Cancer*. 2011;11(12):865-878.

PDGFRA GISTs : D842V vs others

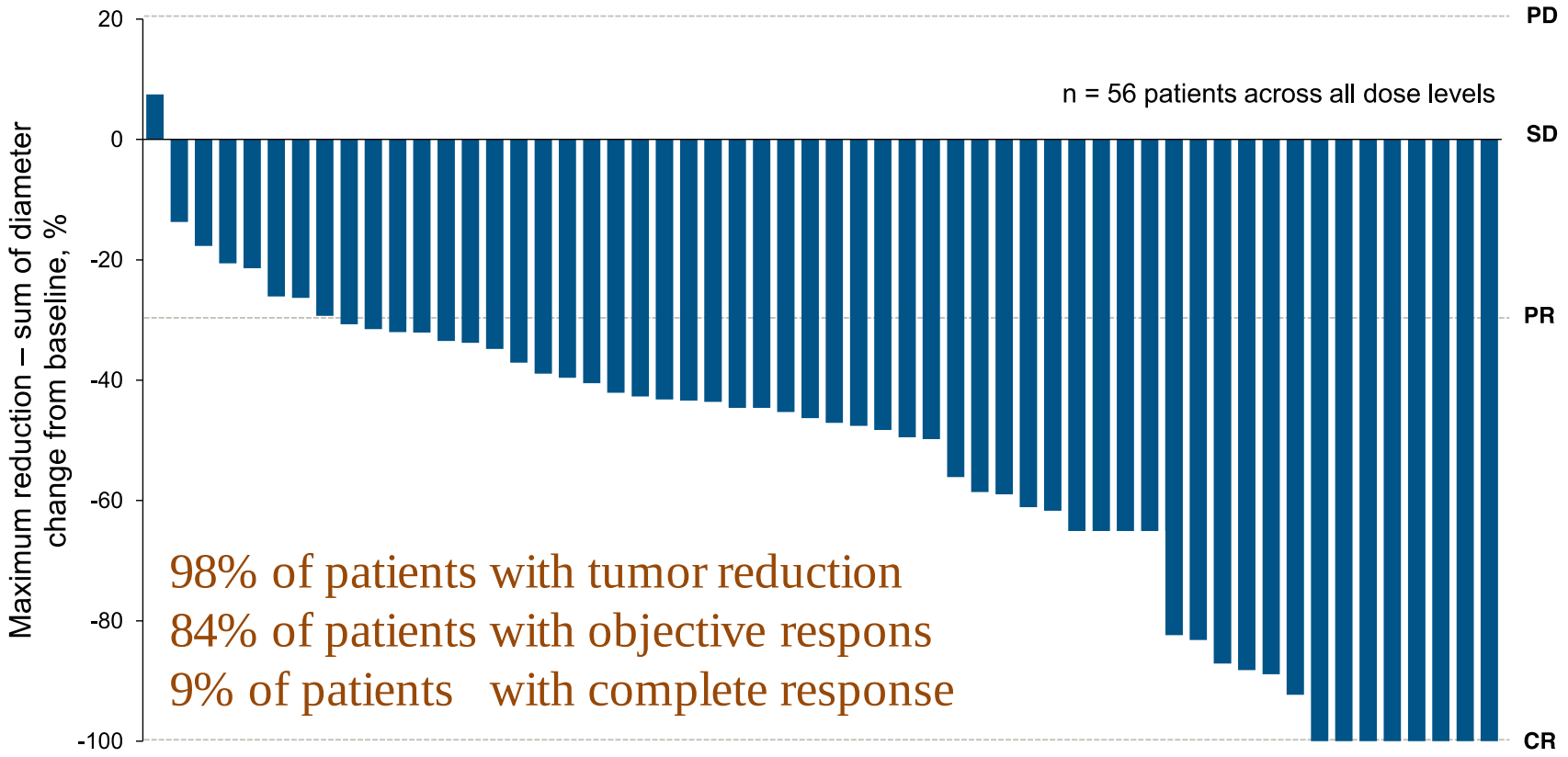
Characteristic	N	%
Total	**58**	**100**
Gender		
Male	34	58,6%
Female	24	41,4%
Primary tumor location		
Stomach	40	69,0%
Small bowel	7	12,1%
Peritoneum/Mesentery	2	3,4%
Rectum/Anus	1	1,7%
Other	4	6,9%
Unknown	4	6,9%
KIT/CD117 expression		
Positive	38	65,5%
Negative	7	12,1%
Unknown	13	22,4%
Type of mutation		
Exon 18 D842V substitution	32	55,2%
Other exon 18 mutation	17	29,3%
Exon 12 mutation	8	13,8%
Exon 4 mutation	1	1,7%
Metastatic sites		
Liver	36	62,1%
Peritoneum	33	56,9%
Liver & periotneum	15	25,9%
Other	15	25,9%
WHO PS		
0	28	48,3%
1	19	32,8%
2	2	3,4%
Unknown	9	15,5%







Avapritinib in PDGFRA D842V GIST



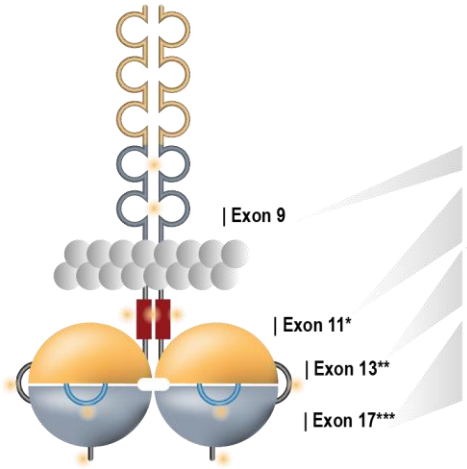
PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

Michael Heinrich,

Connective Tissue Oncology Society 2018 Annual Meeting
Rome, Italy • November 15, 2018

Primary vs Secondary KIT Mutations in GIST

- GIST is a rare sarcoma accounting for 1% to 2% of GI malignancies[1]
- Primary mutations in KIT or PDGFRA occur in >85% of patients with GIST[2]
- Mutations lead to activation of the kinase[3]



Domain	Gene	1° Mutation Frequency	2° Mutation Frequency
D5	*KIT*	10%	
JM	*KIT* *PDGFRA*	67* 1	
TK1 (ATP-binding pocket)	*KIT* *PDGFRA*	1 1	56**
Activation loop	*KIT* *PDGFRA D842* *PDGFRA*	1 5 1	41*** 3

*Exon 11 mutations of the JM domain result in loss of function of the KIT inhibitory switch[4]

**Mutations in the TK1 region of KIT reflect mutations in the ATP-binding pocket ("switch pocket region")[4,5]

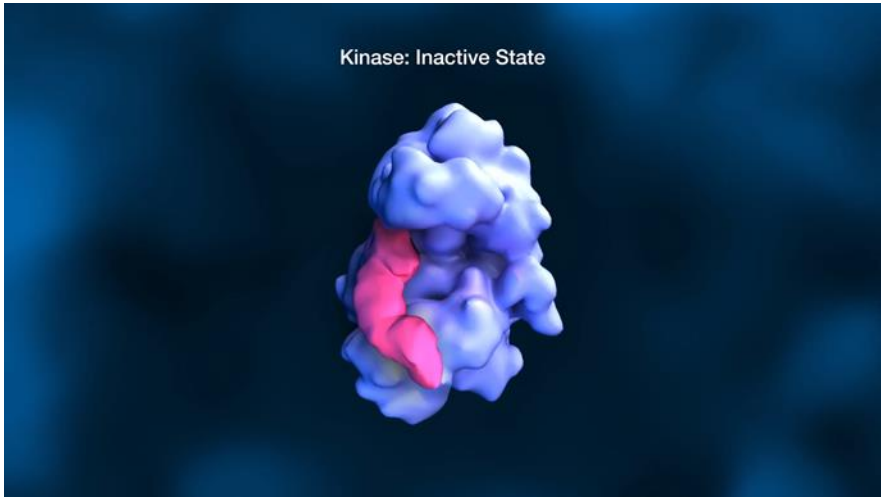
***Mutations in the activation loop of KIT reflect mutations in the KIT activating switch region[4]

From Hemming M, et al. *Ann Oncol.* 2018;29:2037-2045 by permission of Oxford University Press on behalf of the European Society for Medical Oncology.

1. Parab TM, et al. *J Gastrointest Oncol*. 2019;10:144-154. **2.** Hsueh YS, et al. *PLOS One*.2013;e65762. **3**. Smith BD, et al. *Cancer Cell*. 2019;35:738-751
4. Bai Y, et al. *Leukemia*.2013;27:278-285. **5**. Oppelt PJ, et al. *J Gastrointest Oncol*. 2017;8:466-473.

INVICTUS: A Phase 3, *IN*ter*V*ential, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Ripretinib as ≥4th Line Therapy *I*n Patients with Advan*C*ed Gastrointestinal Stromal *TU*mor*S* (GIST) Who Have Received Treatment with Prior Anticancer Therapies (NCT03353753)

Margaret von Mehren, Steven Attia, Sebastian Bauer, Ping Chi, Gina D'Amato, Suzanne George, Hans Gelderblom, Michael C. Heinrich, Robin L. Jones, Peter Reichardt, Patrick Schoffski, Cesar Serrano, John Zalcberg, Julie Meade, Kelvin Shi, Rodrigo Ruiz-Soto, Jean-Yves Blay



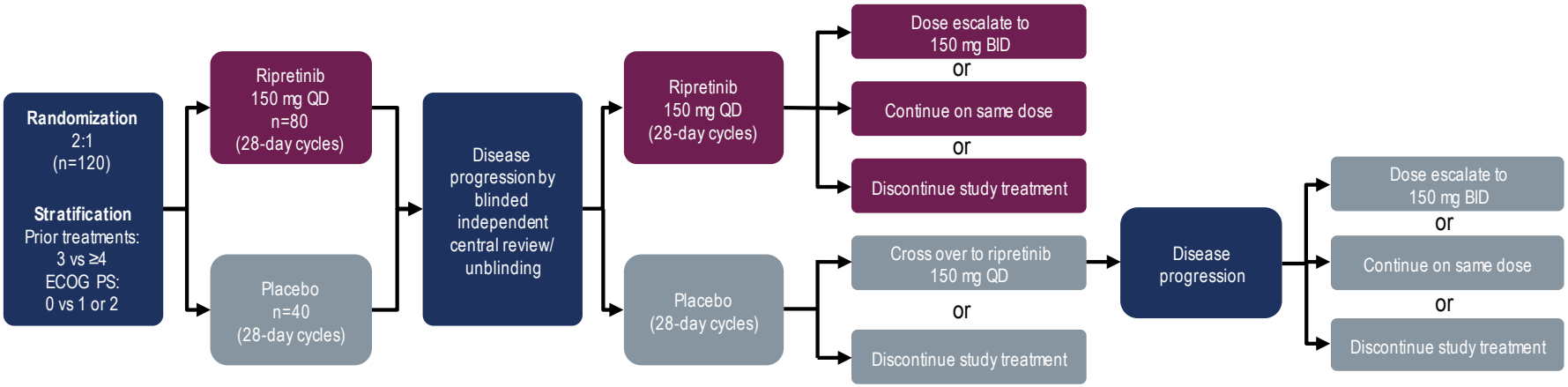
Ripretinib is a novel tyrosine kinase **switch control** inhibitor engineered to broadly inhibit KIT and PDGFRA mutated kinases by using a unique **dual mechanism of action** that regulates the kinase switch pocket and activation loop

BARCELONA 2019 ESMO congress

Smith BD, et al. *Cancer Cell*. 2019;35:738-751.

INVICTUS: Randomized Phase 3 Study Design

Evaluated ripretinib as ≥4th line therapy in patients with advanced GIST



Primary endpoint

PFS

(per modified RECIST based on **B**linded **I**ndependent **C**entral **R**eview [BICR])

Select Secondary endpoints

- **Objective response rate (ORR)** assessed by BICR (Key endpoint)
- **Overall survival (OS)**

Data cutoff
May 31, 2019

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85% Risk Reduction of Disease Progression or Death With Ripretinib Compared With Placebo

	Ripretinib (n=85)	Placebo (n=44)
Events, n (%)	51 (60.0%)	37 (84.1%)
Censored, n (%)	34 (40.0%)	7 (15.9%)
PFS 6 months, % (95% CI)	51.0% (39.4–61.4)	3.2% (0.2–13.8)

*Double-blind period.

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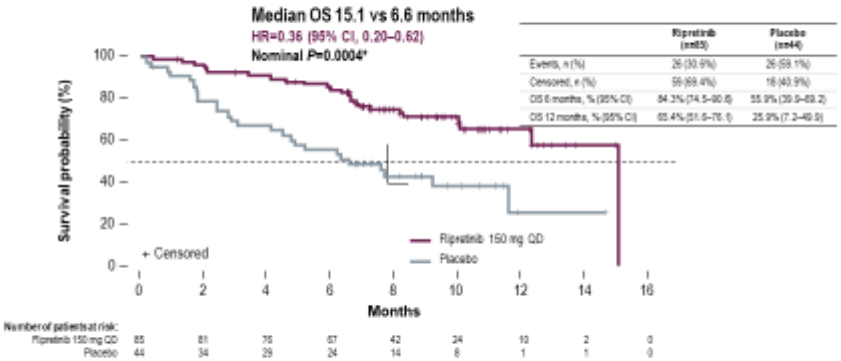
OS Benefit: 64% Risk Reduction of Death Compared With Placebo



	Ripretinib (n=85)	Placebo (n=44)
Events, n (%)	26 (30.6%)	26 (59.1%)
Censored, n (%)	59 (69.4%)	18 (40.9%)
OS 6 months, % (95% CI)	84.3% (74.5–90.6)	55.9% (39.9–69.2)
OS 12 months, % (95% CI)	65.4% (51.5–76.1)	25.9% (7.2–49.5)

*Due to hierarchal testing procedures of the end points, the OS end point could not be formally tested because the ORR was not statistically significant.

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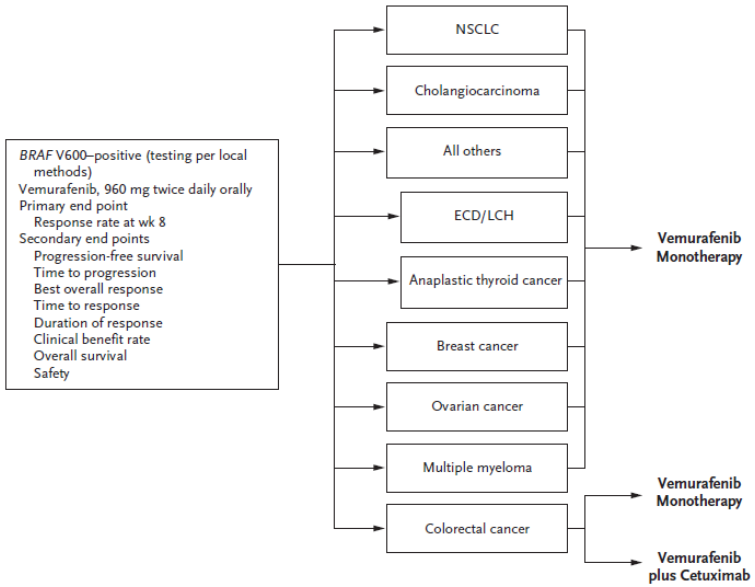
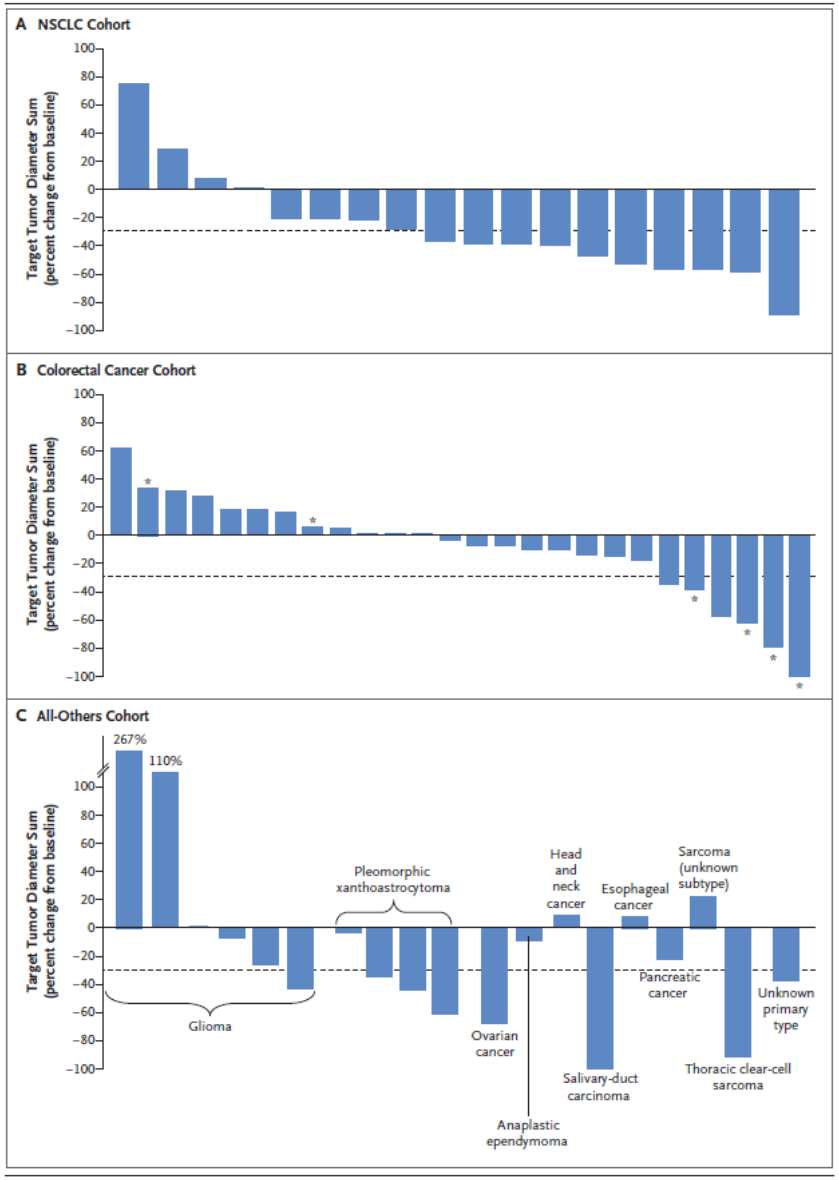
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.





JAMA Oncology | Brief Report

Vemurafenib for *BRAF* V600–Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis

Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study

Eli L. Diamond, MD; Vivek Subbiah, MD; A. Craig Lockhart, MD; Jean-Yves Blay, Prof; Igor Puzanov, MD; Ian Chau, MD; Noopur S. Raje, MD; Jurgen Wolf, Prof Dr; Joseph P. Erinjeri, MD, PhD; Jean Torris, MD; Mario Lacouture, MD; Elena Elez, MD; Ferran Martinez-Valle, MD; Benjamin Durham, MD; Maria E. Arcila, MD; Gary Ulaner, MD, PhD; Omar Abdel-Wahab, MD; Bethany Pitcher; Martina Makrutzki, MD; Todd Riehl, PharmD, BCOP; José Baselga, MD, PhD; David M. Hyman, MD

Figure 1. Efficacy of Vemurafenib in Individual Patients With *BRAF* V600–Mutant Erdheim-Chester Disease (ECD) or Langerhans Cell Histiocytosis (LCH)

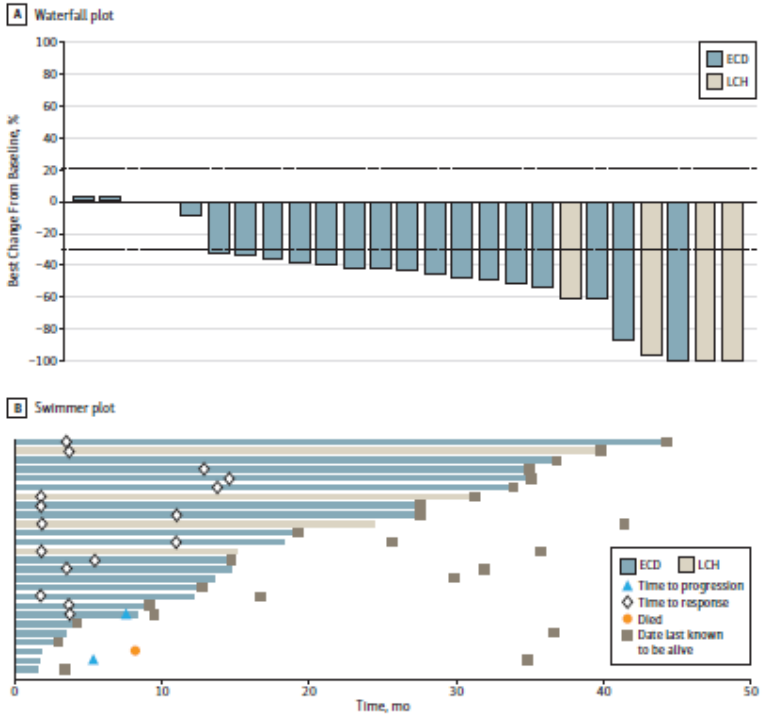


Table. Efficacy of Vemurafenib in Patients With ECD or Langerhans Cell Histiocytosis[a]

Outcome	Patients With ECD (n = 22)	Overall Cohort (n = 26)
Objective response rate (95% CI), %	54.5 (32.2-75.6)	61.5 (40.6-79.8)
Best overall response		
Complete response	1 (5)	2 (8)
Partial response	11 (50)	14 (54)
Stable disease	9 (41)	9 (35)
Progressive disease	0	0
Not evaluable[b]	1 (5)	1 (4)
Clinical benefit rate, No. (%) (95% CI)[c]	16 (73) (49.8-89.3)	20 (77) (56.4-91.0)
Median PFS, % (95% CI)	NE	NE
At 1 year	83 (66-100)	86 (72-100)
At 2 years	83 (66-100)	86 (72-100)
Median OS, % (95% CI)	NE	NE
At 1 year	95 (85-100)	96 (87-100)
At 2 years	95 (85-100)	96 (87-100)
Duration of follow-up, median (range) [IQR], mo	26.6 (3.0-44.3) [9.5-34.9]	28.8 (3.0-44.3) [12.8-35.1]

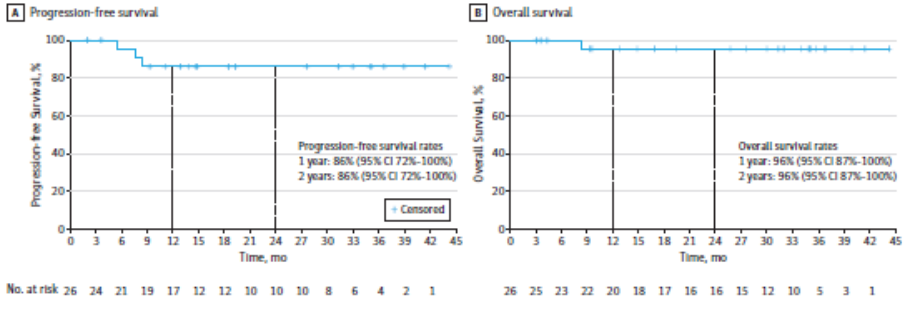
Abbreviations: ECD, Erdheim-Chester disease; IQR, interquartile range; NE, not estimable; OS, overall survival; PFS, progression-free survival.

[a] Unless otherwise indicated, data are reported as number (percentage) of patients.

[b] Patient had no measurable disease at baseline, and response could not be assessed.

[c] Includes complete response, partial response, and stable disease lasting 6 months or longer.

Figure 2. Kaplan-Meier Survival Curves for Patients With *BRAF* V600–Mutant Erdheim-Chester Disease or Langerhans Cell Histiocytosis



Trametinib in Histiocytic Sarcoma with an Activating *MAP2K1* (MEK1) Mutation

Mrinal M. Gounder, M.D.
David B. Solit, M.D.
William D. Tap, M.D.

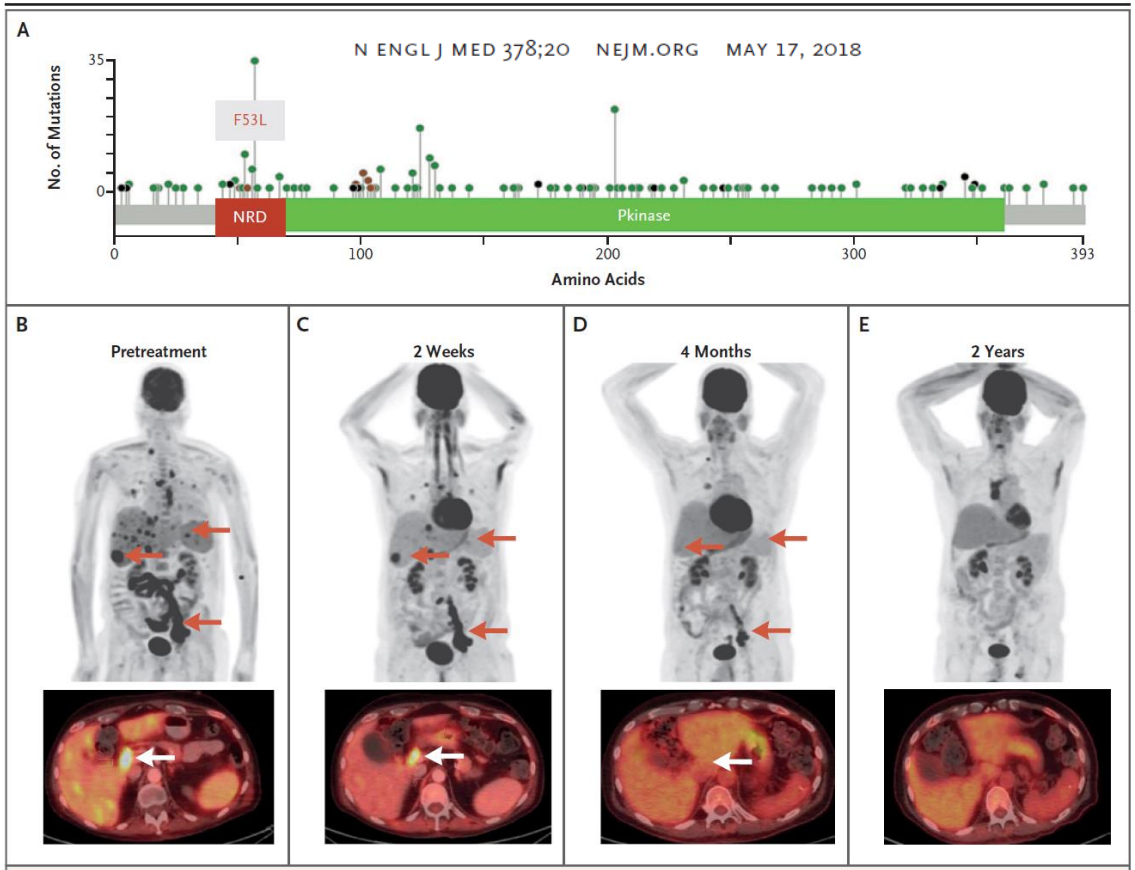
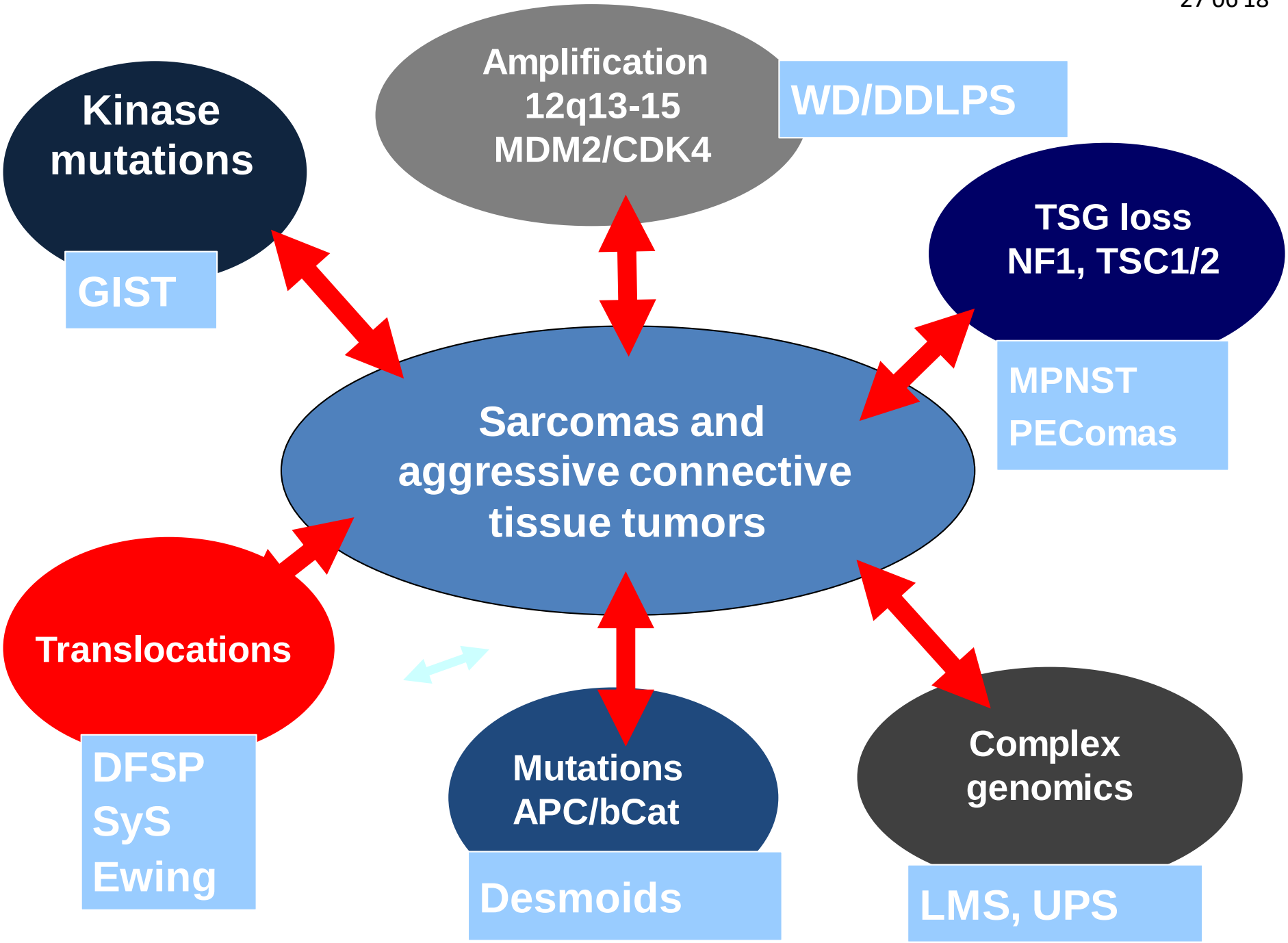


Figure 1. Mutations in *MAP2K1* across many Tumor Types and Pretreatment and Posttreatment Imaging in the Patient.

The MAP2K1 (MEK1) protein structure as well as mutations seen in the negative regulatory domain (NRD) and the protein kinase domain (Pkinase) are shown (Panel A). Locations of mutations and domains in proteins are shown by lollipop structures, with the mutation type indicated by color. Protein domains are also distinguished by color. Red denotes in-frame, black truncating, and green missense mutations. Maximum intensity projection (MIP) coronal and axial fused images from combined positron-emission tomography and computed tomography (PET–CT) with ^{18}F-fluorodeoxyglucose (FDG) before treatment show splenomegaly and widespread hypermetabolic lesions (red and white arrows) in the liver (maximum standardized uptake value [SUV], 9.8), spleen, lungs, and pelvic nodes (Panel B). Images obtained 2 weeks after the initiation of trametinib show interval resolution of splenomegaly and a decrease in the number, size, and metabolism of lesions in the liver (maximum SUV, 5.9), spleen, lungs, and pelvic nodes (Panel C). Images obtained 4 months after treatment show further response to treatment, with resolution of multiple lesions and a decrease in the size and ^{18}F-FDG avidity of the residual sites of disease. A lesion in the liver had a maximum SUV of 3.4 (Panel D). Coronal MIP and an axial PET–CT fused image after 2 years of treatment show a complete response to treatment, with no evidence of FDG neoplastic disease (Panel E); the foci of intense FDG activity uptake in the mediastinum correspond with biopsy-proven aspergillus infection, and the foci of intense FDG activity uptake in the left groin correspond to benign inflammation. Images courtesy of Dr. Lorenzo Mannelli, Department of Radiology, Memorial Sloan Kettering Cancer Center.

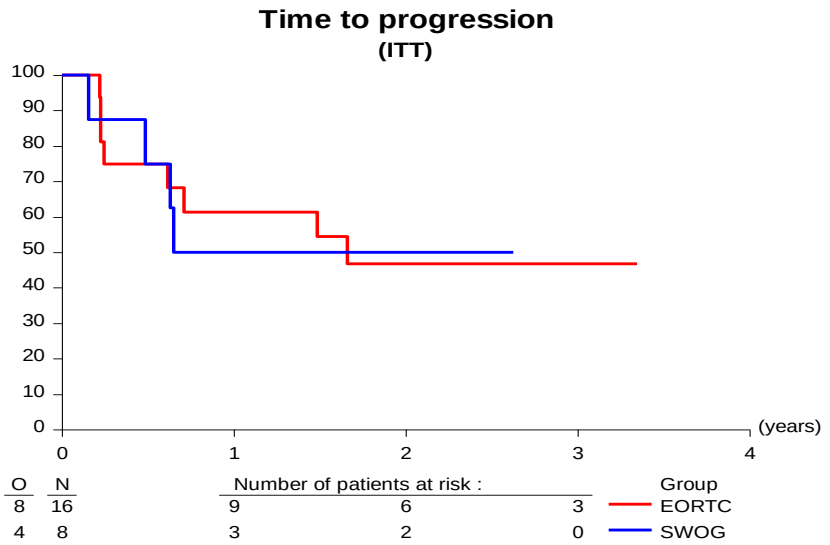

Kinase mutations
GIST
Amplification 12q13-15 MDM2/CDK4
WD/DDLPS
TSG loss NF1, TSC1/2
MPNST
PEComas
Sarcomas and aggressive connective tissue tumors
Translocations
DFSP
SyS
Ewing
Mutations APC/bCat
Desmoids
Complex genomics
LMS, UPS

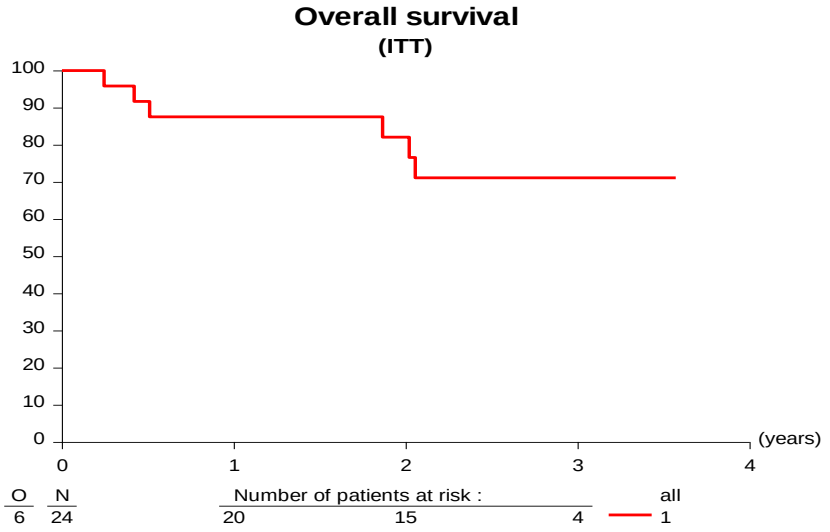
Imatinib mesylate in advanced dermatofibrosarcoma protuberans (DFSP) – pooled analysis of two phase II clinical trials

P. Rutkowski, et al ;
for the EORTC Soft Tissue/Bone Sarcoma Group and South-West Oncology Group

	Study		
	EORTC (N=16)	SWOG (N=8)	Total (N=24)
	N (%)	N (%)	N (%)
Response at 14 weeks			
PR	5 (31.3)		
SD	6 (37.5)		
PD	3 (18.8)		
Not evaluable	2 (12.5)		
Best overall response			
PR (confirmed)	3 (18.8)	4 (50.0)	7 (29.2)
PR (resected)	4 (25.0)	0 (0.0)	4 (16.7)
SD	4 (25.0)	2 (25.0)	6 (25.0)
PD	3 (18.8)	1 (12.5)*	4 (16.7)
Not evaluable	2 (12.5)	1 (12.5)	3 (12.5)

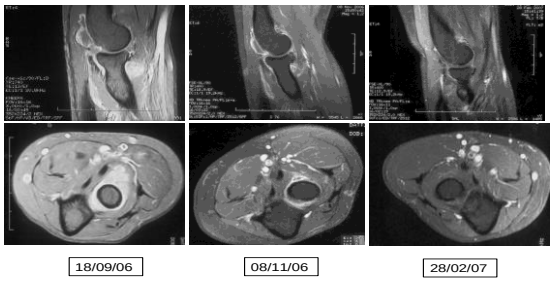
FDA approved in 2009





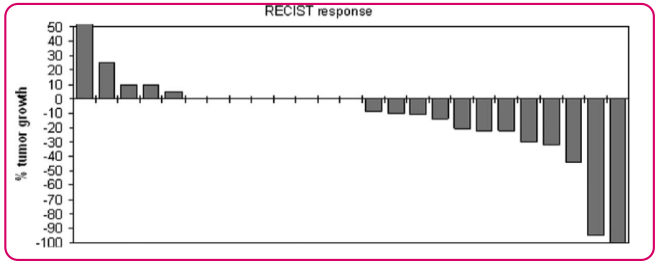
M-CSFR inhibitors (TKI & Ab) in PVNS with t(1,2), col3A6-CSF1 fusions

- Case report in 2008
  - (Ann Oncol 2008)



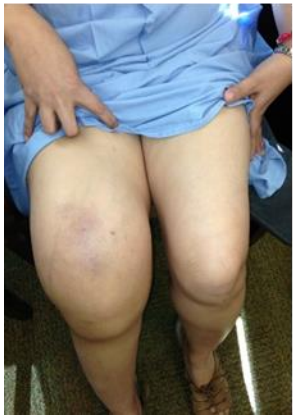
Response to imatinib in PVNS

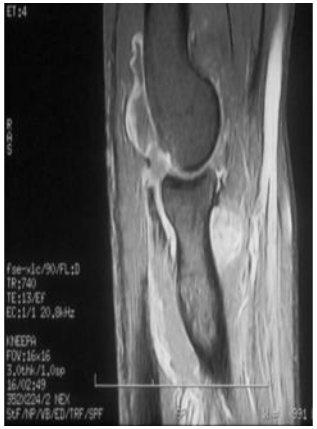
- Retrospective study 2011
  - (Cancer 2011)

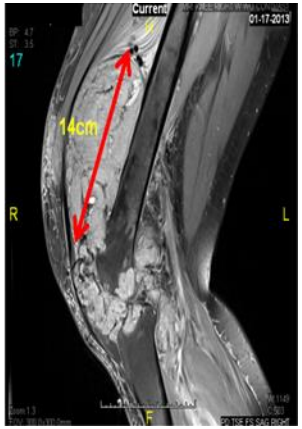


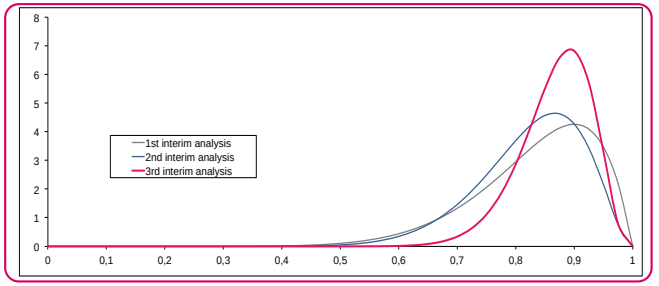
The best tumor shrinkage is illustrated according to RECIST

- Prospective study 2012
  - (Proc ASCO 2012)







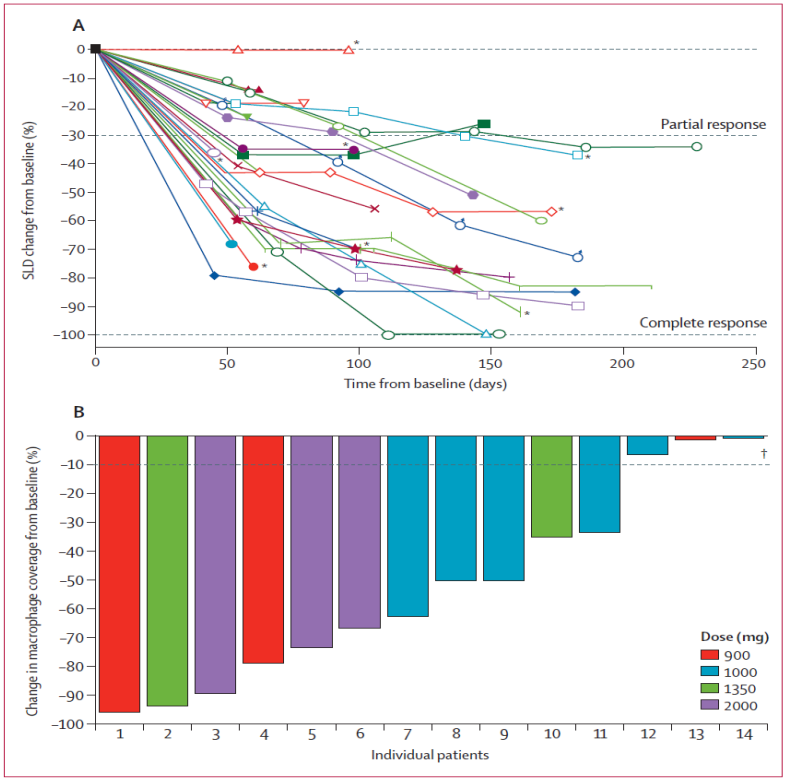


Distribution of the probability of efficacy of nilotinib (Bayesian design)

CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study

Philippe A Cassier*, Antoine Italiano*, Carlos A Gomez-Roca, Christophe Le Tourneau, Maud Toulmonde, Michael A Cannarile, Carola Ries, Anne Brillouet, Claudia Müller, Anna-Maria Jegg, Ann-Marie Bröske, Markus Dembowski, Katharine Bray-French, Christine Freilinger, Georgina Meneses-Lorente, Monika Baehner, Ross Harding, Jayantha Ratnayake, Keelara Abiraj, Nathalie Gass, Karen Noh, Randolph D Christen, Lidia Ukarma, Emmanuelle Bompas, Jean-Pierre Delord, Jean-Yves Blay†, Dominik Rüttinger†

Lancet Oncol 2015; 16: 949–56



Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial

Hans Gelderblom, Claire Cropet, Christine Chevreau, Richard Boyle, Martin Tattersall, Silvia Stacchiotti, Antoine Italiano, Sophie Piperno-Neumann, Axel Le Cesne, Virginia Ferraresi, Nicolas Penel, Florence Duffaud, Philippe Cassier, Maud Toulmonde, Paolo Casali, Sophie Taieb, Séverine Guillemaut, Séverine Metzger, David Pérol, Jean-Yves Blay

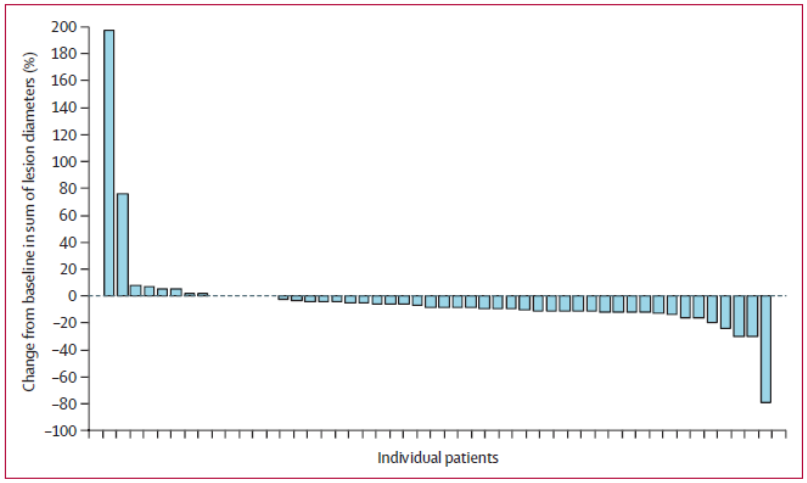


Figure 3: **Best overall response to nilotinib treatment during the treatment period in 50 patients**
One patient was reported to have stable disease by the investigator, but no precise measurement of the lesions were done after treatment.

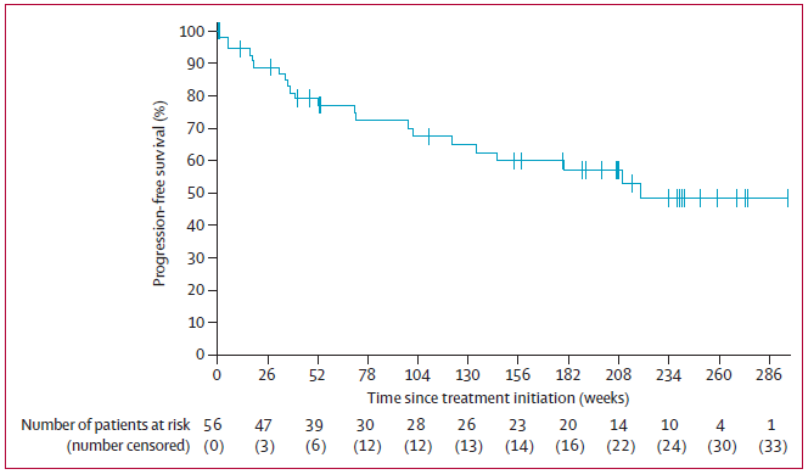


Figure 4: **Kaplan-Meier analysis of progression-free survival**

Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial

William D Tap, Hans Gelderblom, Emanuela Palmerini, Jayesh Desai, Sebastian Bauer, Jean-Yves Blay, Thierry Alcindor, Kristen Ganjoo, Javier Martín-Broto, Christopher W Ryan, David M Thomas, Charles Peterfy, John H Healey, Michiel van de Sande, Heather L Gelhorn, Dale E Shuster, Qiang Wang, Antoine Yver, Henry H Hsu, Paul S Lin, Sandra Tong-Starksen, Silvia Stacchiotti, Andrew J Wagner*, on behalf of the ENLIVEN investigators†*

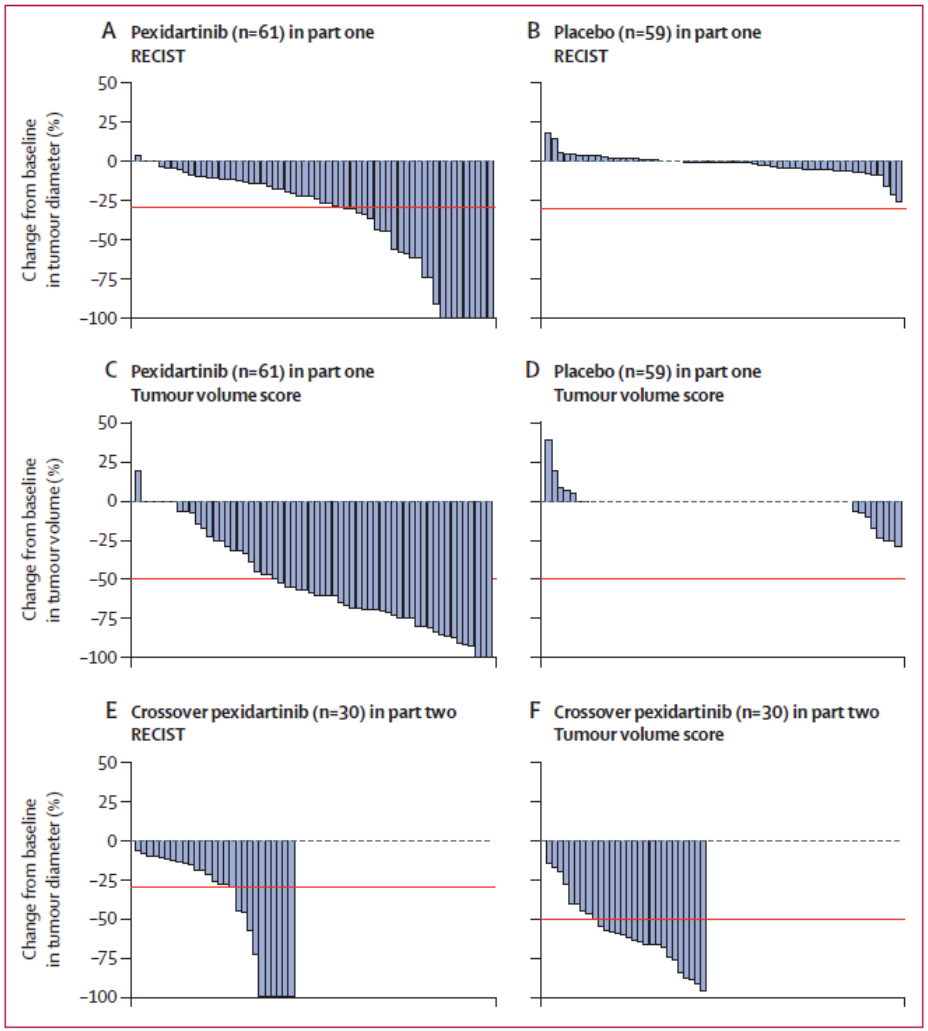


Figure 3: **Maximum change in tumour size according to RECIST and tumour volume score**

« Benign disease ??»

ENLIVEN Patient

- 56-year-old female diagnosed w/TGCT Jun 10, 1988
- Multiple prior surgeries, regular RBC transfusions
- Started pexidartinib Sep 5, 2016, and still ongoing
- Baseline pain: 5.6, decreased to 0.6 at week 25

October 2016 | November 2016 | June 2017 | September 2017 | May 2018

Courtesy of **Dr Silvia Stacchiotti,** Istituto Nazionale Tumori Milano

Crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumours with and without anaplastic lymphoma kinase gene alterations (European Organisation for Research and Treatment of Cancer 90101 CREATE): a multicentre, single-drug, prospective, non-randomised phase 2 trial

Patrick Schöffski, Jozef Sufliarsky, Hans Gelderblom, Jean-Yves Blay, Sandra J Strauss, Silvia Stacchiotti, Piotr Rutkowski, Lars H Lindner, Michael G Leahy, Antoine Italiano, Nicolas Isambert, Maria Debiec-Rychter, Raf Sciot, Thomas Van Cann, Sandrine Marréaud, Axelle Nzokirantevye, Sandra Collette, Agnieszka Wozniak

	ALK-positive patients (n=12)	*ALK*-negative patients (n=7)	Total (n=19)
Best RECIST 1.1 response			
Confirmed complete response	2 (17%)	0	2 (11%)
Confirmed partial response	4 (33%)	1 (14%)	5 (26%)
Non-confirmed partial response	1 (8%)	0	1 (5%)
Stable disease	5 (42%)	5 (71%)	10 (53%)
Progressive disease	0	1 (14%)	1 (5%)
Confirmed objective response	6 (50%; 21·1–78·9)	1 (14%; 0·0–57·9)	7 (37%; 16·3–61·6)
Disease control	12 (100%; 73·5–100·0)	6 (86%; 42·1–99·6)	18 (95%; 74·0–99·9)
Progression-free survival			
Alive without progression of IMFT	8 (67%)	3 (43%)	11 (58%)
Progression of IMFT or died	4 (33%)	4 (57%)	8 (42%)
12-month progression-free survival	9 (73%; 37·9–90·6)	4 (54%; 13·2–82·5)	13 (67%; 39·9–83·5)
Survival status			
Alive	10 (83%)	4 (57%)	14 (74%)
Dead	2 (17%)	3 (43%)	5 (26%)
Reason of death			
Progression of IMFT	1 (8%)	3 (43%)	4 (21%)
Cardiovascular disease	1 (8%)	0	1 (5%)
12-month survival	10 (82%; 44·7–95·1)	6 (83%; 27·3–97·5)	16 (82%; 54·7–93·9)

Data are n (%) or n (%, 95% CI). *ALK*=anaplastic lymphoma kinase. RECIST=Response Evaluation Criteria in Solid Tumors. IMFT= inflammatory myofibroblastic tumours.

Table 4: **Response assessment and activity summary according to investigator assessment**

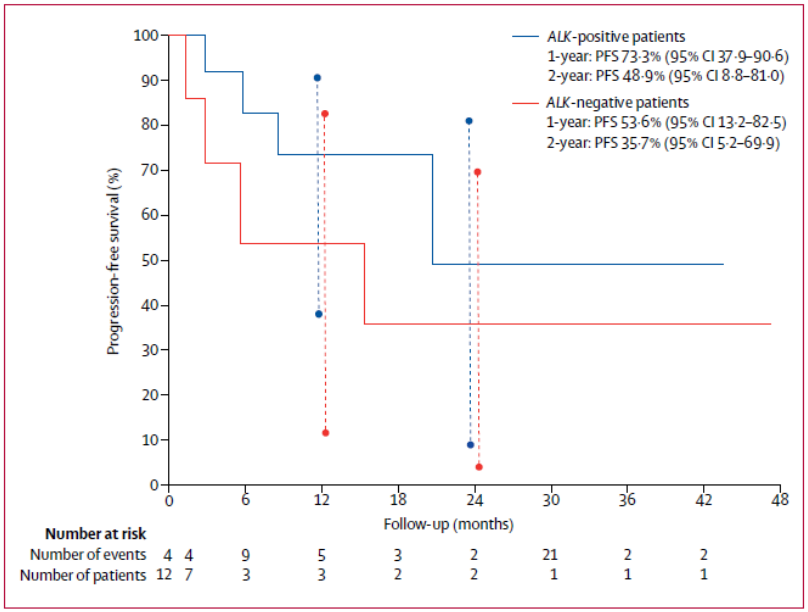
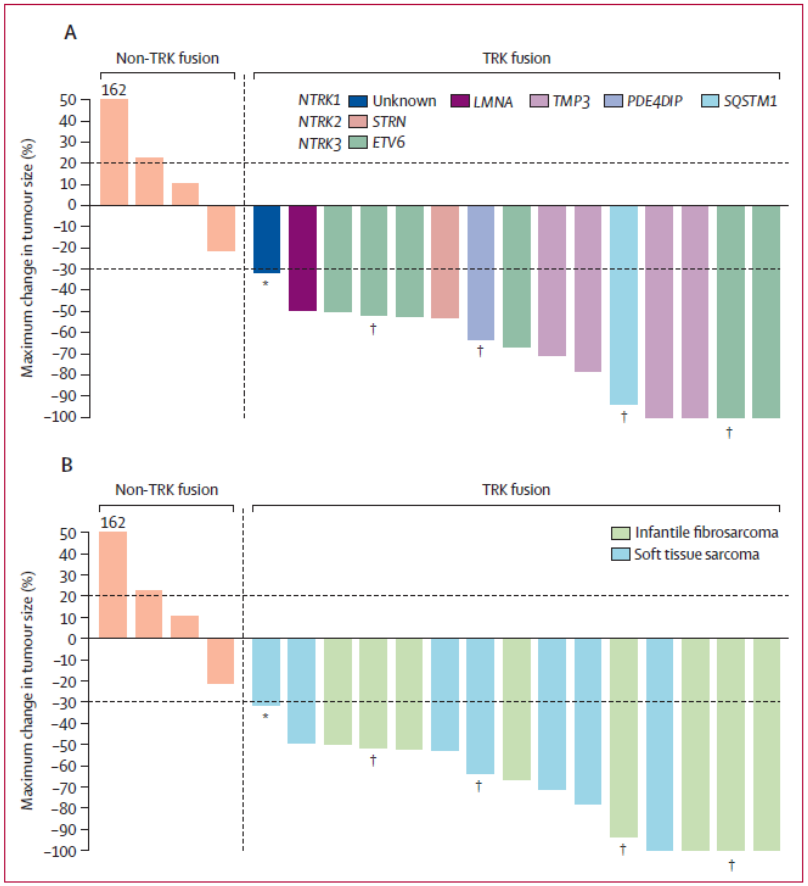


Figure 2: **Progression-free survival**

Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study

Theodore W Laetsch, Steven G DuBois*, Leo Mascarenhas, Brian Turpin, Noah Federman, Catherine M Albert, Ramamoorthy Nagasubramanian, Jessica L Davis, Erin Rudzinski, Angela M Feraco, Brian B Tuch, Kevin T Ebata, Mark Reynolds, Steven Smith, Scott Cruickshank, Michael C Cox, Alberto S Pappo*, Douglas S Hawkins**

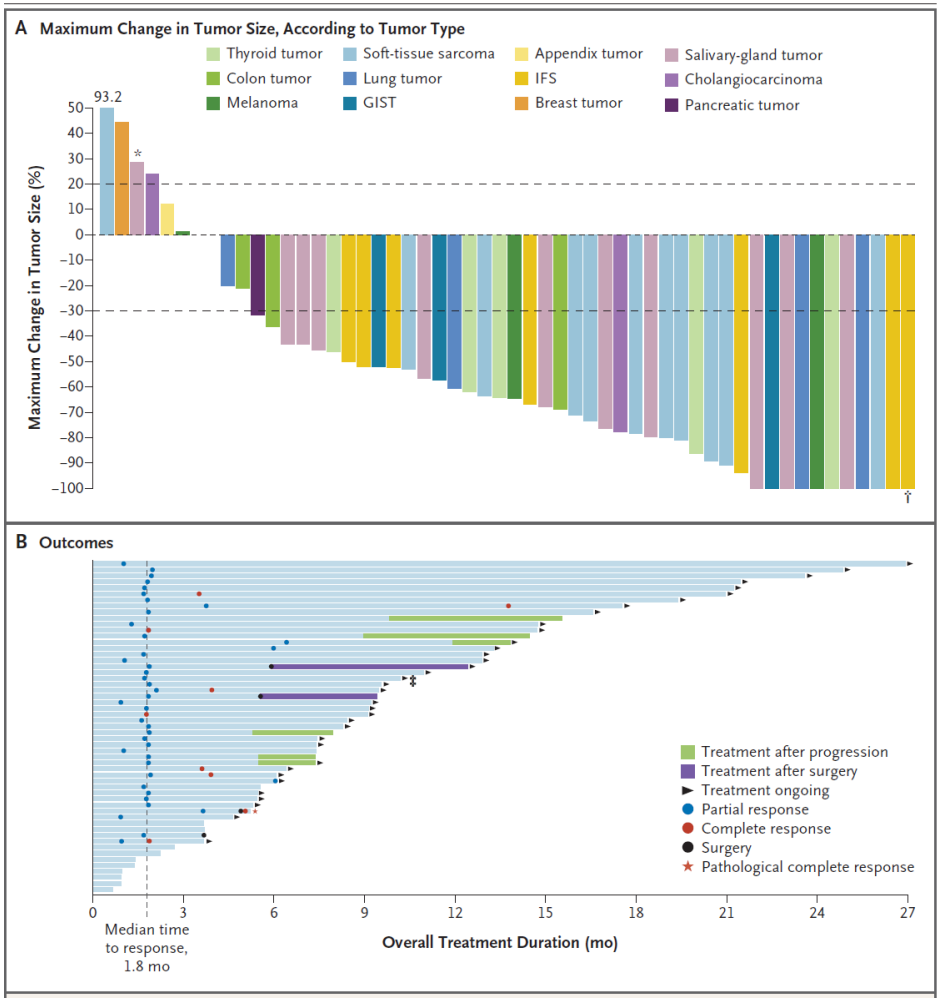
Lancet Oncol 2018; 19: 705–14



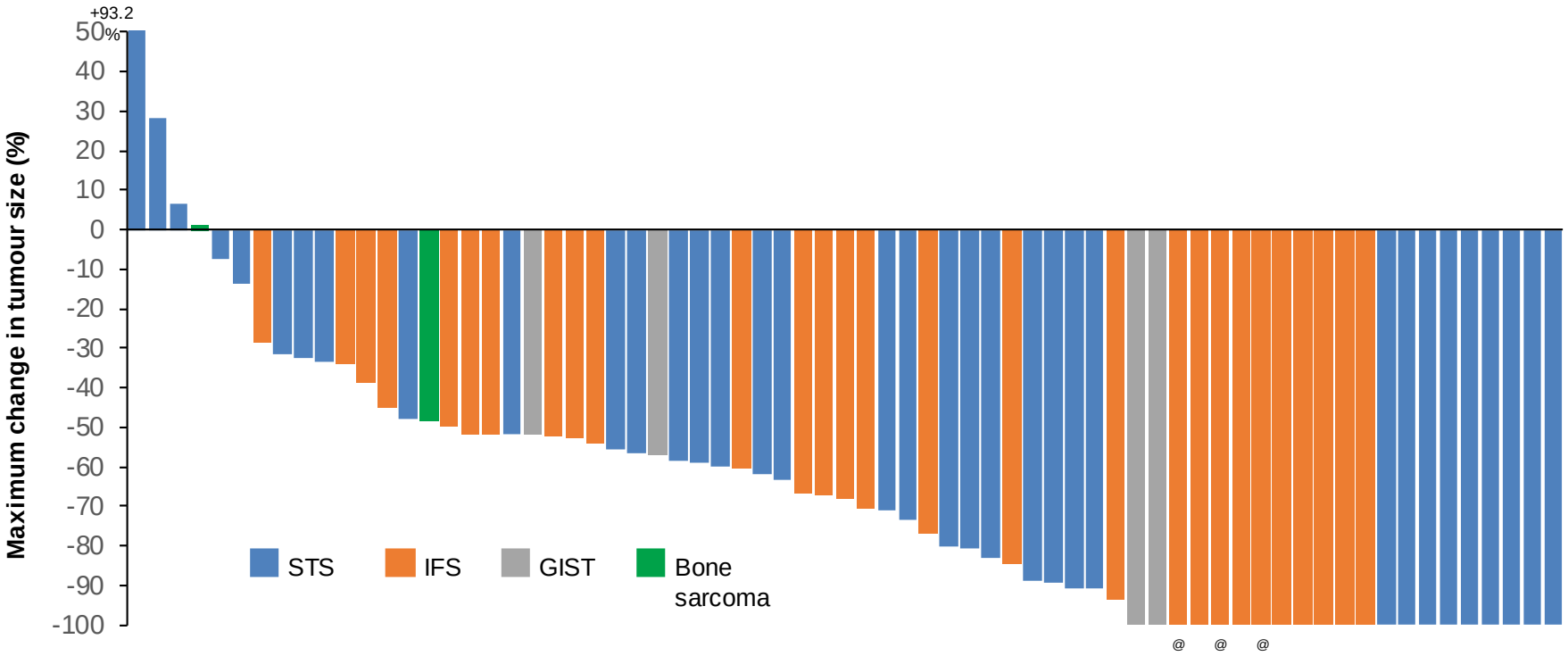
Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

N Engl J Med 2018;378:731-9.
DOI: 10.1056/NEJMoa1714448



Efficacy of Larotrectinib in Sarcomas Harbouring TRK fusions: Best Change in Target Lesions
(Investigator assessed)

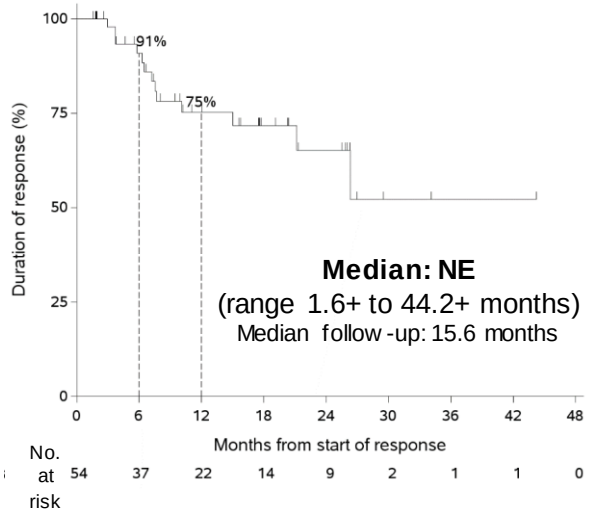


Data cut-off: Feb 19, 2019

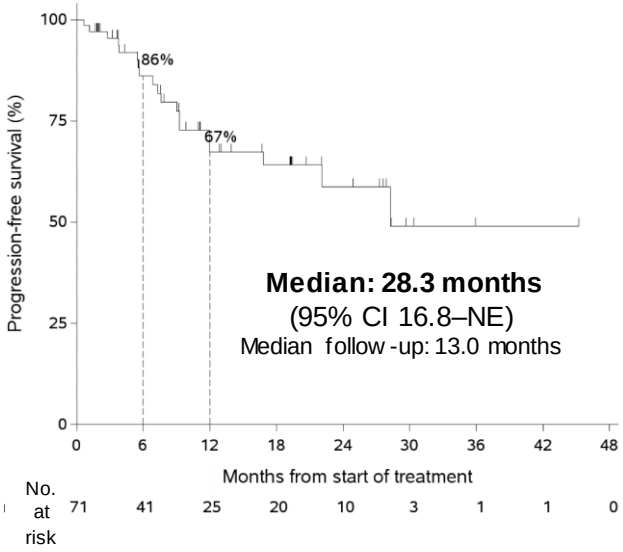
Tumour responses in patients with measurable disease and tumour values recorded at data cut-off, based on RECIST 1.1 sum of longest diameter.
Excludes one patient because post-baseline assessments were not yet done at data cut-off; one patient continued on treatment. @Patients with a pathological complete response.
GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; RECIST, Response Evaluation Criteria in Solid Tumors; STS, soft tissue sarcoma.

Efficacy Endpoints

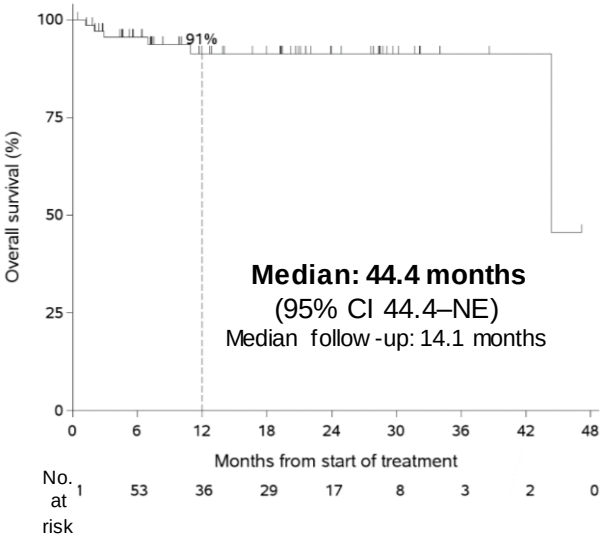
Duration of response



Progression-free survival



Overall survival



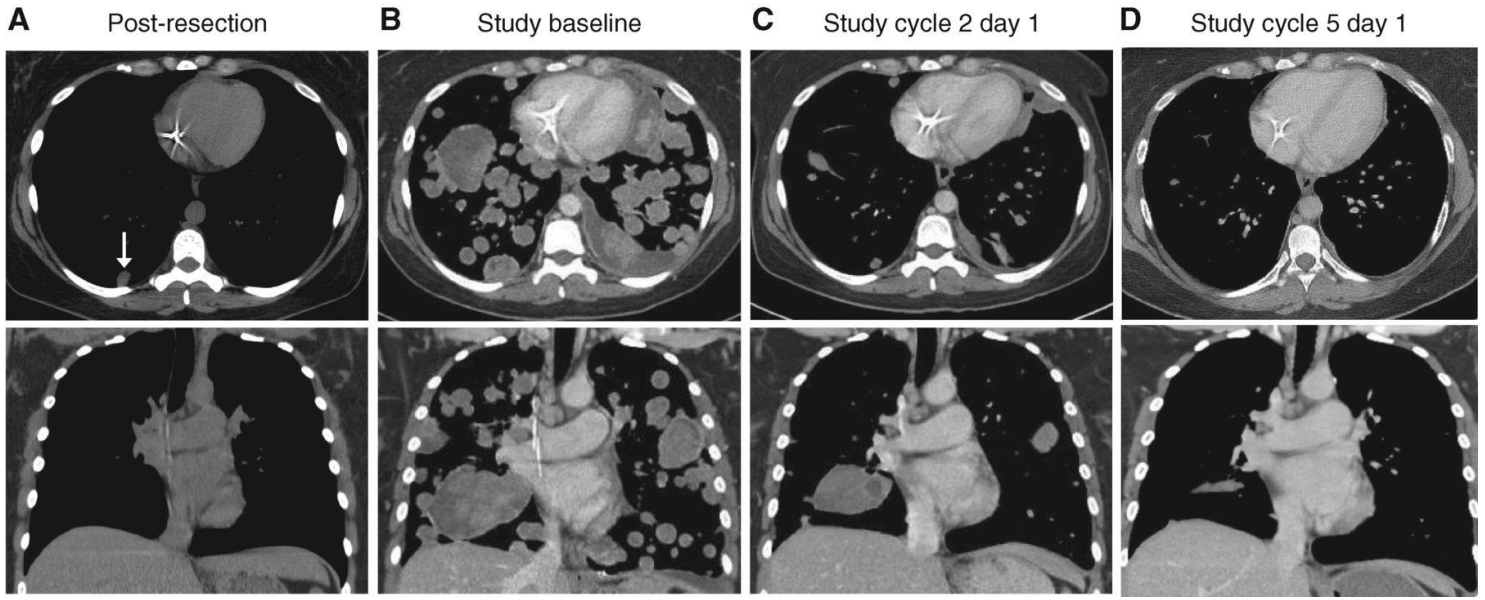
Data cut-off: Feb 19, 2019

Vertical tick marks represent censored patients. NE, not estimable.

60 year old woman with widely metastatic, refractory MPNST

TPM4-NTRK3 fusion

Enrolled in Phase II trial of larotrectinib – ASCO 2017 Oral Developmental Therapeutics

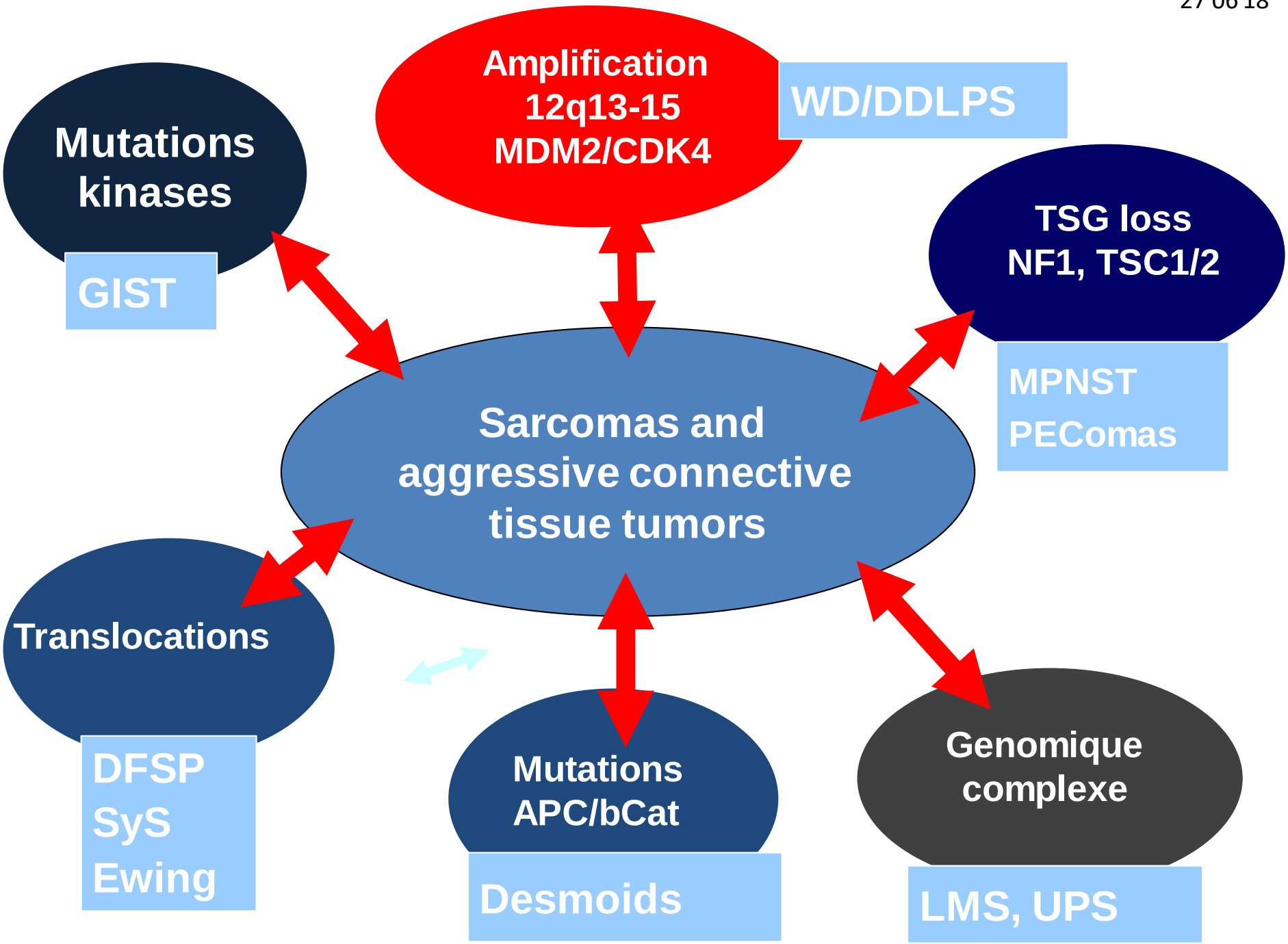


RC Doebele et al. Cancer Discovery 2015;5:1049-1057

M Gounder ASCO 2017

How to identify these patients?

- Translocation frequently present in very rare sarcomas (IFS, QNGIST, IMT)
- Translocations very rare (1%) in other sdarcomas (which are rare…)

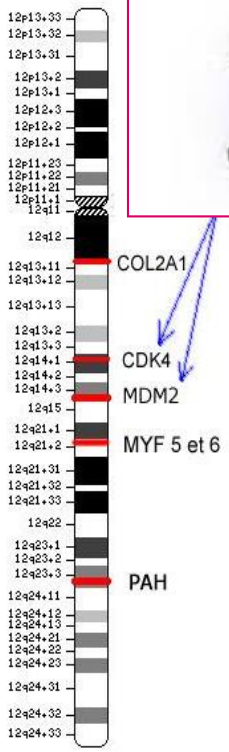

Amplification
12q13-15
MDM2/CDK4
WD/DDLPS
Mutations
kinases
GIST
TSG loss
NF1, TSC1/2
MPNST
PEComas
Sarcomas and
aggressive connective
tissue tumors
Translocations
DFSP
SyS
Ewing
Mutations
APC/bCat
Desmoids
Genomique
complexe
LMS, UPS

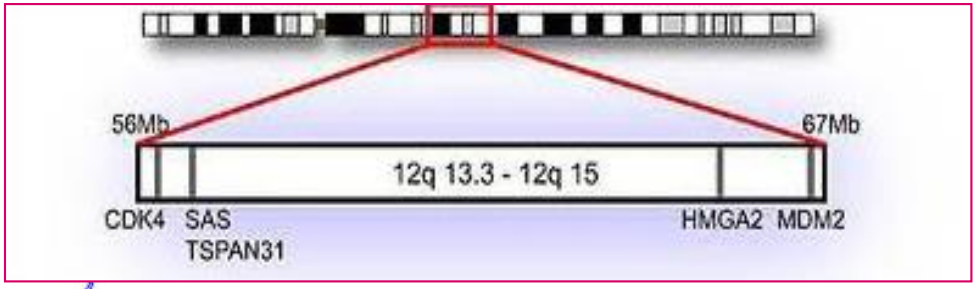
Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with *MDM2*-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study

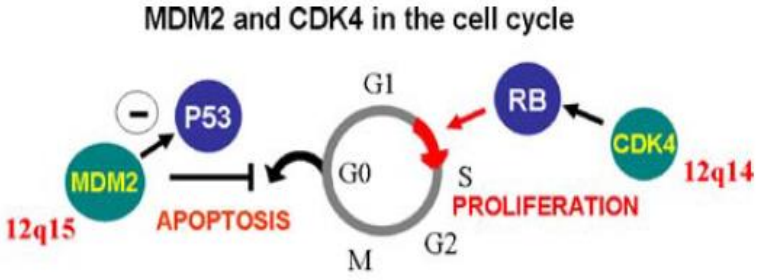
Isabelle Ray-Coquard, Jean-Yves Blay, Antoine Italiano, Axel Le Cesne, Nicolas Penel, Jianguo Zhi, Florian Heil, Ruediger Rueger, Bradford Graves, Meichun Ding, David Geho, Steven A Middleton, Lyubomir T Vassilev, Gwen L Nichols, Binh Nguyen Bui

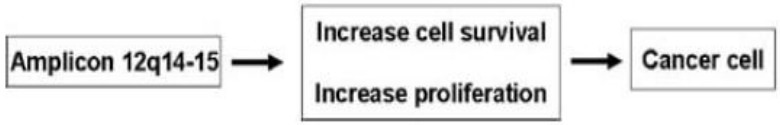
Structure

Chromosome 12



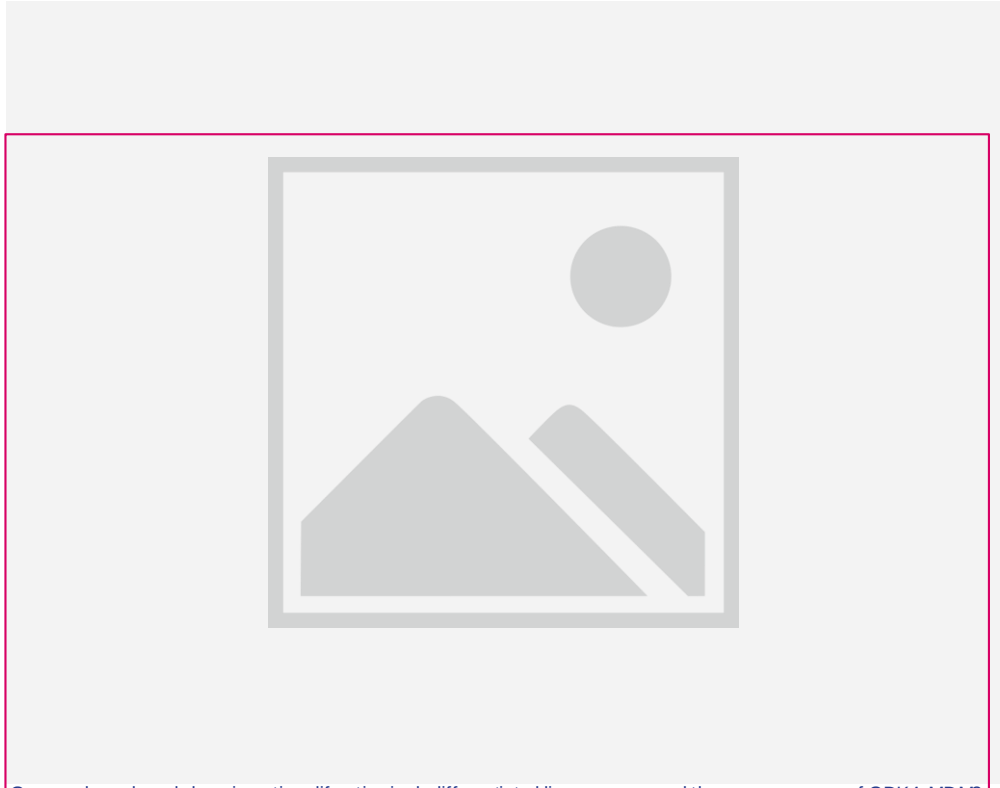




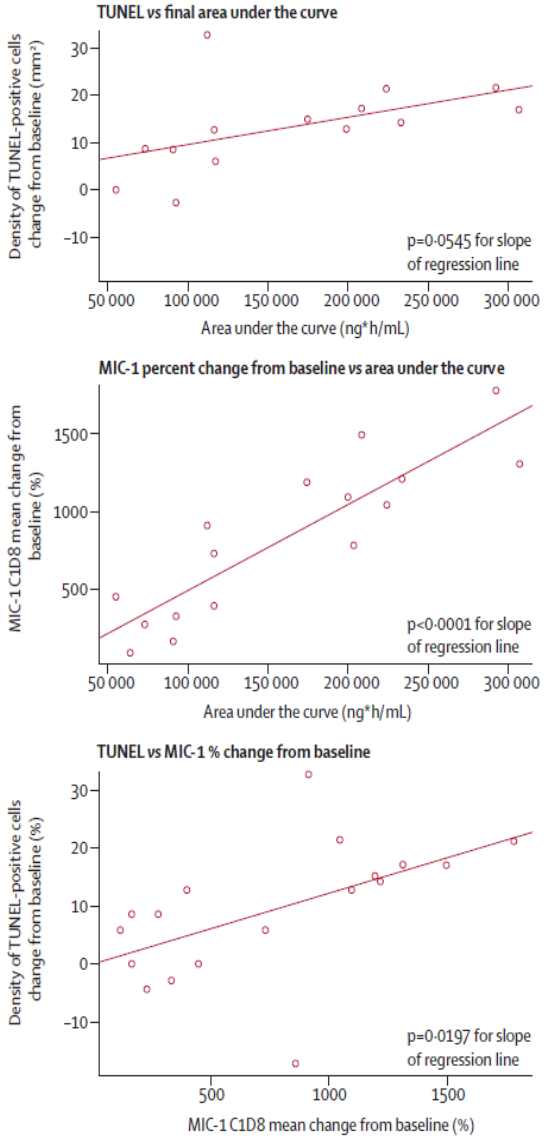


Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with *MDM2*-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study

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



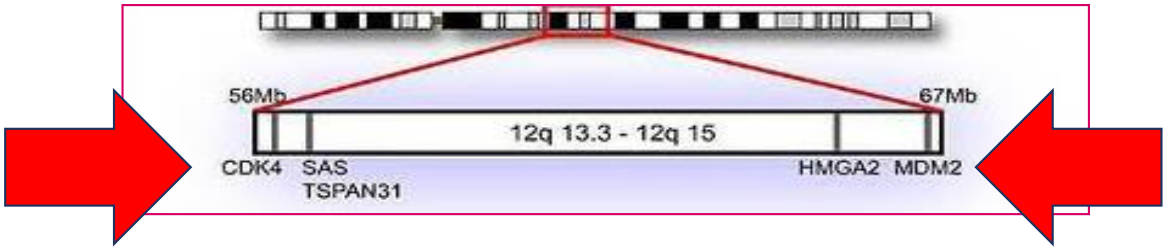
Genes whose knockdown is anti-proliferative in dedifferentiated liposarcoma, and the consequences of CDK4, MDM2 and YEATS4 knockdown in dedifferentiated liposarcoma

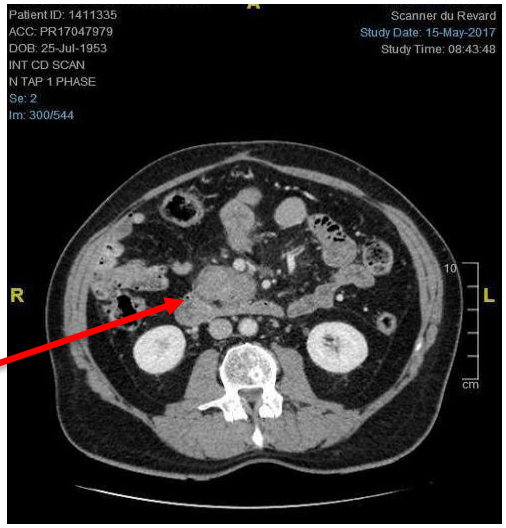


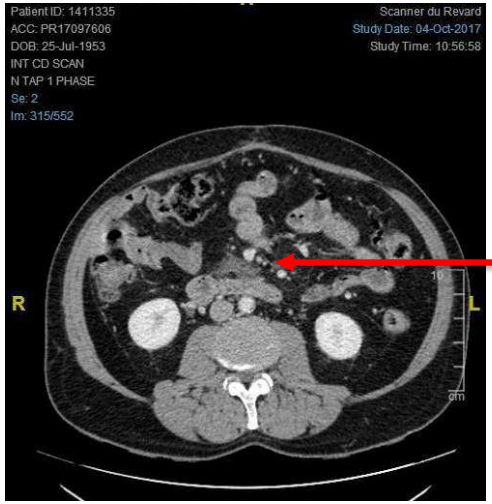
Phamacokinetic and pharmacodynamic data

Nat Gen 2010

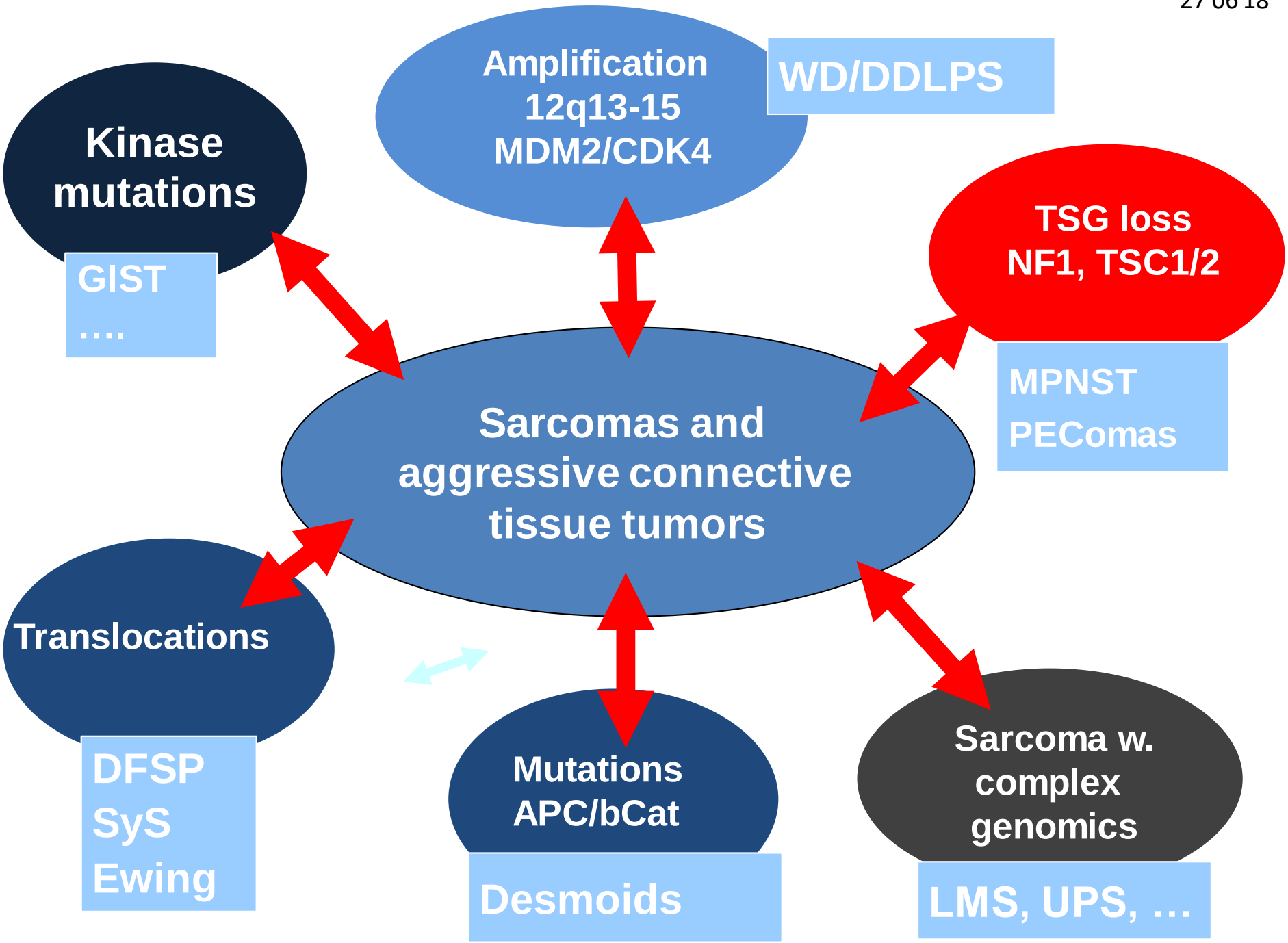
Phase I combinations of MDM2/CDK4 ongoing







First example of the need for a dual oncogene blockade (from a single amplicon) ?


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

Clinical Cancer Research

Role of Chemotherapy, VEGFR Inhibitors, and mTOR Inhibitors in Advanced Perivascular Epithelioid Cell Tumors (PEComas)

Roberta Sanfilippo[1], Robin L. Jones[2], Jean-Yves Blay[3], Axel Le Cesne[4], Salvatore Provenzano[1], Georgios Antoniou[2], Olivier Mir[4], Giovanni Fucà[1], Elena Fumagalli[1], Rossella Bertulli[1], Silvia Stacchiotti[1], Mehdi Brahmi[3], Federica Grosso[5], Armelle Dufresne[3], Nadia Hindi[6,7], Marta Sbaraglia[8], Alessandro Gronchi[9], Paola Collini[10], Angelo P. Dei Tos[8,11], and Paolo G. Casali[1,12]

Table 1. Patients and disease characteristics at time of first-line systemic treatment initiation

Characteristics	Total ($N = 53$) N (%)
Center	
INT/RTR	32 (60.4)
Royal Marsden	10 (18.8)
French sarcoma group	9 (17)
Spanish sarcoma group	2 (3.8)
Sex	
Male	16 (30.2)
Female	37 (69.8)
Age (years)	
Median (range)	54 (26–76)
Histopathology	
Malignant PEComa	42 (79.2)
Epithelioid angiomyolipoma	11 (20.8)
Primary site	
Kidney	6 (11.3)
Retroperitoneum	11 (20.8)
Uterus	11 (20.8)
Soft tissue	7 (13.2)
Gastrointestinal	5 (9.4)
Pelvis	6 (11.3)
Lung	1 (1.9)
Other	6 (11.3)
Primary tumor resection	
No	8 (15.1)
Yes	45 (84.9)
Stage	
Locally advanced	3 (5.7)
Metastatic	50 (94.3)
Synchronous metastases	
No	29 (54.7)
Yes	24 (45.3)
Metastatic sites	
Lymph nodes	4 (7.5)
Lung	12 (22.6)
Soft tissue	5 (9.4)
Liver	10 (18.8)
Peritoneum	9 (17)
Other	14 (26.4)
Not applicable	3 (5.7)

Abbreviations: INT, Istituto Nazionale dei Tumori di Milano; RTR, Italian Rare Cancer Network.

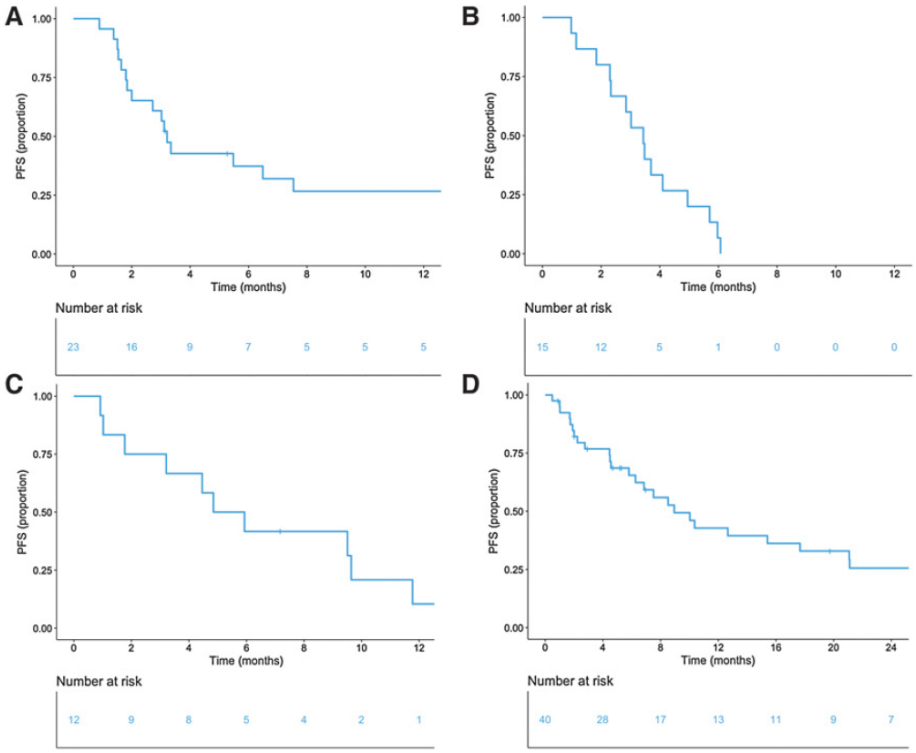
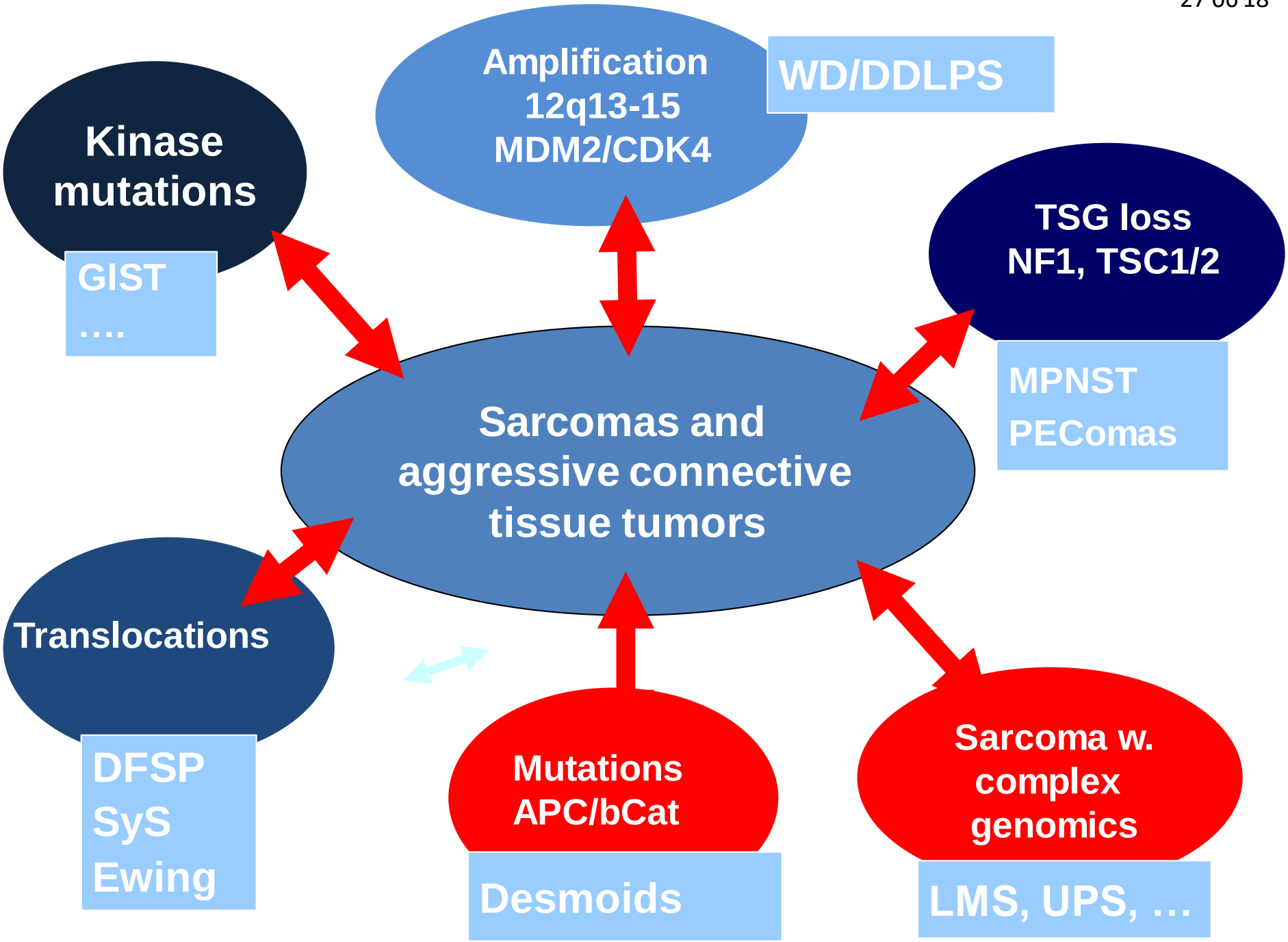


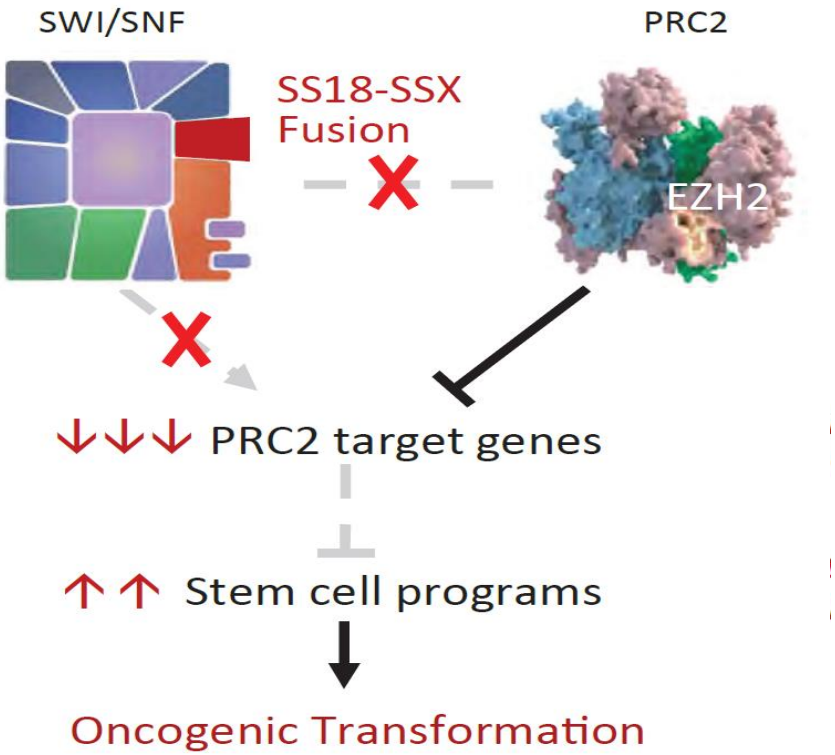
Figure 2.
Kaplan–Meier curves for PFS of patients treated with anthracycline-based chemotherapy (**A**), gemcitabine-based chemotherapy (**B**), VEGFR inhibitors (**C**), and mTOR inhibitors (**D**).


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

Epigenetic "Next Generation" Targets in Sarcomas

Tazemetostat (EZH2 inhibitor) for INI-1 deficient malignant rhabdoid tumors and epithelioid sarcomas

Epithelioid sarcoma



EZH2 inhibitor, tazemetostat

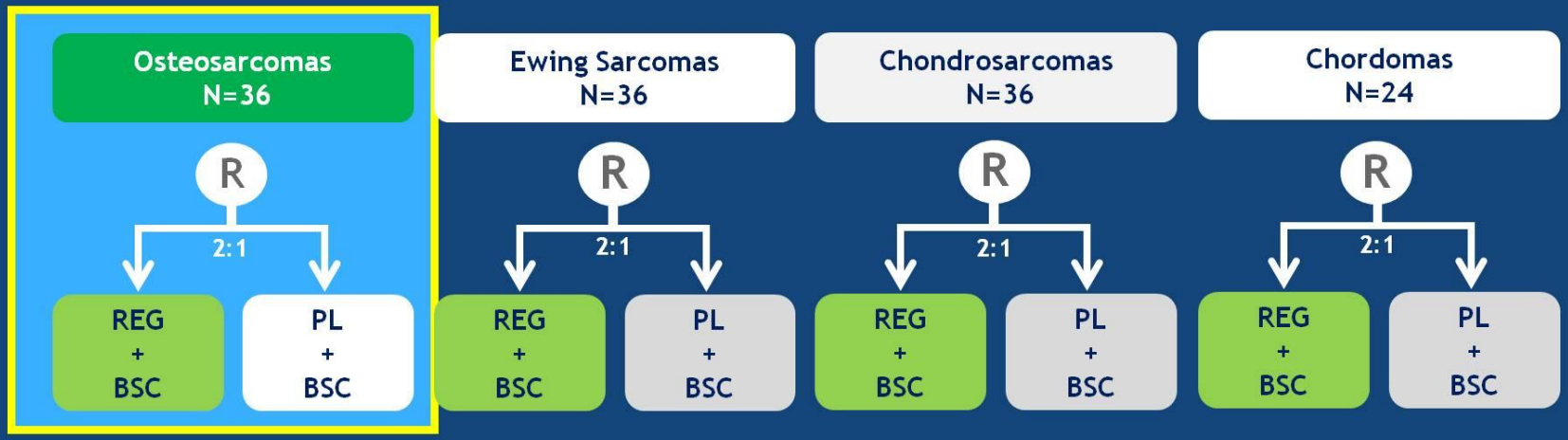
Endpoint Category, n (%)	No Prior Anticancer Therapy N=24	Prior Anticancer Therapy N=38	Total N=62
DCR [CR + PR + (SD≥32 weeks)]	9 (38)	6 (16)	15 (24)
90% CI	(21.2, 56.3)	(7.1, 28.8)	(15.5, 34.8)
ORR (CR + PR)	5 (21)	3 (8)	8 (13)
90% CI	(8.6, 38.9)	(2.2, 19.2)	(6.6, 22.1)
Best Response			
CR	0	0	0
PR	5 (21)	3 (8)	8 (13)
SD	16 (67)	20 (53)	36 (58)
PD	2 (8)	11 (29)	13 (21)
NE, missing, or unknown	1 (4)	4 (11)	5 (8)
Median duration of response, weeks	41	48+	48+
Range	(7.1+, 48.1+)	(40.1, 95.0+)	(7.1+, 95.0+)
Median progression-free survival, weeks	25.7	14.7	16.1
90% CI	(23.7, NE)	(8.3, 16.0)	(15.1, 25.3)
Median overall survival, weeks	NE	47.4	82.4
90% CI		(33.7, 64.1)	(47.7, NE)

Gounder M, et al. CTOS 2018

REGOBONE: study design

Regorafenib for Advanced/Metastatic Bone Sarcomas

- Basket of 4 parallel *non-comparative* randomized phase II trials

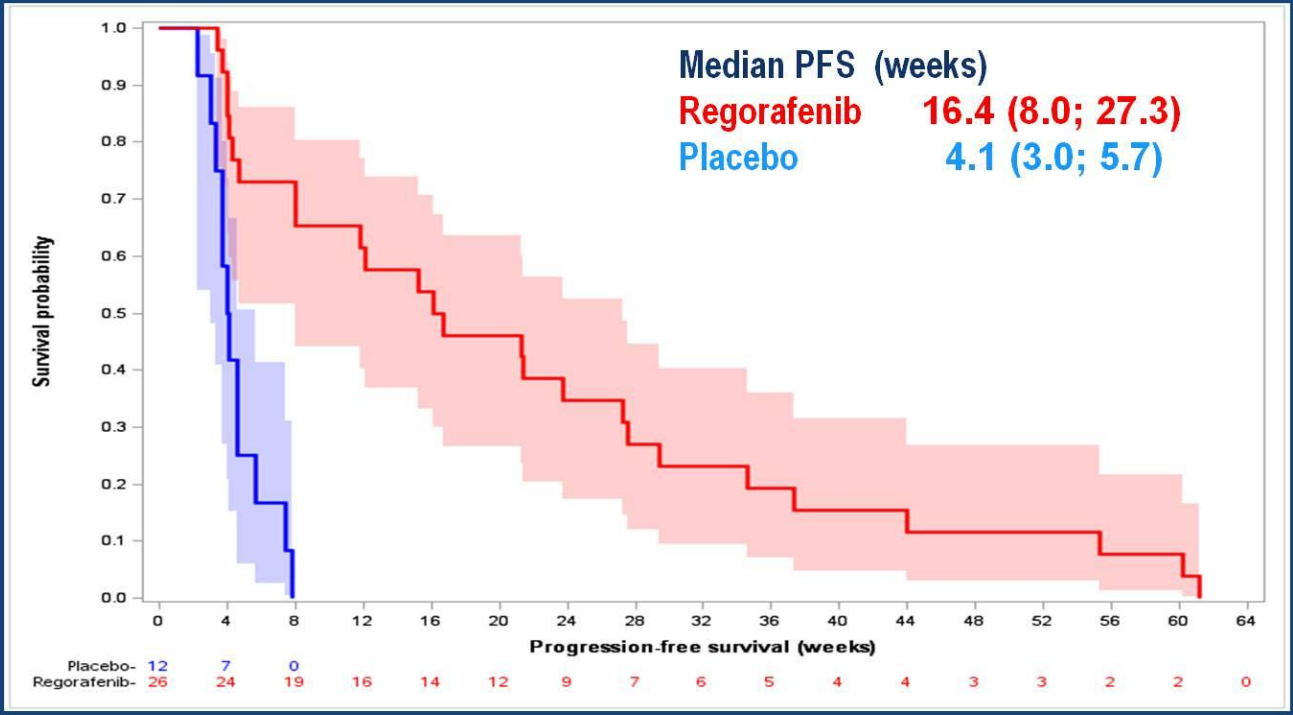


REGORAFENIB or PLACEBO dosed until progression or unacceptable toxicity

Pts initially randomized to PL could cross-over to open-label REG after PD confirmation

Osteosarcoma in REGOBONE: Progression-Free Survival

Primary end-point per blinded central review



Presented By Florence Duffaud at 2018 ASCO Annual Meeting

ORIGINAL ARTICLE

Sorafenib for Advanced and Refractory Desmoid Tumors

Mrinal M. Gounder, M.D., Michelle R. Mahoney, M.S., Brian A. Van Tine, M.D., Ph.D., Vinod Ravi, M.D., Steven Attia, D.O., Hari A. Deshpande, M.D., Abha A. Gupta, M.D., Mohammed M. Milhem, M.D., Robert M. Conry, M.D., Sujana Movva, M.D., Michael J. Pishvaian, M.D., Ph.D., Richard F. Riedel, M.D., Tarek Sabagh, M.D., William D. Tap, M.D., Natally Horvat, M.D., Ethan Basch, M.D., Lawrence H. Schwartz, M.D., Robert G. Maki, M.D., Ph.D., Narasimhan P. Agaram, M.B., B.S., Robert A. Lefkowitz, M.D., Yousef Mazaheri, Ph.D., Rikiya Yamashita, M.D., Ph.D., John J. Wright, M.D., Ph.D., Amylou C. Dueck, Ph.D., and Gary K. Schwartz, M.D.

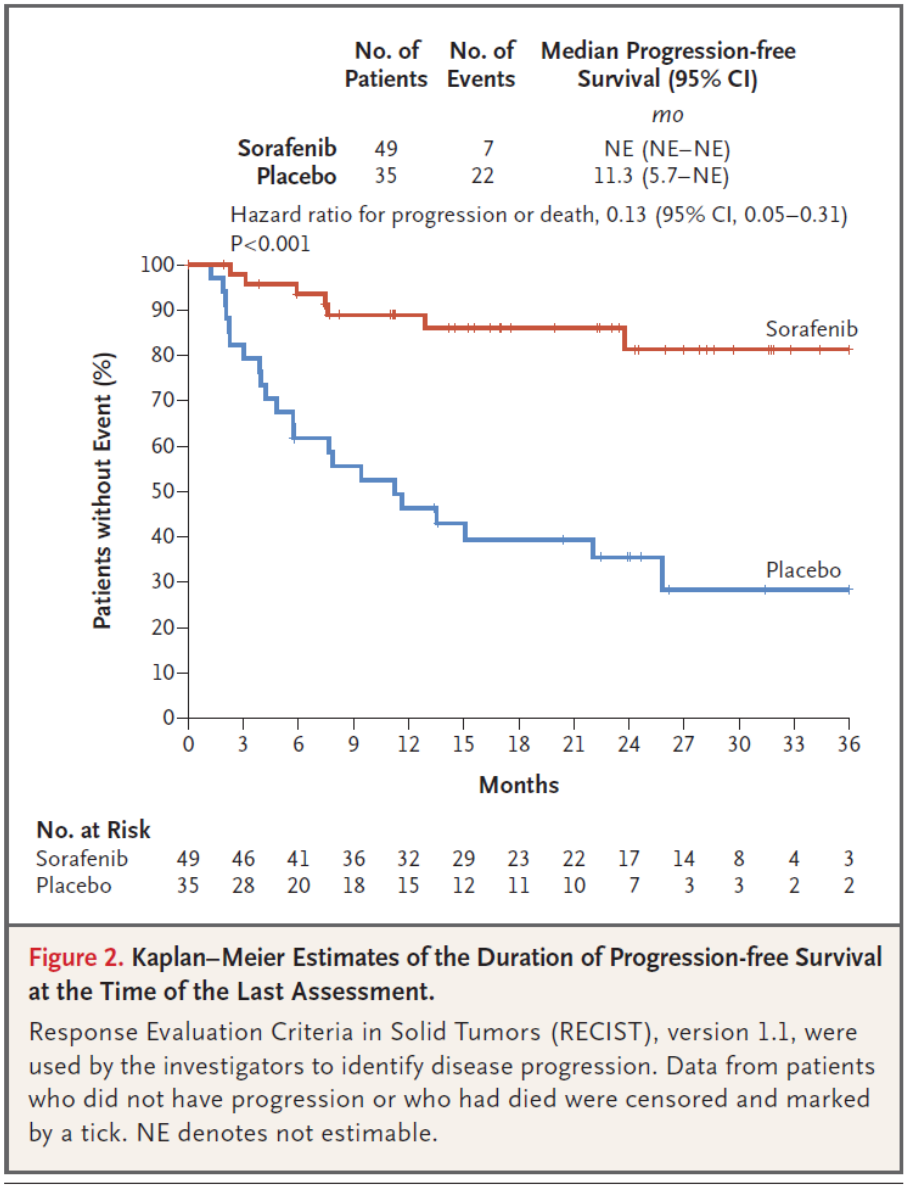


Figure 2. Kaplan–Meier Estimates of the Duration of Progression-free Survival at the Time of the Last Assessment.

Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were used by the investigators to identify disease progression. Data from patients who did not have progression or who had died were censored and marked by a tick. NE denotes not estimable.

Immunotherapy in Sarcoma?

William Coley

"… on May 2, 1891, i inoculated a case of sarcoma"

"At the end of two weeks, the tumor had disappeared"

AMERICAN JOURNAL

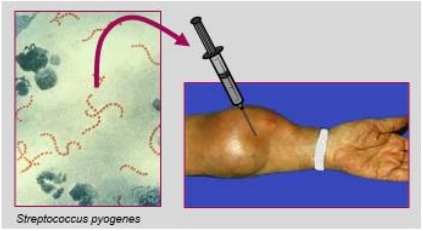
OF THE MEDICAL SCIENCES.

MAY, 1893.

THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYSIPELAS: WITH A REPORT OF TEN ORIGINAL CASES.[1]

By William B. Coley, M.D.,

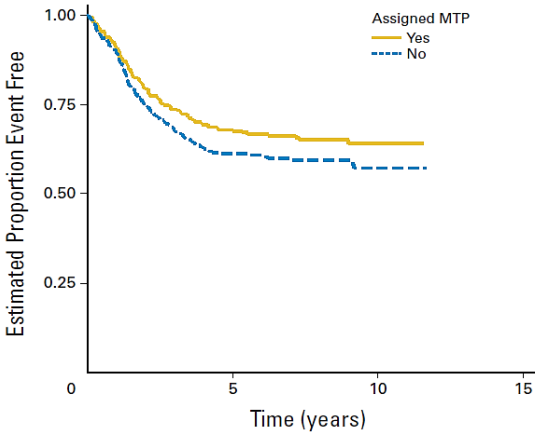
Assistant Surgeon to the Hospital for Ruptured and Crippled; Instructor in Surgery in the Post-Graduate Medical School, New York.



Streptococcus pyogenes

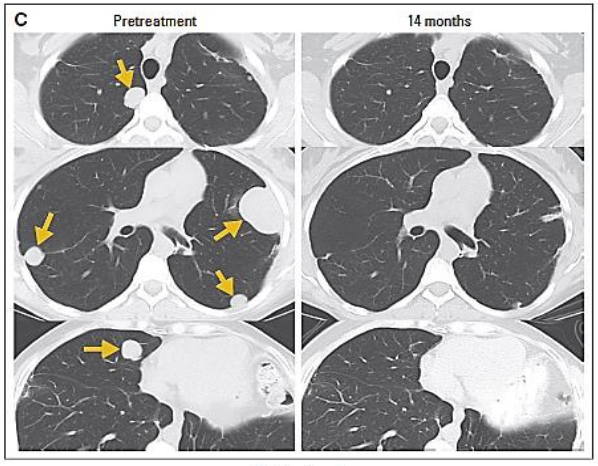
Osteosarcoma: A Randomized, Prospective Trial of the Addition of Ifosfamide and/or Muramyl Tripeptide to Cisplatin, Doxorubicin, and High-Dose Methotrexate

Paul A. Meyers, Cindy L. Schwartz, Mark Krailo, Eugenie S. Kleinerman, Donna Betcher, Mark L. Bernstein, Ernest Conrad, William Ferguson, Mark Gebhardt, Allen M. Goorin, Michael B. Harris, John Healey, Andrew Huvos, Michael Link, Joseph Montebello, Helen Nadel, Michael Nieder, Judith Sato, Gene Siegal, Michael Weiner, Robert Wells, Lester Wold, Richard Womer, and Holcombe Grier



Tumor Regression in Patients With Metastatic Synovial Cell Sarcoma and Melanoma Using Genetically Engineered Lymphocytes Reactive With NY-ESO-1

Paul F. Robbins, Richard A. Morgan, Steven A. Feldman, James C. Yang, Richard M. Sherry, Mark E. Dudley, John R. Wunderlich, Azam V. Nahvi, Lee J. Helman, Crystal L. Mackall, Udai S. Kammula, Marybeth S. Hughes, Nicholas P. Restifo, Mark Raffeld, Chyi-Chia Richard Lee, Catherine L. Levy, Yong F. Li, Mona El-Gamil, Susan L. Schwarz, Carolyn Laurencot, and Steven A. Rosenberg



Meyers PA, et al. *J Clin Oncol.* 2005;23:2004-2011. Robbins PF, et al. *J Clin Oncol.* 2011;29:917-924.

Negative trials?

Immunotherapy with Single Agent Nivolumab for Advanced Leiomyosarcoma of the Uterus: Results of a Phase 2 Study

Eytan Ben-Ami, MD[1]; Constance M. Barysauskas, MS[2]; Sarah Solomon, BA[1]; Kadija Tahlil, BS[1]; Rita Malley, BA[1]; Melissa Hohos, RN, BSN, OCN[1]; Kathleen Polson, ANP-BC[1]; Margaret Loucks, FNP[1]; Mariano Severgnini, MS[3]; Tara Patel, BA[3]; Amy Cunningham, BA[3]; Scott J. Rodig, MD, PhD[3,4]; F. Stephen Hodi, MD[3,5]; Jeffrey A. Morgan, MD[1]; Priscilla Merriam, MD[1]; Andrew J. Wagner, MD, PhD[1]; Geoffrey Shapiro, MD, PhD[6,7]; and Suzanne George, MD[1]

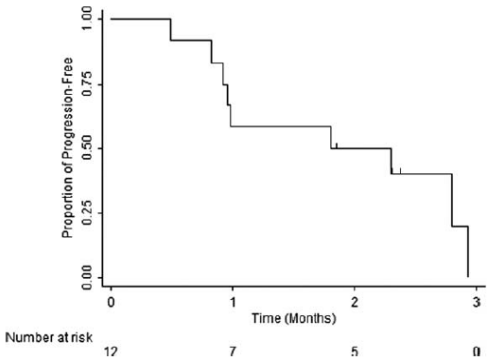


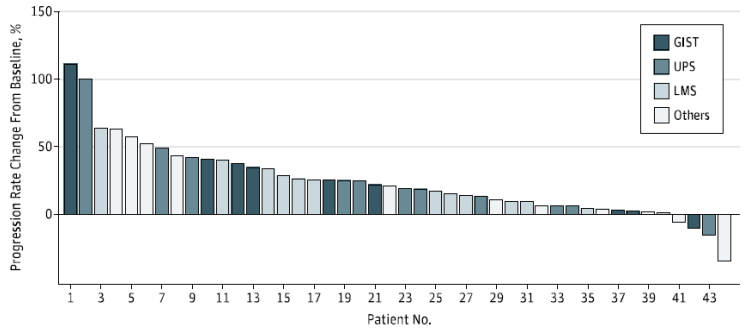
Figure 1. Progression-free survival.

JAMA Oncology | Brief Report

Resistance to PD-1 Targeting, Macrophage Infiltration, and IDO Pathway Activation in Sarcomas

Maud Toulmonde, MD; Nicolas Penel, MD, PhD; Julien Adam, MD, PhD; Christine Chevreau, MD; Jean-Yves Blay, MD, PhD; Axel Le Cesne, MD; Emmanuelle Bompas, MD; Sophie Piperno-Neumann, MD; Sophie Cousin, MD; Thomas Grellety, MD; Thomas Ryckewaert, MD; Alban Bessede, PhD; François Ghiringhelli, MD, PhD; Marina Pulido, MSc; Antoine Italiano, MD, PhD

Figure 2. Change in Progression Rate for 44 Patients



GIST indicates gastrointestinal stromal tumor; LMS, leiomyosarcoma; others, other sarcomas; UPS, undifferentiated pleomorphic sarcoma.

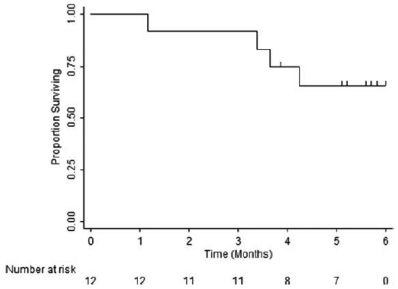


Figure 2. Overall survival.

TABLE 2. Grade 3 or Higher Toxicities

Patient	Toxicity	Grade	Relationship to Drug
1	Dyspnea	3	Unrelated
1	Dyspnea	5	Unrelated
2	Small intestinal obstruction	3	Unrelated
3	Hematuria	3	Unrelated
3	Depression	4	Unrelated
4	Abdominal pain	3	Possible
6	Renal colic	3	Unrelated
9	Serum amylase increased	4	Definite
9	Lipase increased	4	Definite
10	Dyspnea	3	Unrelated
10	Cardiac arrest	5	Unrelated
11	Fatigue	3	Probable
12	Cough	3	Unrelated
12	Dyspnea	3	Unrelated

Article

B cells are associated with survival and immunotherapy response in sarcoma

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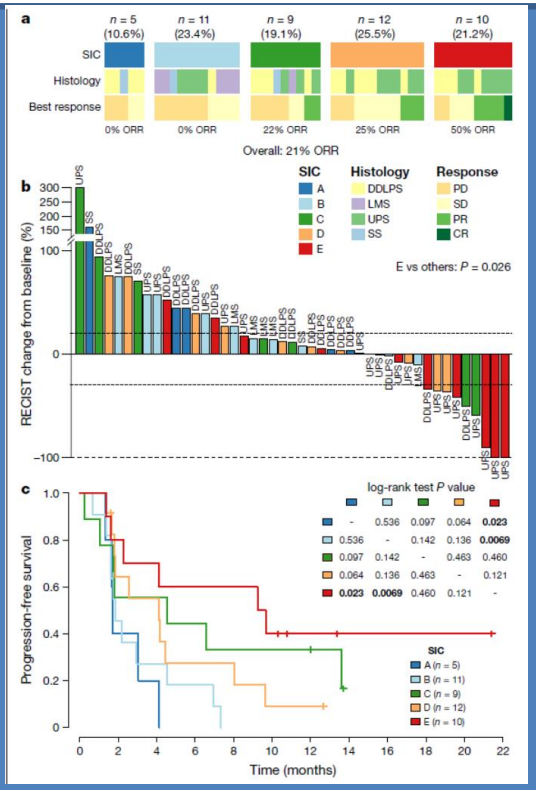
Florent Petitprez[1,2,3,4], Aurélien de Reyniès[4,34], Emily Z. Keung[5,34], Tom Wei-Wu Chen[6,7,8,9], Cheng-Ming Sun[1,2,3], Julien Calderaro[10,11], Yung-Ming Jeng[8,12], Li-Ping Hsiao[7], Laetitia Lacroix[1,2,3], Antoine Bougouïn[1,2,3], Marco Moreira[1,2,3], Guillaume Lacroix[1,2,3], Ivo Natario[1,2,3], Julien Adam[13], Carlo Lucchesi[14,15], Yec'han Laizet[14,16], Maud Toulmonde[14,16], Melissa A. Burgess[17], Vanessa Bolejack[18], Denise Reinke[19], Khalid M. Wani[20], Wei-Lien Wang[20], Alexander J. Lazar[20,21], Christina L. Roland[5], Jennifer A. Wargo[6,21], Antoine Italiano[14,16,22], Catherine Sautès-Fridman[1,2,3], Hussein A. Tawbi[23]* & Wolf H. Fridman[1,2,3]*



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16190

High clinical benefit rates of single agent pembrolizumab in selected rare sarcoma histotypes: First results of the AcSé Pembrolizumab study

• **Jean-Yves BLAY**, I. RAY-COQUARD, N. PENEL, F. BERTUCCI , E. BOMPAS, E. SAADA BOUZID, J-C. EYMARD, J-P. LOTZ, E. COQUAN, R. SCHOTT, P. SOULIE, C. LINASSIER, A. LECESNE, M. BRAHMI, N. HOOG-LABOURET, F. LEGRAND, C. SIMON, A. LAMRANI-GHAOUTI, S. CHEVRET, C. MASSARD

Immuno-Oncology Group

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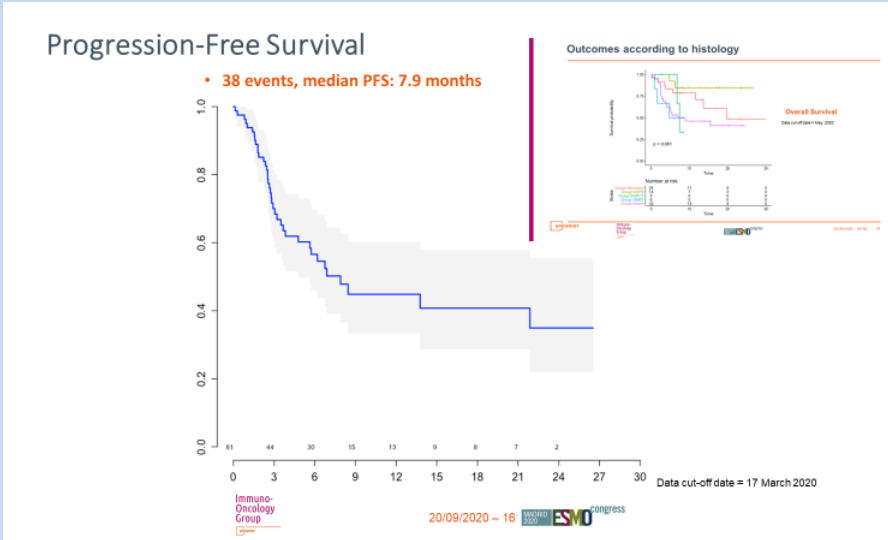


Ordered incidences of sarcomas and connective tissue tumors in NETSARC & published clinical trials

Histotypes	Total	Incidence	Ph III	RPh II	Ph II
	(2013-2016)	/10e6/year			
	25172	95,104			
Incidence >10/10e6/year					
Fibroblastic and myofibroblastic tumours	5274	19,977			
Gastrointestinal stromal tumors (GIST).	3272	12,394			
Adipocytic tumours	3247	12,299			
ALL Undifferentiated sarcoma	2717	10,292			
ALL smooth muscle tumours	2679	10,148			
Incidence <10/10e6/year					
Undifferentiated pleomorphic sarcoma	1556	5,894			
All vascular tumor	1520	5,758			
Liposarcoma – dedifferentiated	1345	5,095			
Desmoid fibromatosis	1339	5,072			
Atypical lipomatous tumour/WDLPS	1266	4,795			
Uterine sarcoma	1138	4,311			
Leiomyosarcoma	1094	4,144			
Dermatofibrosarcoma Protuberans	1040	3,939			
Leiomyosarcoma -differentiated	945	3,580			
Solitary fibrous tumour (all)	925	3,504			
Undifferentiated sarcoma NOS	853	3,231			
Sarcoma NOS	844	3,197			
Solitary fibrous tumor	751	2,845			
Angiosarcoma	728	2,758			
Kaposi sarcoma	663	2,511			
Conventional osteosarcoma	661	2,504			
Myxofibrosarcoma	630	2,386			
Ewing sarcoma	614	2,326			
ALL Rhabdomyosarcoma	608	2,303			
Chondrosarcoma NOS	572	2,167			
Uterine leiomyosarcoma	545	2,064			
Leiomyosarcoma – poorly differentiated	516	1,955			
ALL Synovial sarcoma	442	1,674			
Atypical fibroxanthoma	429	1,625			
Myxoid or round cell liposarcoma	409	1,549			
Liposarcoma - myxoid	355	1,345			
All GCTB	330	1,250			
Giant cell tumour of bone	324	1,227			
Undifferentiated spindle cell sarcoma	308	1,167			
ALL Peripheral nerve sheath tumours	286	1,083			

Histotypes	Total	Incidence	Ph III	RPh II	Ph II
	(2013-2016)	/10e6/year			
		95,104			
Incidence <1/10e6/year					
Synovial sarcoma - monophasic	244	0,924			
Endometrial stromal sarcoma, low grade	238	0,902			
Embryonal RMS	179	0,678			
High risk SFT	174	0,659			
Malignant peripheral nerve sheath tumour	173	0,655			
Other histological subtypes of bone sarcoma	171	0,648			
Osteosarcoma NOS	168	0,636			
Conventional chordoma	164	0,621			
Adenosarcoma	156	0,591			
All undifferentiated sarcoma of bone	152	0,576			
Inflammatory myofibroblastic Tumour	145	0,549			
Pleomorphic RMS	144	0,545			
Undifferentiated uterine sarcoma	141	0,534			
Liposarcoma - pleomorphic	139	0,527			
Phyllode sarcoma	138	0,523			
Embryonal rhabdomyosarcoma usual type	137	0,519			
Low grade fibromyxoid sarcoma	136	0,515			
Alveolar RMS	123	0,466			
Smooth muscle tumour of undetermined ma	122	0,462			
Epithelioid sarcoma	120	0,455			
Central chondrosarcoma, grades 2 and 3	117	0,443			
So-called fibrohistiocytic tumours	106	0,402			
Epithelioid hemangioEndothelioma	100	0,379			
Epithelioid sarcoma	98	0,371			
Extraskeletal osteosarcoma	96	0,364			
Myoepithelioma, myoepithelial carcinoma,	96	0,364			
Dedifferentiated chondrosarcoma	93	0,352			
RMS NOS	88	0,333			
Myoepithelioma	85	0,322			
Central atypical cartilaginous tumour / chon	76	0,288			
Clear cell sarcoma of soft tissue	71	0,269			
Giant cell tumour of soft tissue	70	0,265			
Synovial sarcoma - biphasic	70	0,265			
Undifferentiated pleomorphic sarcoma of bo	69	0,261			
PECOMA - NOS	67	0,254			
Extraskeletal myxoid chondrosarcoma	58	0,220			
Round cell sarcoma with EWSR1-non-ETS fus	56	0,212			
Liposarcoma - round cell	54	0,205			
Aneurysmal bone cyst	53	0,201			
Desmoplastic small round cell tumour	52	0,197			
Tumors of intermediate malignancy NOS ALL	52	0,197			
Chondroblastoma	52	0,197			
Extrarenal rhabdoid tumour	51	0,193			
Intimal sarcoma	46	0,174			
Angiomatoid fibrous histiocytoma	43	0,163			
Sclerosing epithelioid fibrosarcoma	41	0,155			
Endometrial stromal sarcoma - high-grade	41	0,155			
All parosteal osteosarcoma	40	0,152			
Leiomyosarcoma of bone	40	0,152			
Spindle cell RMS	39	0,148			
Peripheral chondrosarcoma	39	0,148			
Synovial sarcoma - poorly Differentiated	37	0,140			
Malignant rhabdoid tumor	36	0,136			
Ossifying fibromyxoid Tumour	32	0,121			
Alveolar soft part sarcoma	31	0,117			
Mesenchymal chondrosarcoma	31	0,117			
Osteoblastoma	31	0,117			
Plexiform fibrohistiocytic tumors	29	0,110			
Embryonal rhabdomyosarcoma spindle cell	29	0,110			
Angiosarcoma of bone	29	0,110			
Adult fibrosarcoma	28	0,106			
Parosteal osteosarcoma	27	0,102			

Histotypes	Total	Incidence	Ph III	RPh II	Ph II
	(2013-2016)	/10e6/year			
Incidence <0.1/10e6/year					
Osteoblastoma-like osteosarcoma					
Chondromyxoid fibroma	26	0,098			
Undifferentiated spindle cell sarcoma	26	0,098			
Periosteal chondrosarcoma	25	0,095			
High-grade surface osteosarcoma	25	0,095			
Myxoinflammatory Fibroblastic Sarcoma	23	0,087			
Embryonal RMS sarcoma - botryoid type	23	0,087			
Undifferentiated epithelioid sarcoma	22	0,083			
Langerhans cell histiocytosis	20	0,076			
Malignant PECOMA	19	0,072			
Low grade central osteosarcoma (ALL)	19	0,072			
Adamantinoma	19	0,072			
UTROSC	17	0,064			
Endometrial stromal nodule	16	0,061			
Telangiectasic osteosarcoma	16	0,061			
SMARCA4-deficient thoracic sarcoma	15	0,057			
Clear cell chondrosarcoma	14	0,053			
Low grade Myofibroblastic Sarcoma	13	0,049			
Dedifferentiated parosteal osteosarcoma	13	0,049			
Dedifferentiated low grade central osteosar	12	0,045			
Giant cell Fibroblastoma	11	0,042			
Sclerosing RMS	11	0,042			
CIC-rearranged sarcoma	11	0,042			
Infantile fibrosarcoma	10	0,038			
Pericytic (perivascular) tumours	10	0,038			
Malignant Triton tumour	10	0,038			
Retiform hemangio-endothelioma	9	0,034			
Ectomesenchymoma : Malignant mesenchym	9	0,034			
Malignant granular cell Tumour	9	0,034			
Haemosiderotic fibrolipomatous tumour	9	0,034			
Synovial sarcoma of bone	9	0,034			
RMS of bone	9	0,034			
Lipofibromatosis	8	0,030			
Sarcoma with BCOR genetic alterations	7	0,027			
Low-grade central osteosarcoma	7	0,027			
Pseudomyogenic hemangioendothelioma	6	0,023			
Intermediate vascular tumours	6	0,023			
MPNST - epithelioid type	6	0,023			
Mixed tumour	6	0,023			
Desmoplastic fibroma of bone	6	0,023			
Malignant/dedifferentiated GCTB	6	0,023			
BCOR Sarcoma of bone	6	0,023			
Intermediate fibrohistiocytic tumors	5	0,019			
Adult spindle cell RMS	5	0,019			
Phosphaturic mesenchymal tumour	5	0,019			
Low grade sinonasal sarcoma	5	0,019			
Periosteal osteosarcoma	5	0,019			
Kaposiform hemangioendothelioma	4	0,015			
Small cell osteosarcoma	4	0,015			
Myoepithelioma of bone	4	0,015			
Liposarcoma of bone	4	0,015			
Composite hemangioendothelioma	3	0,011			
Malignant perineurioma	3	0,011			
Adult fibrosarcoma of bone	3	0,011			
Liposarcoma - mixed type	2	0,008			
Malignant tenosynovial giant cell tumors	2	0,008			
Metastatic leiomyoma	2	0,008			
Malignant myoepithelial Tumour	2	0,008			
Osteoblastoma-like osteosarcoma	2	0,008			
Dedifferentiated chordoma	2	0,008			
Lipomatous spindle cell/pleomorphic tum	1	0,004			
Papillary intralymphatic angioendotheliom	1	0,004			
Melanotic neuroectodermal tumour of infan	1	0,004			
Osteogenic tumor of uncertain prognosis	1	0,004			
Fibro-osseous tumour of bone NOS	1	0,004			
Undifferentiated epithelioid sarcoma	1	0,004			

Sarcomas: why slow progresses?

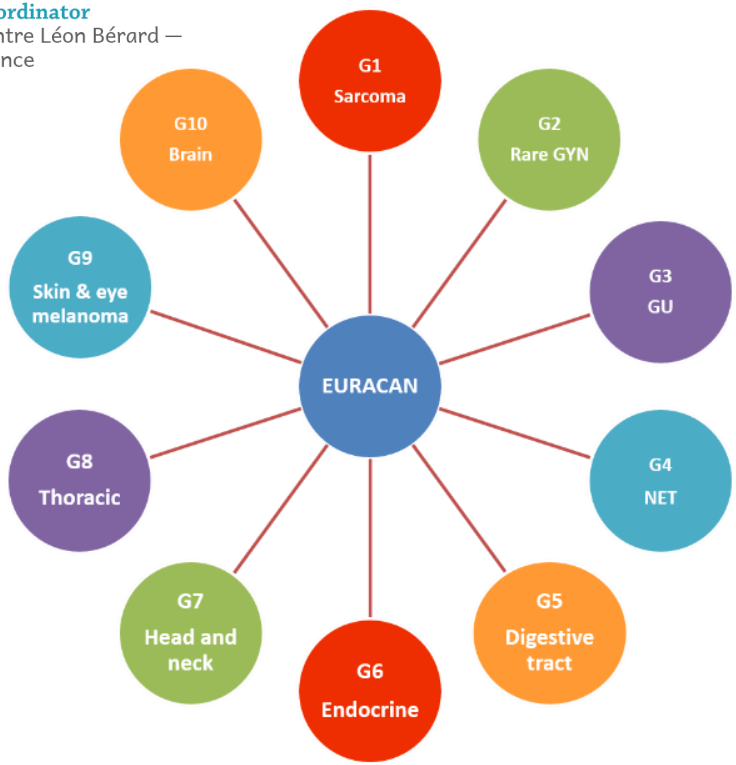
- About 150 subtypes/ complex diagnostic, value of molecular biology
- Local treatments : optimize management =first goal
- Very efficient targeted treatments in a variety of sarcoma histotypes and molecular subsets (incl.immunotherapy)
- But poor rates of approval and reimbursement in these rare cancers

European Reference Network
for rare or low prevalence complex diseases

ERN EURACAN

Network
Adult Cancers
(ERN EURACAN)

Coordinator
Centre Léon Bérard — France



10 domains

17 European countries

RARE ADULT SOLID CANCERS

Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial

Breelyn A Wilky, Matteo M Trucco, Ty K Subhawong, Vaia Florou, Wungki Park, Deukwoo Kwon, Eric D Wieder, Despina Kolonias, Andrew E Rosenberg, Darcy A Kerr, Efrosyni Sfakianaki, Mark Foley, Jaime R Merchan, Krishna V Komanduri, Jonathan C Trent

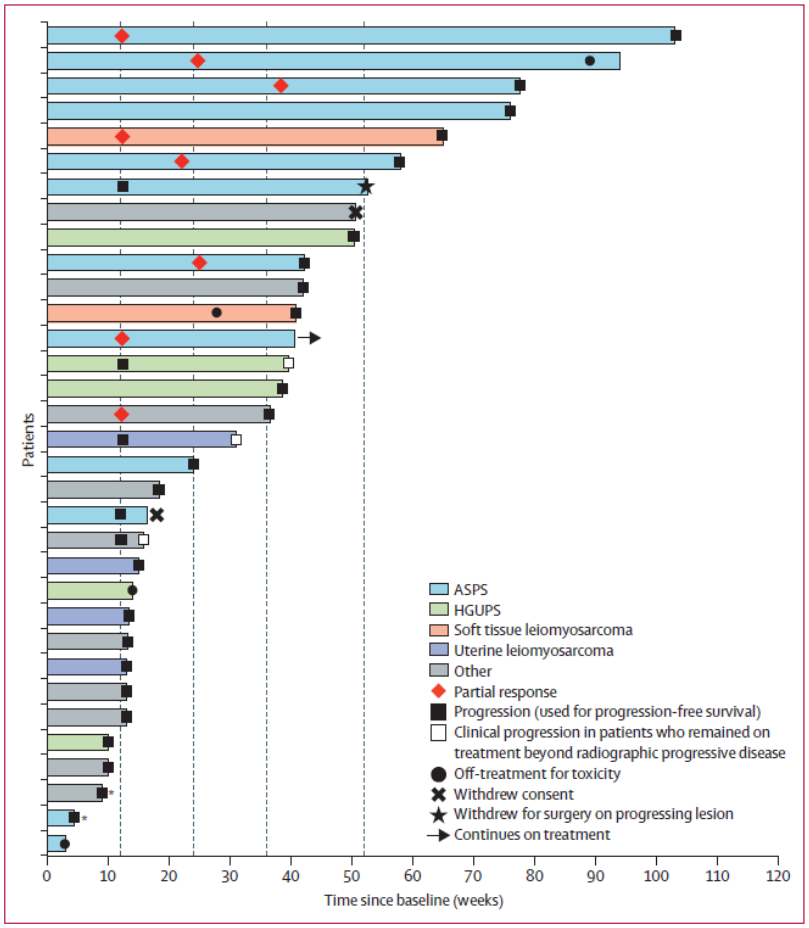


Figure 4: Duration of responses

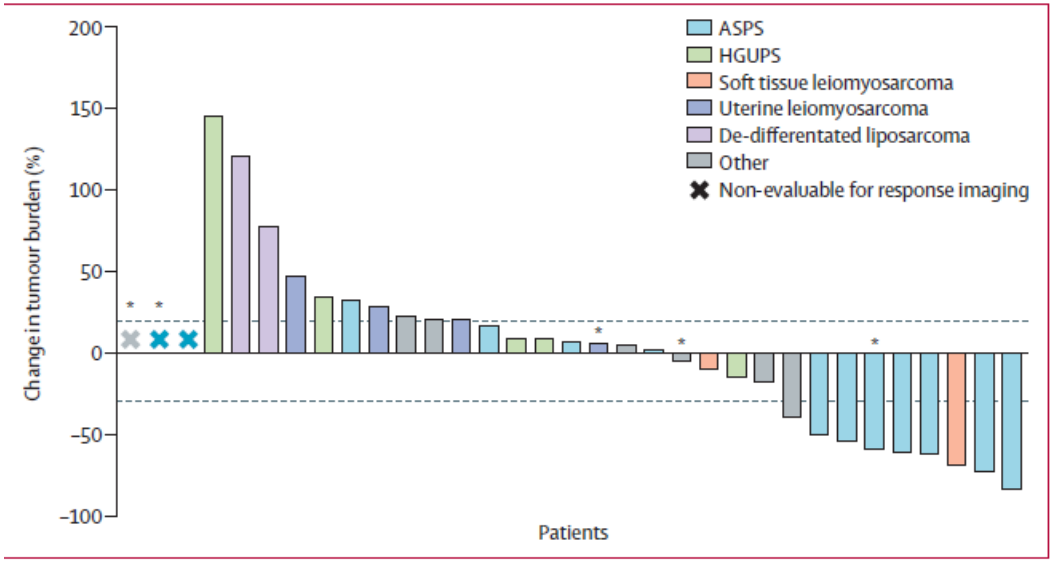


Figure 3: Change from baseline in tumour burden