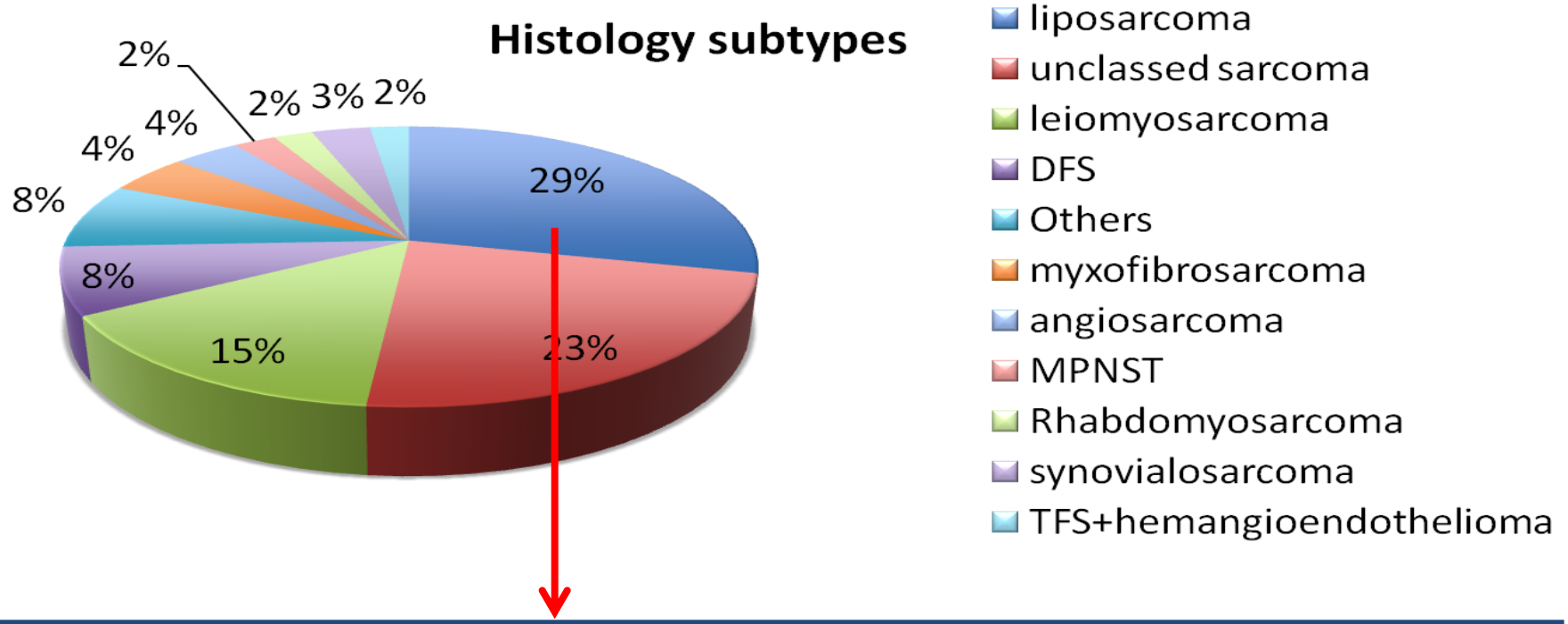
Liposarcoma: medical treatment

JY Blay

Disclosures

Research support or honoraria from:

Novartis, Roche, Pharmamar, GSK, Amgen, Pfizer, MSD, Cytheris



• 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.

Annals of Oncology 25: 1854–1860, 2014
doi:10.1093/annonc/mdu202
Published online 8 June 2014

ESMO 2016

Adjuvant radiotherapy for extremity and trunk wall atypical lipomatous tumor/well-differentiated LPS (ALT/WD-LPS): a French Sarcoma Group (GSF-GETO) study

P. A. Cassier[1,2*], G. Kantor[3], S. Bonvalot[4], E. Lavergne[5], E. Stoeckle[6], C. Le Péchoux[7], P. Meeus[8], M.-P. Sunyach[9], G. Vaz[10], J.-M. Coindre[11], C. Linassier[12], A. Labib[13], C. Delcambre[14], J.-O. Bay[15], S. Leyvraz[16], T. Dubergé[17], J.-L. Lagrange[18], A. Duret[1,†] & J.-Y. Blay[1,2]

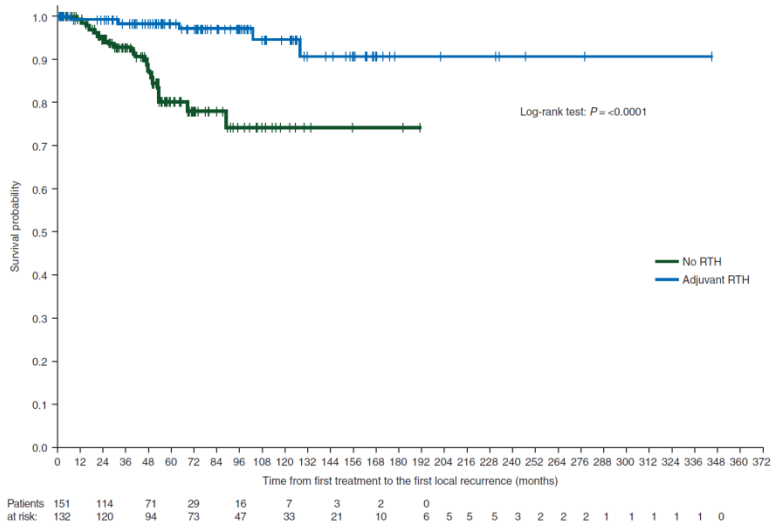


Figure 2. Time to local recurrence according to adjuvant therapy (log rank, $P < 0.0001$).

Table 2. Multivariate model for time to local recurrence (TTLR)

Variables	*N*	HR	95% CI	*P*
Adjuvant radiotherapy for primary tumor	245			
No		1	–	0.0166
Yes		0.26	0.08–0.78	
Site of primary tumor				
Trunk or girdles		1	–	0.0137
Extremities		0.32	0.13–0.79	
Margin status				
R0		1	–	0.0030
R1 or R2		6.49	1.89–22.25	

Table 3. Multivariate model for progression-free survival

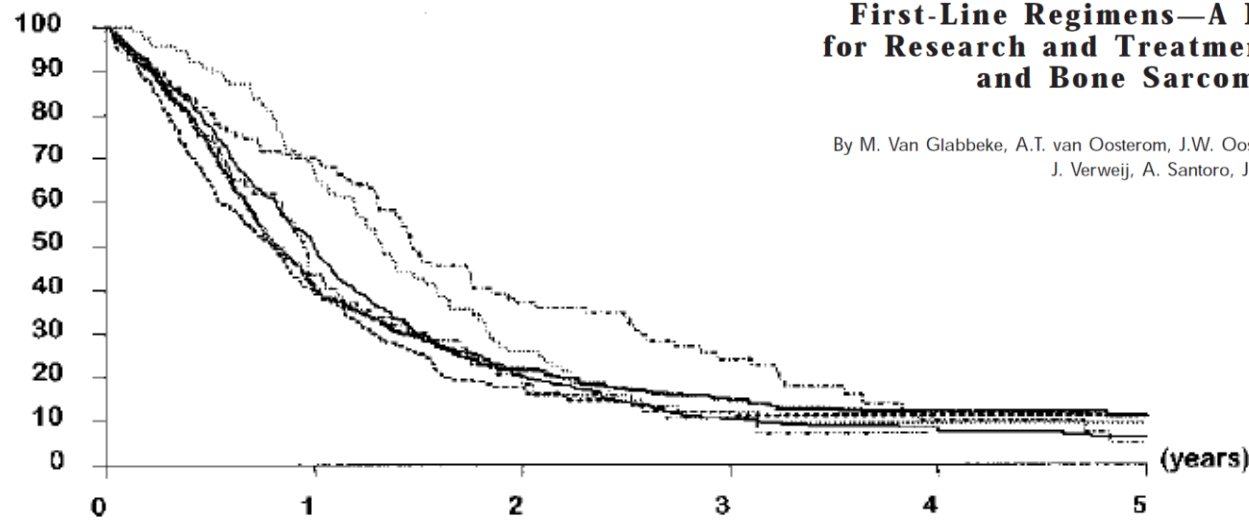
Variables	*N*	HR	95% CI	*P*
Adjuvant radiotherapy for primary tumor	245			
No		1	–	0.0003
Yes		0.23	0.10–0.51	
Margin status				
R0		1	–	0.0146
R1 or R2		2.54	1.20–5.36	

WD/DD LPS : not so indolent!

Van Glabbeke et al, JCO 1999 N=111, med OS 16 mos

Prognostic Factors for the Outcome of Chemotherapy in Advanced Soft Tissue Sarcoma: An Analysis of 2,185 Patients Treated With Anthracycline-Containing First-Line Regimens—A European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study

By M. Van Glabbeke, A.T. van Oosterom, J.W. Oosterhuis, H. Mouridsen, D. Crowther, R. Somers, J. Verweij, A. Santoro, J. Buesa, and T. Tursz



O	N	Number of patients at risk :				Histologic cell type
449	540	241	87	34	17	Leio
181	218	79	29	11	8	MFH
92	120	74	23	6	2	Synov
86	111	73	34	15	5	Lipo
56	69	28	8	3	0	Fibro
403	512	187	86	42	26	Other

Annals of Oncology 23: 1601–1607, 2012
doi:10.1093/annonc/mdr485
Published online 29 October 2011

Advanced well-differentiated/dedifferentiated liposarcomas: role of chemotherapy and survival

A. Italiano[1,2*], M. Toulmonde[1], A. Cioffi[2,3], N. Penel[4], N. Isambert[5], E. Bompas[6], F. Duffaud[7], A. Patrikidou[3], B. Lortal[1], A. Le Cesne[3], J.-Y. Blay[8], R. G. Maki[2,9], G. K. Schwartz[2], C. R. Antonescu[10], S. Singer[11], J.-M. Coindre[12] & B. Bui[1]

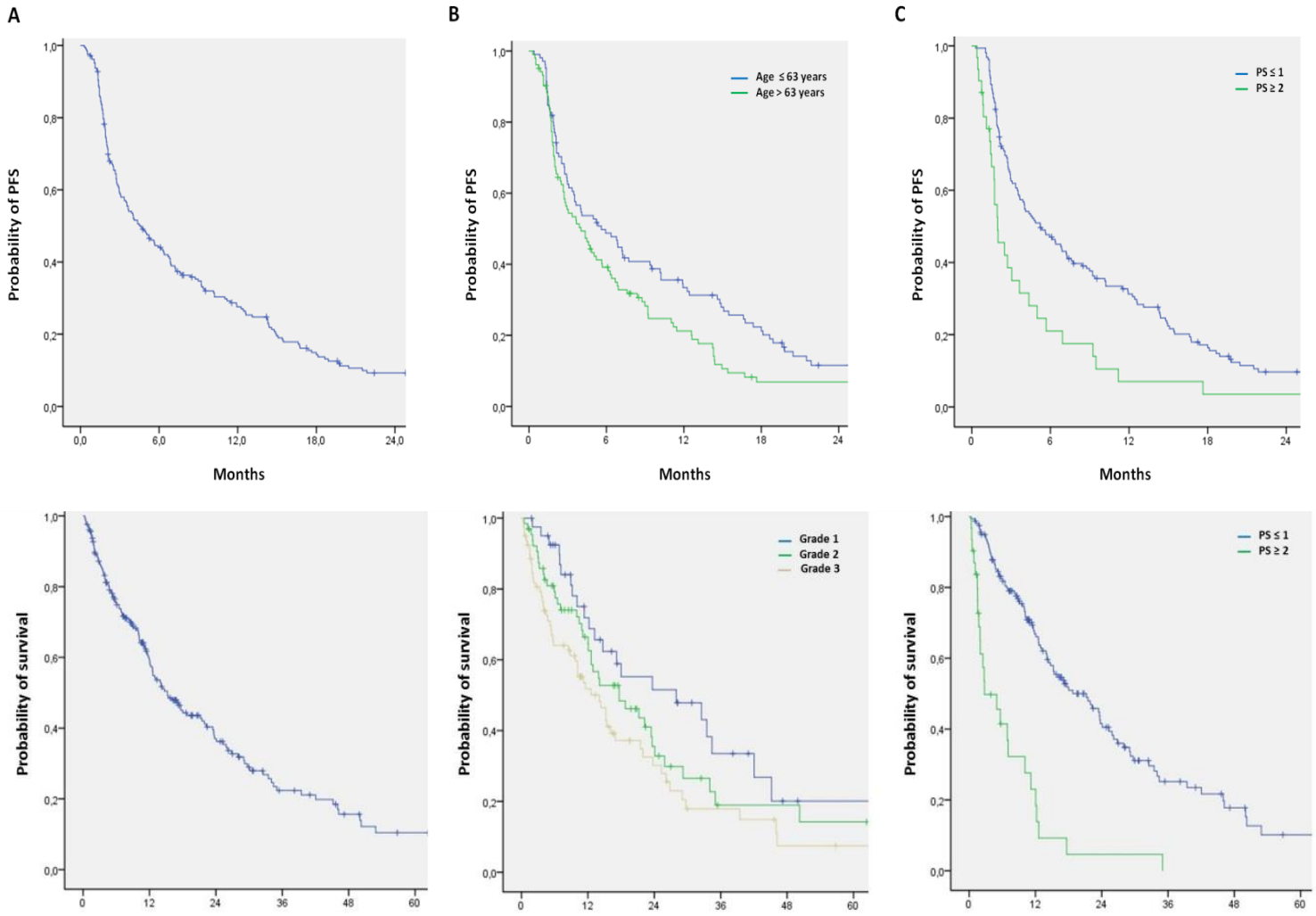
	No. of patients (%)
Age (years)	
Median (range)	63 (32–84)
Sex	
Male	127 (61.0)
Female	81 (39.0)
Performance status	
≤1	159 (76.5)
≥2	31 (15)
Unknown	18 (8.5)
Histology	
Well-differentiated liposarcoma	37 (18)
Dedifferentiated liposarcoma	171 (82)
Grade	
1	41 (20.0)
2	65 (31.0)
3	79 (38.0)
Unknown	23 (11.0)
Tumor location	
Limb	20 (9.5)
Retroperitoneum	161 (77.5)
Other	18 (8.5)
Unknown	9 (4.5)
Number of metastatic sites	
0	55 (26.5)
1	110 (53.0)
2	43 (20.5)
Site of metastasis	
Peritoneal sarcomatosis	153 (73.5)
Lung	40 (19.0)
Liver	25 (12.0)

Table 2. Chemotherapy regimens in patients with WDLPS/DDLPS

Protocol	Drugs	*N* (%)
Anthracyline-containing regimen		
Doxorubicin	Doxorubicin 60–75 mg/m^2; 21-day cycle	72 (34.5)
Pegylated liposomal doxorubicin	Pegylated liposomal doxorubicin 40–50 mg/m^2; 28-day cycle	20 (9.5)
AI	Doxorubicin 20–25 mg/m^2 (d1–d3); Ifosfamide 2.5–3 g/m^2(d1-d3); 21-day cycle	25 (12)
MAID	Doxorubicin 20 mg/m^2 (d1–d3); Ifosfamide 2.5 g/m^2 (d1); Dacarbazine 300 mg/m^2 (d1); 21-day cycle	14 (7)
AD	Doxorubicin 20 mg/m^2 (d1–d3); Dacarbazine 300 mg/m^2 (d1); 21-day cycle	8 (4)
Other regimens	Doxorubicin + miscellaneous cytotoxic or investigational agent	32 (16)
Non-anthracycline regimen		
Metronomic cyclophosphamide	Oral daily cyclophosphamide 50 mg/day on 21 of 28-day cycle	12 (5.5)
Docetaxel–Gemcitabine	Gemcitabine 900 mg/m^2 J1, J8; Docetaxel 100 mg/m^2 J8; 21-day cycle	4 (2)
Trabectedin	Trabectedin 1.5 mg/m^2; 21-day cycle	4 (2)
Other regimens	Doxorubicin + miscellaneous cytotoxic or investigational agent	16 (7.5)

WD/DD LPS : not so indolent!

Italiano et al Ann Oncol 2012, N=208, Med PFS=3.7 mos
Med OS=15.2 mos



Retroperitoneal sarcomas: patterns of care in advanced stages, prognostic factors and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group

M. Toulmonde[1*], S. Bonvalot[2], I. Ray-Coquard[3], E. Stoeckle[4], O. Riou[5], N. Isambert[6], E. Bompas[7], N. Penel[8], C. Delcambre-Lair[9], E. Saada[10], A. Lecesne[11], C. Le Péchoux[12], J. Y. Blay[3], S. Piperno-Neumann[13], C. Chevreau[14], J. O. Bay[15], V. Brouste[16], P. Terrier[17], D. Ranchère-Vince[18], A. Neuville[19] & A. Italiano[1] on behalf of the French Sarcoma Group

ESMO 2016

Table 1. Response rates to first line of palliative chemotherapy in all patients assessable for response ($n = 255$), and across histological subtypes: DDLPS ($n = 102$), WDLPS ($n = 35$), LMS ($n = 65$), US ($n = 26$) and other ($n = 27$)

	Progression		Stable disease		Response	
	n	%	*n*	%	*n*	%
All patients	69	27	145	57	41	16
DDLPS	25	24	64	63	13	13
WDLPS	11	31	20	57	4	11
LMS	13	20	40	62	12	18
US	8	31	17	65	1	4
Other	12	44	4	15	11	41

n, number; DDLPS, dedifferentiated liposarcoma; WDLPS, well-differentiated liposarcoma; LMS, leiomyosarcoma; US, unclassified sarcoma.

Table 2. Time to progression and overall survival from first line of palliative chemotherapy of all patients ($n = 299$) and across histological subtypes: DDLPS ($n = 124$), WDLPS ($n = 38$), LMS ($n = 73$), US ($n = 30$) and other ($n = 34$)

	Time to progression (months) [95% CI]		Overall survival (months) [95% CI]	
All patients	5.0	[4.0–7.3]	15.8	[13.0–18.0]
DDLPS	5.8	[3.9–8.3]	13.5	[11.1–16.9]
WDLPS	5.0	[2.2–13.2]	26.8	[12.2–65.1]
LMS	7.0	[5.0–9.2]	19.6	[15.8–25.0]
US	3.2	[2.0–7.6]	14.4	[6.1–19.2]
Other	5.4	[1.9–8.2]	11.8	[5.4–16.3]

TTP, time to progression; DDLPS, dedifferentiated liposarcoma; WDLPS, well-differentiated liposarcoma; LMS, leiomyosarcoma; US, unclassified sarcoma.

Table 3. Multivariate analysis of factors associated with overall survival after first line of palliative chemotherapy, in all patients overall ($n = 299$), in patients with DDLPS ($n = 124$) and LMS ($n = 73$), respectively (reference)

	Overall survival		
	HR	[95% CI]	*P*
	All patients		
Male gender	1.5	[1.1–1.9]	0.009
PS (0)			
1	1.7	[1.2–2.2]	<0.001
≥2	3	[1.9–4.8]	
Grade (1)			
2	1.7	[1.1–2.7]	0.001
3	2.3	[1.5–3.7]	
Histology		Not retained	
	DDLPS		
PS (0)			
1	1.6	[1–2.5]	0.017
≥2	3	[1.3–6.9]	
Grade (2)			
3	1.6	[1–2.6]	0.04
	LMS		
PS		Not retained	
Grade (1)			
2	3	[1.1–9.2]	0.006
3	5	[1.6–15.4]	
Stage (LR)			
Sarcomatosis	0.8	[0.3–2]	0.01
Distant metastasis	0.4	[0.2–0.7]	

HR: hazard ratio; CI: confidence interval; DDLPS: dedifferentiated liposarcoma; PS: performance status; LMS: leiomyosarcomass; LR: locoregional.

Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial

Lancet Oncol 2014; 15: 415–23

Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarsky, Jeremy Whelan, Peter Hohenberger, Anders Krarup-Hansen, Thierry Alcindor, Sandrine Marreaud, Saskia Litière, Catherine Hermans, Cyril Fisher, Pancras C W Hogendoorn, A Paolo dei Tos, Winette T A van der Graaf, for the European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group*

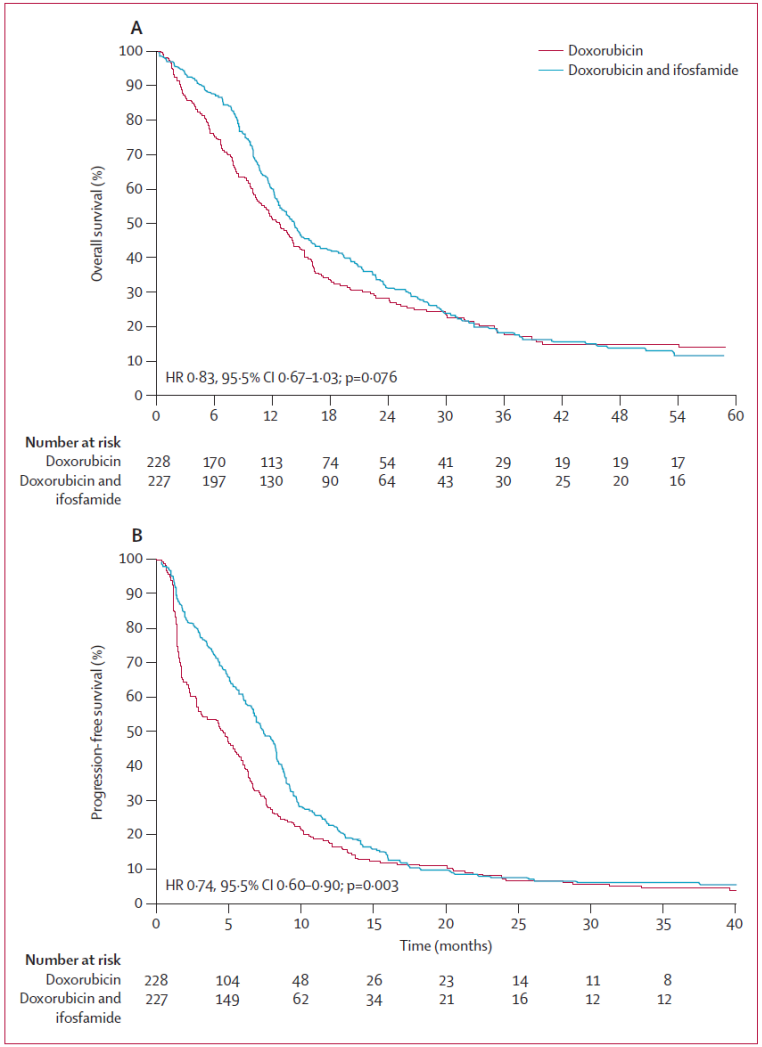


Figure 2: Kaplan-Meier curves for overall survival (A) and progression-free survival (B)
HR=hazard ratio.

	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
Complete response	1 (<1%)	4 (2%)
Partial response	30 (13%)	56 (25%)
Stable disease	105 (46%)	114 (50%)
Progressive disease	74 (32%)	30 (13%)
Early death (progression)	4 (2%)	5 (2%)
Early death (other cause)	3 (1%)	2 (1%)
Not evaluable	11 (5%)	16 (7%)

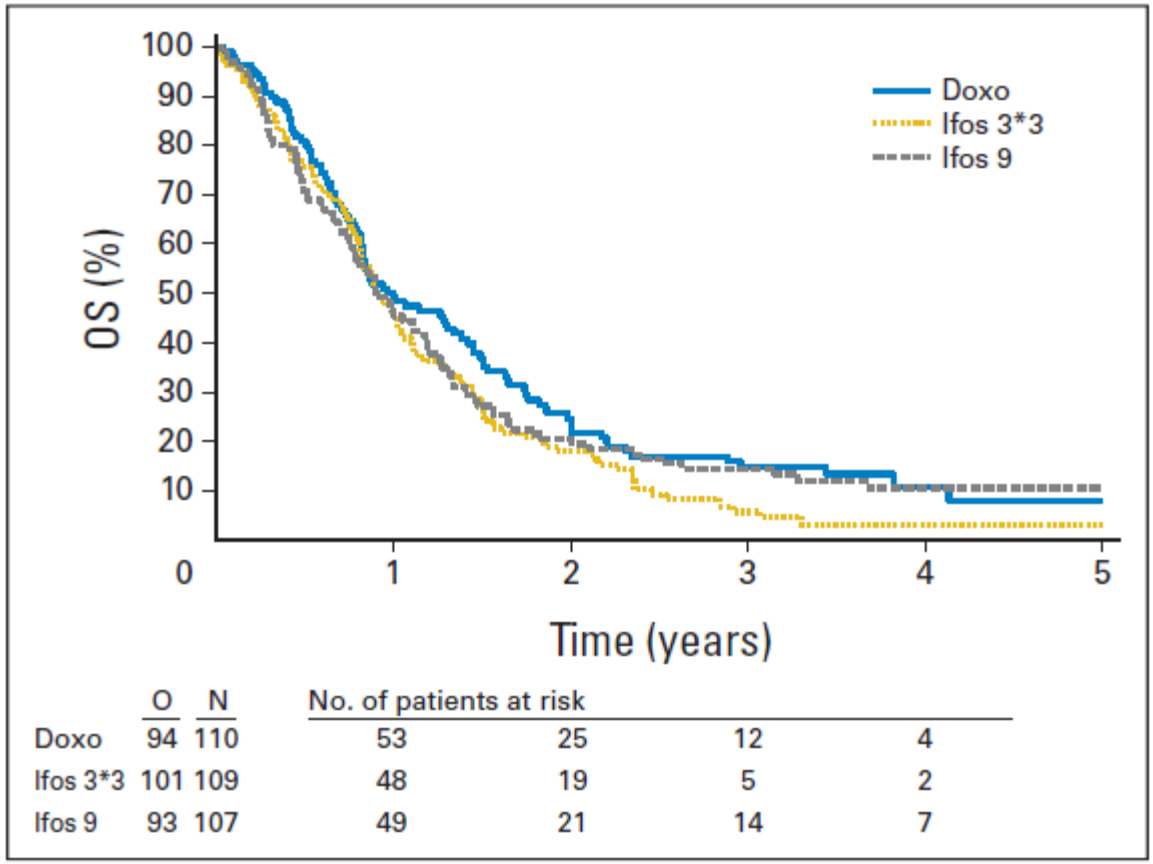
Data are n (%).

Table 3: Responses to treatment

High doses when response or PFS is the most important enpoint (eg presurgery)

Phase III Trial of Two Investigational Schedules of Ifosfamide Compared With Standard-Dose Doxorubicin in Advanced or Metastatic Soft Tissue Sarcoma: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study

Paul Lorigan, Jaap Verweij, Zsuzsa Papai, Sjoerd Rodenhuis, Axel Le Cesne, Michael G. Leahy, John A. Radford, Martine M. Van Glabbeke, Anne Kirkpatrick, Pancras C.W. Hogendoorn, and Jean-Yves Blay

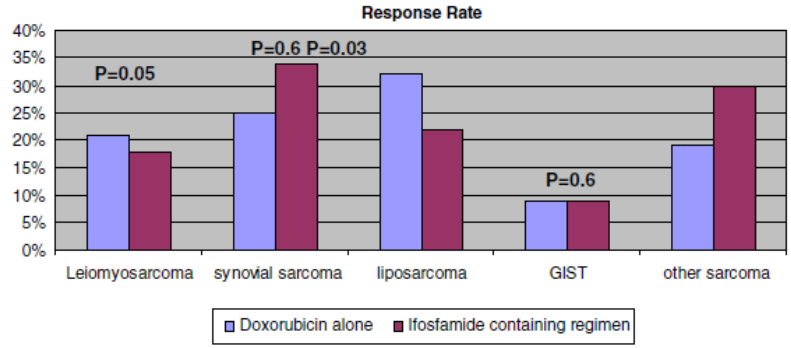


	O	N	No. of patients at risk			
Doxo	94	110	53	25	12	4
Ifos 3*3	101	109	48	19	5	2
Ifos 9	93	107	49	21	14	7

Ifosfamide

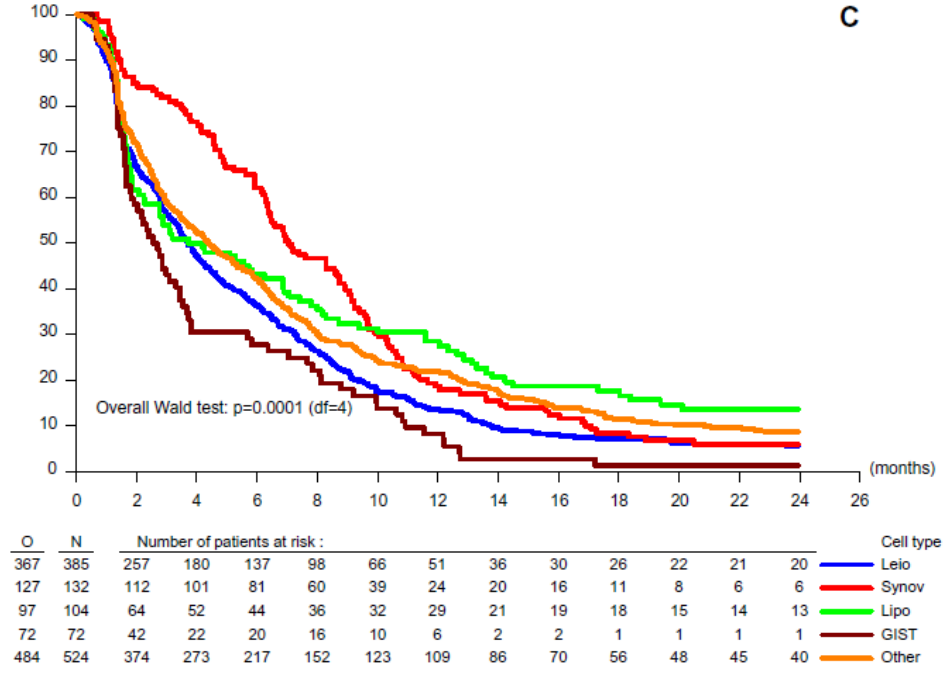
Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas
An exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG)

Stefan Sleijfer [a,], Monia Ouali [b], Martine van Glabbeke [b], Anders Krarup-Hansen [c], Sjoerd Rodenhuis [d], Axel Le Cesne [e], Pancras C.W. Hogendoorn [f], Jaap Verweij [a], Jean-Yves Blay [g]*



Abbreviations p: the p-value for the interaction test

Fig. 4 – Responses to doxorubicin alone and ifosfamide-based therapies by histological entity.



After failure of anthracyclins

Trabectedine

Pazopanib

Gemcitabine and Docetaxel

Dacarbazine and Gem

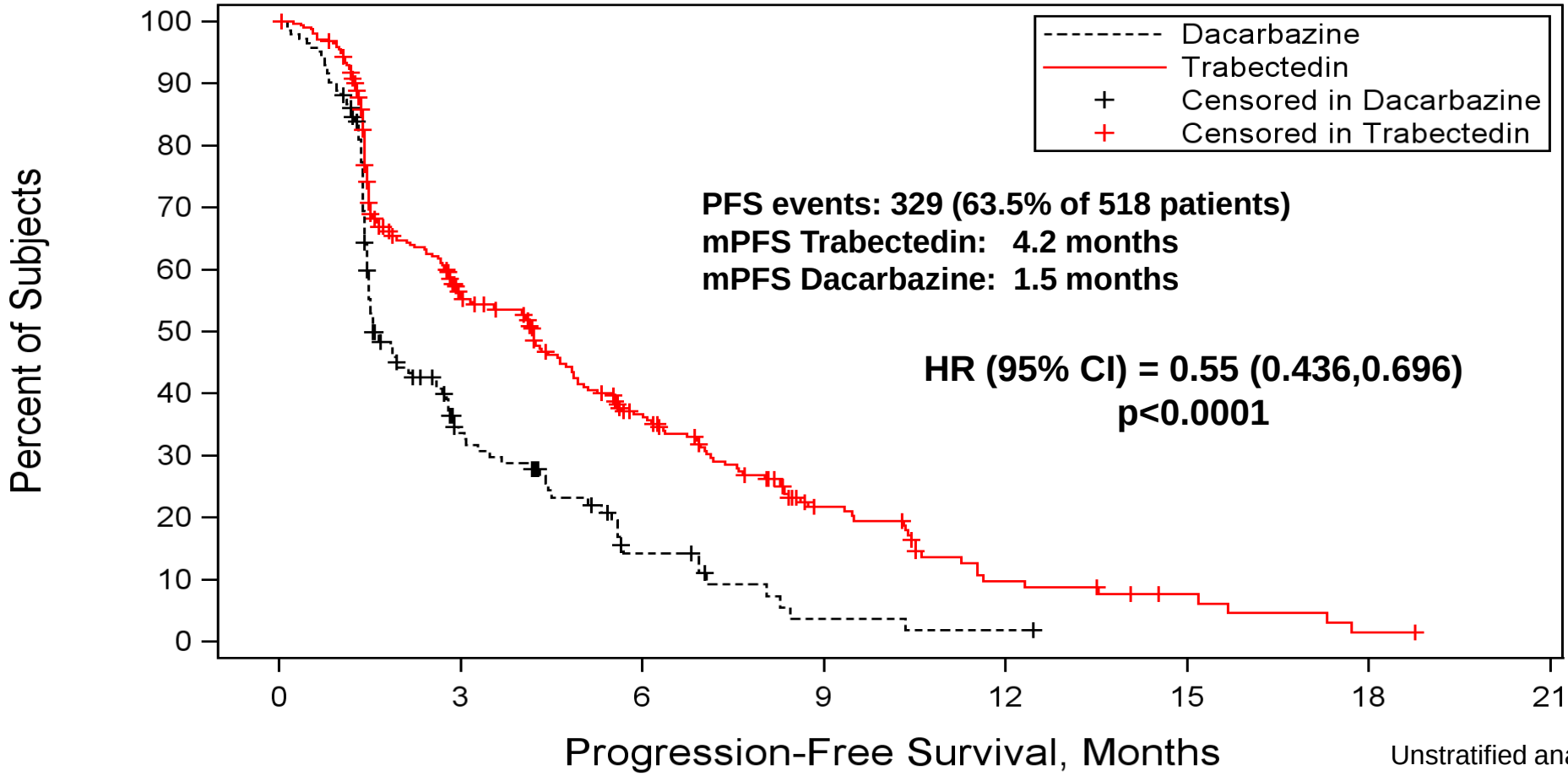
A Randomized Phase 3 Study of Trabectedin or Dacarbazine for the Treatment of Patients With Advanced Liposarcoma (LPS) or Leiomyosarcoma (LMS)

George D. Demetri, Margaret von Mehren, Robin Lewis Jones, Martee Leigh Hensley, Scott Schuetze, Arthur P. Staddon, Mohammed M. Milhem, Anthony D. Elias, Kristen N. Ganjoo, Hussein Abdul-Hassan Tawbi, Brian Andrew Van Tine, Alexander I. Spira, Andrew Peter Dean, Nushmia Z. Khokhar, Youn Choi Park, Roland E. Knoblauch, Trilok V. Parekh, Robert G. Maki, Shreyaskumar Patel

Dana-Farber Cancer Institute and Ludwig Center at Harvard Medical School, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; Seattle Cancer Care Alliance, Seattle, WA; Memorial Sloan Kettering Cancer Center, New York, NY; University of Michigan, Ann Arbor, MI; University of Pennsylvania, Philadelphia, PA; University of Iowa Hospitals and Clinics, Iowa City, IA; University of Colorado Cancer Center, Aurora, CO; Stanford Univ, Stanford, CA; University of Pittsburgh Cancer Institute, Pittsburgh, PA; Washington University in St Louis, St Louis, MO; Virginia Cancer Specialists, Fairfax, VA; St. John of God Hospital Subiaco, Subiaco, Australia; Janssen Pharmaceuticals, Raritan, NJ; Janssen Research &Development, LLC, Raritan, NJ; Mount Sinai School of Medicine, New York, NY; MD Anderson Cancer Center, Houston, TX

Final Analysis of PFS

(Investigator Assessed)

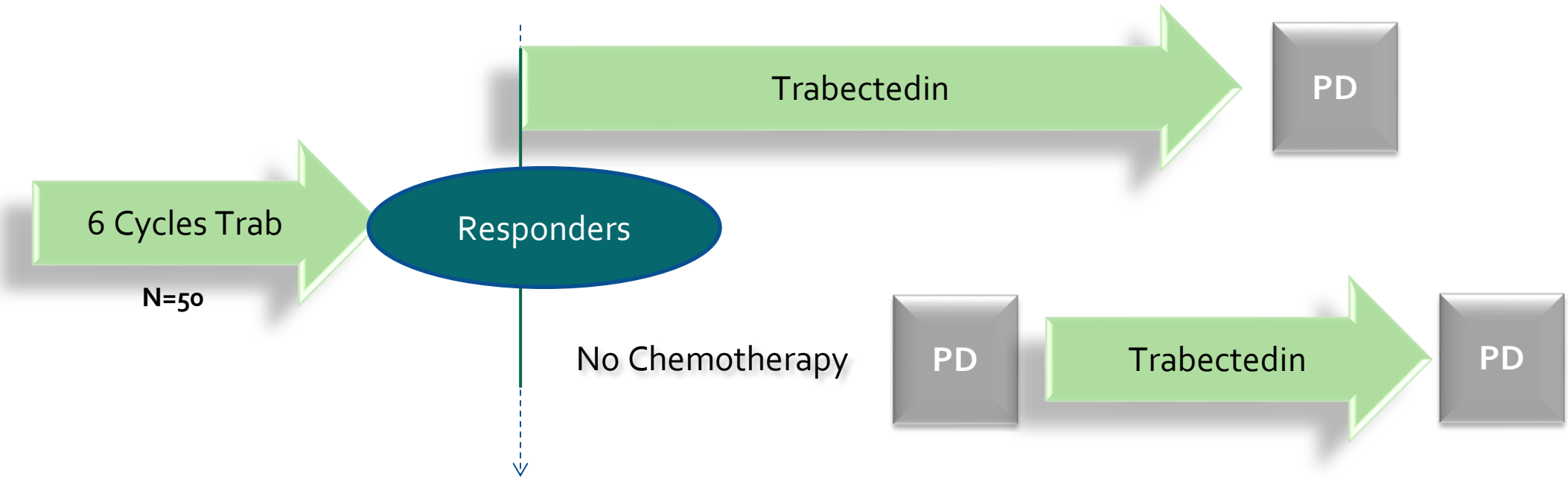


No. Subjects at Risk

Dacarbazine	173	35	10	2	1	0		
Trabectedin	345	133	71	29	10	5	1	0

Trabectedin : T-DIS study – Drug Holiday and Rechallenge

Interruption vs Continuation in Responding Patients After 6 Courses of Trabectedin



Primary endpoint:

- PFR 24 weeks post Randomization

Secondary endpoints:

- ORR
- PFR at 12 & 54 weeks
- Survival at 12 & 24 months

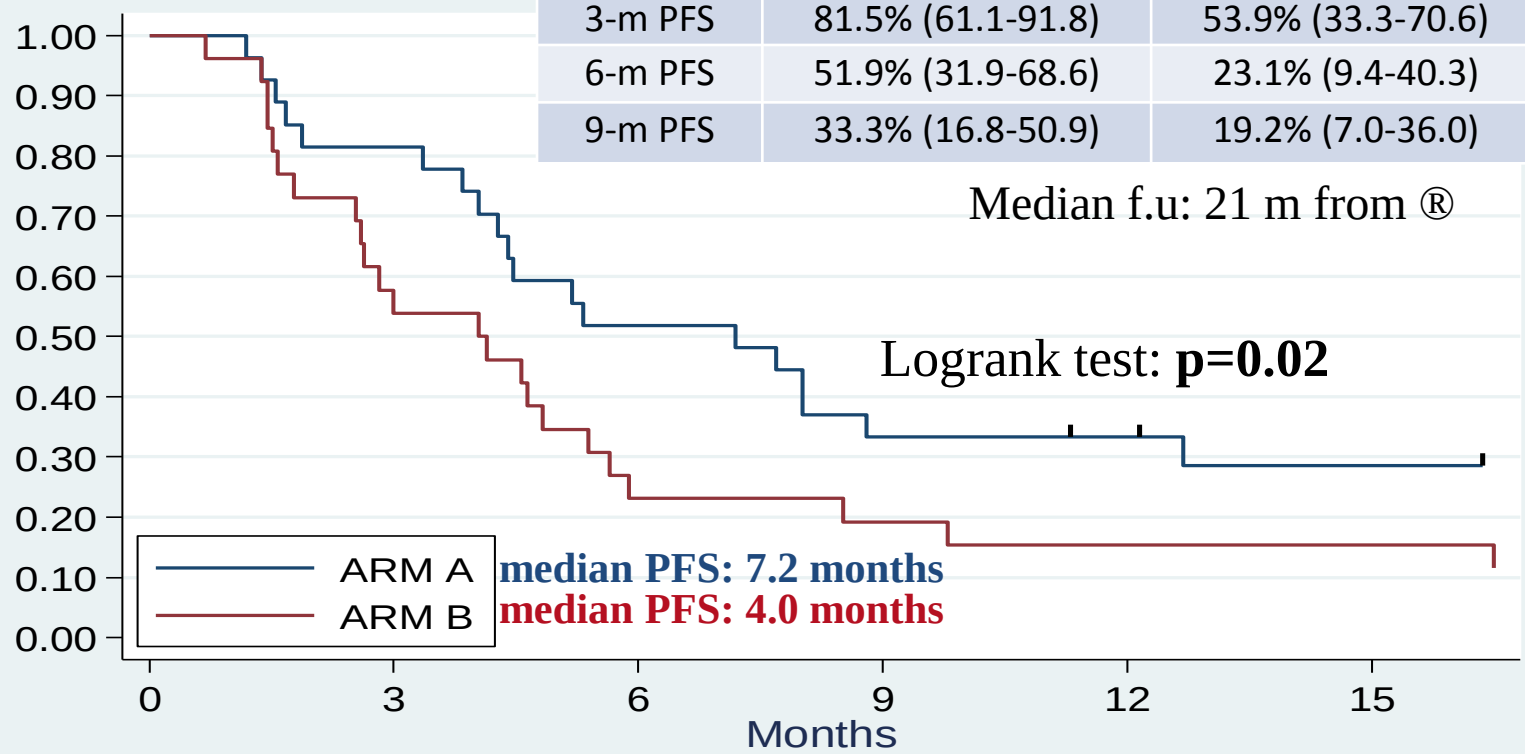
N=156 at inclusion
® = 50

Le Cesne et al, ASCO 2014 Abs Nº 10523; Le Cesne et al, ESMO 2014, Annals of Oncol 25(Supl 4): 494 Abs. Nº 1414
Le Cesne et al, Lancet Oncol 2015

T-Dis Maintenance Study

Results: Progression Free Survival (ITT)

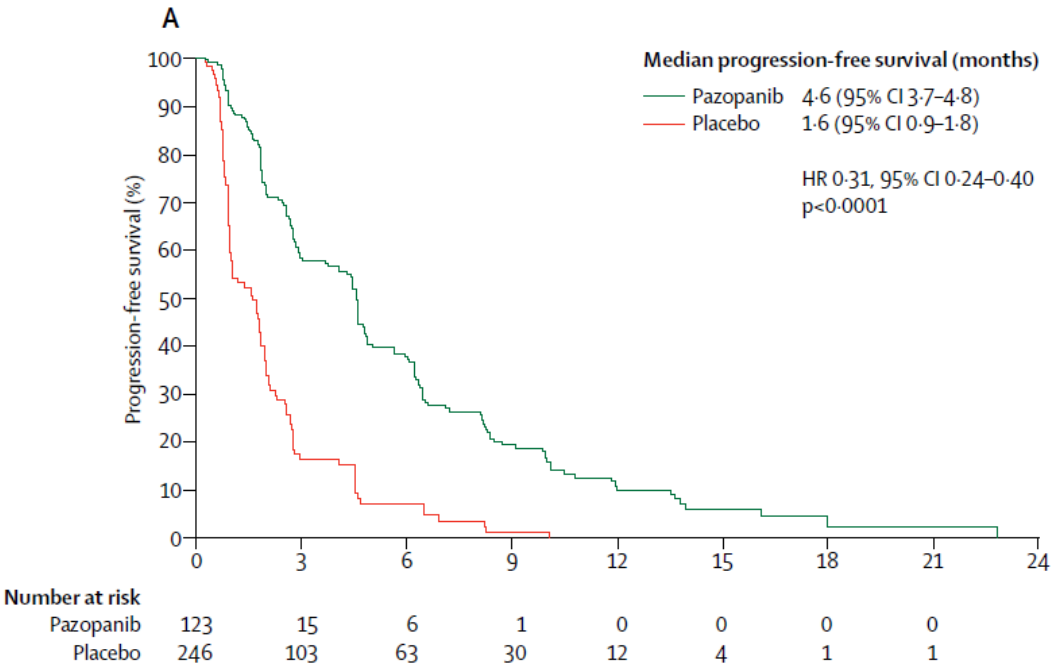
	Arm A (cont)	Arm (discont)
3-m PFS	81.5% (61.1-91.8)	53.9% (33.3-70.6)
6-m PFS	51.9% (31.9-68.6)	23.1% (9.4-40.3)
9-m PFS	33.3% (16.8-50.9)	19.2% (7.0-36.0)

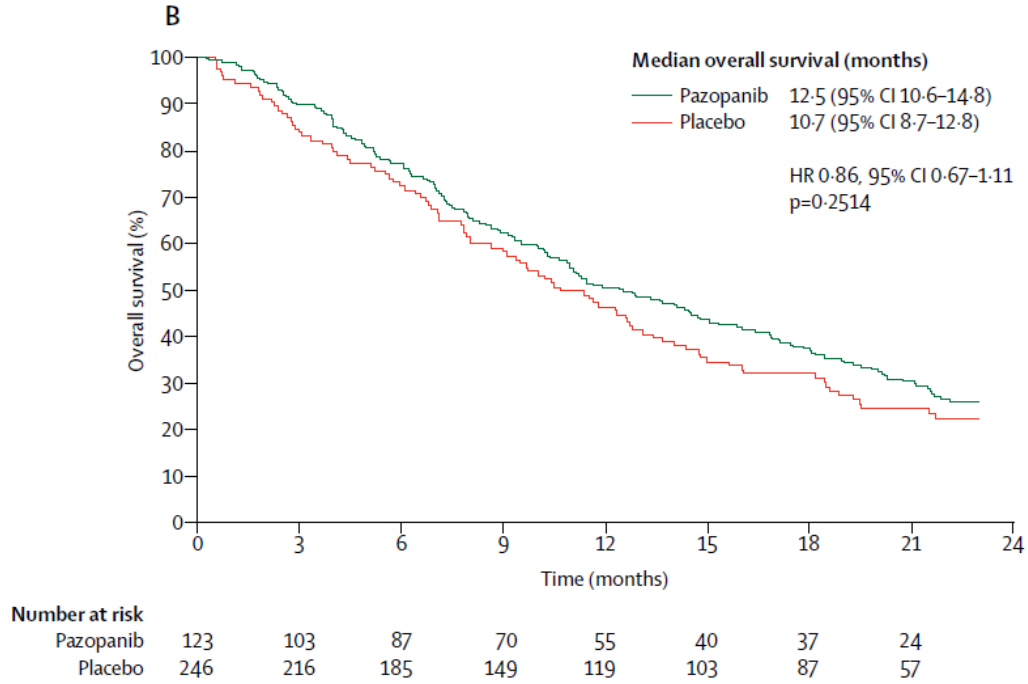


Le Cesne et al, ASCO 2014 Abs Nº 10523; Le Cesne et al, ESMO 2014, Annals of Oncol 25(Supl 4): 494 Abs. Nº 1414
Le Cesne et al, Lancet Oncol 2015

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





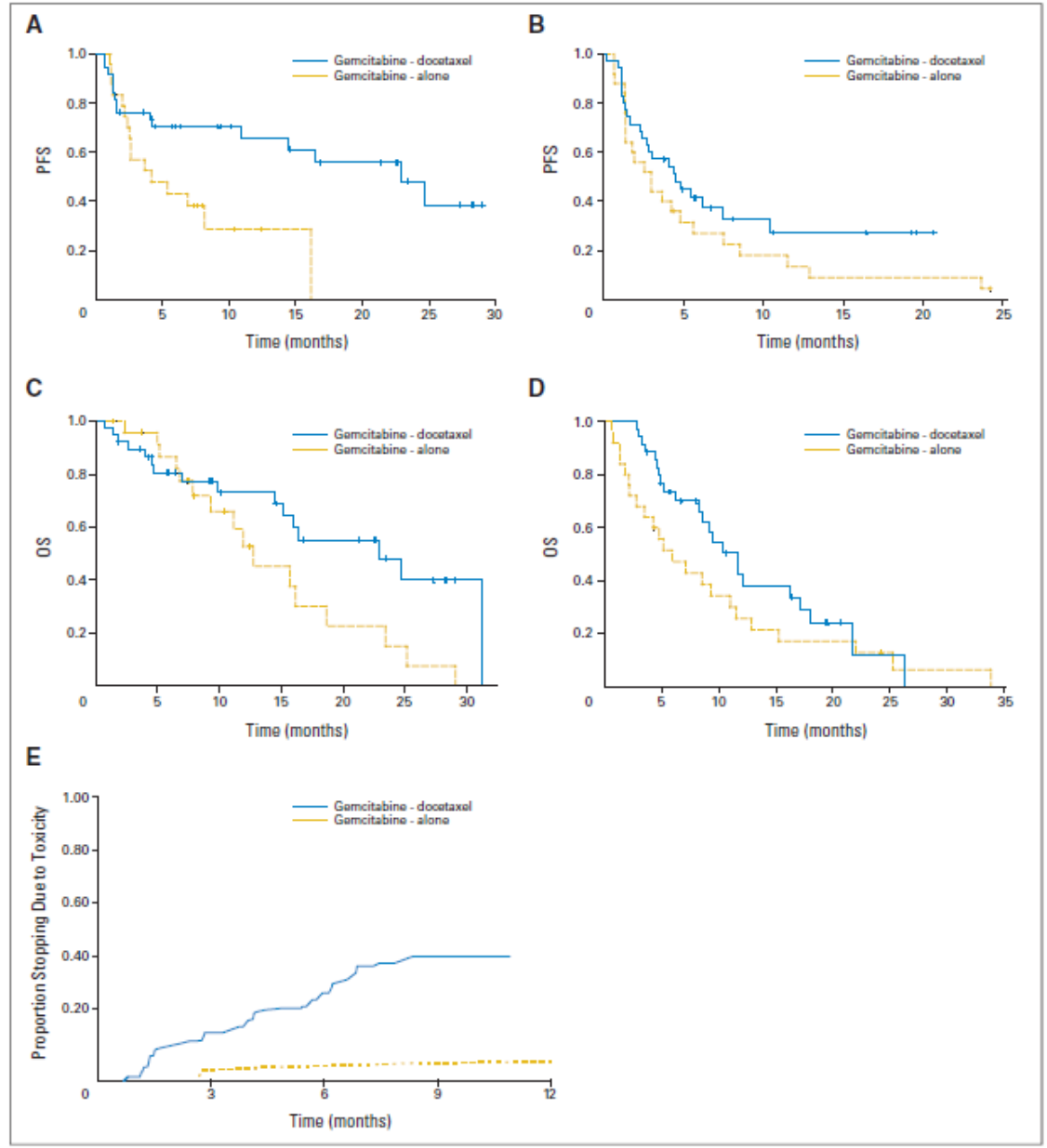
Randomized Phase II Study of Gemcitabine and Docetaxel Compared With Gemcitabine Alone in Patients With Metastatic Soft Tissue Sarcomas: Results of Sarcoma Alliance for Research Through Collaboration Study 002

Robert G. Maki, J. Kyle Wathen, Shreyaskumar R. Patel, Dennis A. Priebat, Scott H. Okuno, Brian Samuels, Michael Fanucchi, David C. Harmon, Scott M. Schuetze, Denise Reinke, Peter F. Thall, Robert S. Benjamin, Laurence H. Baker, and Martee L. Hensley

Table 4. Best Response by Treatment Arm and Histology*

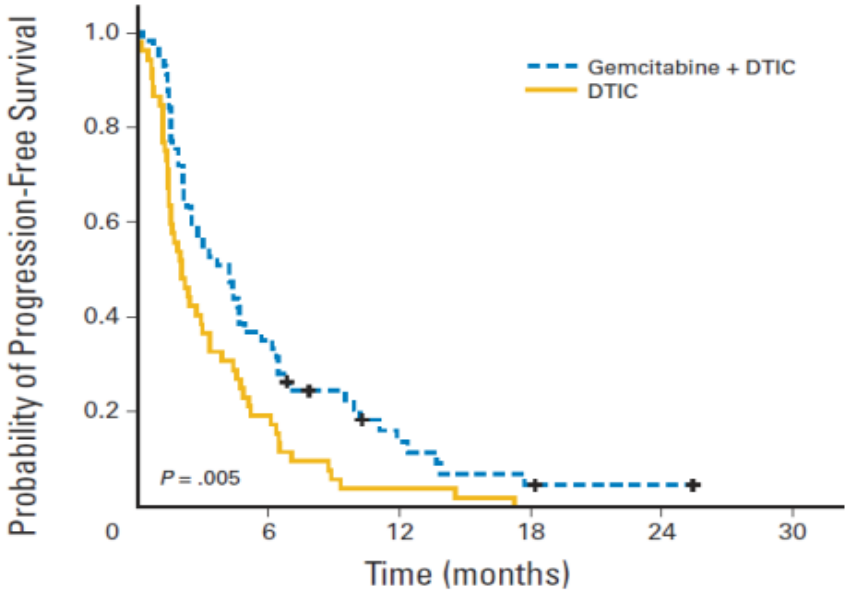
Histology	Gemcitabine						Gemcitabine-Docetaxel					
	CR	PR	Stable Disease ≥ 24 Weeks	Stable Disease < 24 Weeks	Progressive Disease	Not Assessable	CR	PR	Stable Disease ≥ 24 Weeks	Stable Disease < 24 Weeks	Progressive Disease	Not Assessable
Leiomyosarcoma		1	2	5	1			5	3	13	8	
MFH/HGUPS												
Liposarcoma												
Well differentiated/dedifferentiated			2	3	3					4		1
Myxoid-round cell				2	1	1						
Pleomorphic								2		1		
Synovial sarcoma												
Malignant peripheral nerve sheath tumor				1	1				1		3	
Unclassified sarcoma			1	2	1					1		
Fibrosarcoma			1		2				1	2		
Rhabdomyosarcoma							1				1	
Other sarcoma histology	1			2	4				2	4	4	

Abbreviations: CR, complete response; PR, partial response; MFH/HGUPS, malignant fibrous histiocytoma/high-grade undifferentiated pleomorphic sarcoma.
*Includes one Response Evaluation Criteria in Solid Tumors Group unconfirmed PR on each arm: gemcitabine (MFH/HGUPS); gemcitabine-docetaxel (uterine leiomyosarcoma).



Randomized Phase II Study Comparing Gemcitabine Plus Dacarbazine Versus Dacarbazine Alone in Patients With Previously Treated Soft Tissue Sarcoma: A Spanish Group for Research on Sarcomas Study

) 2016



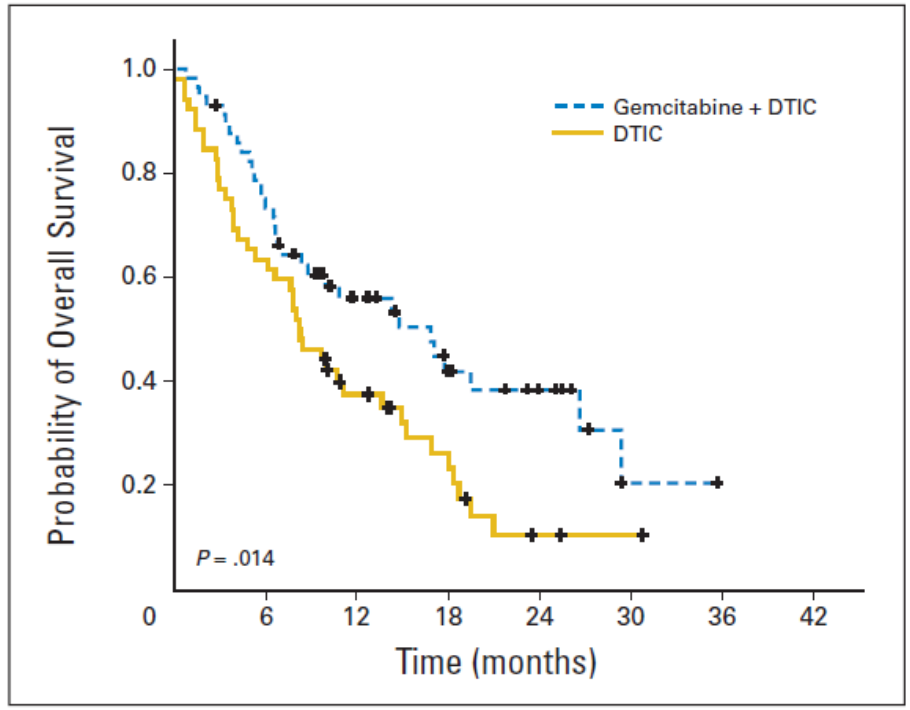


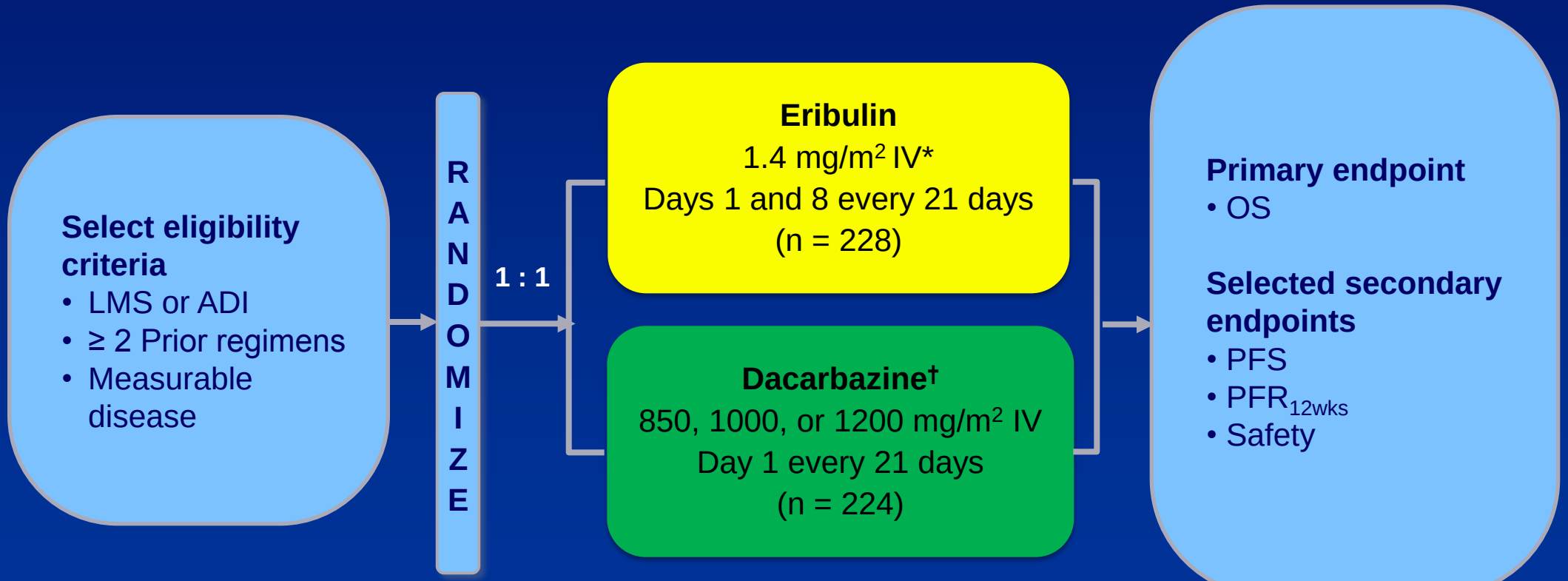
Fig 3. Kaplan-Meier curves for overall survival. DTIC, dacarbazine.

- 113 pts with STS (2 previous lines of CT; adria & ifosfamide)
- Gem 1800mg/m² fixed + DTIC 500 mg/m² q2 weeks or DTIC 1200 mg/m² q3 weeks
- Primary endpoint, PFR @ 3 months (40% to 60%)

García-del-Muro et al. J Clin Oncol 29:2528-2533

A randomized, open-label, multicenter, phase 3 study in patients with advanced/metastatic STS

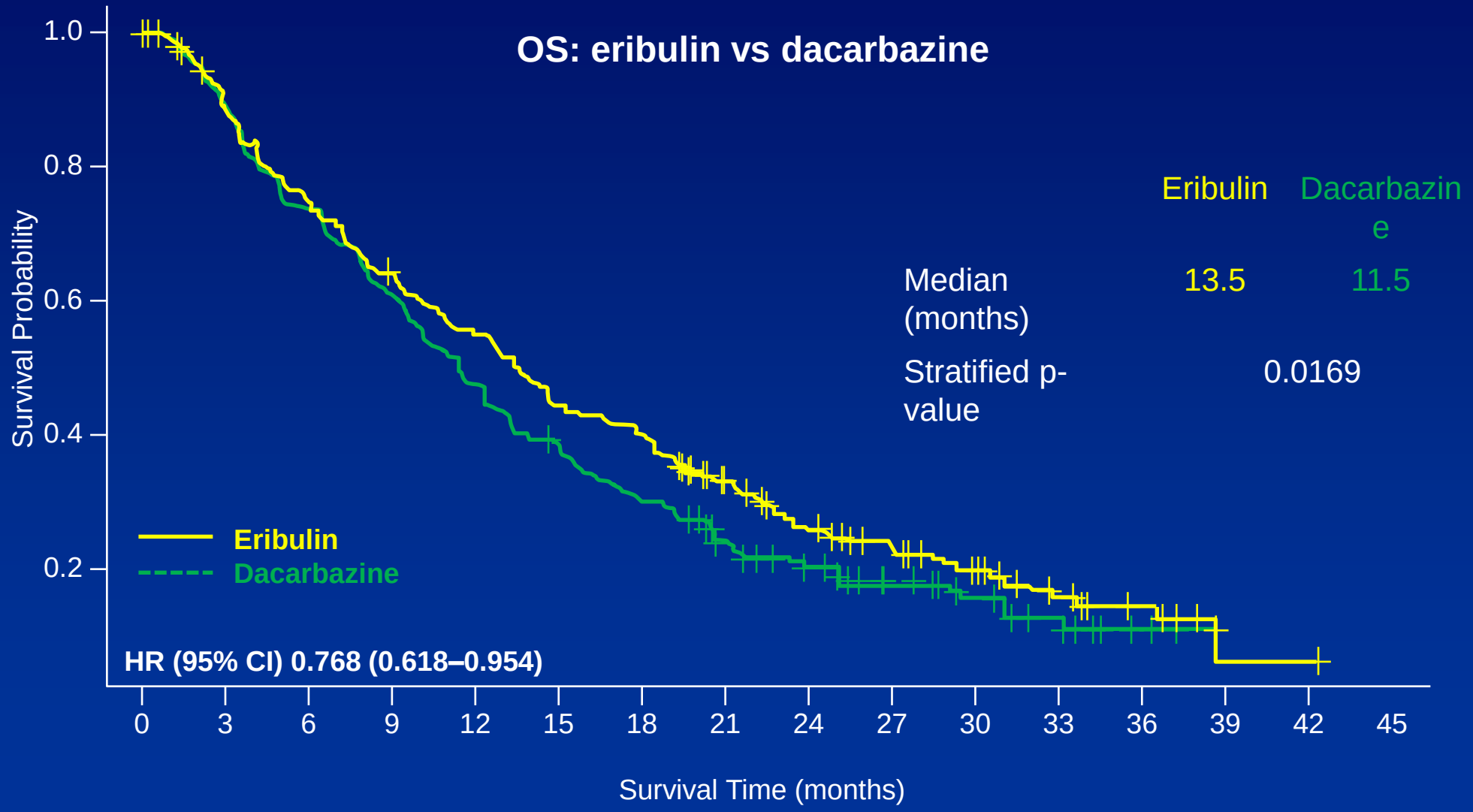
- **The aim is to discuss OS and PFS in various patient subgroups following treatment with eribulin versus dacarbazine**



*Dose for eribulin mesilate. †Starting dose selected by the local investigator at study initiation.

ADI, adipocytic sarcoma; IV, intravenous; LMS, leiomyosarcoma; OS, overall survival; PFR_{12wks}, progression-free rate at 12 weeks; PFS, progression-free survival; STS, soft tissue sarcoma.

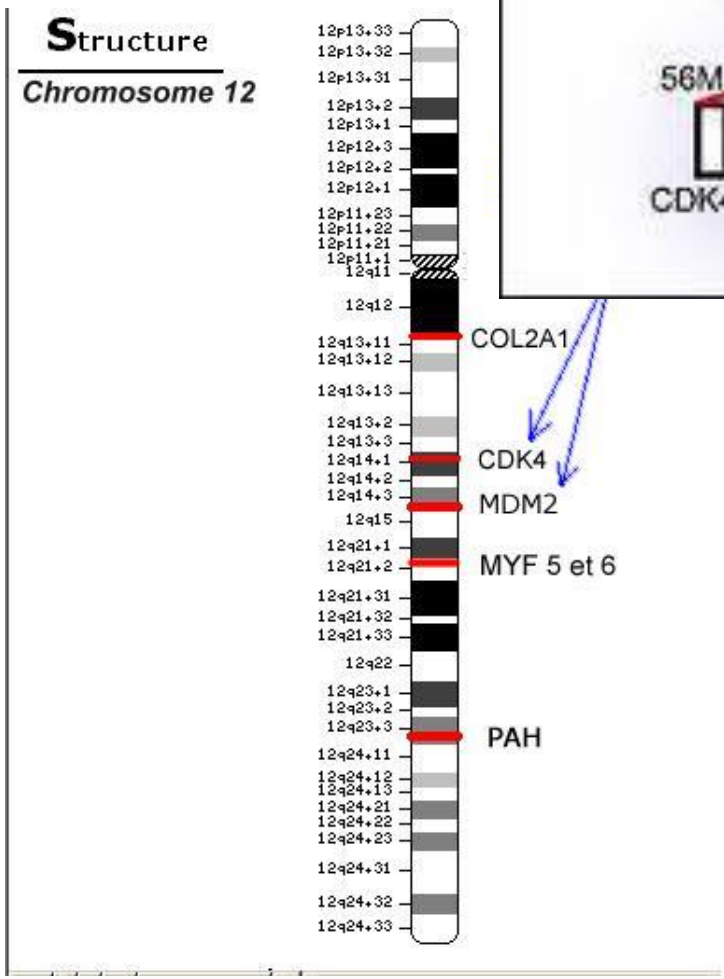
Eribulin significantly prolonged OS in comparison to dacarbazine, in the overall population

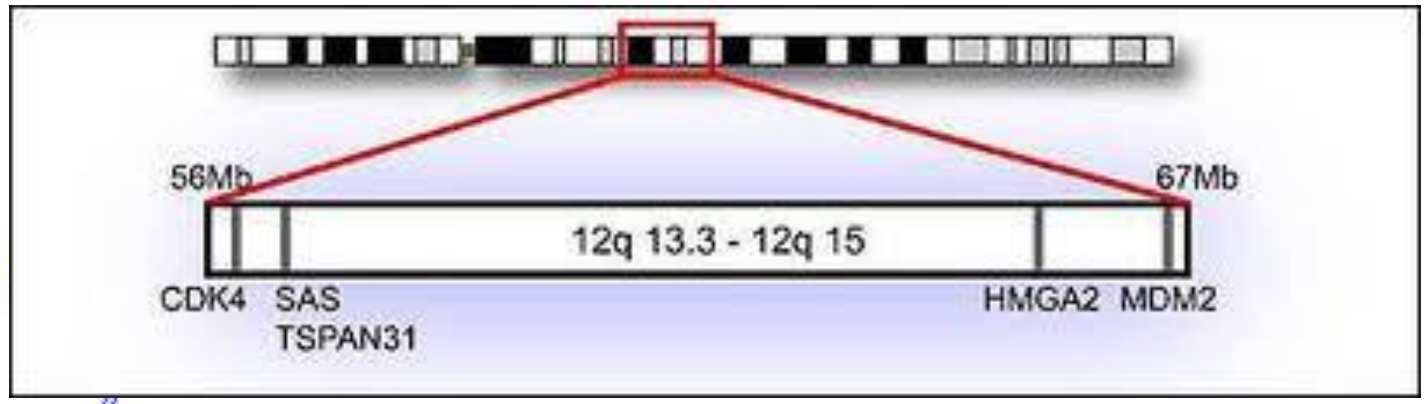


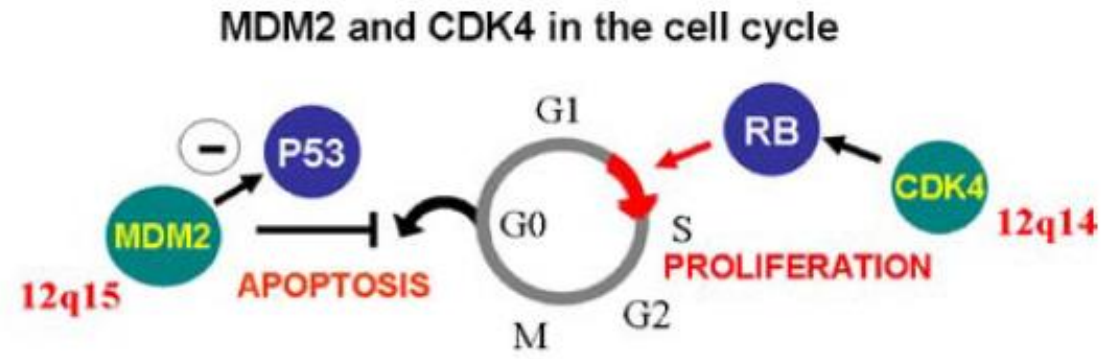
CI, confidence interval; HR, hazard ratio.

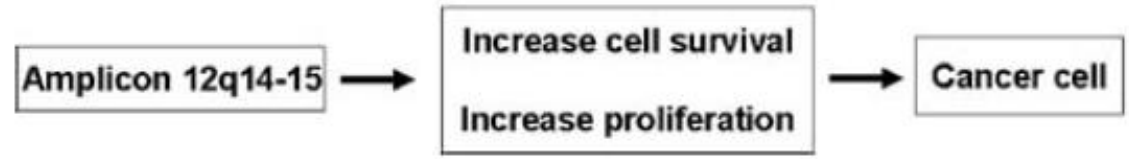
Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with *MDM2*-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study

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],

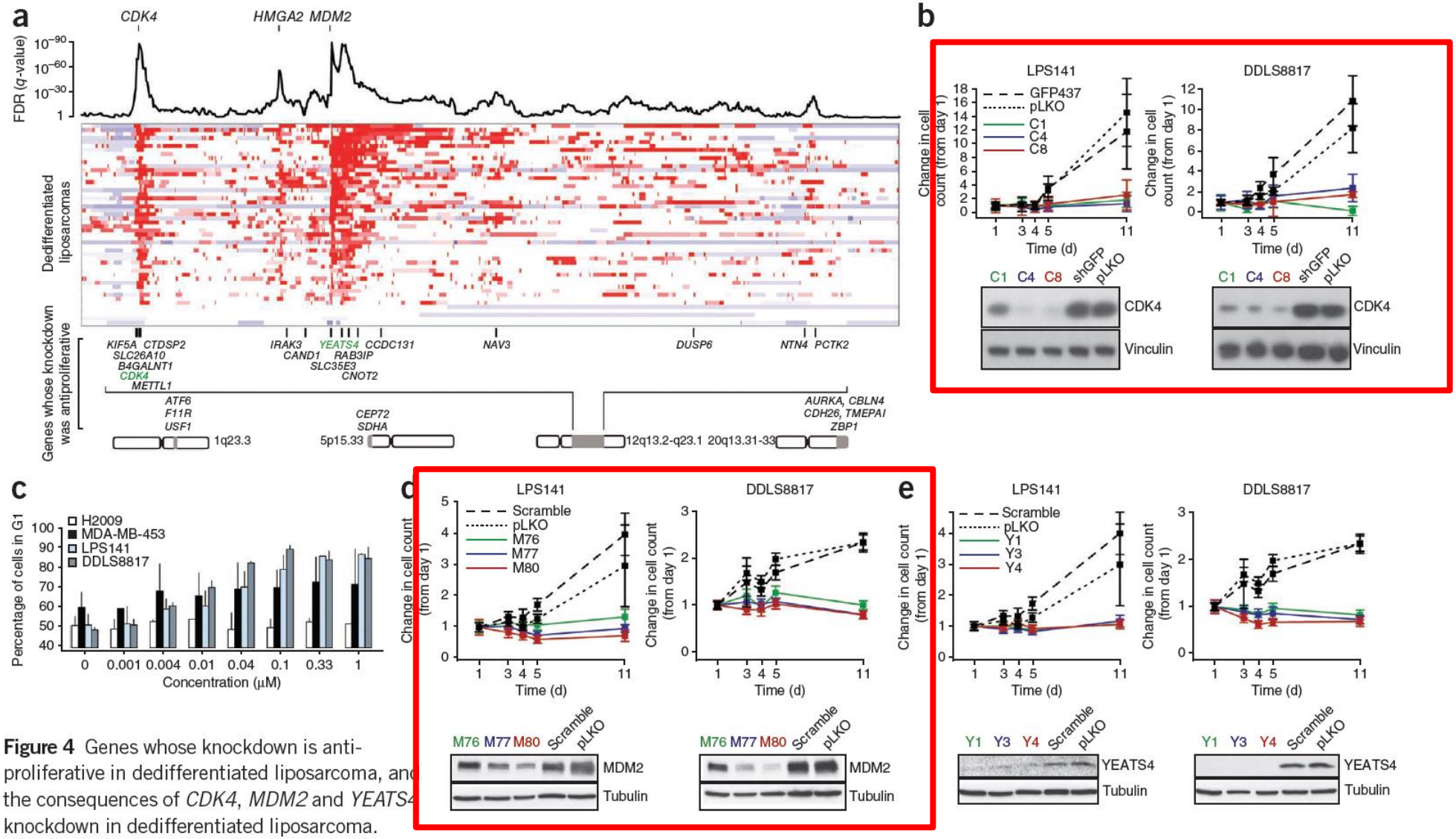


Figure 4 Genes whose knockdown is anti-proliferative in dedifferentiated liposarcoma, and the consequences of *CDK4*, *MDM2* and *YEATS4* knockdown in dedifferentiated liposarcoma.

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

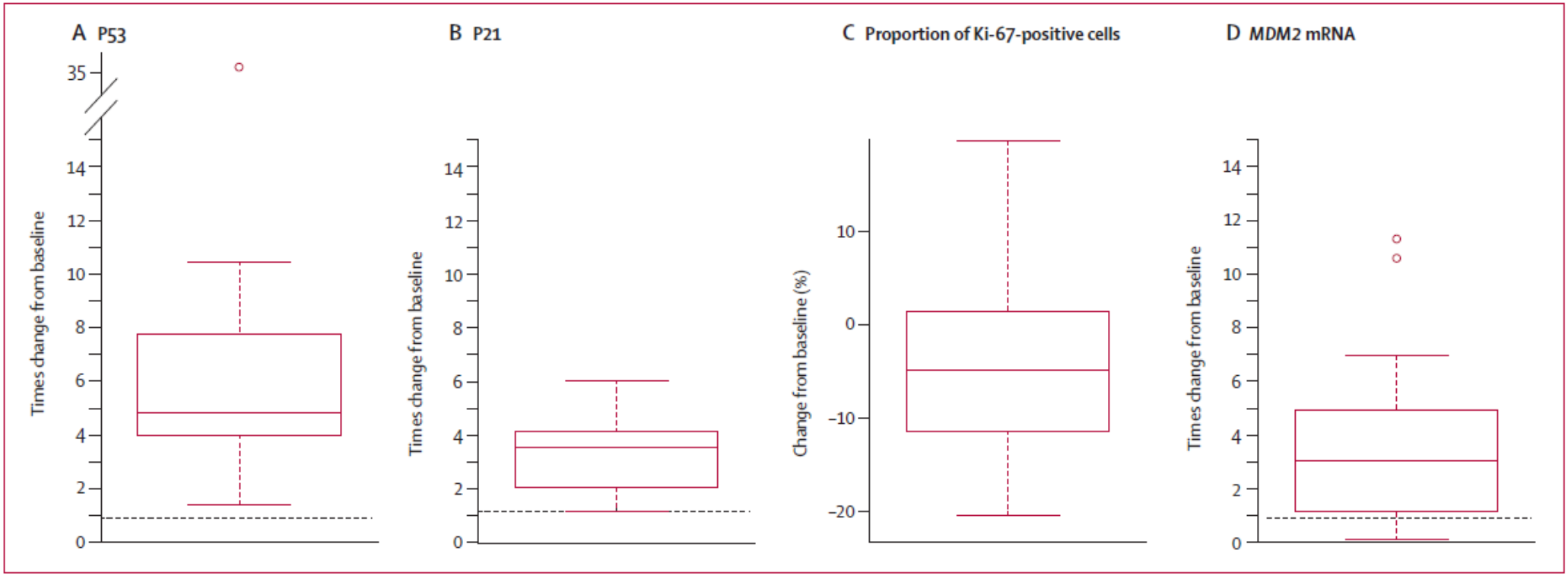
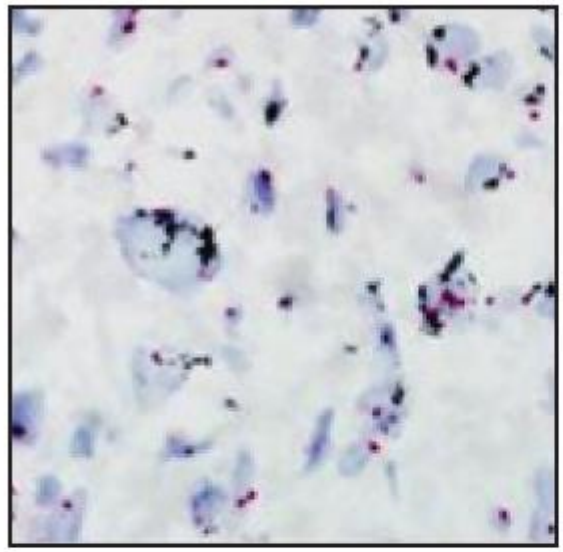


Figure 2: **Changes from baseline in P53 and P21 concentrations, proportion of Ki-67-positive cells, and *MDM2* RNA concentrations**
Horizontal dashed line corresponds to the point at which there is no change from baseline.

A



MDM2/Chr12=10
(*MDM2* amplified)

B

Biomarker	Baseline Biopsy	Biopsy at Day 8 (+/-2 days)
TUNEL [Density of TUNEL+ Cells (mm^2)]	0	17.9
Ki-67 [Percent of Cells Positive for Ki-67]	4.4	0.7

Lancet Oncol 2012; 13: 1133–40

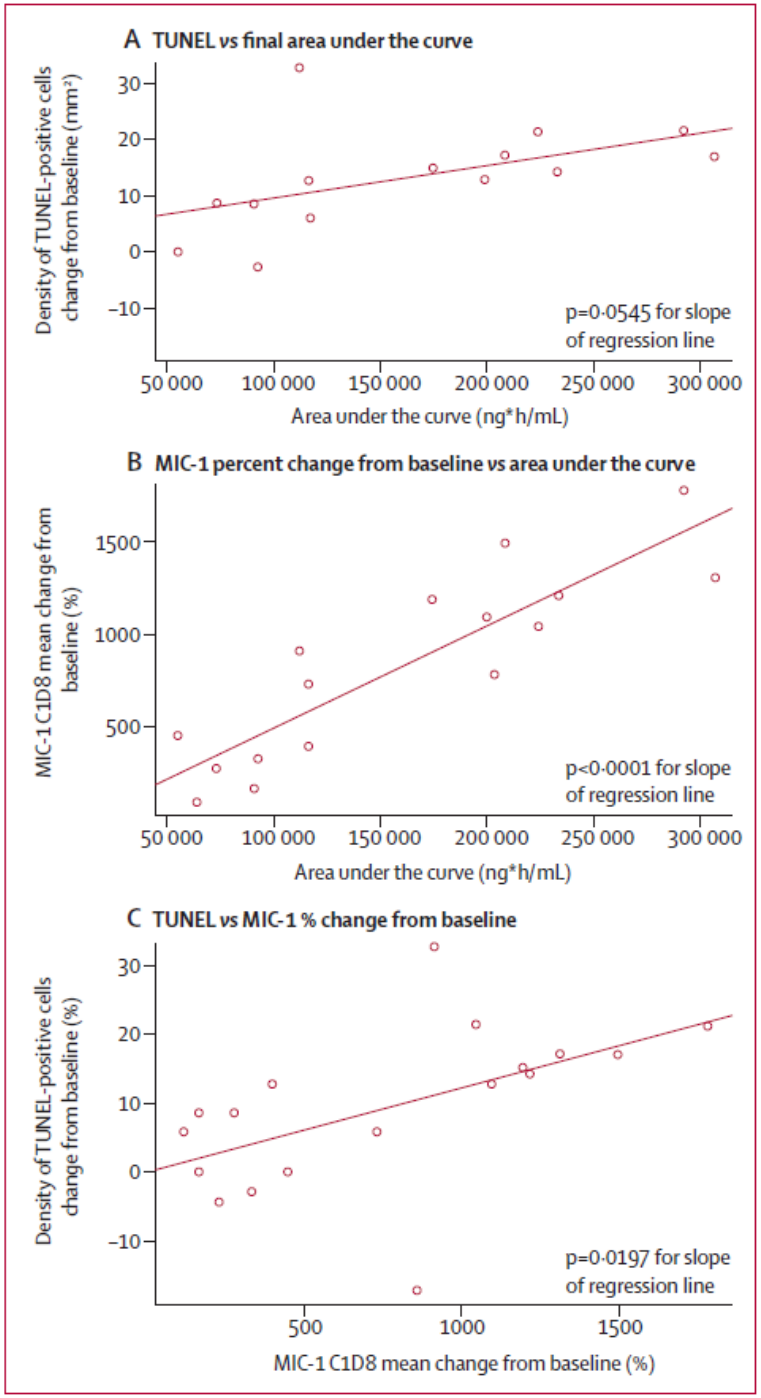


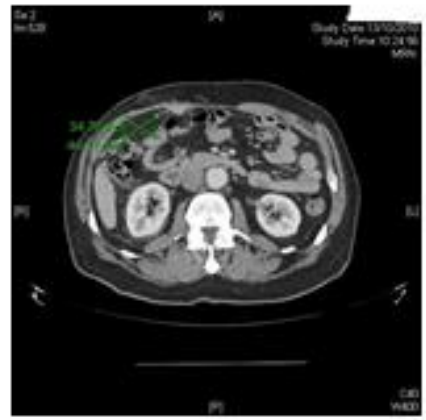
Figure 3: Pharmacokinetic and pharmacodynamic data

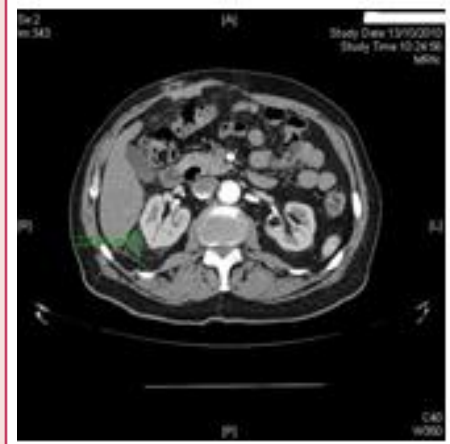
Response in a WD LPS

	Outcome (n=20)
Best response before surgery*	
Partial response	1
Stable disease	14
Progressive disease	5
Surgery†	
Yes	10
Complete resection	8
Partial resection	2
Biopsy only	2
No surgery	8
Status at last follow-up	
No evidence of disease	8
On study	2
Deceased	4
Off study	6
Progressive disease	5
Phlebitis	1

Data are number of patients. *Assessed by RECIST. †One patient died from postoperative haemorrhage after a complete resection.

Table 1: **Clinical response and outcome after treatment with RG7112**

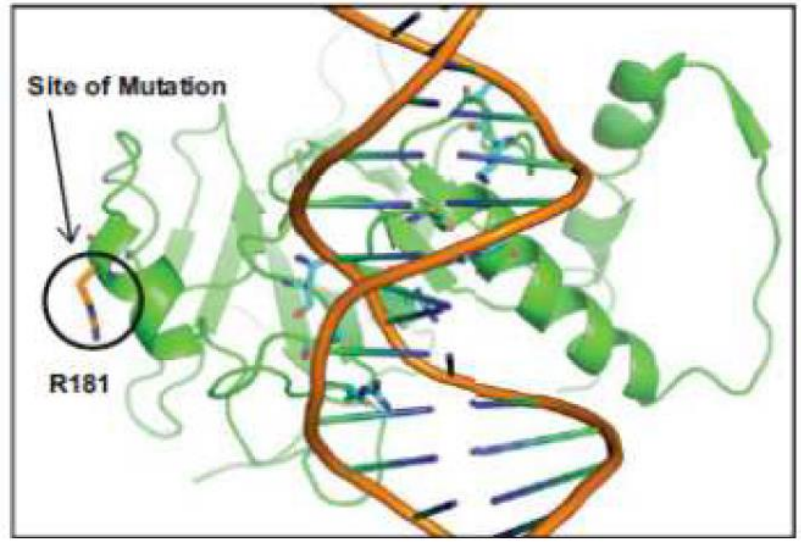




Biological responses in a p53 mutated WD/DDLPS

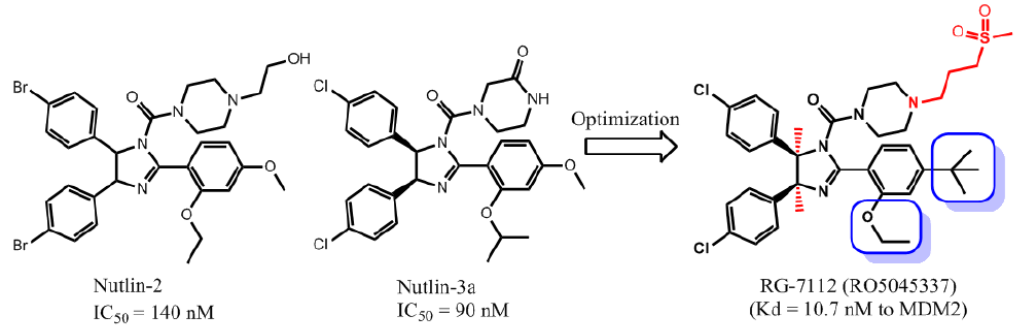
- Two patients with p53 mutations: R181L,G266R
- Biological response in the R181L pt (G266R NE)
- P53-independent role for MDM2?

Figure S4. Crystal structure of p53 bound to DNA and site of the R181 mutation



MDM2/p53 inhibitors

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



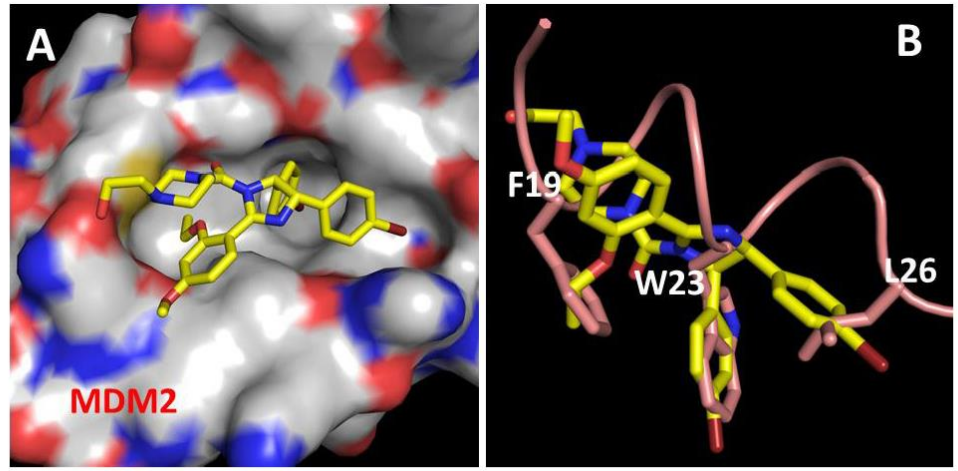


Figure 3. A) Crystal structure of nutlin-2 (shown as sticks) and MDM2 (PDB: 1RV1). B) Aligned orientation of p53 and Nutlin-3a. p53 residues essential for interaction are shown as sticks.

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

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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.

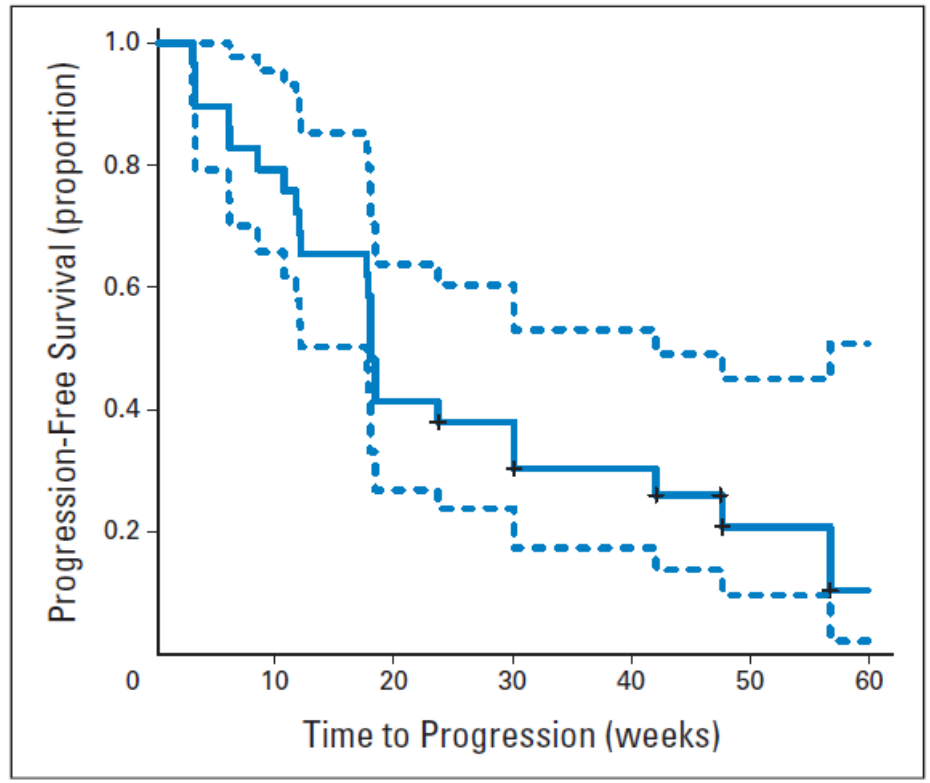

Fig 2. Kaplan-Meier curve of progression-free survival. Dashed lines indicate 95% CI.

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ESMO 2016

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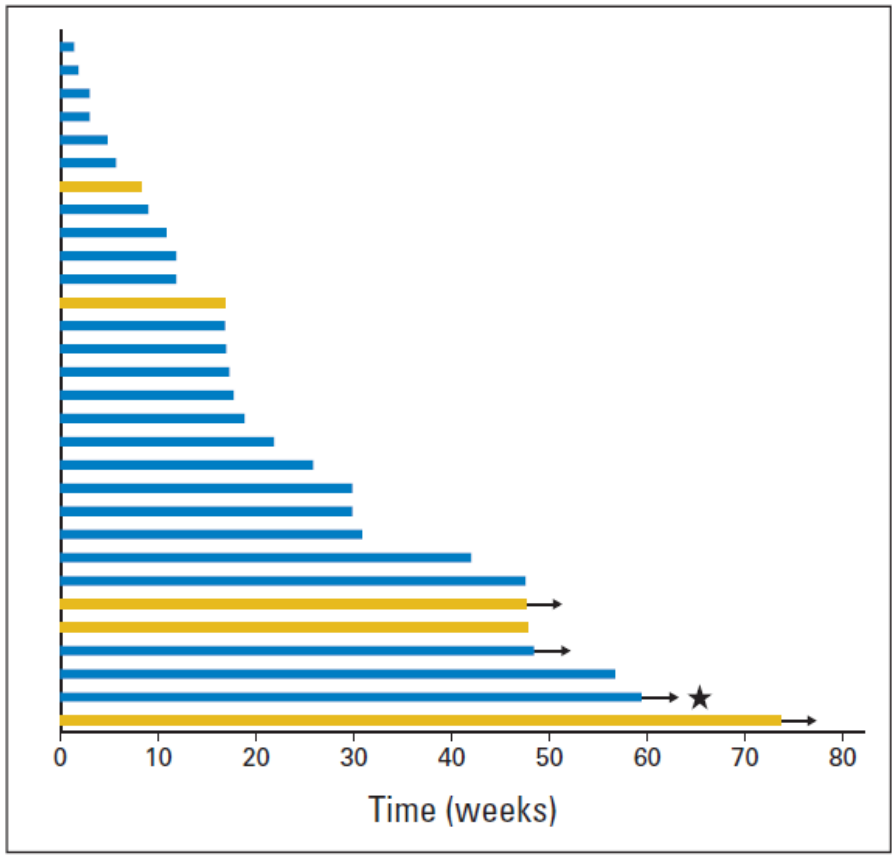
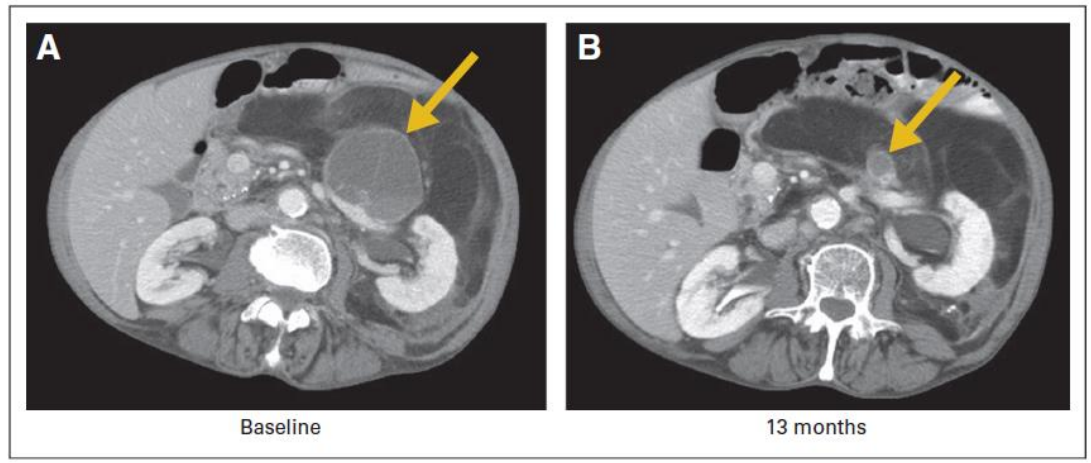


Fig 3. Time in study for all evaluable patients. Gold bars represent patients with purely well-differentiated liposarcoma; blue bars represent dedifferentiated tumors. Arrows indicate patients who remained in study at the data cutoff. Star indicates patient with partial response.

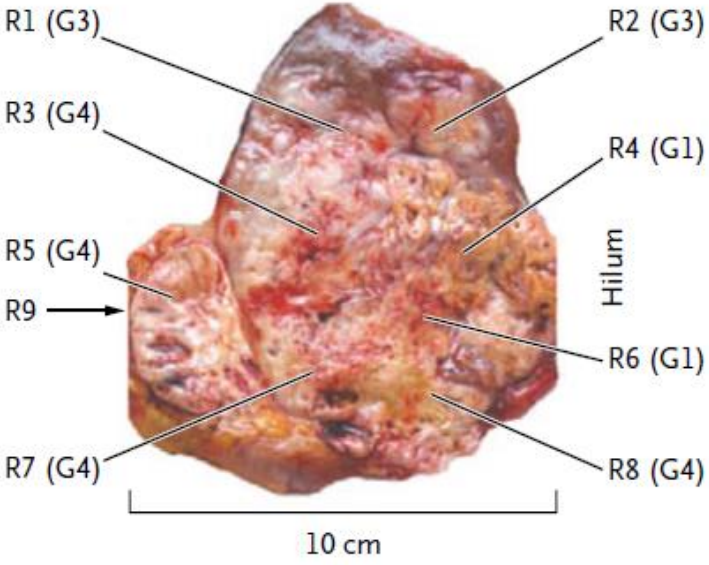


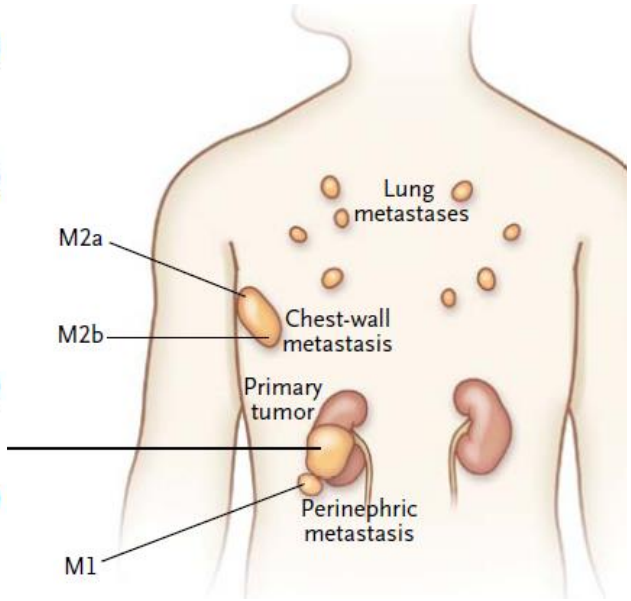
Study of Safety and Efficacy of HDM201 in Combination With LEE011 in Patients With Liposarcoma

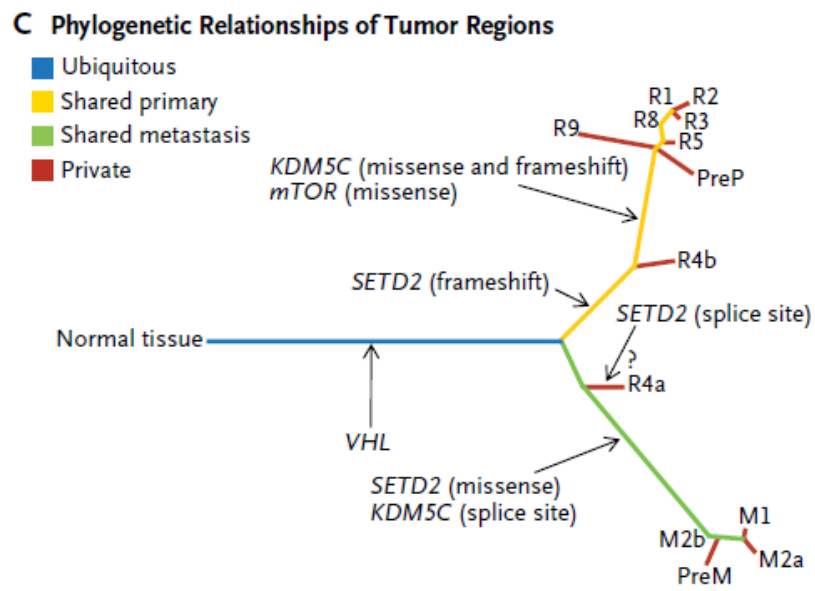
ClinicalTrials.gov Identifier
NCT02343172

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.







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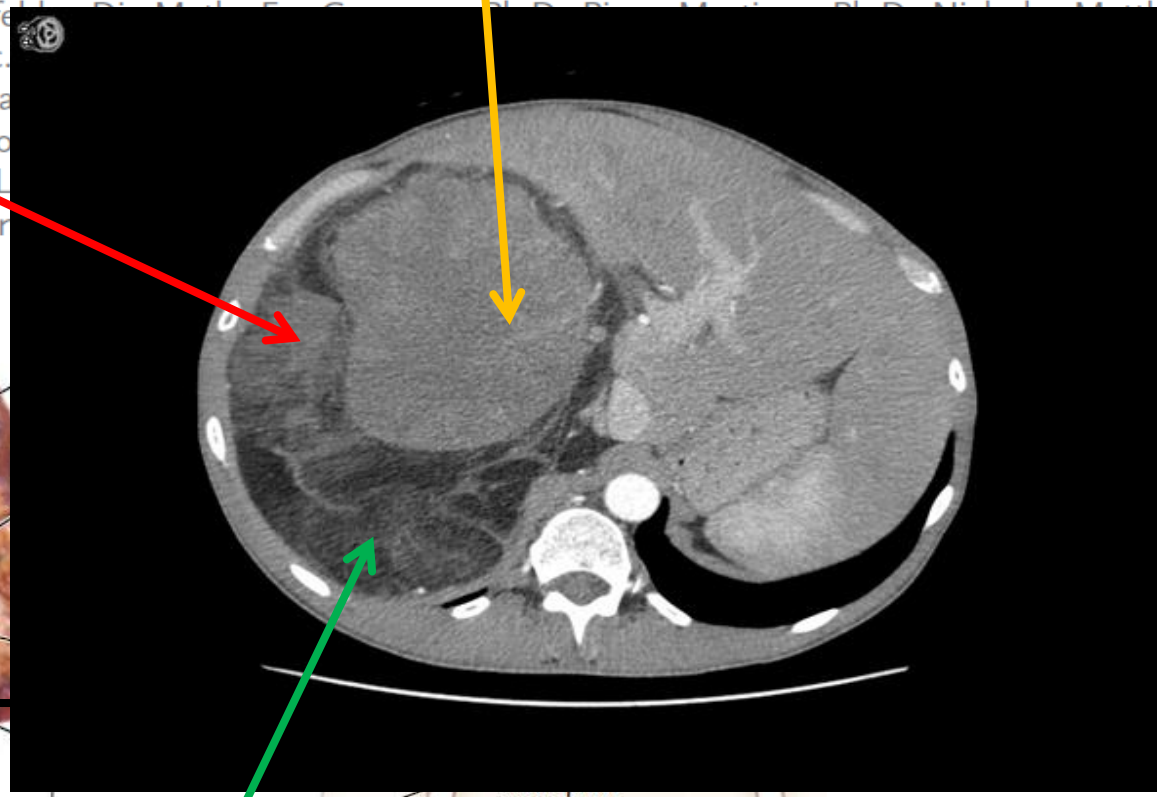
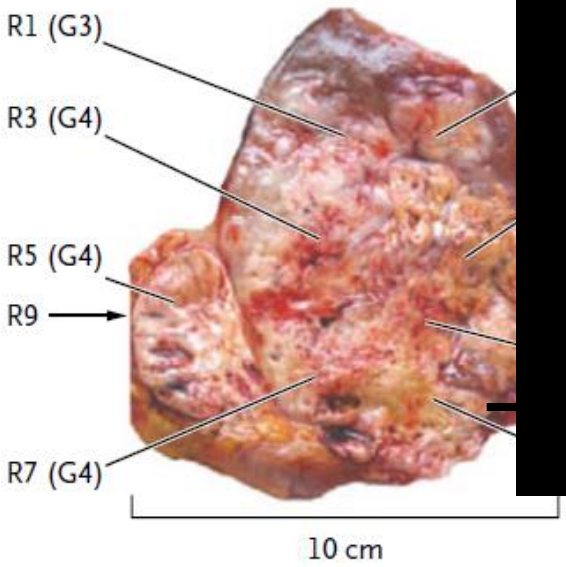
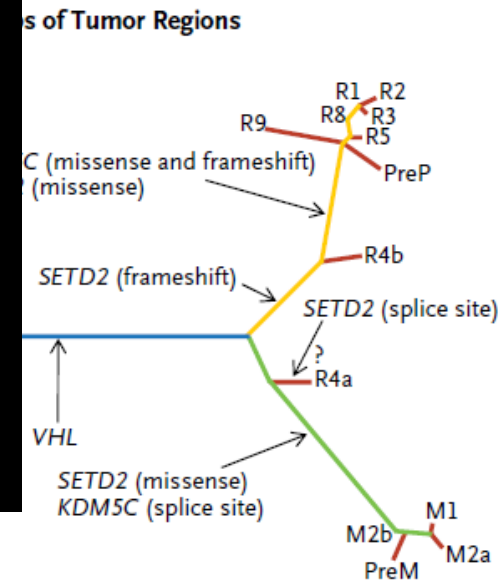
Claudio R. Santo… …-Dene, Ph.D.,
Graham Clark, B.Sc. L… …oltan Szallasi, M.D.,
Julian… …D.

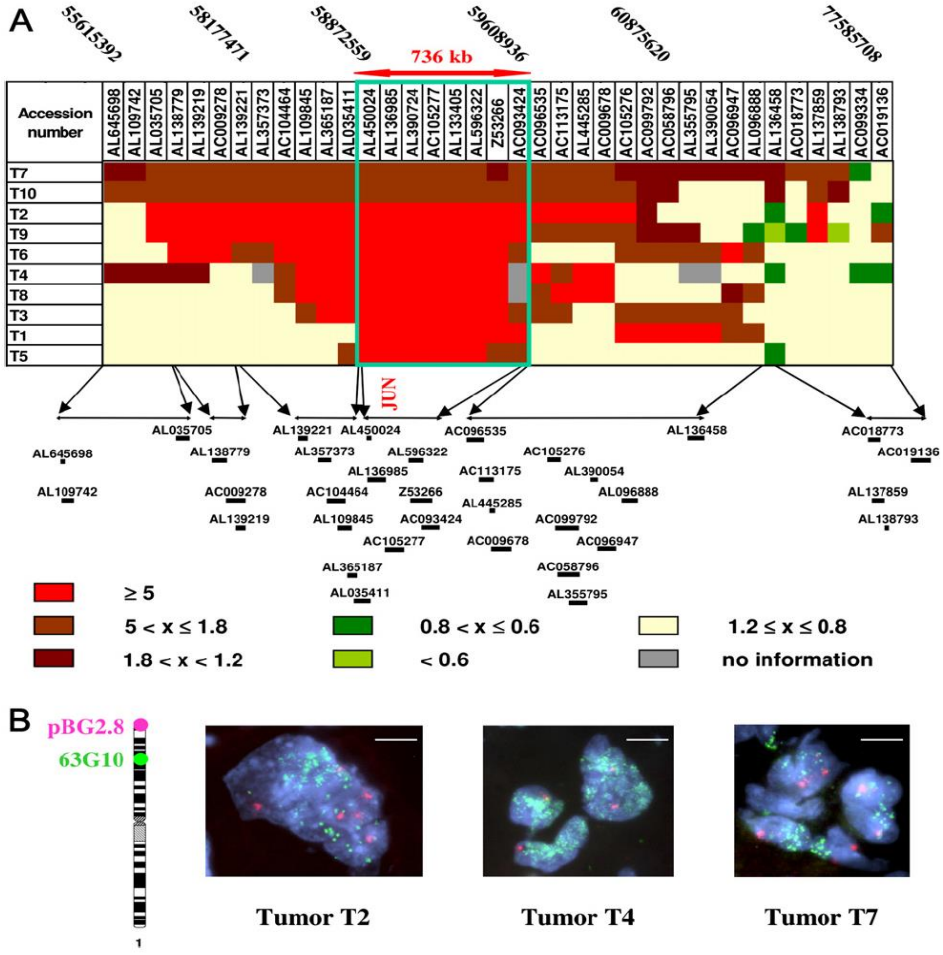






JUN Oncogene Amplification and Overexpression Block Adipocytic Differentiation in Highly Aggressive Sarcomas

Odette Mariani,[1,2] Caroline Brennetot,[1,2] Jean-Michel Coindre,[3] Nadège Gruel,[4] Carine Ganem,[1,2] Olivier Delattre,[1,2] Marc-Henri Stern,[1,2] and Alain Aurias[1,2,*]



Genomic Amplification of the JUN Locus

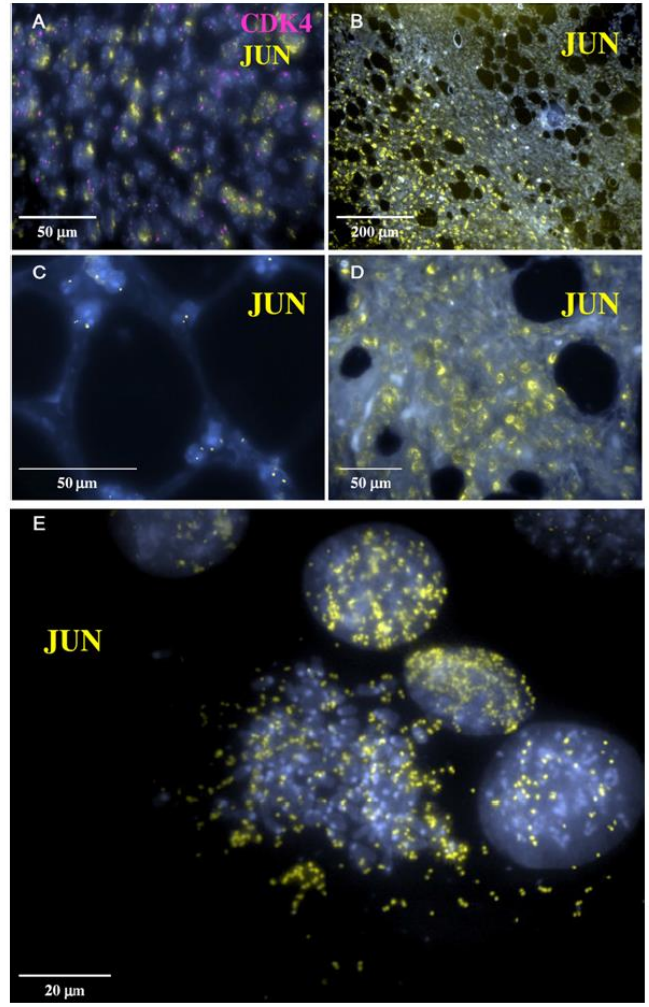
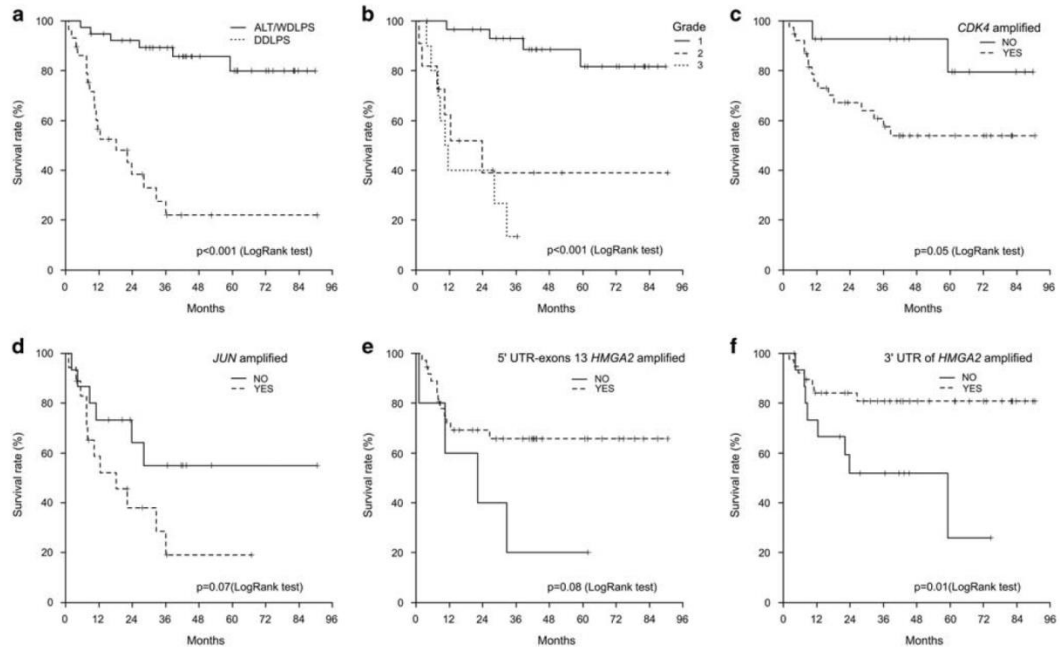


Figure 7. FISH Experiments Performed on Tumors Obtained after 3T3-L1 Cell Injection into Nude Mice

Cancer Cell 2007

Prognostic value of *HMGA2*, *CDK4*, and *JUN* amplification in well-differentiated and dedifferentiated liposarcomas

Esma Saâda-Bouzid[1,2,3], Fanny Burel-Vandenbos[4], Dominique Ranchère-Vince[5], Isabelle Birtwisle-Peyrottes[6], Bruno Chetaille[7], Corinne Bouvier[8], Marie-Christine Château[9], Michel Peoc'h[10], Maxime Battistella[11], Audrey Bazin[1], Jocelyn Gal[12], Jean-François Michiels[4], Jean-Michel Coindre[13], Florence Pedeutour[1,2,14] and Laurence Bianchini[1,2,14]



	MDM2	*HMGA2*	*CDK4*	*JUN*	*MAP3K5*
Primary tumor: WDLPS 1999	Amplified Log $R = 3.01$	Gained Log $R = 1.04$	Amplified Log $R = 3.01$	Not amplified	Not amplified
First recurrence: DDLPS 2008	Amplified Log $R = 1.72$	Not gained	Amplified Log $R = 1.25$	Amplified Log $R = 1.83$	Not amplified
Second recurrence: DDLPS 2009	Amplified Log $R = 4.41$	Gained Log $R = 0.73$	Amplified Log $R = 3.22$	Amplified Log $R = 4.22$	Not amplified
Third recurrence: DDLPS 2011	Amplified Log $R = 2.03$	Not gained	Gained Log $R = 0.49$	Amplified Log $R = 2.03$	Not amplified
Fourth recurrence: DDLPS 2014	Amplified Log $R = 3.14$	Amplified Log $R = 2.0$	Amplified Log $R = 2.39$	Amplified Log $R = 1.98$	Amplified Log $R = 1.20$

Conclusions

Chemotherapy of WD/DD liposarcomas

- Rare relapses for WDLPS if not RPS
- CT of WD/DDLPS : similar strategies
- Similar results
- Trabectedine
- Eribuline
- No antiangiogenics yet (why?)
- So far target limited impact of MDM2/CDK4 inhibitors
  - Challenging the concept of “driver” alterations