MADRID 2014 ESMO congress

Is there a role for neo-adjuvant systemic treatment in STS?

Dr. J Martin-Broto
Universitary Hospital Virgen del Rocío
Sevilla, Spain

Disclosure slide

- Participant in advisory board for PharmaMar, GSK, Amgen and Novartis.

AGENDA

1) Is there room for systemic treatment in localized STS?

2) If so, then Is the neo-adjuvant systemic therapy the best choice?

For any succesful co-adjuvant treatment we need:

1.- To test adjuvant treatment in a prognostic homogeneous population (Adequate patient selection).

2.- To offer the most active treatment (Adequate drug selection)

3.- To know predictive biomarkers (Adequate target selection)

Prognostic Factors in Localized STS

Cox Multivariate Analysis for Metastasis-free Survival (n= 1199)

Factor	No. patients	Relative Risk	95% CI	p
Grade				
1	154	1		
2	492	3.12	1.83-5.35	3.2×10^{-5}
3	553	7.81	4.63-13.17	1.1×10^{-14}
Tumor Size				
< 5 cm	260	1		
5-9 cm	415	1.5	1.11-2.09	0.01
≥ 10 cm	524	2.02	1.47-2.76	1.2×10^{-5}
Neurovascular involvement				
No	985	1		
Yes	214	1.5	1.21-1.89	0.0003
Tumor Depth				
Superficial	165	1		
Deep	1034	1.47	1.00-2.18	0.048

J M Coindre, Cancer 2001, 91: 1914-26

Prognostic Factors in Localized STS

5-Year Metastasis free survival in the main histologic types

Factors	UPS	LIPOS.	LEIOM.	SYNOV.	MPNST	UNCLASS.
Tumor Size	p= 0.005	p=0.0061	p=0.0001	p=0.0104	p=0.67	p=0.053
<5 cm	88.2 (78)	92.6 (14)	88.0 (41)	66.8 (39)	61.2 (12)	72.4 (21)
5-9 cm	65.4 (117)	94.7 (39)	52.7 (48)	56.3 (54)	57.6 (28)	58.2 (49)
≥ 10 cm	53.6 (147)	72.8 (130)	41.2 (59)	27.3 (26)	44.5 (29)	34.5 (66)
Tumor Depth	p=0.0043	p= 0.07	p=0.0002	p=0.0407	nd	p=0.042
Superficial	82.2 (69)	100 (11)	86.0 (35)	100 (5)		78.6 (14)
Depth	60.7 (279)	77.8 (177)	50.9 (112)	50.6 (120)		46.0 (125)
Grade	p< 0.0001	p<0.0001	p=0.002	p=<0.0001	p=0.33	p<0.0001
1	89.8 (33)	93.8 (85)	92.9 (16)	--	77.8 (5)	82.0 (18)
2	76.5 (160)	71.6 (71)	66.6 (65)	74.8 (56)	56.1 (26)	69.0 (75)
3	48.1 (156)	58.7 (32)	44.7 (67)	35.1 (69)	52.1 (41)	36.5 (65)

J M Coindre, Cancer 2001, 91: 1914-26

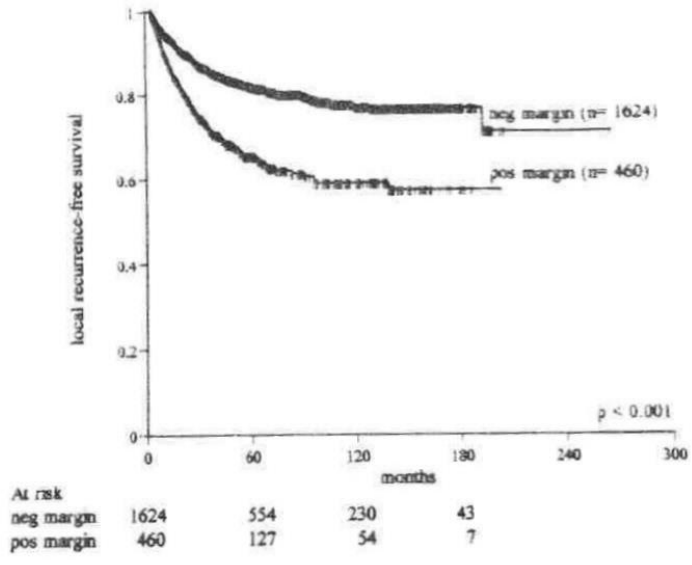
MADRID 2014

Analysis of the Prognostic Significance of Microscopic Margins in 2,084 Localized Primary Adult Soft Tissue Sarcomas

Alexander Stojadinovic, MD,* Denis H. Y. Leung, PhD,† Axel Hoos, MD, PhD,* David P. Jaques, MD,*
Jonathan J. Lewis, MD, PhD, and * Murray F. Brennan, MD*

*From the Departments of *Surgery and †Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York*

LR



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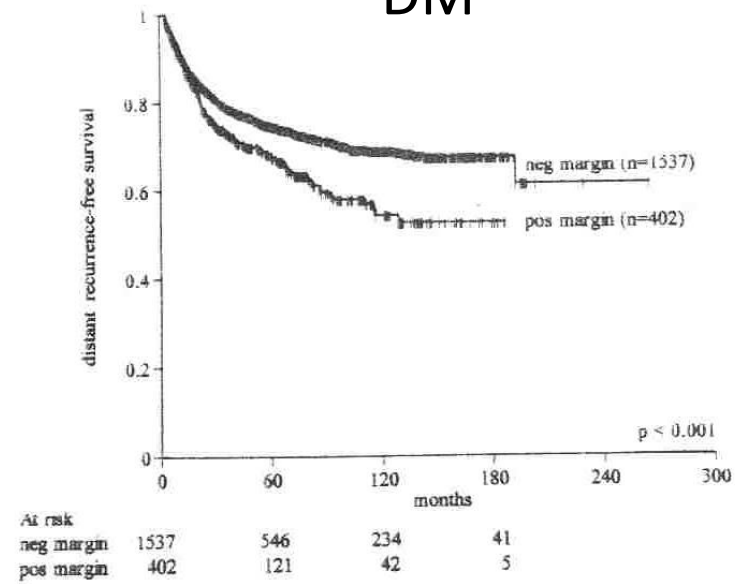


A Stojadinovic , Ann Surg 2002, 235: 424-34

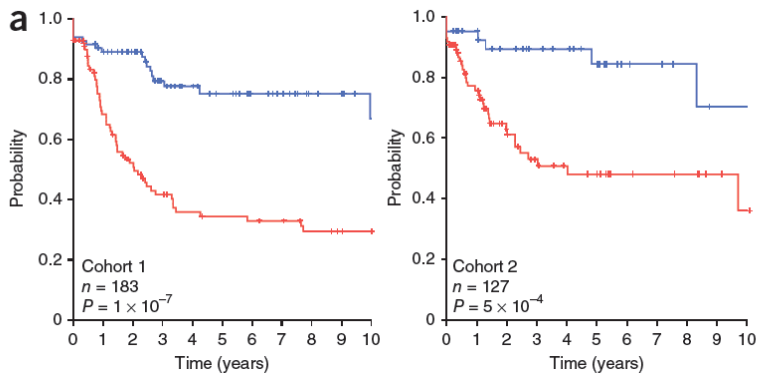
Prognostic Factors in Localized STS

Multivariate analysis (Overall Survival)

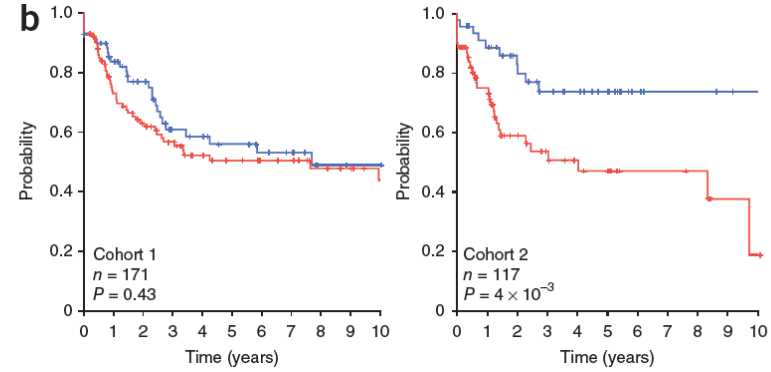
	GRADO 2 (N=625) HR (95% IC)	p	GRADO 3 (N=627) HR (95% IC)	p
EDAD > 51 años	2.1 (1.6-2.8)	< 0.0001	1.6 (1.2-2.1)	0.0002
TUMOR > 5 cm	1.8 (1.3-2.5)	0.0003	1.6 (1.2-2.2)	0.003
Local superficial	NS		0.6 (0.4-0.9)	0.02
Invasión neurovascular	1.9 (1.3-2.6)	0.0001	1.5 (1.1-2.1)	0.003
QTP adyuvante	0.8 (0.6-1.1)	0.15	0.6 (0.5-0.8)	0.0002

A Italiano , Ann Surg 2002, 235: 424-34

Metastasis-free survival analysis(Overall Survival)



CINSARC



FNCLCC Grade

F Chibon, Nature Medicine, 2010, 12: 2436-41

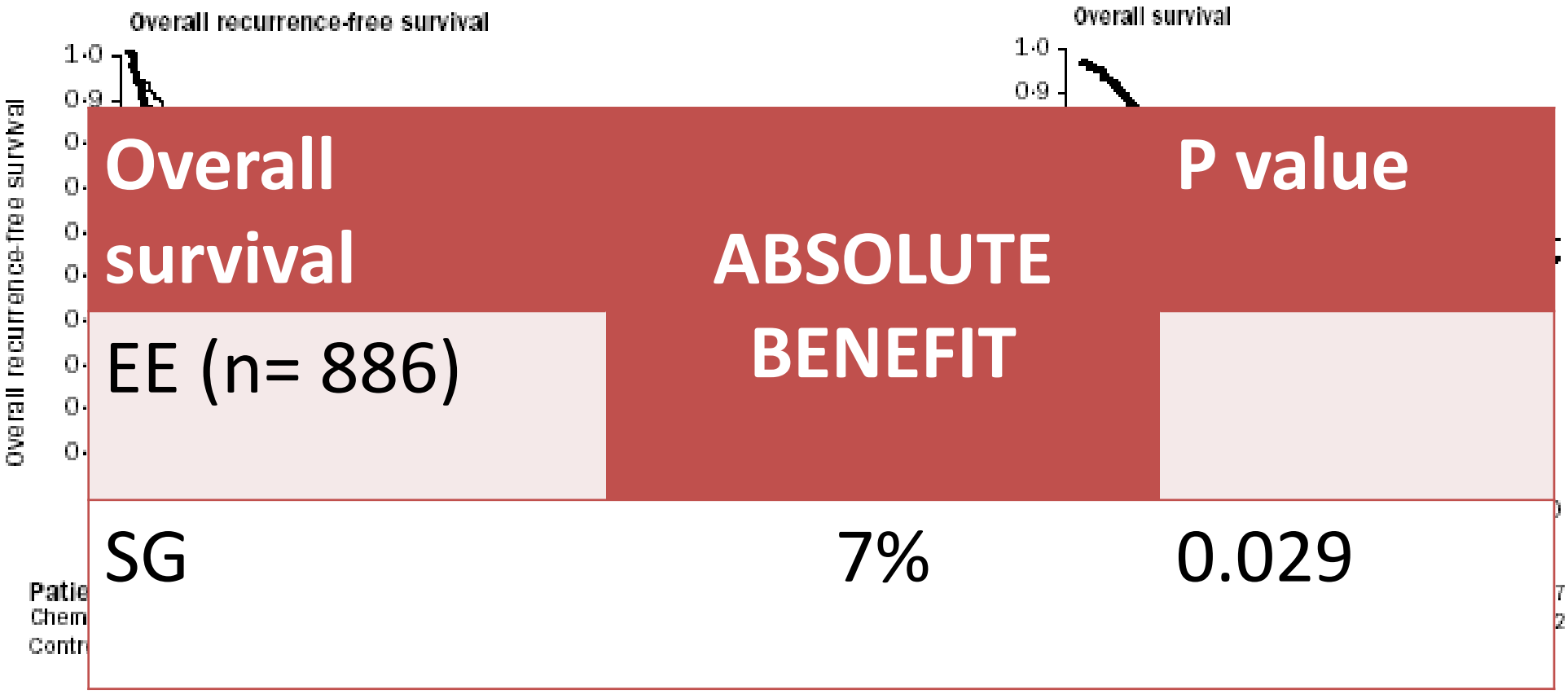
FIRST GENERATION TRIALS. MONOCHEMOTHERAPY

GROUP	SCHEME	N	Fup	RFS	OS
Scandin.	A 60 d1/4s/x9	77	40	62 nS	75 nS
1981-86	control	77		56	70
UCLA	A 45 d1-2/4s/x5	56	28	58 nS	85 nS
1981-84	control	63		54	80
InterG	A 35 d1-3/3s/x6	32	20	67 nS	82 nS
1983-87	control	32		67	77
Rizzoli	A 25 d1-3/3s/x6	32	106	56 pS	?? pS
1981-86	control	44		32	??

FIRST GENERATION TRIALS. POLYCHEMOTHERAPY

GROUP	SCHEME	N	Fup	RFS		OS	
•EORT	VC-A-C-D	145	80	56	ps	63	ns
	control	172		43		55	
•NCI	A-C-MTx	39	85	75	ps	82	ns
	control	28		54		60	
•MAYO	VC-C-Dact/A-D	26	64	ns		90	ns
	control	26		ns		77	
•MDAn	VC-A-C-Dact	20	120	54	ps	65	ns
	control	23		35		57	ns
•F.Berg.	VC-A-C-D	31	52	ns		87	ps
	control	28		ns		53	

Sarcoma Meta-analysis Collaboration
(Lancet, 350:1647-54, 1997)



Overall survival	ABSOLUTE BENEFIT	P value
EE (n= 886)		
SG	7%	0.029

Endpoint	results		Absol benefit	P value
	Treatm.	Control		
RFS	55%	45%	10%	0.0001

Endpoint	results		Absol benefit	P value
	Treatm.	Control		
OS	54%	50%	4%	0.12

Criticism of first generation trials

- Inadequate patient selection:
  - Heterogeneous population: Different grade, locations; depth; surgical margins.
- Inadequate drug selection:
  - Only 3% of patients had received Ifosfamide
  - Low dose-intensity for anthracyclines

SECOND GENERATION TRIALS: Anthracyclines+Ifosfamide

GROUP	SCHEME	TIME INTERVAL	D.I. (mg/m2/s)
NCI 92	ADR 70 IFOS 4	4 W X 5	ADR 17.5 IFOS 1000
EORTC 62931	ADR 75 IFOS 5	3 W X 5	ADR 25 IFOS 1667
RTOG 9514	ADR 20 D1-3 IFOS 2,5 D1-3 DTIC 225 D1-3	3 W X2 +4	ADR 20 IFOS 2500 DTIC 225
ITALY (Frustaci et. al)	EPI 60 D1-2 IFOS 1,8 D1-5	3W X 5	EPI 40 IFOS 3000

Systematic Meta-analysis

(Includes 2nd generation trials)

RELATIVE RISK 95% CI FOR LR, DR, OR, OS								
	LOCAL RECURRENCE		DISTANT RECURRENCE		OVERALL RECURRENCE		OVERALL SURVIVAL	
	RR	95%IC	RR	95%IC	RR	95%IC	RR	95%IC
DOXO	0.75	0.56-1.01	0.69	0.56-0.86	0.75	0.56-0.86	0.84	0.68-1.03
DOXO+IFOS	0.66	0.39-1.12	0.61	0.41-0.92	0.61	0.41-0.92	0.56	0.36-0.85
ALL	0.73	0.56-0.94	0.67	0.56-0.82	0.67	0.56-0.82	0.77	0.64-0.93
	5%	NTT 25	10%	NTT 10	10%	NTT 10	6%	NTT 17

Cancer, 113: 573-581. 2008

ISG FIRST TRIAL: EPI+IFOS

G3, deep, ≥ 5 cm

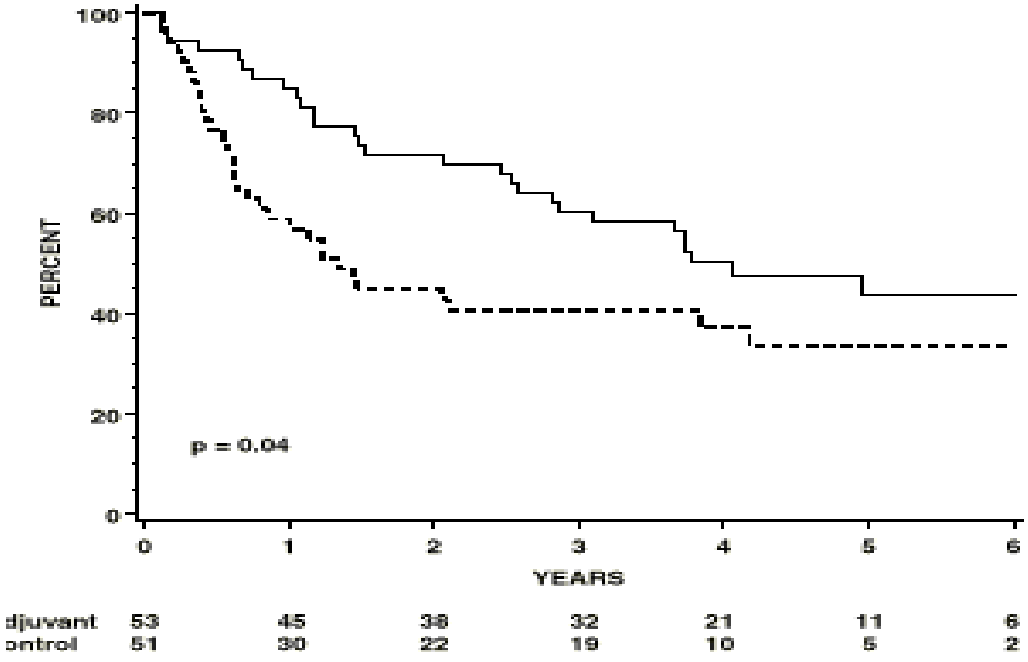


Figure 2. Disease-free Survival by Treatment

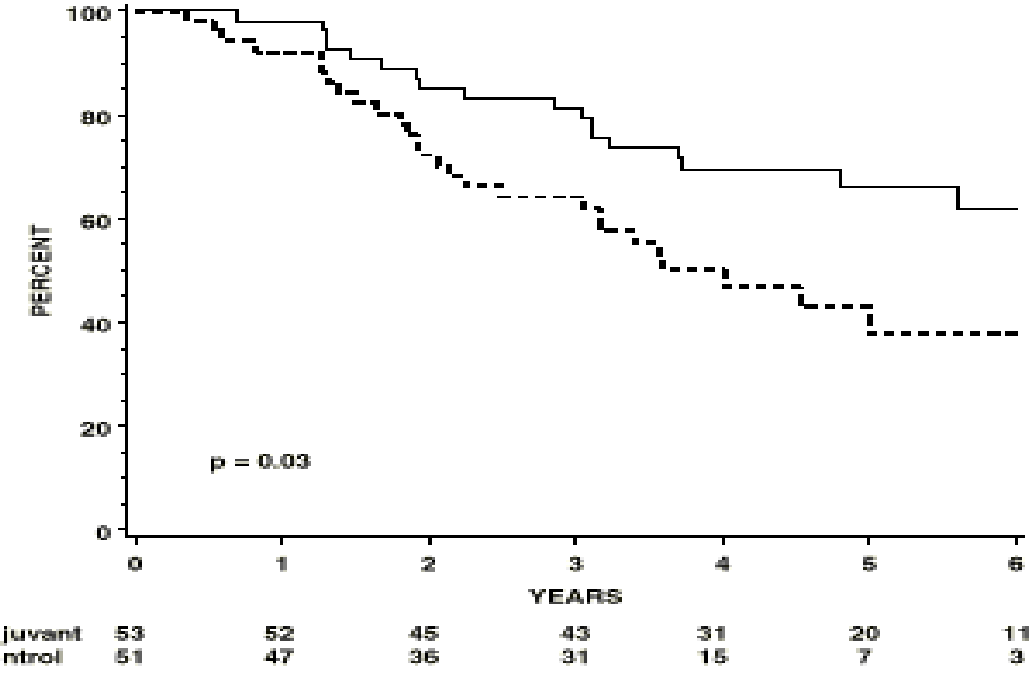


Figure 4. Overall Survival by Treatment

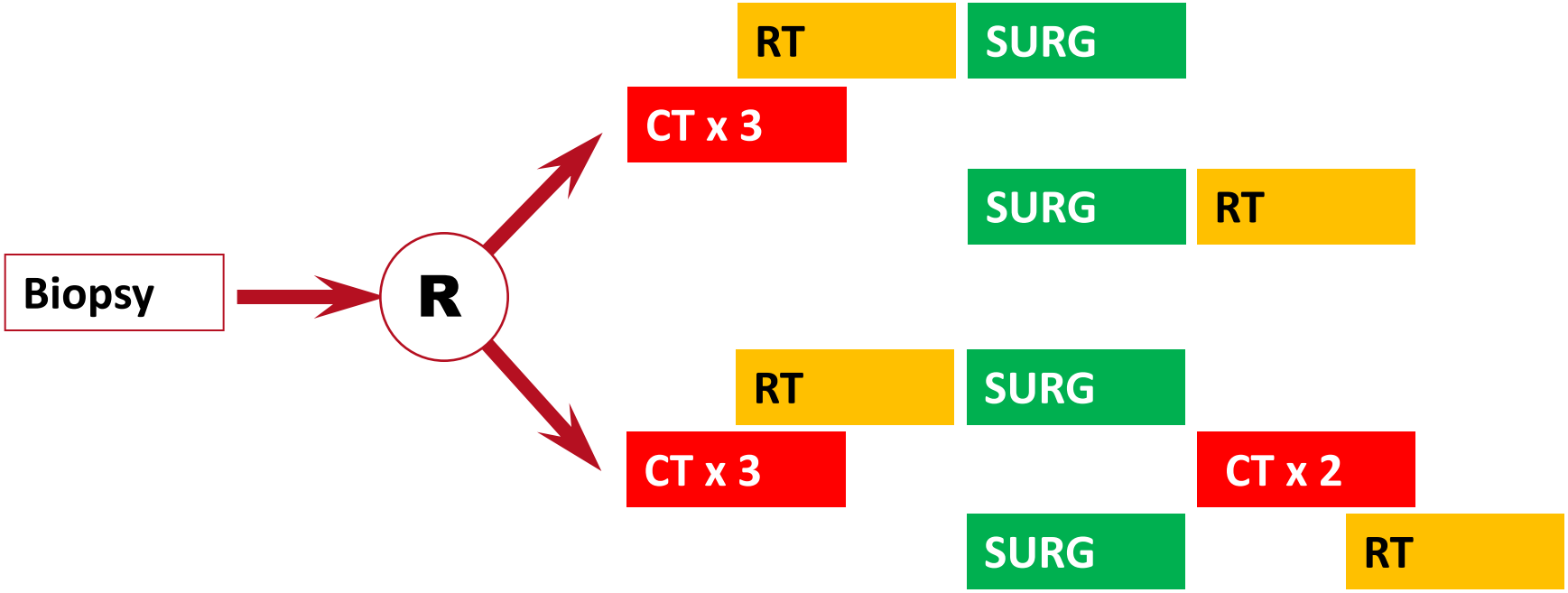
P=0.04

Median F.U.=59 m
Minimum F.U.=36 m

P = 0.03

S. Frustaci et al, JCO, 2001, Vol. 19, 5

ISG Second TRIAL: EPI+IFOS
G3, deep, ≥ 5 cm



A. Gronchi, J Clin Oncol 30:850-856. 2012

ISG First & Second TRIAL
Equivalent OS

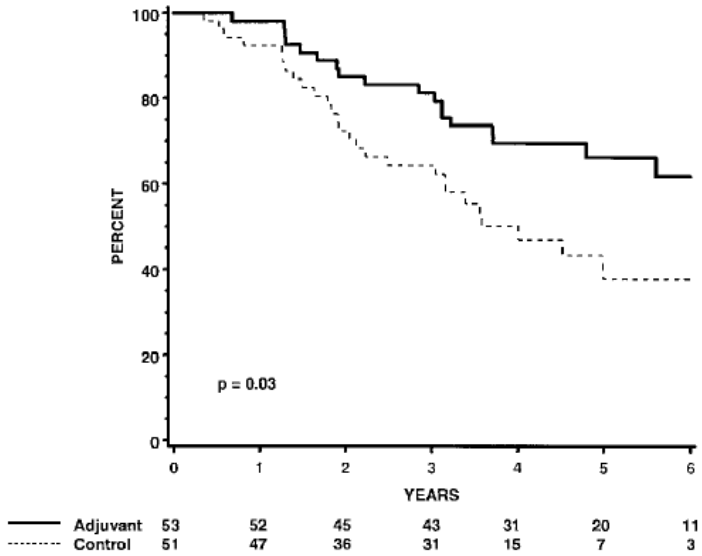
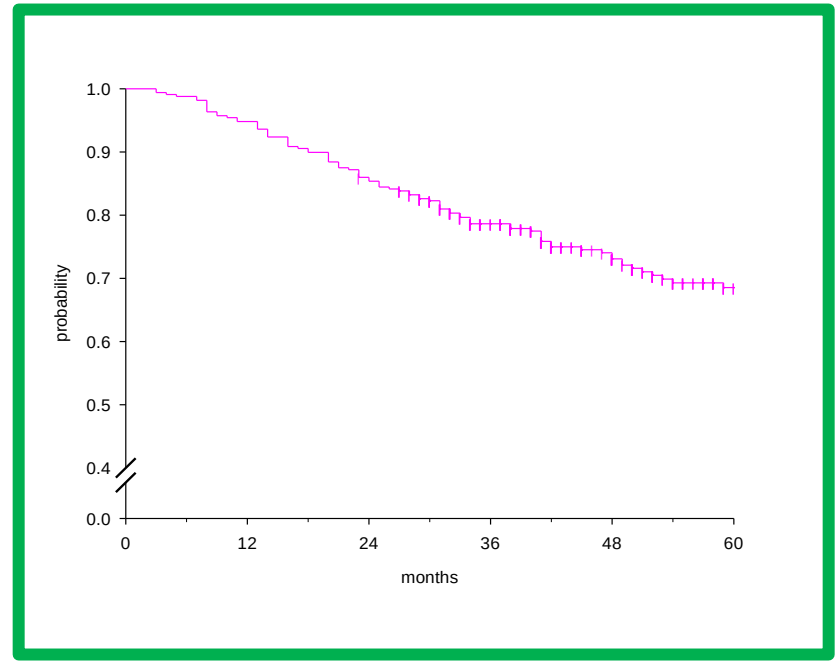


Fig 4. OS by treatment



1) Is there room for systemic treatment in localized STS?

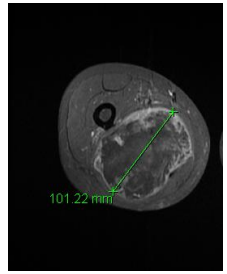
- Yes if adequate patient and drug selection:
  - G3, deep, ≥ 5 cm (limbs/trunk wall)
  - Full dose of Anthracyclines plus Ifosfamide
  - Chemosensitive histologies
- Individualizing decision-making process
- Enrolment in randomized clinical trials

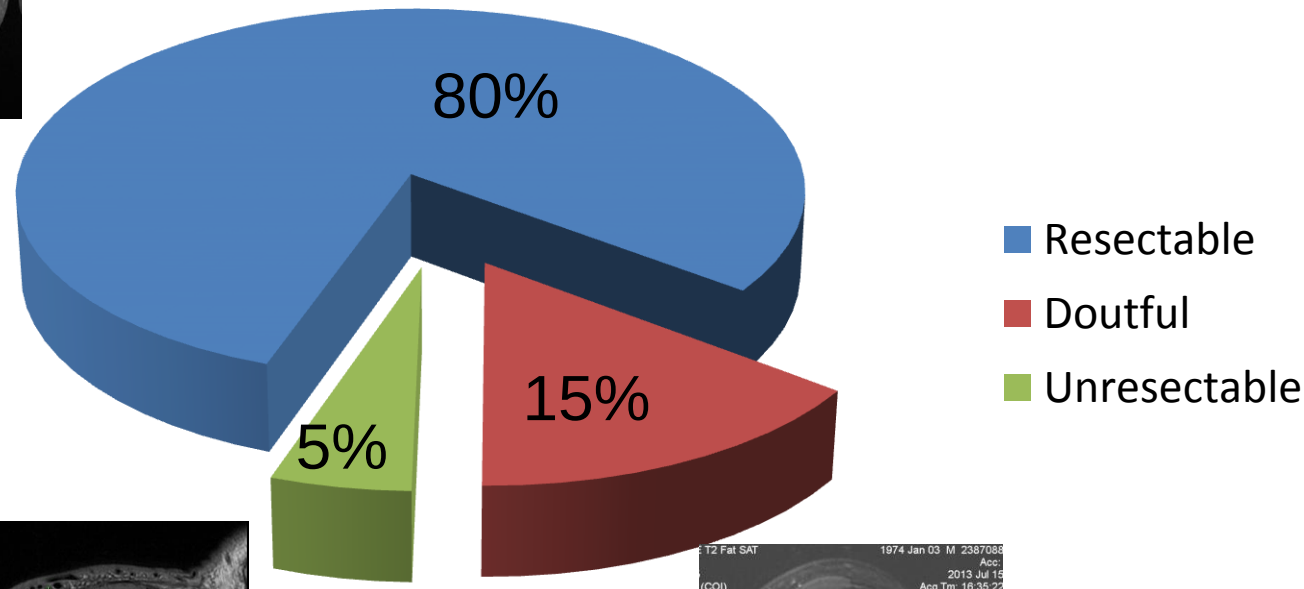
2) If so, then Is the neo-adjuvant systemic therapy the best choice?

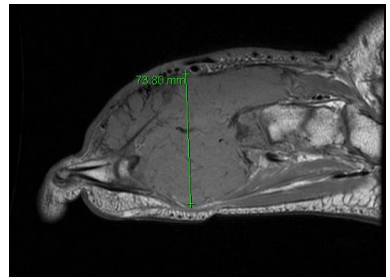
- Does it implicate clinical benefit?
- Does it implicate prognostic information?
- It could increase the knowledge?

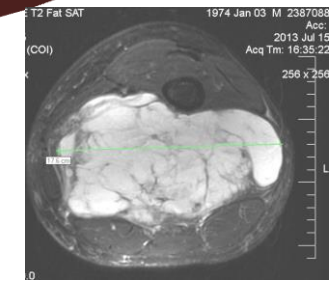
Neo-Adjuvant chemotherapy:

It does improve resectability?

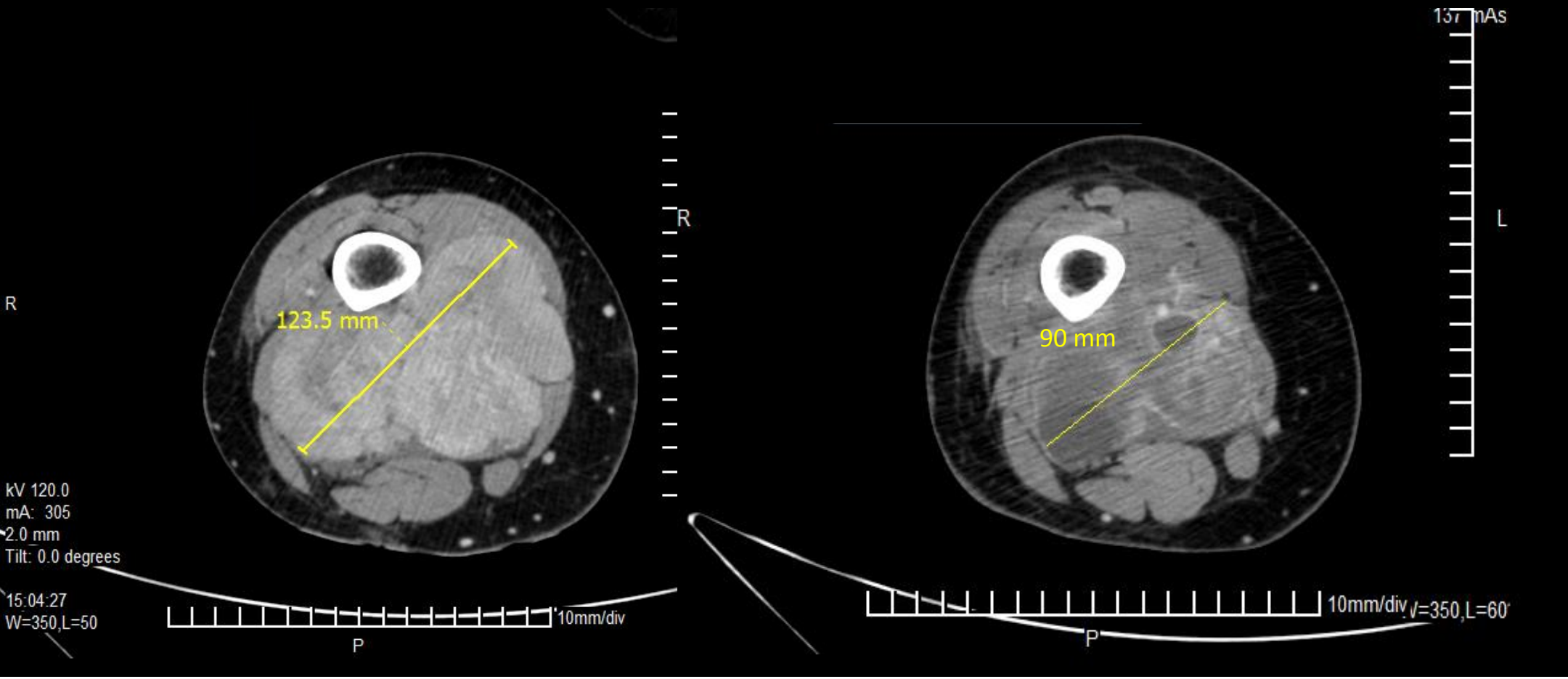








Sometimes yes… but not usually



3 courses CT (E.I.) + RT (50 Gy)

Annals of Oncology Advance Access published October 30, 2012

original article

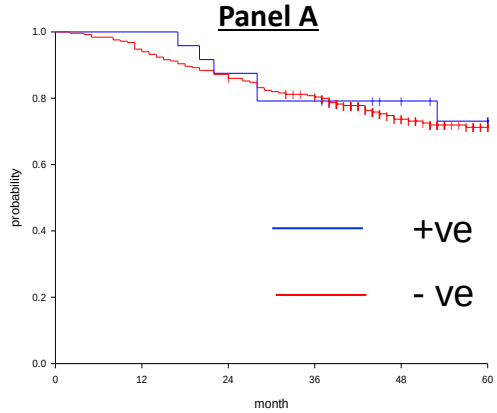
Annals of Oncology 0: 1–7, 2012
doi:10.1093/annonc/mds501

PROSPECTIVE

Quality of surgery and neoadjuvant combined therapy in the ISG-GEIS trial on soft tissue sarcomas of limbs and trunk wall

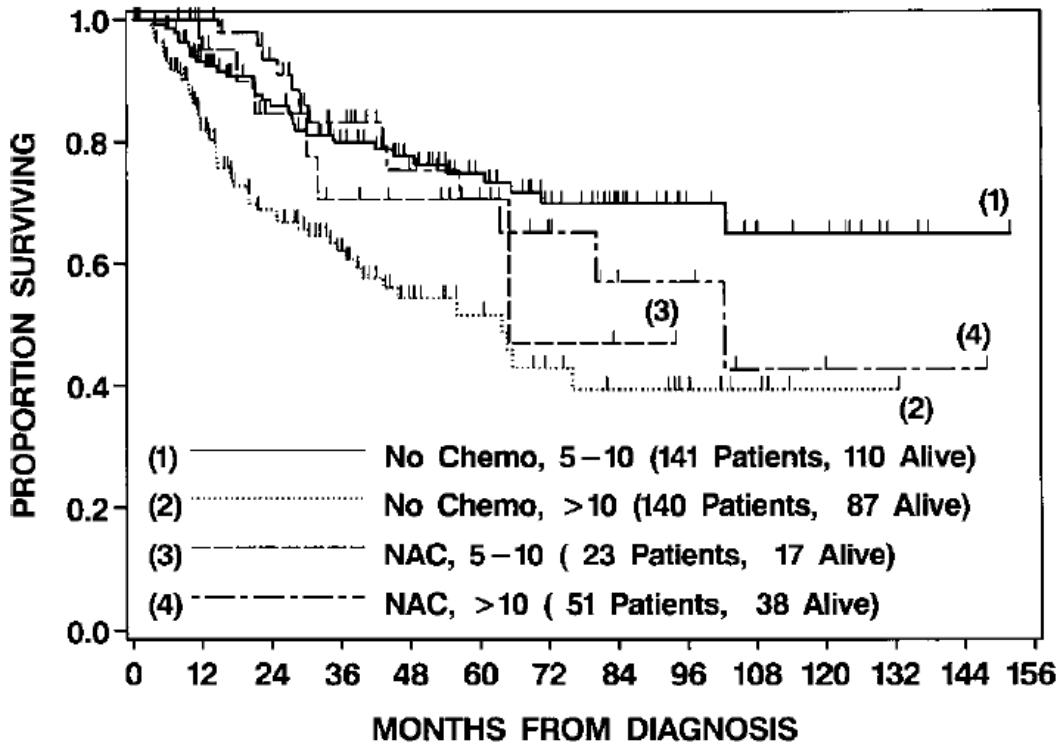
A. Gronchi[1*], P. Verderio[2], A. De Paoli[3], A. Ferraro[4], O. Tendero[5], J. Majò[6], J. Martin[5], A. Comandone[7], G. Grignani[8], S. Pizzamiglio[2], V. Quagliuolo[9], P. Picci[10], S. Frustaci[11], A. P. Dei Tos[12], E. Palassini[13], S. Stacchiotti[13], S. Ferrari[14], M. Fiore[2] & P. G. Casali[13]

5-year OS



With Neo-adjuvant Chemo-RTP the impact of positive margins seems to be prevented

Neoadjuvant chemo impact on DSS in >10 cm; G3

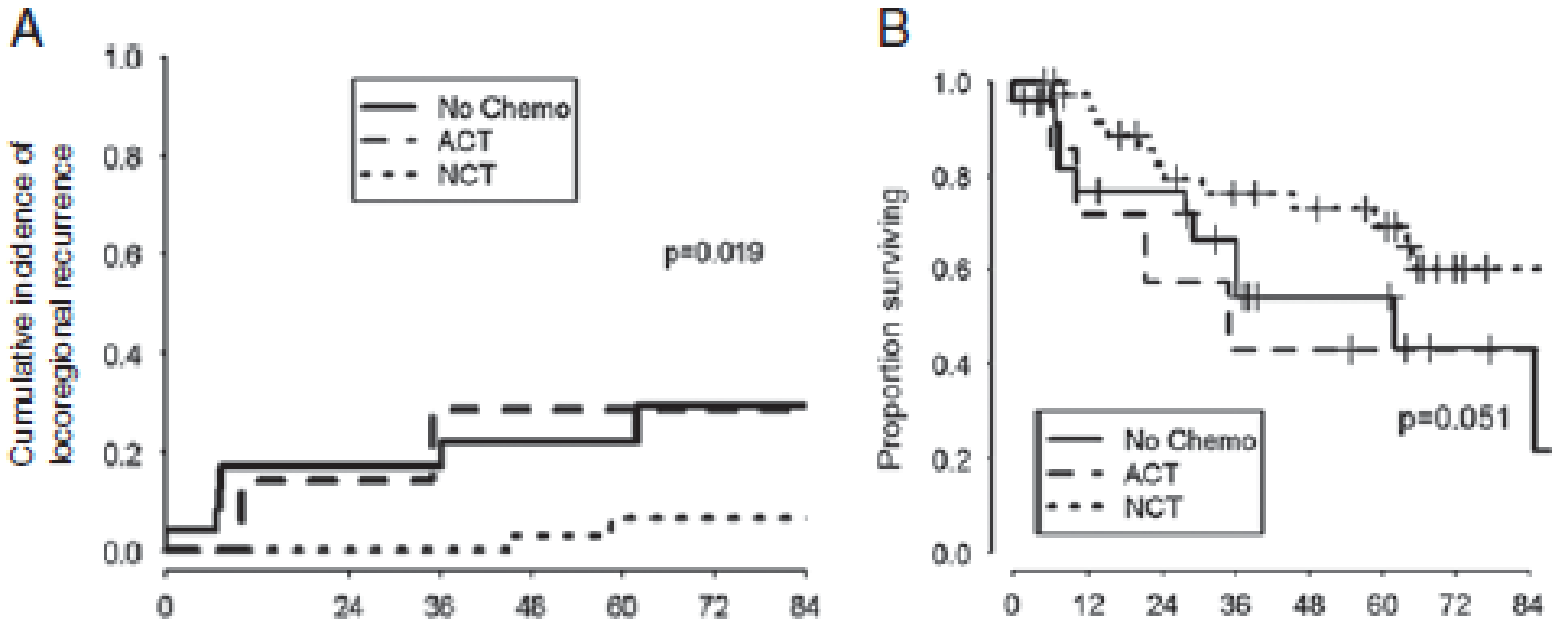


3-year DSS:

0.83 (NAC) vs
0.62 (No chemo)

Grobmayer et al. Ann Oncol 2004; 15: 1667-72

Neoadjuvant chemo impact in local control more than adjuvant



A Mahmoud et al, Am J Clin Oncol 2014

Neoadjuvant studies: some benefits

Author	Scheme	Patients	RTP timing	Study nature	Clinical benefit
Mahmaud	Doxo + ifosf x 4-6	G2-3 borderline resectable	Post Surgery	Retrospective N=97	Local control Trends DFS
Grobmayer	Doxo 75 + Ifos 6-9 x 3	G2-3; ≥ 5 cm; deep	no	Retrospective N=74	DSS in ≥ 10 cm
Delaney	MAID X 3	G2-3; ≥ 8 cm	Pre	Retrospective N=48	Distal M1* and OS*
Gortzak	Doxo 50 + Ifos 5 x 3	"High risk"	Post (some)	Prospective N= 150	No
Italiano	Doxo 50-60+ Ifos 6-7 g x 3	G2-3;	Post	Retrospective N=60	No
Curtis	Several: Doxo+Ifos; MAID…	ST II/III	Pre/Post	Prospective N=112	OS in > 5 cm
Gronchi	Epi 120 + Ifos 9	G3; ≥ 5 cm; deep	Pre/Post	Prospective N=252	In +ve Surgical margins

(*) Confirmed with long-term follow-up

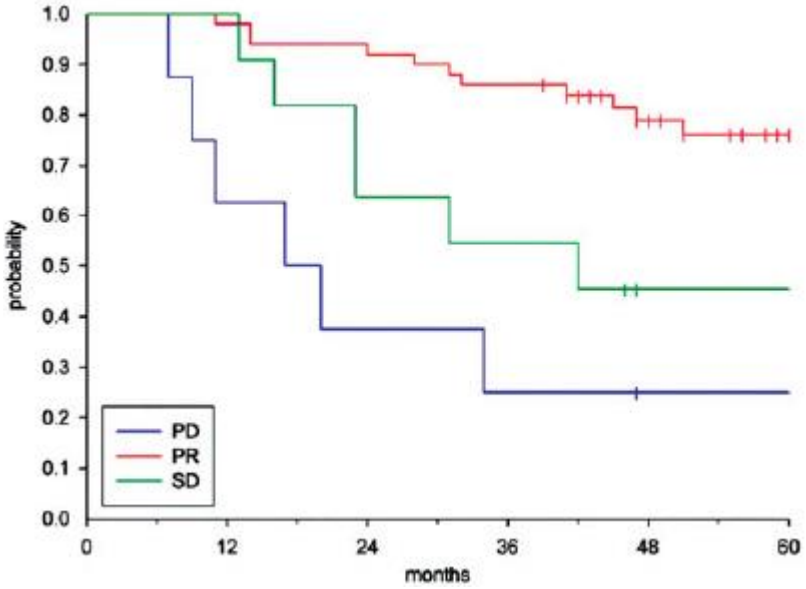
Neoadjuvant: It does offer prognostic information?

Author	Scheme	Patients	RTP timing	Study nature	Prognostic?
Eilber, 2001	Doxo 90 based	G2-3 limbs	Pre	Retrospective N=496 (309)	If necrosis ≥ 95%: better LR and OS
Vaynrub, 2014	NA	G2-3 limbs	Pre (some)	Retrospective N=207	Better DFS in Univariate
Lucas, 2008	Doxo-Ifosfamide	G3, ≥ 5 cm, limbs	Post	Retrospective N=31	No correlation
Scmitt, 2011	Etoposide, Ifosfamide & Doxorubicin	G2-3, Deep, ≥ 5 cm;	IORT/POST	Retrospective in Prospective. N= 50	No correlation
Stacchiotti, 2012	Epi 120+Ifos9 x3	G3, Deep; ≥ 5 cm	Pre/Post	Retrospective in Prospective; N=243	Correlation (Choi) with OS and DFS
Martin-Broto 2014	Epi 120+Ifos9 x3	G3, Deep; ≥ 5 cm	Pre/Post	Retrospective in Prospective; N= 101	Correlation MRP1 with RFS and OS

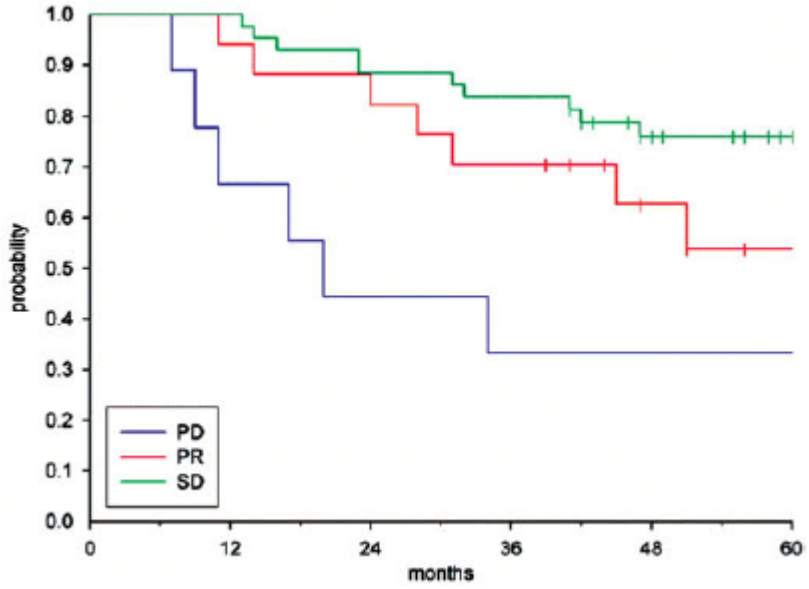
Prognostic information?

Tumor Response Assessment by Modified Choi Criteria in Localized High-Risk Soft Tissue Sarcoma Treated With Chemotherapy

Silvia Stacchiotti, MD[1]; Paolo Verderio, PhD[2]; Antonella Messina, MD[3]; Carlo Morosi, MD[3]; Paola Collini, MD[4]; Antonio Llombart-Bosch, MD[5]; Javier Martin, MD[6]; Alessandro Comandone, MD[7]; Jurado Cruz, MD[8]; Andrea Ferraro, MD[9]; Giovanni Grignani, MD[10]; Sara Pizzamiglio, MSc[2]; Vittorio Quagliuolo, MD[11]; Piero Picci, MD[12]; Sergio Frustaci, MD[13]; Angelo Paolo Dei Tos, MD[14]; Paolo G. Casali, MD[1]; and Alessandro Gronchi, MD[15]



CHOI CRITERIA



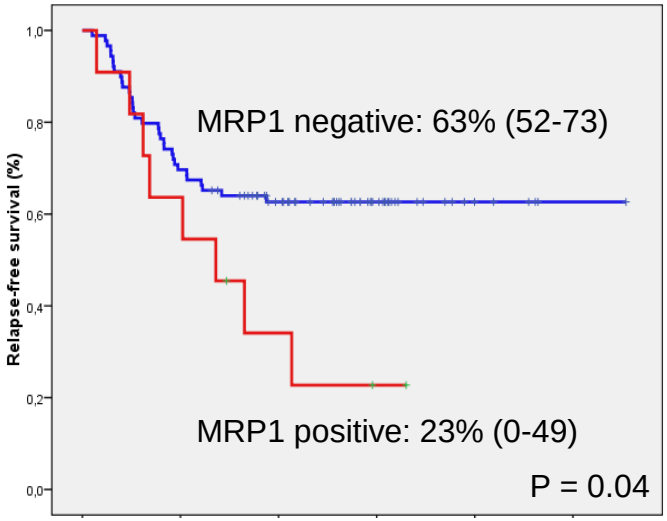
RECIST CRITERIA

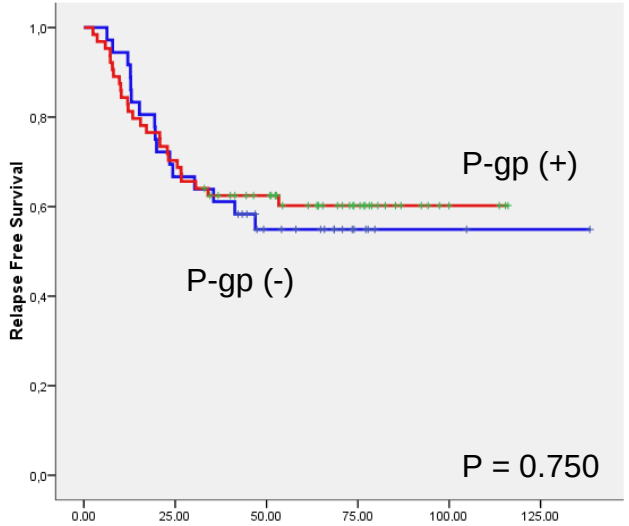
S. Stacchiotti, Cancer 2012;118:5857-66

MADRID 2014 ESMO congress

Relapse Free Survival Analysis

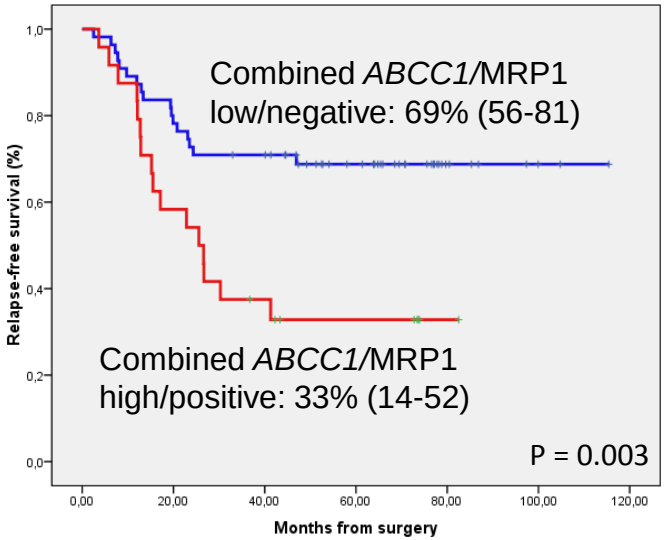
Protein expression curves

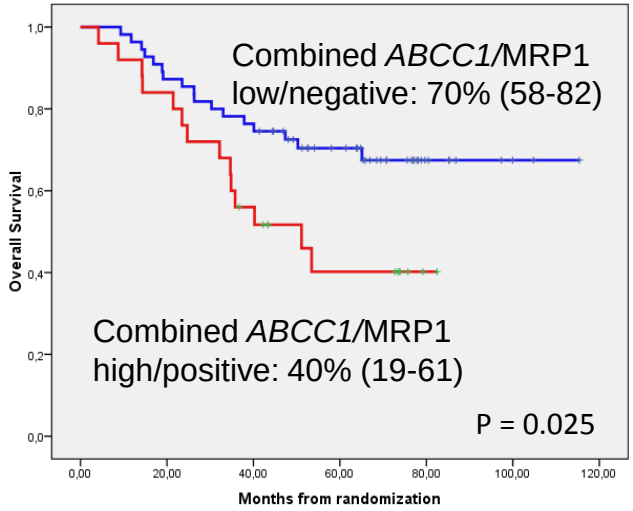




Relapse Free Survival and Overall Survival Analysis

Combined ABCC1/MRP1 expression curves





J Martin-Broto Mol Cancer Ther 2014;13:249-259.

HISTOTYPE TAILORED CT

- ❑ Leiomyosarcoma → gemcitabine + dacarbazine
- ❑ Round cell liposarcoma → adriamicine
- ❑ Synovial sarcoma → ifosfamide
- ❑ MFH, pleomorphic s → gemcitabine+taxotere
- ❑ MPNST → Ifo + VP16 (SARC study)

- ❑ Myxofibrosarcoma
- ❑ Unclassified Spindle Cell Sarcoma
- ❑ Pleomorphic Liposarcoma
- ❑ Pleomorphic Rabdomiosarcoma

REMARKS

- Co-adjuvant chemotherapy could be advisable if:
  - Localized high risk STS limbs/trunk wall
  - Full doses anthracycline+ifosfamide
  - Individualizing decision-making process
- Neo-adjuvant chemotherapy better than adjuvant:
  - If can be anticipated R1 margins
  - More prognostic information (Radiological and Molecular)
  - We need to gain more knowledge (prospective clinical trials)