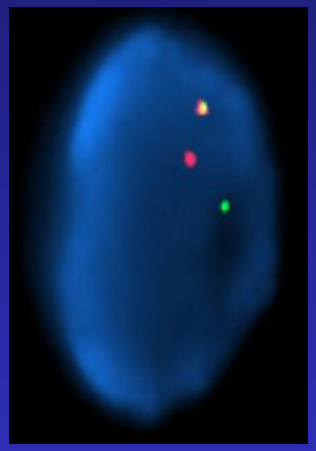
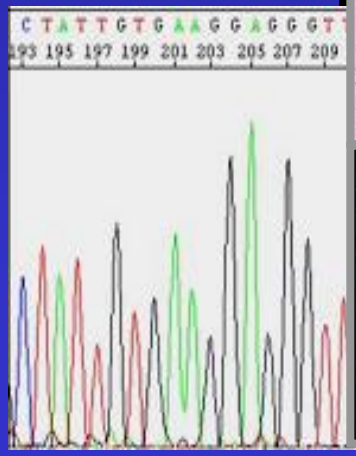
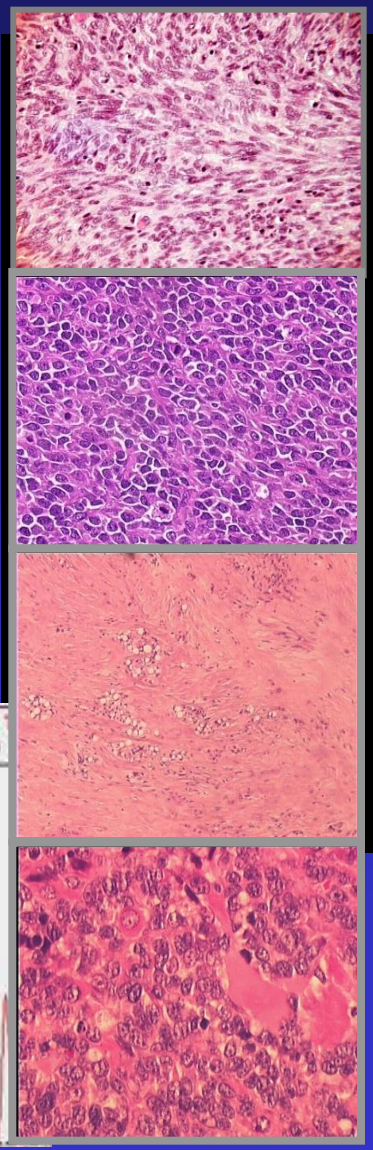
Personalising adjuvant chemotherapy choices in sarcomas

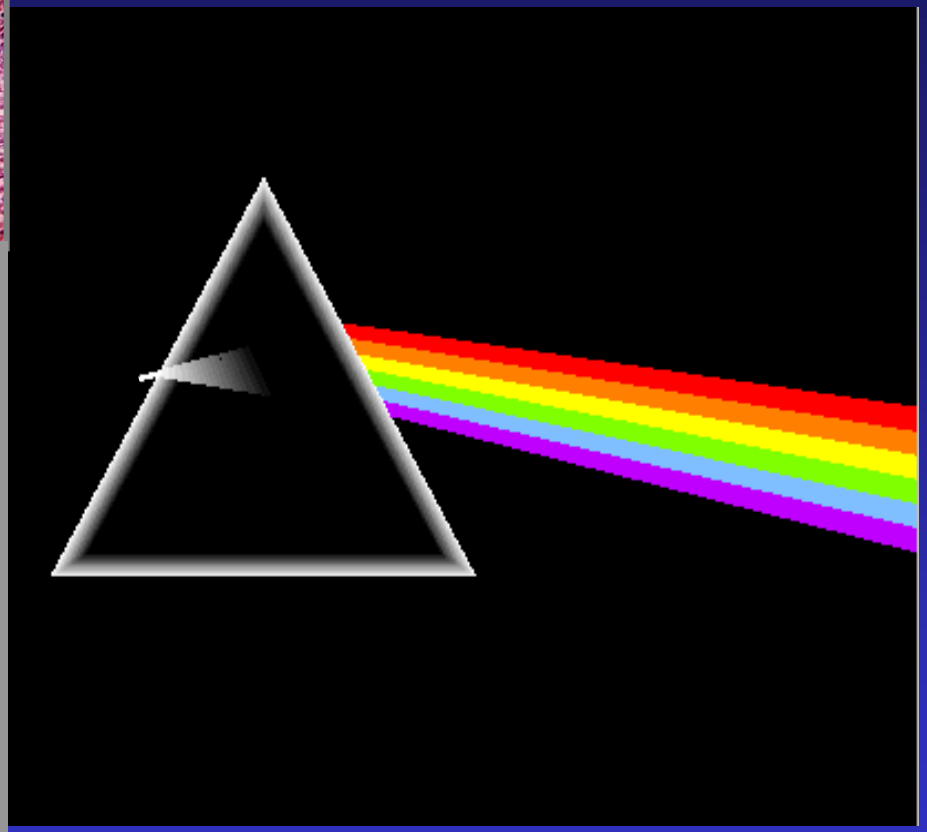
Axel Le Cesne & JY Blay
Institut Gustave Roussy, Villejuif
Centre Leon Berard, Lyon

21st century: to understand our mistakes and sarcoma complexity









A

Rainbow

Of

Different

Sarcoma

Subtypes

At least 50 histological subtypes, multiple sites, size, grade

100 patients included in ® trials = 100 different diseases!!

Courtesy of G. Demetri

Mass in a soft part

- **The first step:** I don't know what it is
- **The second step:** I operate you within a few hours
- **The third step:** whoops, it was a STS!
- **The fourth step:** I did my job, I send you to an oncologist

No Induction TT

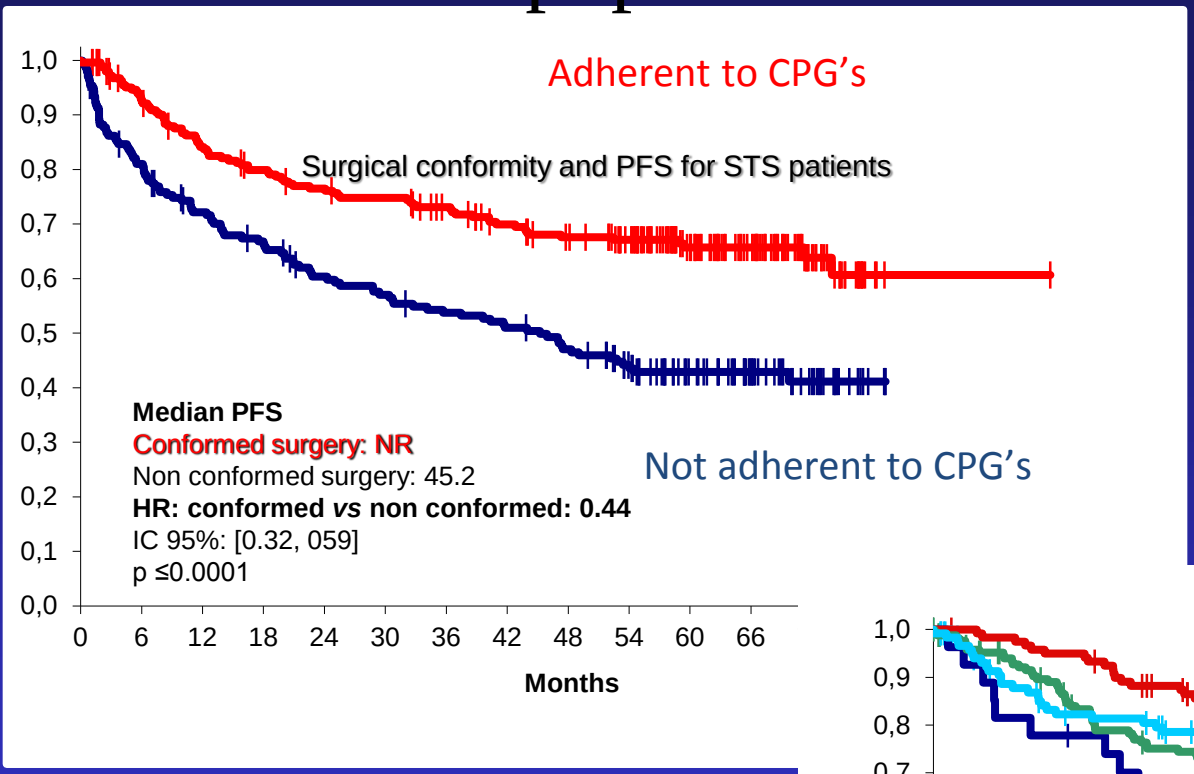
Inadequate Surgery

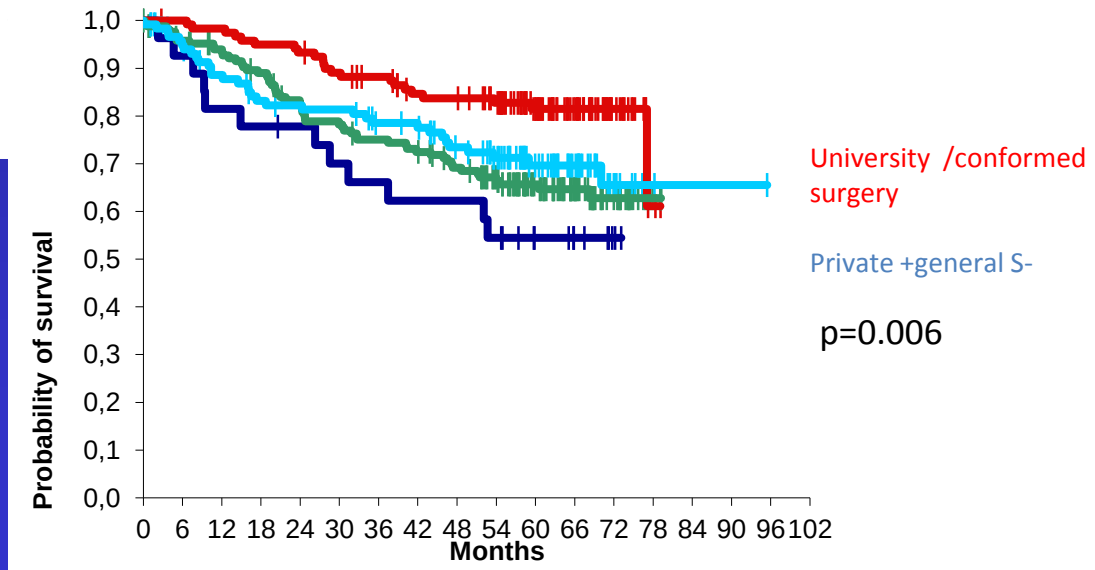
Salvage Surgery

« adjuvant » CT/RT: case per case discussion

→ Minority of tumors are seen initially in referral centers!
Less than one third of pts are taken in charge according to CPGs

Adherence to CPG and pt outcome in a population based series

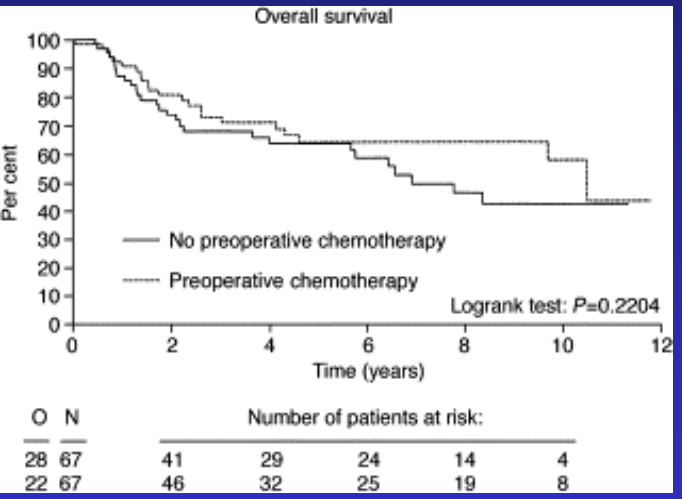


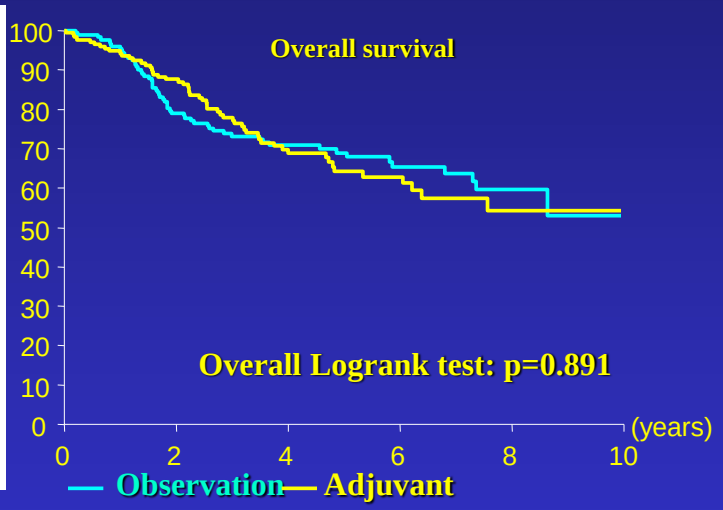


Derbel et al 2012 ESMO

Localized resectable STS

Adjuvant and neo-adjuvant ?





EORTC 62871
Gortzak, EJC 2001

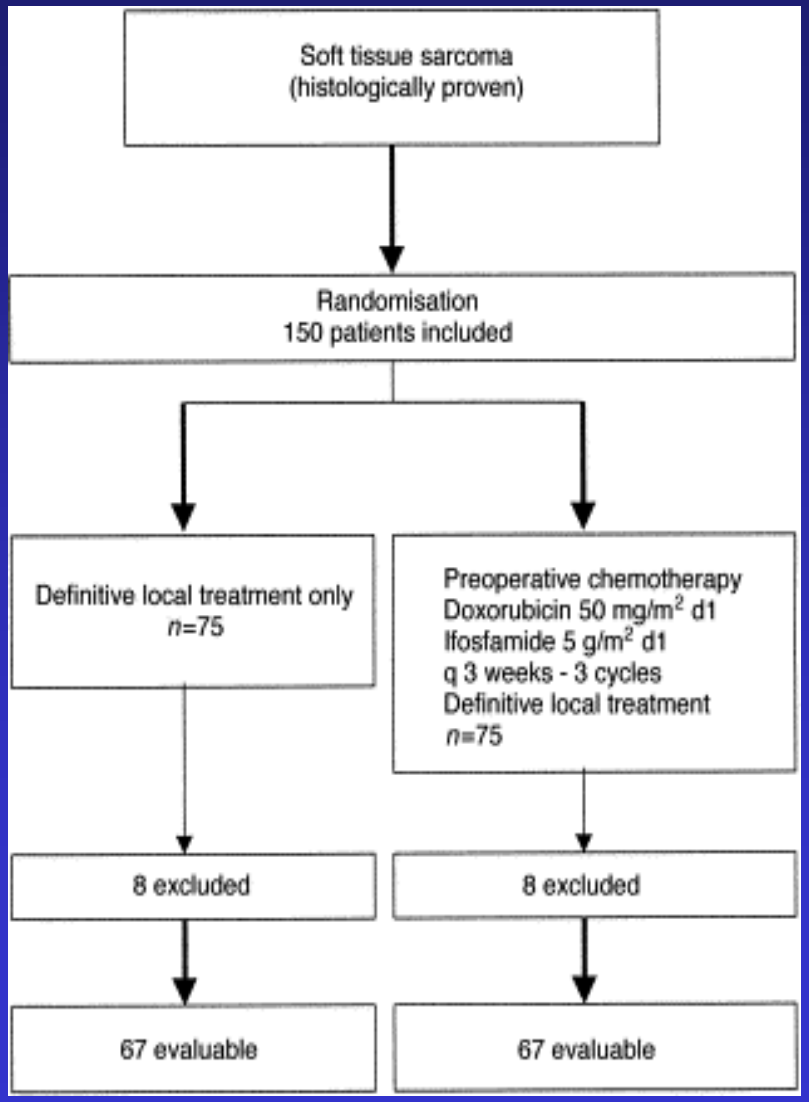
Impact on metastases unknown

EORTC 62031
Woll, Lancet Oncol 2012

Impact on metastases unknown

Gortzak E, et al. A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. Eur J Cancer. 2001 Jun;37(9):1096-103.

- 134 evaluable patients
- Randomisation
  - 3 courses of CT + surgery
  - Surgery alone



A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma

E. Gortzak [a], A. Azzarelli [b], J. Buesa [c], V.H.C. Bramwell [d], F. van Coevorden [a,*], A.N. van Geel [e], A. Ezzat [f,l], A. Santoro [b], J.W. Oosterhuis [e], M. van Glabbeke [g], A. Kirkpatrick [g], J. Verweij [e], the E.O.R.T.C. Soft Tissue Bone Sarcoma Group and the National Cancer Institute of Canada Clinical Trials Group/Canadian Sarcoma Group

Table 1
Patient characteristics ($n = 150$)

	No preoperative chemotherapy *n* (%)	Preoperative chemotherapy *n* (%)
Stratification according to risk factor		
<8 cm, group II/III	18 (24)	18 (24)
>8 cm, group I	6 (8)	6 (8)
>8 cm, group II/III	31 (41)	33 (44)
Inadequate surgery, group II/II	13 (17)	13 (17)
Local recurrence	7 (9)	5 (7)
Distribution according to localisation		
Limbs	61 (81)	62 (83)
Head/neck	4 (5)	1 (1)
Trunk	7 (9)	10 (13)
Pelvis	3 (4)	2 (3)
Eligibility		
Eligible	67 (89)	67 (89)
Ineligible	8 (11)	8 (11)
Reasons for ineligibility		
Retroperitoneal localisation	2	–
T. category	–	1
Distant metastases	2	2
Age	–	1
Other histology	4	2
Cardiovascular disease	–	1
Grade unknown	–	1
Total	75 (100)	75 (100)

A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma

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Table 4
Response to chemotherapy ($n = 49$)

Response	n (%)
Complete remission	4 (8)
Partial remission	10 (20)
Stable disease	26 (53)
Progression	9 (18)
Total	49

A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma

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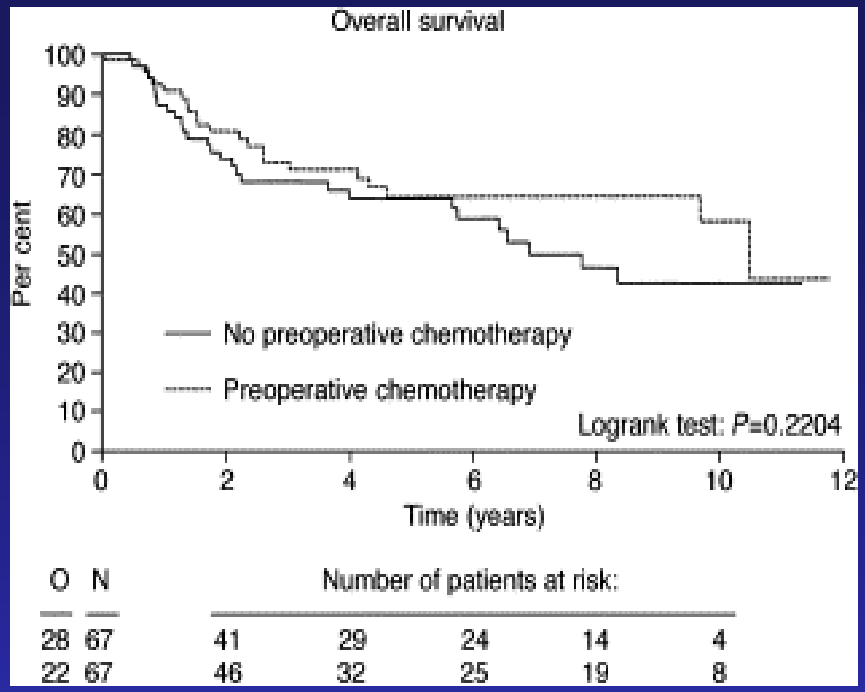
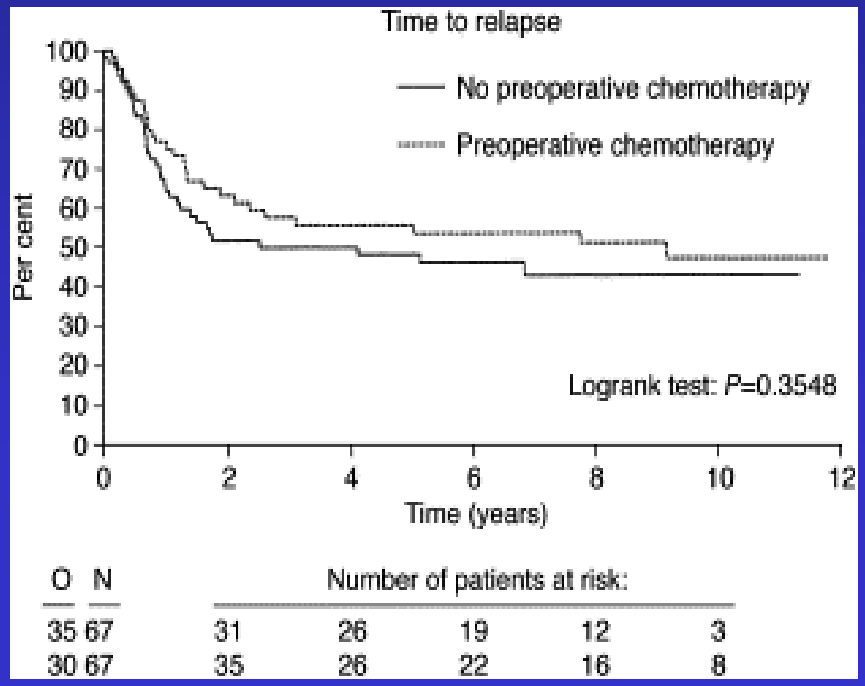
Table 5
Surgery ($n = 129$)[a]

	No preoperative chemotherapy	Preopetative adjuvant chemotherapy
Planned/performed surgery		
Amputation	6/6	9/9
Compartimental resection	22/24	13/17
Wide excision	27/24	32/28
Marginal excision	7/11	9/10
No information	3/0	1/0
Total	65/65	64/64
Microscopical radicality		
Radical	57 (88%)	58 (91%)
Irradical	8 (12%)	6 (9%)
Postoperative complications		
Superficial infection	9 (14%)	9 (14%)
Deep infection	3 (5%)	–
Vascular complication	2 (3%)	1 (2%)
Neurological	2 (3%)	2 (3%)
Skin necrosis	7 (11%)	4 (6%)

[a] The surgery on these two patients missed in the database and were not taken into these calculations.

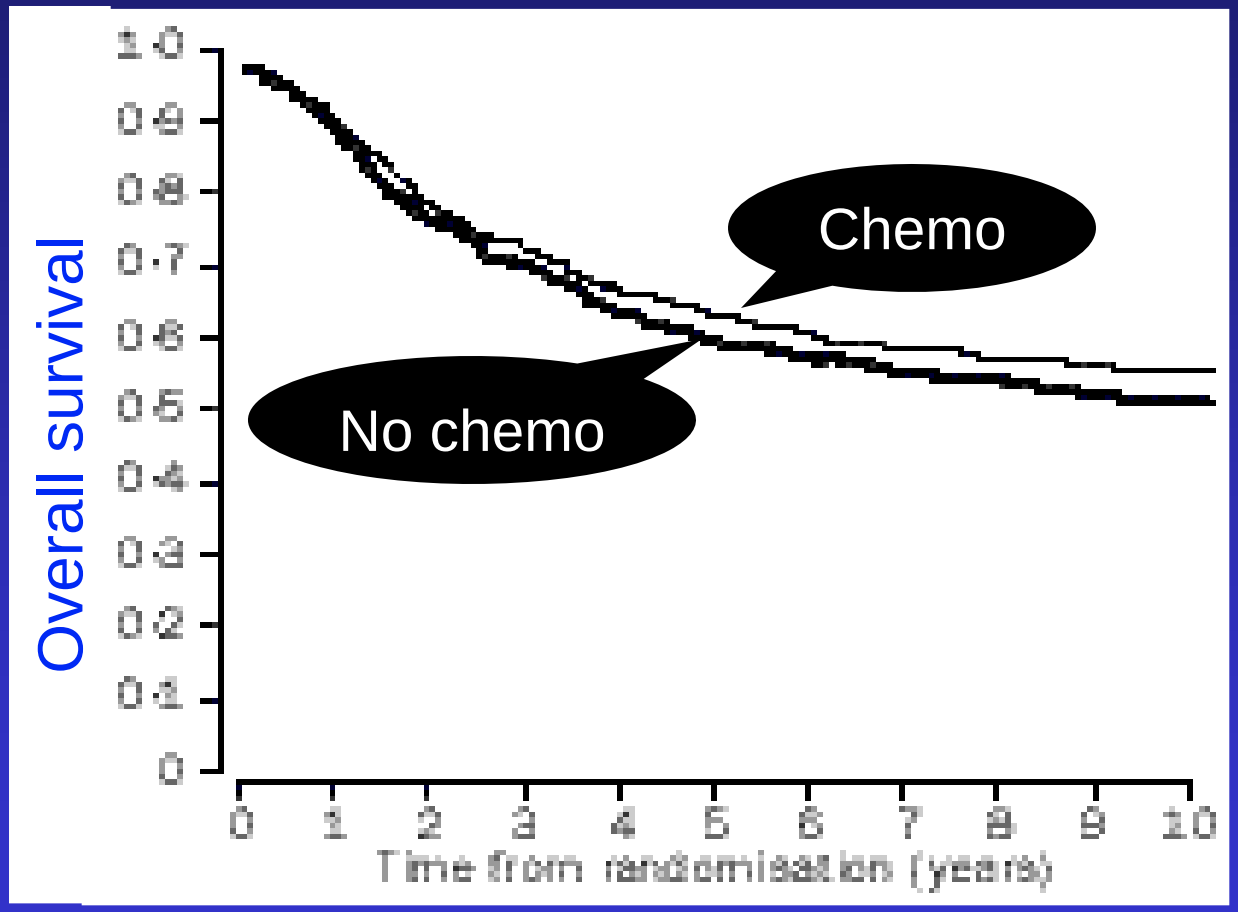




- At a median follow-up of 7.3 years:
  - 5 year disease-free survival is 52% for the no chemotherapy and 56% for the chemotherapy arm (P=0.3548).
  - 5 year overall survival for both arms is 64 and 65%, respectively (standard error 7%) (P=0.2204).

Meta-analysis of adjuvant chemotherapy for soft tissue sarcoma

1568 patients in 14 randomised trials comparing chemo with no chemo



SMAC 1997, Lancet 350:1647-54

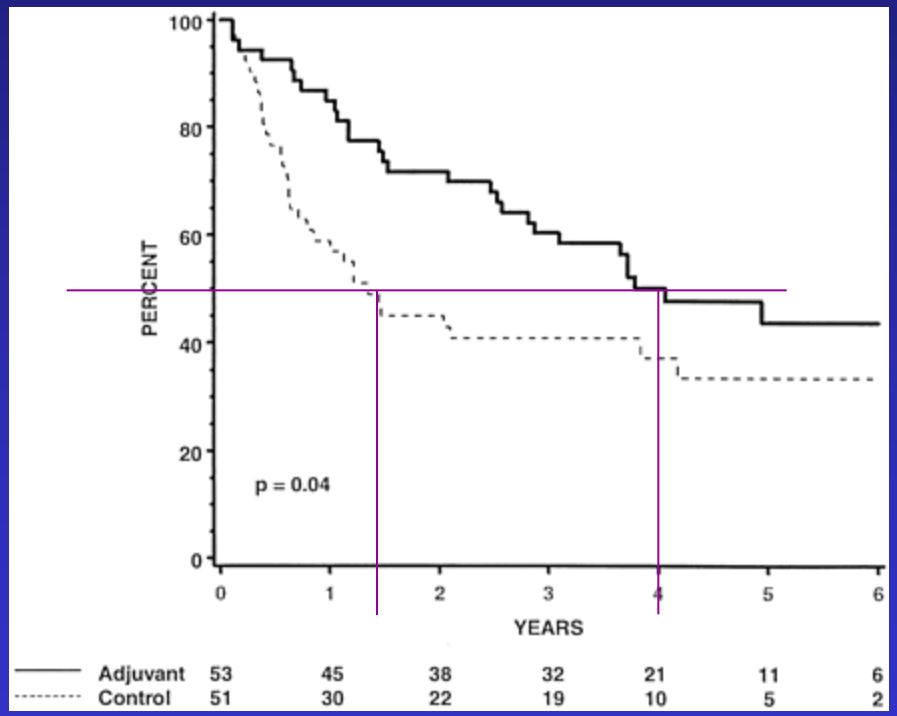
Neoadjuvant for early systemic treatment? Meta- analyses

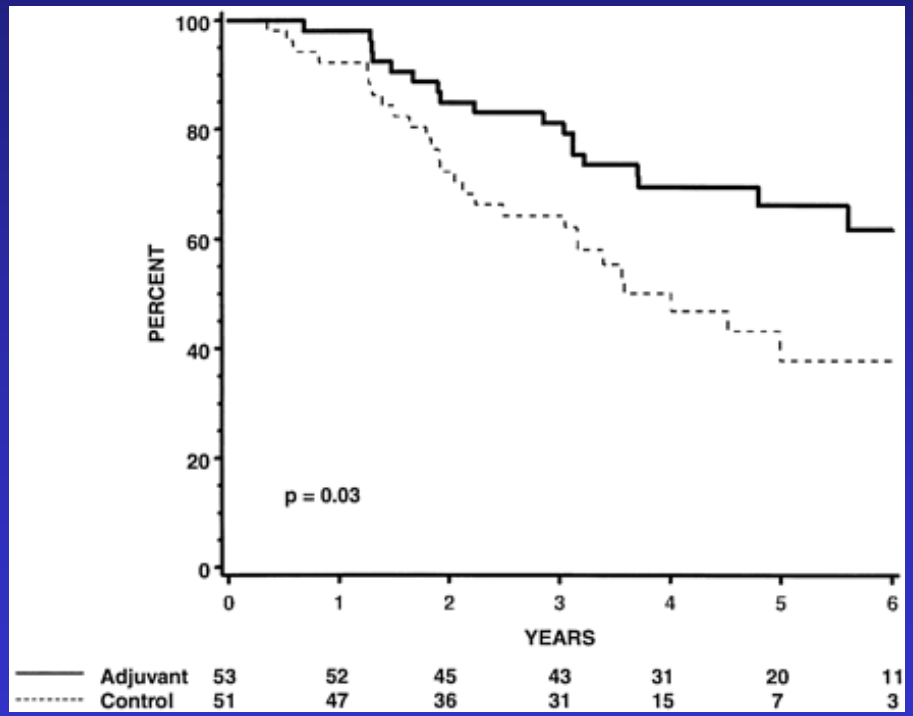
Lancet, 1997
13 trials
1502 patients

Met Free survival 5 yrs : 50%
Survival 5 yrs : 60 %

Loc rel	**p = 0.024**	**HR = 0.74 (0.57-0.96)**	**5 % à 5 ans**
Mets	**p = 0.0003**	**HR = 0.69 (0.57-0.84)**	**9 % à 5 ans**
SSR	**p = 0.00008**	**HR = 0.74 (0.63-0.86)**	**10 % à 5 ans**
SG	**p = 0.087**	**HR = 0.87 (0.75-1.02)**	**4 % à 5 ans**

Adjuvant therapy: ISG trial

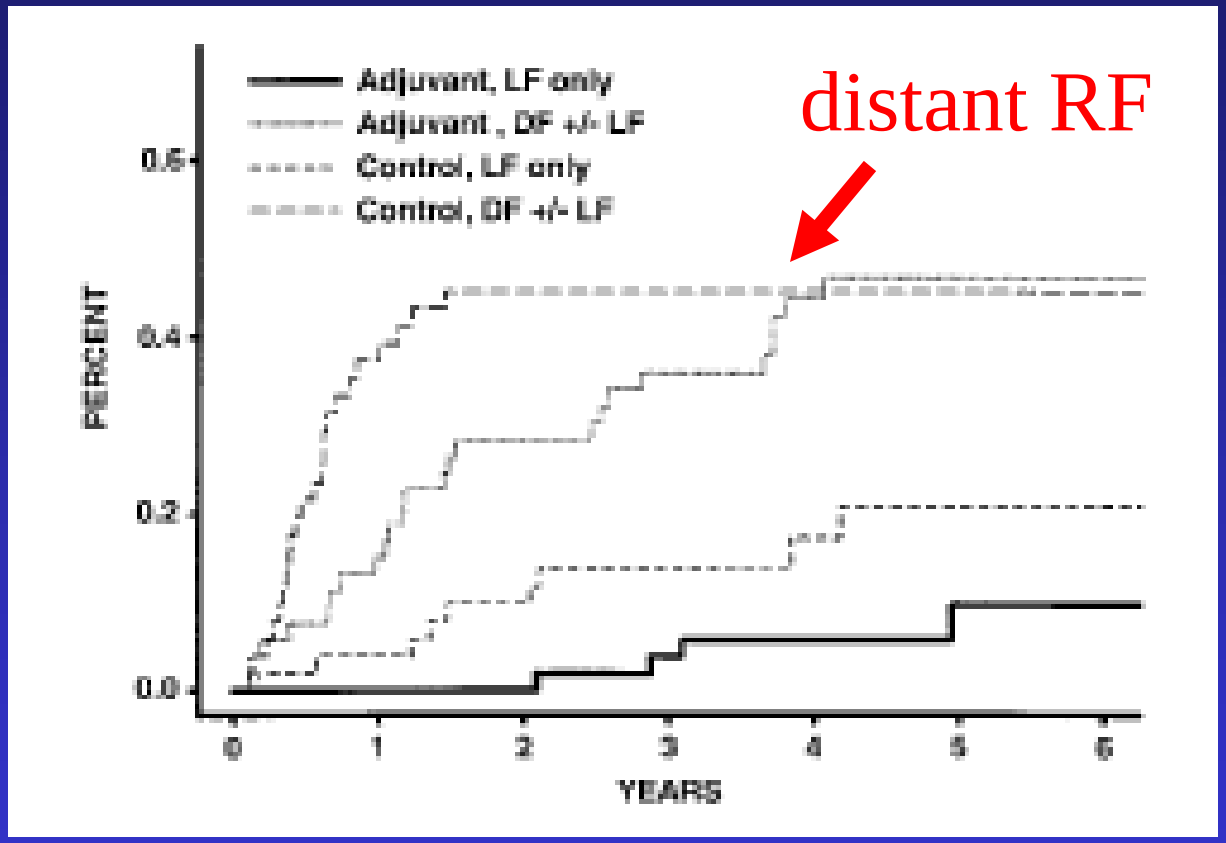




Frustaci et al. JCO 2001; 19:1238

STS – Adjuvant CT - Follow-up ?

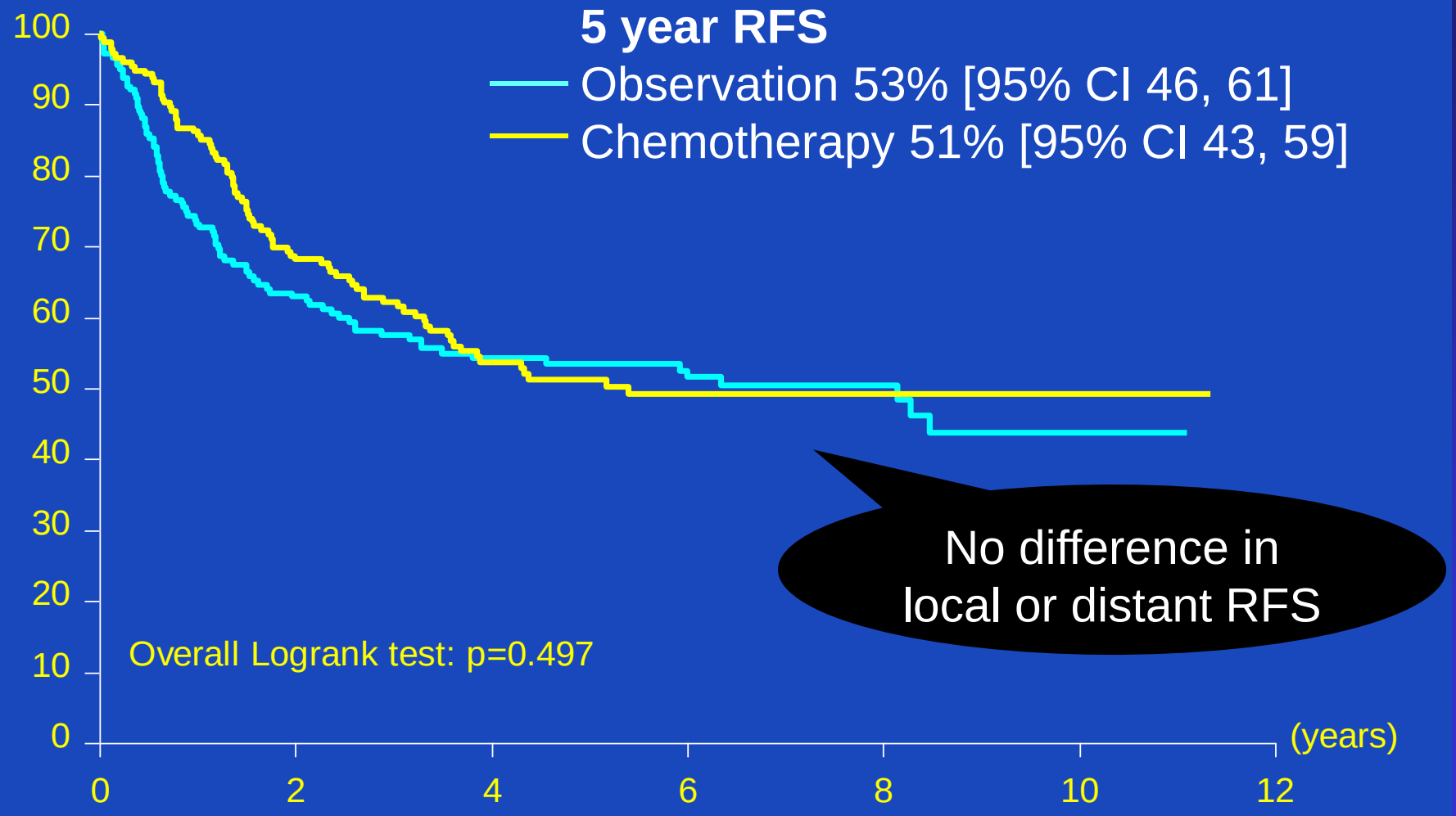
Frustaci S et al. JCO 2001; 19: 1238



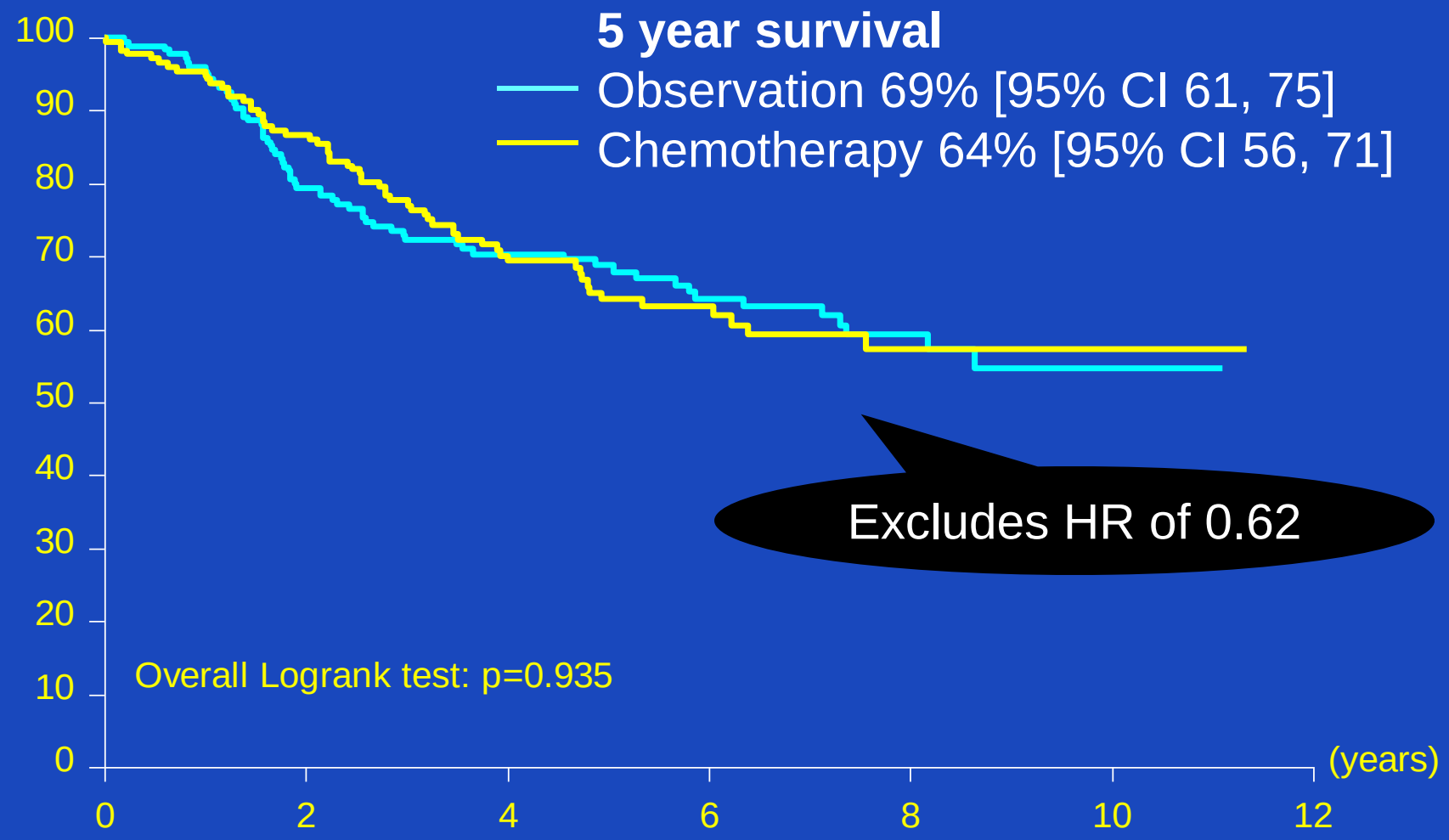
Positif impact of adjuvant CT only in the first 2-3 years after surgery?

Cormier (MDACC, MSKCC), JCO 2004

EORTC 62931 - Relapse free survival



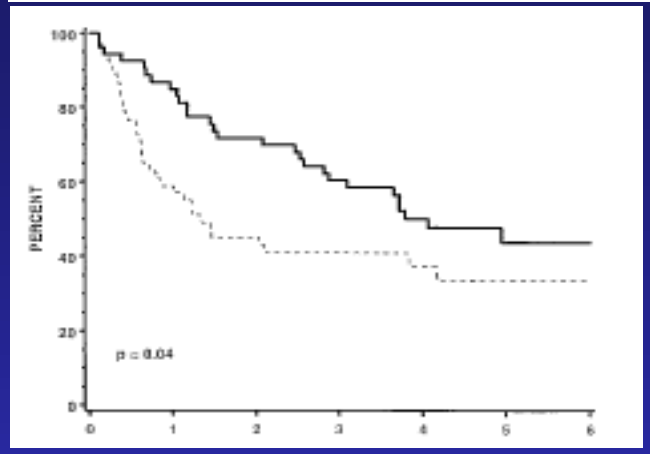
EORTC 62931 - Overall survival

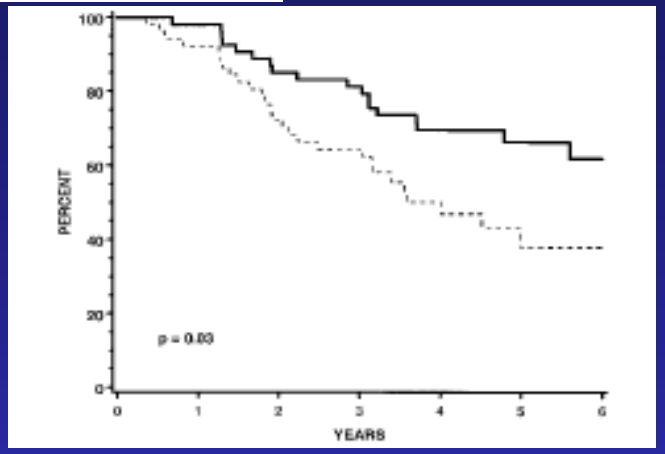


Adjuvant Chemotherapy for Adult Soft Tissue Sarcomas of the Extremities and Girdles: Results of the Italian Randomized Cooperative Trial

Journal of Clinical Oncology, Vol 19, No 5 (March 1), 2001

By Sergio Frustaci, Franco Gherlinzoni, Antonino De Paoli, Marco Bonetti, Alberto Azzarelli, Alessandro Comandone, Patrizia Olmi, Angela Buonadonna, Giovanni Pignatti, Enza Barbieri, Gaetano Apice, Hassan Zmerly, Diego Serraino, and Piero Picci

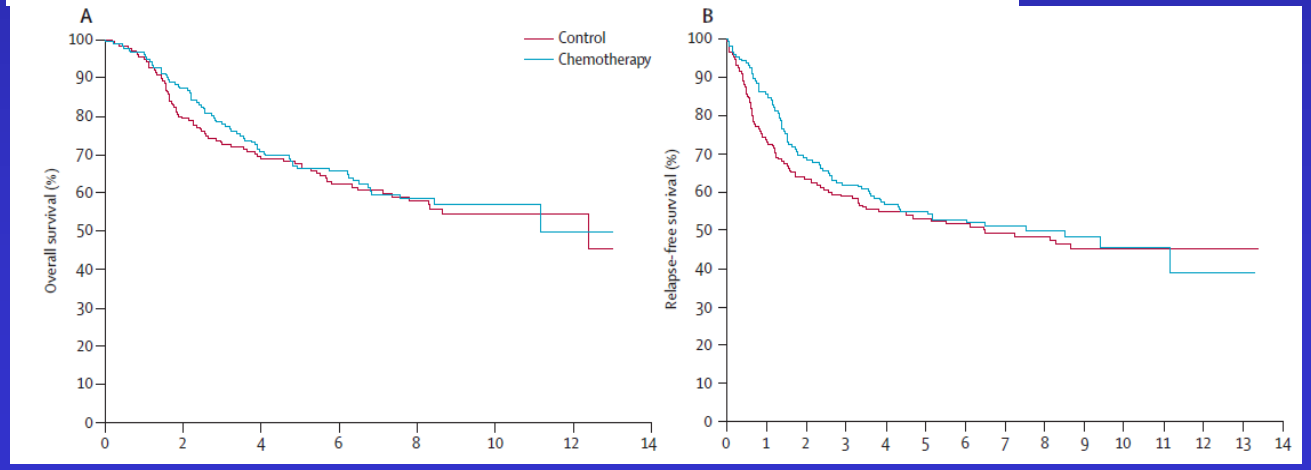




Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial

Lancet Oncol 2012; 13: 1045–54

Penella J Woll, Peter Reichardt, Axel Le Cesne, Sylvie Bonvalot, Alberto Azzarelli†, Harald J Hoekstra, Michael Jaap Verweij, Pancras C W Hogendoorn, Monia Ouali, Sandrine Marreaud, Vivien H C Bramwell, Peter Hohenberger, for the EORTC Soft Tissue and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee



Subsets?

Age>40

Males

R1

EORTC metaanalysis

Le Cesne et al (submitted)

STS- Increase of OS?
Control arm

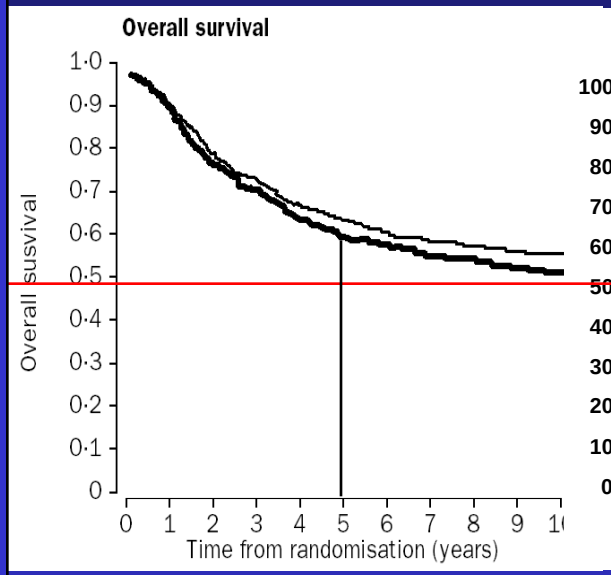
SMAC.
Lancet 1997; 350: 1647

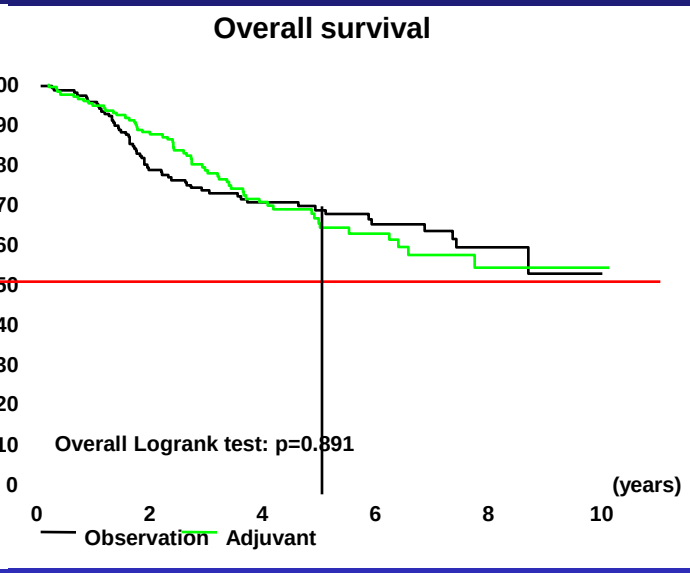
EORTC 62931
ASCO 07

1) Surgical techniques improvement

2) Optimization of the « beginning »

3) Referral centers



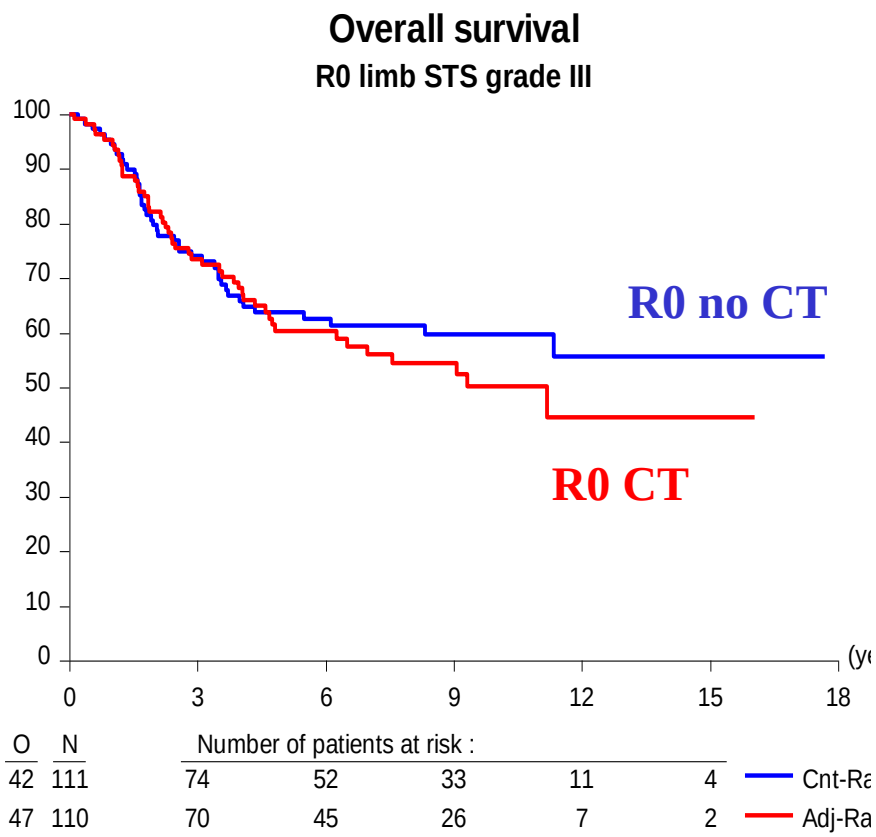


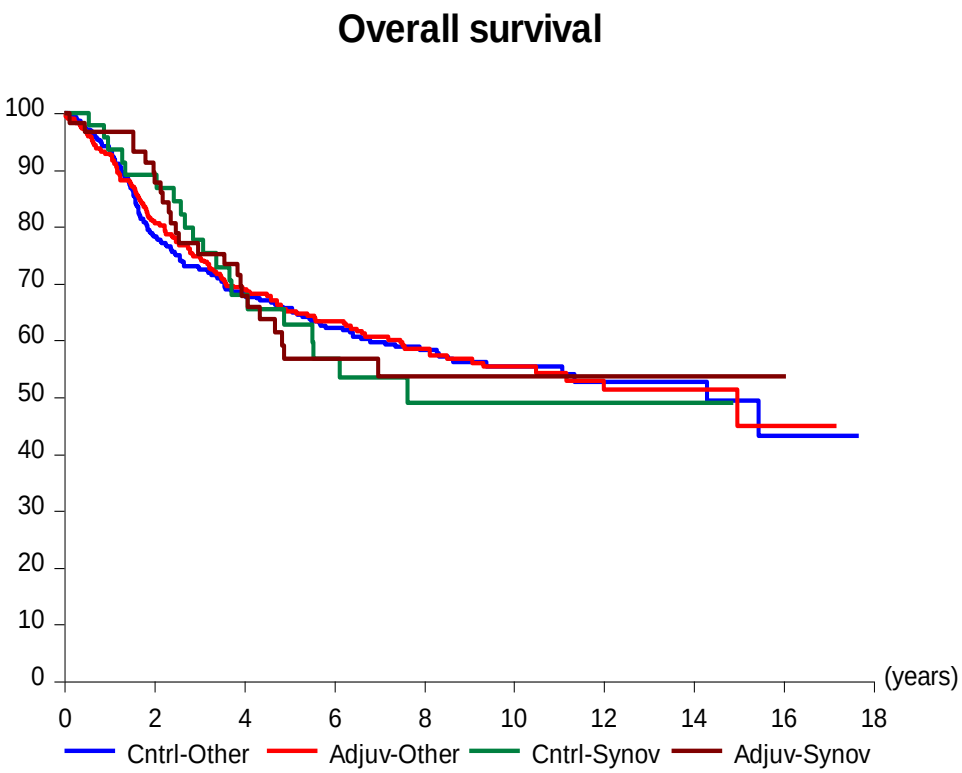
5-yr OS	**59%**	**69%**

10% absolute increase of OS in 10 yrs

Trials on adjuvant CT improved….. Surgeons/surgery !

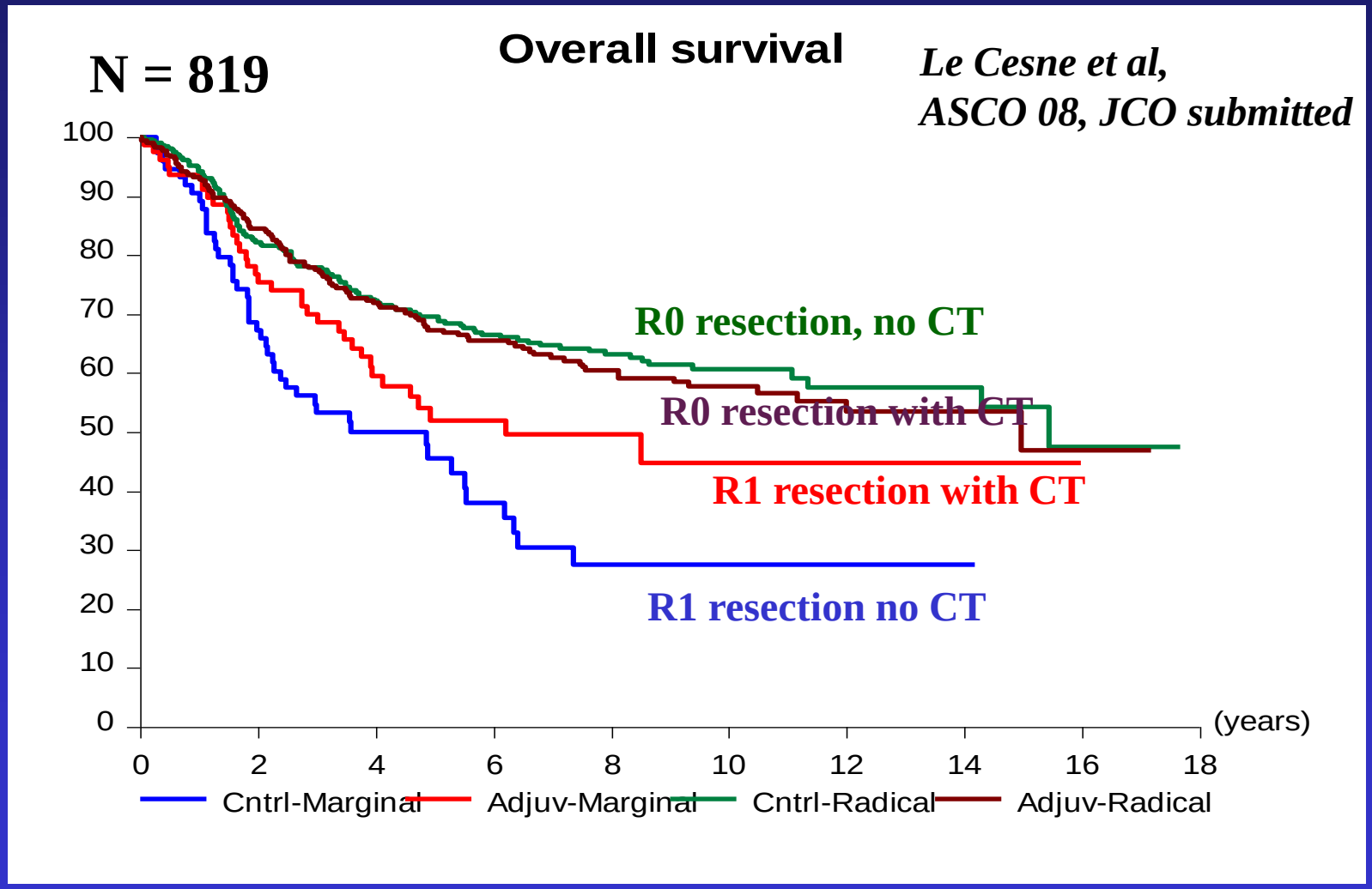
EORTC Adjuvant trials in STS





No impact of site, size and histological subtype

EORTC adjuvant trials in STS
Predictive factor of resection on OS by treatment

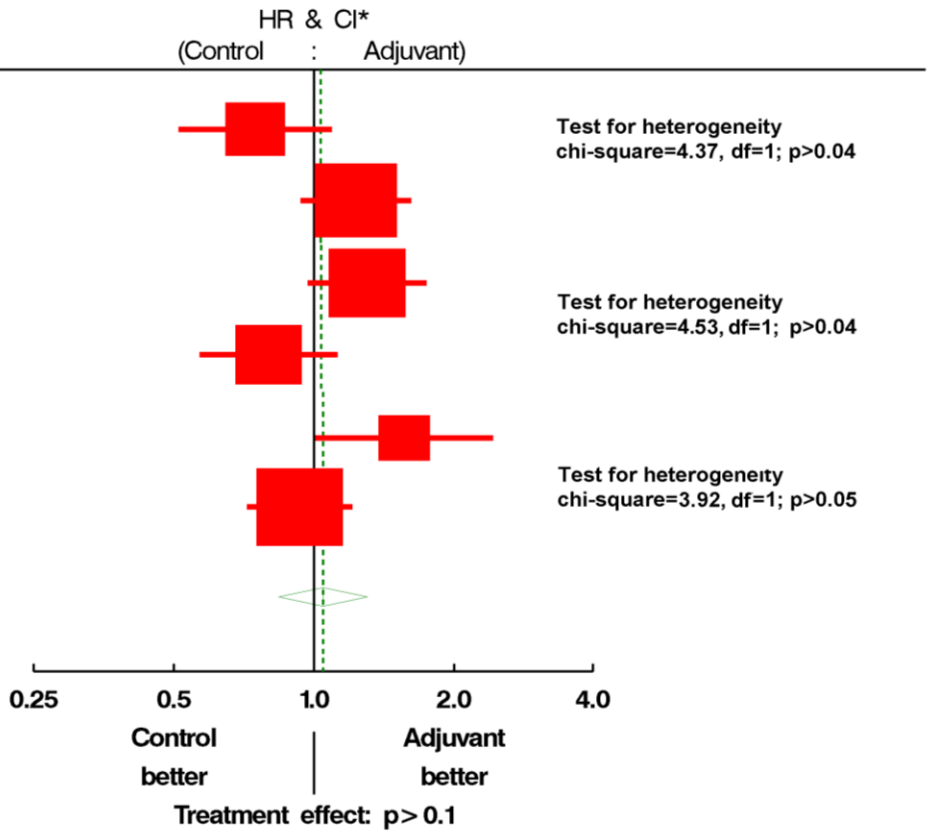


EORTC Adjuvant trials in STS
Predictive factors for OS

Overall survival

		Events / Patients Control	Events / Patients Adjuvant	Statistics (O−E)	Statistics Var.
Age	< 40 yrs	50 / 153	58 / 143	−7.8	26.7
	> 40 yrs	112 / 248	94 / 249	10.6	51.2
Sex	Male	102 / 223	77 / 211	11.7	44.6
	Female	60 / 176	73 / 175	−7.5	33.2
Resection	Marginal	45 / 74	36 / 79	8.9	19.9
	Radical	114 / 317	113 / 301	−4	56.6
Total		**163 / 409 (39.9 %)**	**158 / 407 (38.8 %)**		

*95% CI everywhere



Relative risk of death

Localized resectable STS

Adjuvant CT ?

For whom ?

STS – Adjuvant CT
ESMO CPGs / IGR algorythm (2013)

clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v198–v203, 2010
doi:10.1093/annonc/mdq209

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

P. G. Casali[1] & J.-Y. Blay[2]
On behalf of the ESMO/CONTICANET/EUROBONET Consensus Panel of experts*
[1]Department of Cancer Medicine, Istituto Nazionale dei Tumori, Milan, Italy; [2]INSERM U590, Claude Bernard University and Department of Oncology, Edouard Herriot Hospital, Lyon, France

Adjuvant CT is not recommended routinely in high grade STS

Adjuvant CT can be proposed as an option to the high-risk individual pt

Adjuvant CT	R1 resection (even after salvage surgery) grade 3 specially in males
No adjuvant CT	R0 resection, male/female grade 2-3 R1 resection, grade 2 superficial STS, all grade, all age All retroperitoneal sarcomas All STS > 70 yrs
Induction CT	R2, R1 fragmentated resection before salvage surgery

Future of adjuvant CT

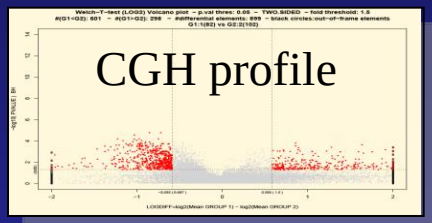
Possible options

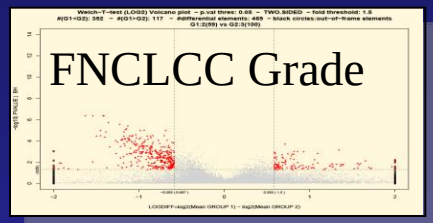
1. Randomized trial in selected groups : R1?
2. Conventional CT in STS with molecular signature
3. Novel agents: trabectedin
4. Antiangiogenics
5. Adapted to histological and molecular subtypes

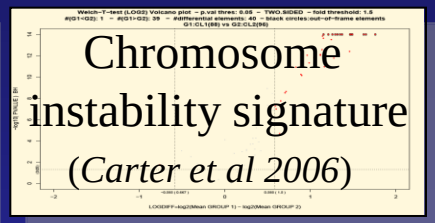
CINSARC: Complexity INdex in SARComas

Chromosome integrity and mitosis control

Identification of genes significantly ($p<0.01$) expressed according to:



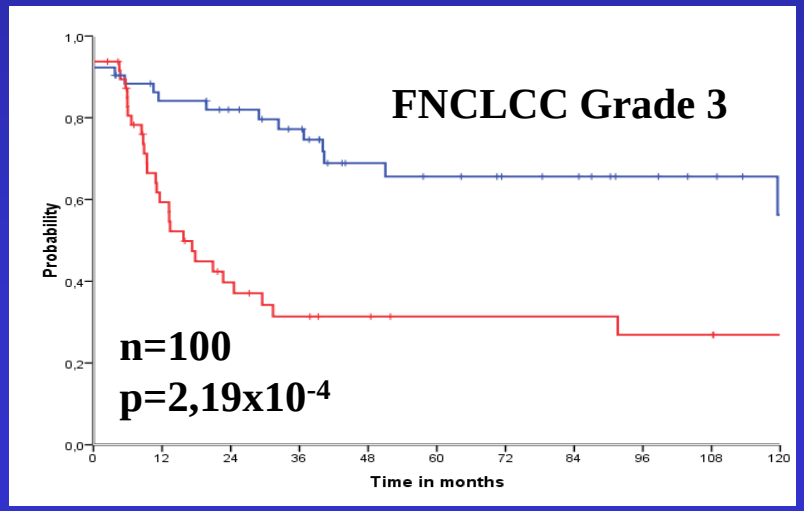


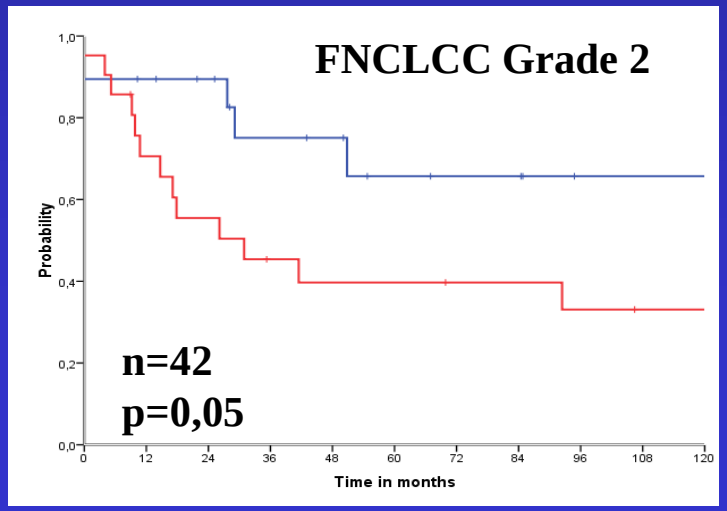


GO analysis: Selection of genes belonging to pathway significantly overrepresented ($p<10^{-5}$)

67 genes: Cinsarc signature

Chibon et al, Nat Med 2010





Future of adjuvant CT in STS?

Cytotoxic drugs

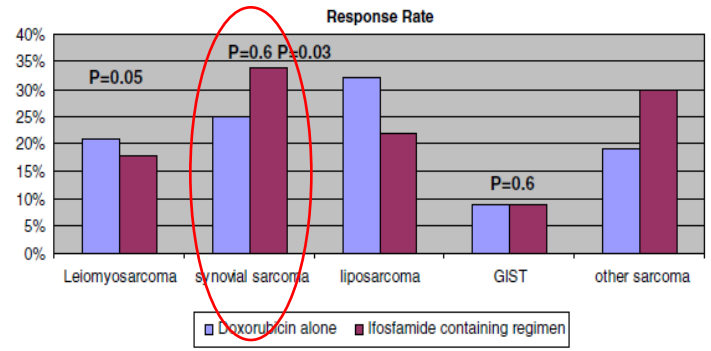
Histological subtype	Agents
Angiosarcoma	Paclitaxel
DD Liposarcoma	Doxorubicine + Ifosfamide
Myxoid liposarcoma	Trabectedin
Leiomyosarcoma	Doxorubicine + Dacarbazine Gemcitabine + Dacarbazine Doxorubicine + Trabectedin Trabectedin
Synovialosarcoma	Ifosfamide

…first step of personalized treatment!

Ifosfamide in Synovial sarcomas

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.

®

Ifosfamide

Surveillance

Paclitaxel in angiosarcomas

Phase II Trial of Weekly Paclitaxel for Unresectable Angiosarcoma: The ANGIOTAX Study

Nicolas Penel, Binh Nguyen But, Jacques-Olivier Bay, Didier Cupissol, Isabelle Ray-Coquard, Sophie Piperno-Neumann, Pierre Kerbrat, Charles Fournier, Sophie Taieb, Maria Jimenez, Nicolas Isambert, Frédéric Peyrade, Christine Chevreau, Emmanuelle Bompas, Etienne G.C. Brain, and Jean-Yves Blay

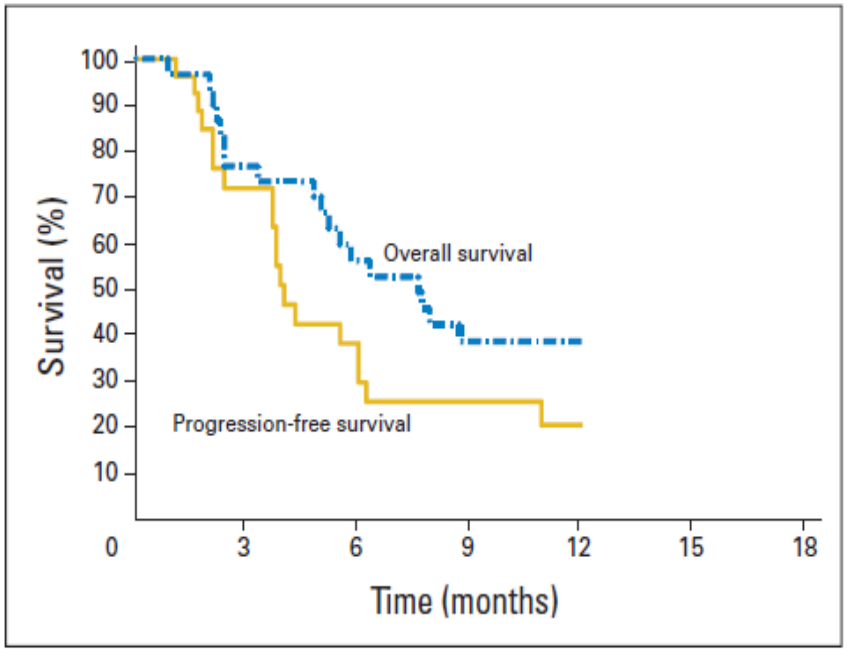


Fig 1. Overall and progression-free survival.

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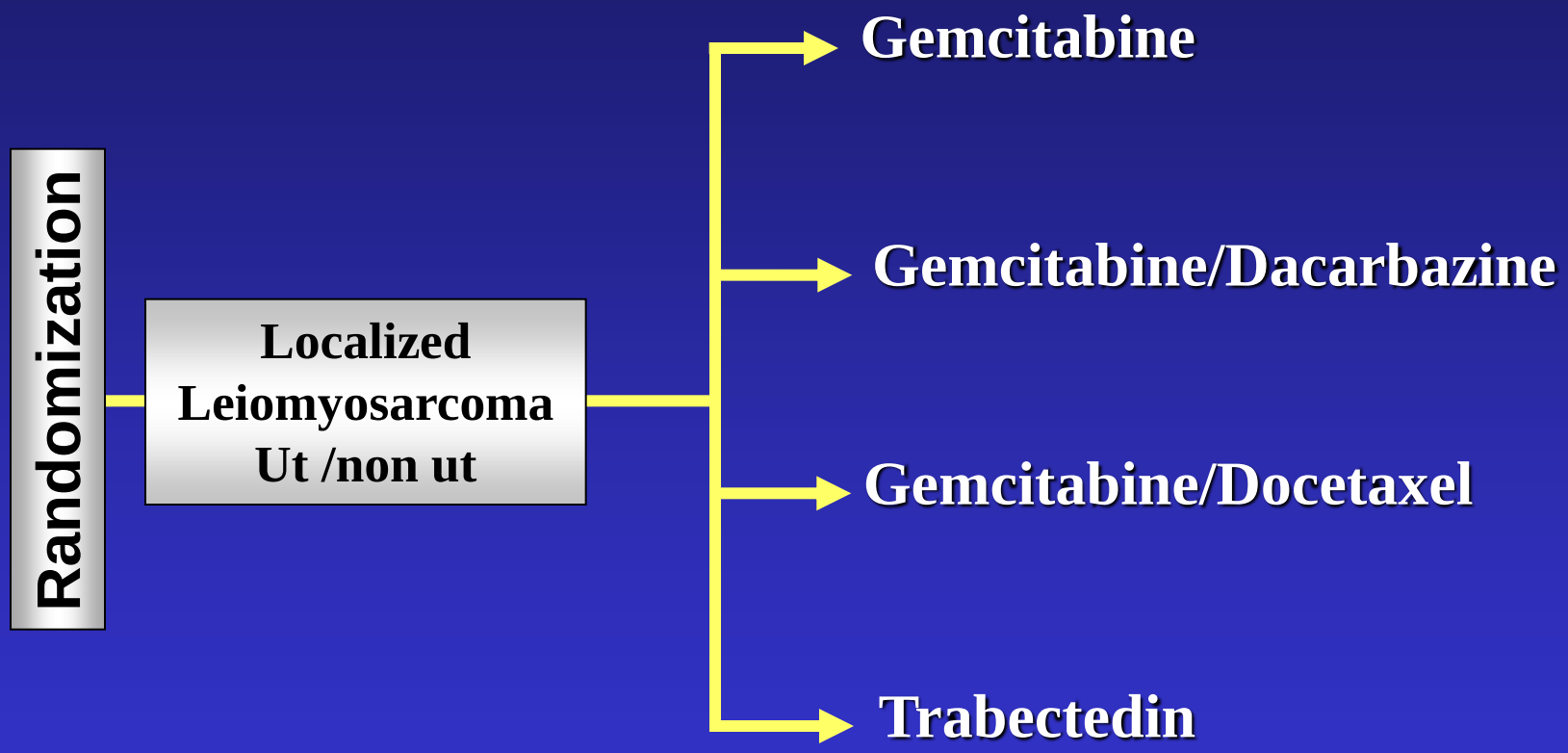
weekly TXL

Surveillance

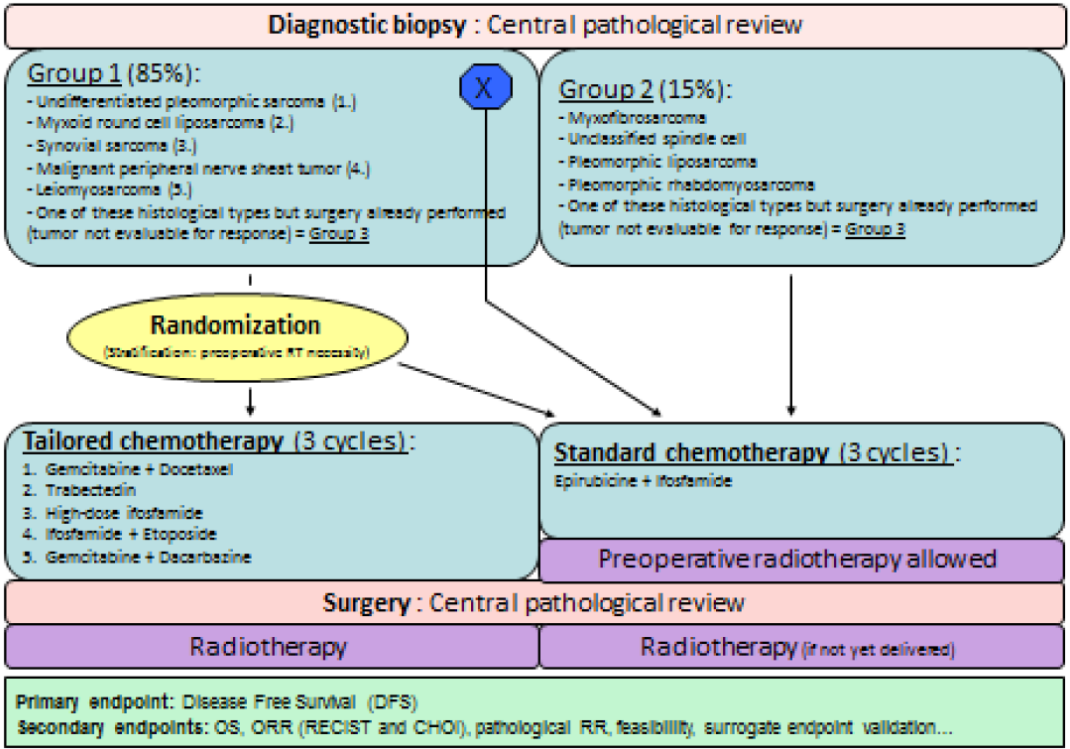
Hypothetical phase III study design in leiomyosarcoma?



Eurosarc ISG STS 10-01

Localized high-risk soft tissue sarcomas of the extremities and trunk wall in adults: an integrating approach comprising standard vs histotype-tailored neoadjuvant chemotherapy (ISG-STS 10-01)

Sponsor	Italian Sarcoma Group Istituto Ortopedico Rizzoli Via Pupilli, 1 40136 Bologna, Italia
Coordinating investigator	Pr Alessandro GRONCHI Fondazione IRCCS - Istituto Nazionale dei Tumori Via venezian, 1 20133 Milano, Italia



Conclusion : Personnalizing adjuvant CT

1. Not a standard option
2. In selected groups
3. Which selected groups? R1, >40? Males?
4. Conventional CT in STS with molecular signature?
5. Adapted to histological and molecular subtypes?

Future of adjuvant CT

Possible options

1. Randomized trial in selected groups
2. Conventional CT in STS with molecular signature
3. Novel agents: trabectedin
4. Antiangiogenics
5. Adapted to histological and molecular subtypes