



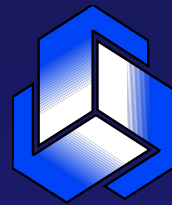
Adjuvant chemotherapy in STS: A never ending or an out-of date issue?

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Disclosures

Novartis, Pfizer, Lilly, Pharmamar, Merck



Adjuvant systemic treatment in STS

A never ending issue?

No, an era is just ended!



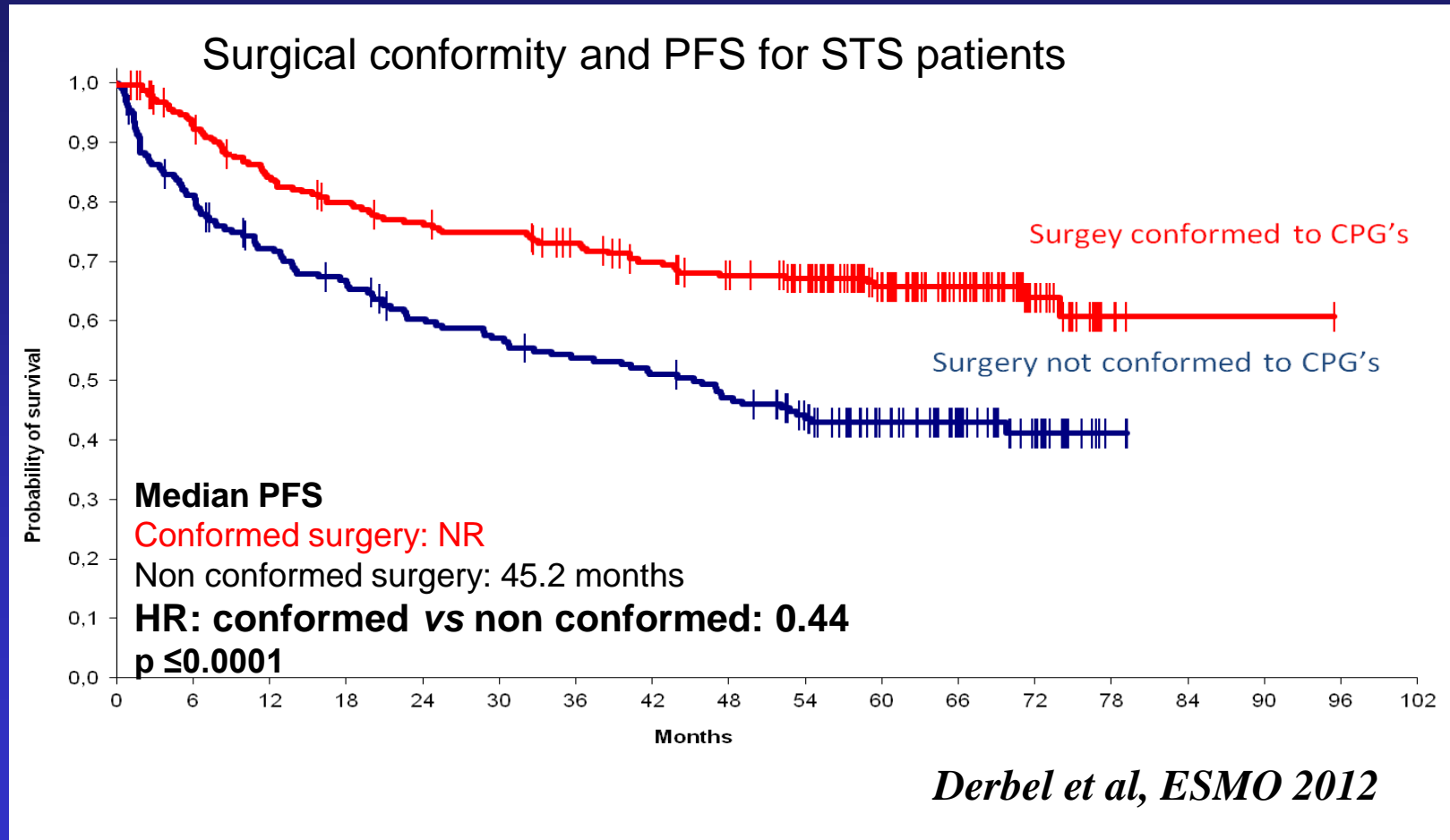
Adjuvant CT in STS

Randomized trials

What we have learnt from the past?

- Inadequate number of patient in clinical prospective trials
- Heterogeneous group of tumors with histological sub types not yet « biologically » characterized and no histological review in « old » trials
- All sites for primary including visceral (GIST) and non visceral sarcomas
- Only two « active » drugs: doxorubicin and ifosfamide (10-20% of OR in metastatic setting)
- Inadequate CT regimen (Dox alone, Ifo non fractionated low dose...)
- Follow-up of patients too short and long term results not given...
- Incomplete or marginal initial surgery (margins unknown)

Adjuvant randomized trials according to surgical conformity?



→ Initial « surgical » take in charge: also a never ending issue?

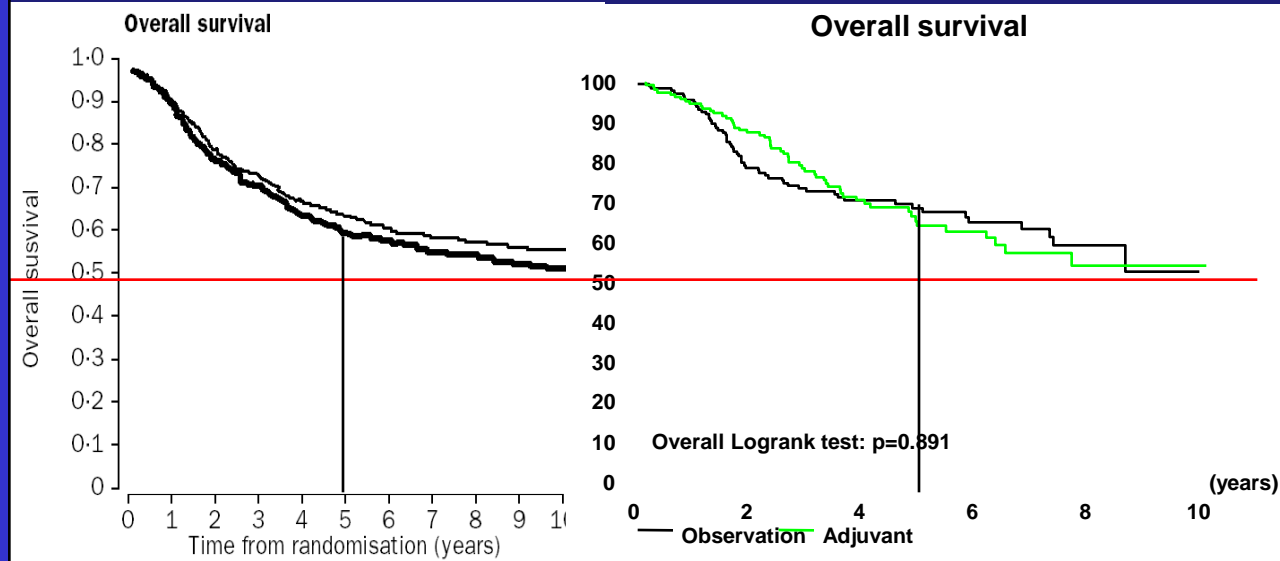
STS- Increase of OS?

Control arm

*SMAC.
Lancet 1997; 350: 1647*

*EORTC 62931
Woll, LO 2012*

- 1) Surgical techniques improvement
- 2) Optimization of the « beginning »
- 3) Referral centers



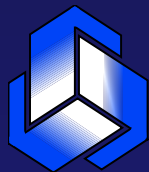
5-yr OS

59%

69%

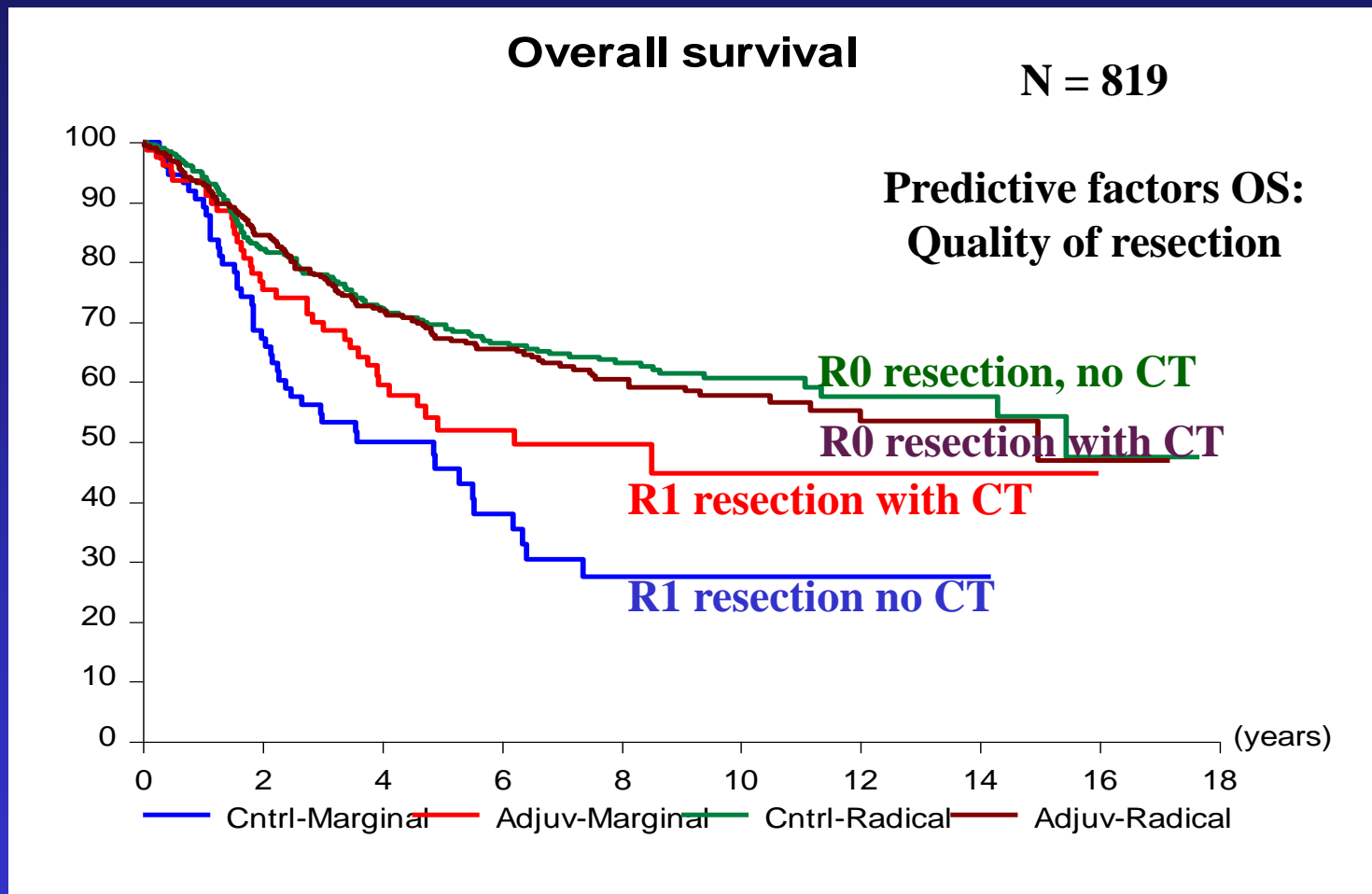
10% absolute increase of OS in 20 yrs

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



EORTC adjuvant trials in STS

Predictive factor of resection on OS by treatment



clinical practice guidelines

Annals of Oncology 25 (Supplement 3): 1102-1112, 2014
doi:10.1093/annonc/mdt284

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

The ESMO/European Sarcoma Network Working Group*

Adjuvant chemotherapy should never be intended to rescue inadequate surgery

Le Cesne et al, Annals of Oncol 2014

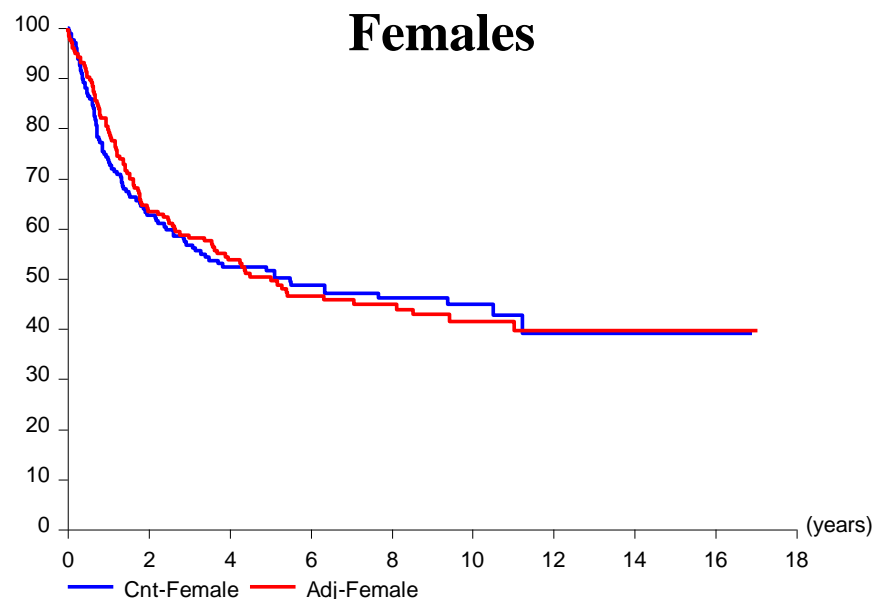
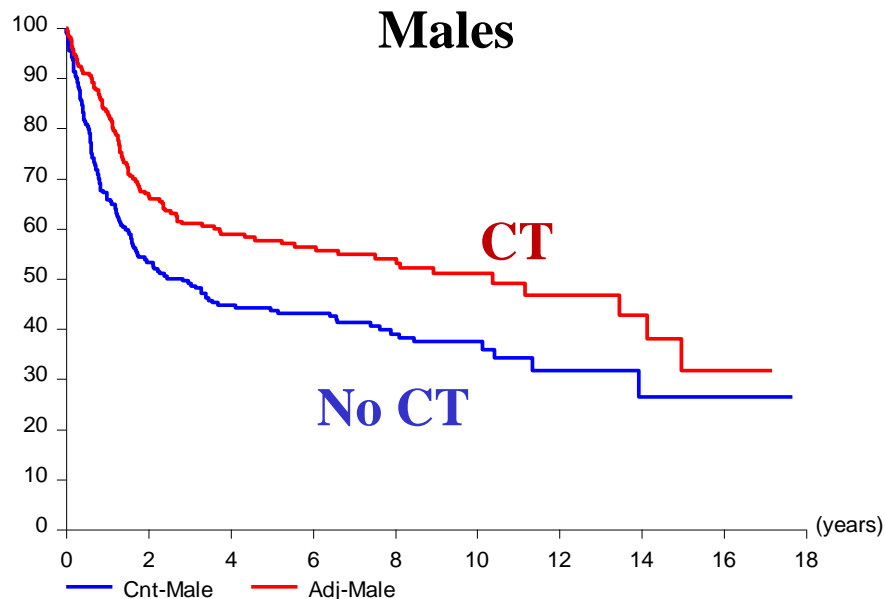


Adjuvant chemotherapy according to gender

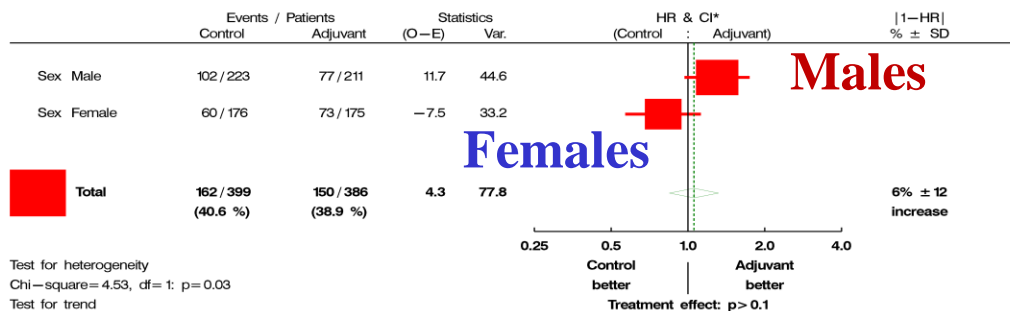
Progression free survival

N = 819

Progression free survival



Overall survival



® trials only in males?

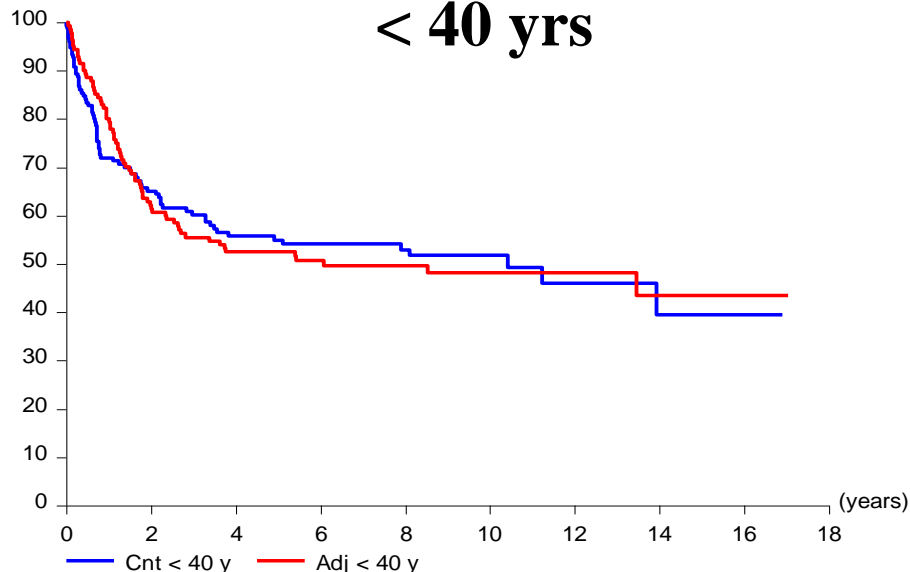
*Le Cesne et al,
Annals of Oncol 2014*



Adjuvant chemotherapy according to age

Progression free survival

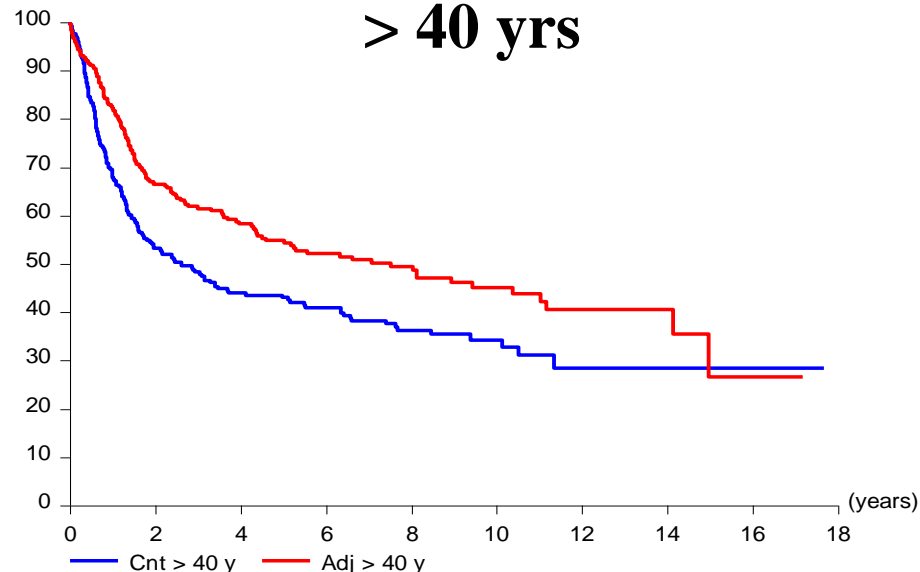
< 40 yrs



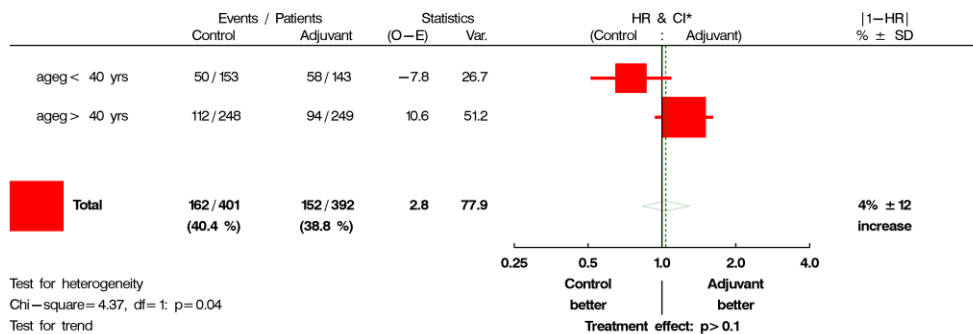
N = 819

Progression free survival

> 40 yrs



Overall survival



® trials in > 40 yrs?

*Le Cesne et al,
Annals of Oncol 2014*

< 40 yrs > 40 yrs

STS - Adjuvant CT- EORTC 62931

OS of women with radical resection (R0) by treatment and by age

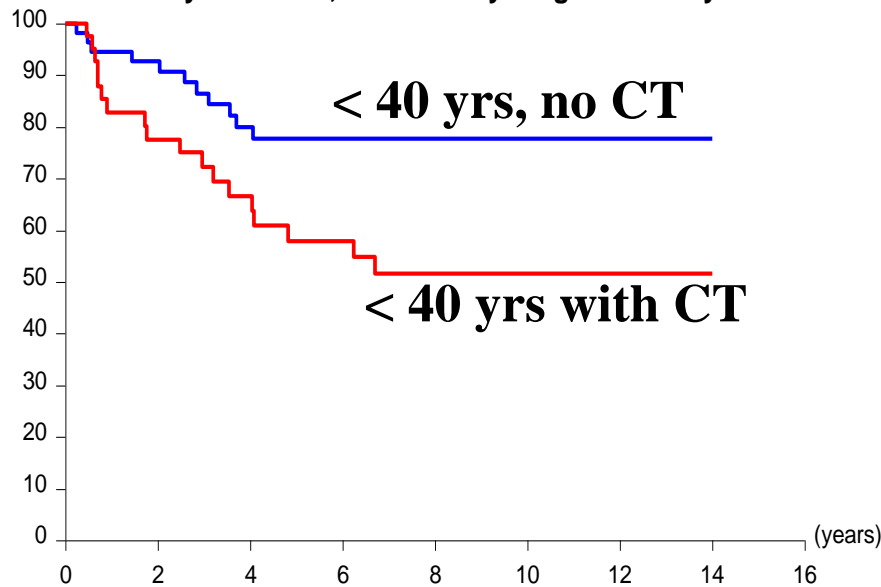


R0 resection

R0 resection

Overall survival

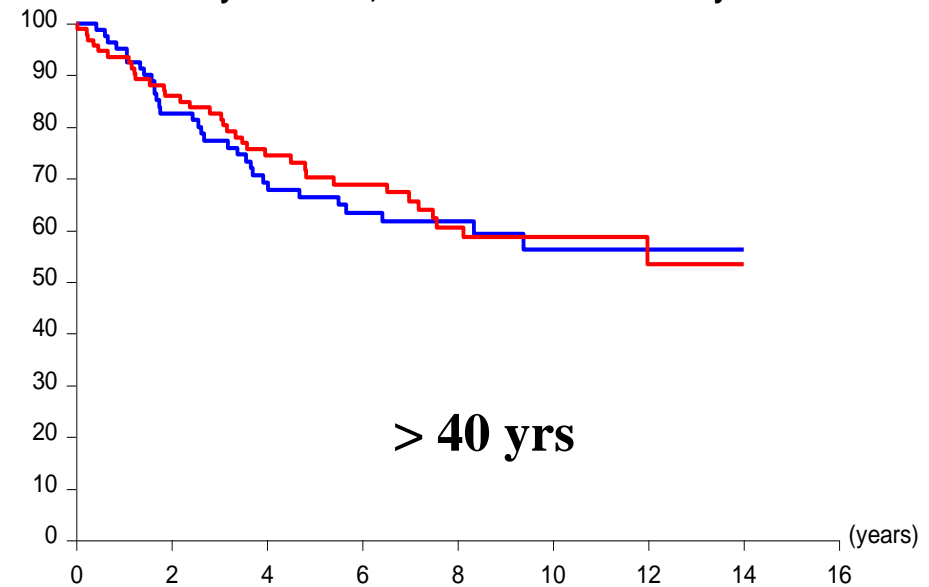
R0 by treatment, for women younger than 40 yrs



| O | N | Number of patients at risk : | | | | | | | | |
|----|----|------------------------------|----|----|----|----|---|---|---|-------------|
| 11 | 55 | 47 | 36 | 29 | 24 | 16 | 7 | 4 | — | Cnt-Radical |
| 18 | 41 | 30 | 23 | 20 | 15 | 11 | 7 | 4 | — | Adj-Radical |

Overall survival

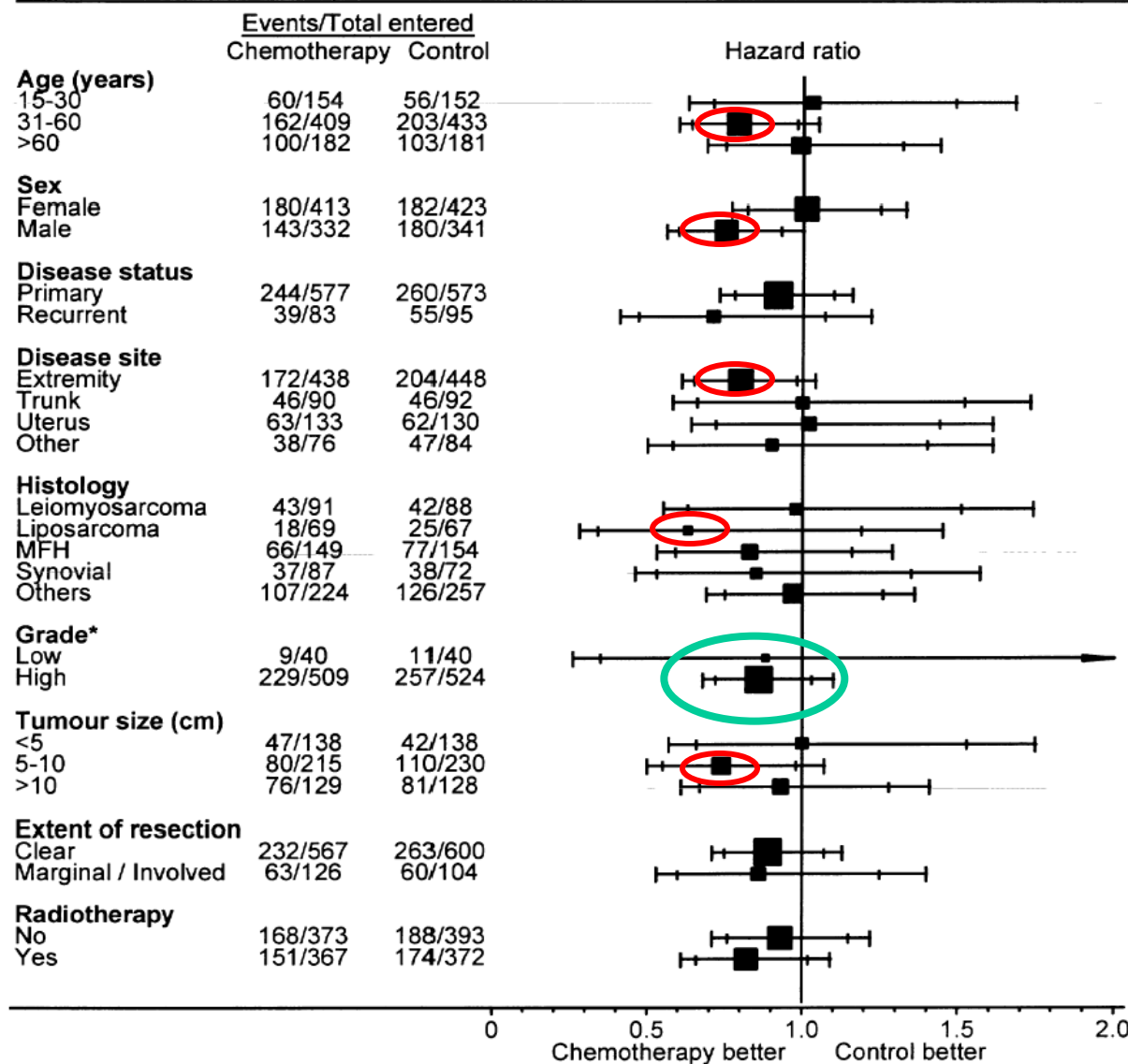
R0 by treatment, for women older than 40 yrs



| O | N | Number of patients at risk : | | | | | | | | |
|----|----|------------------------------|----|----|----|----|----|---|---|-------------|
| 31 | 83 | 66 | 51 | 39 | 29 | 14 | 8 | 5 | — | Cnt-Radical |
| 34 | 95 | 78 | 60 | 45 | 33 | 22 | 10 | 3 | — | Adj-Radical |

Quality of resection remains the most powerful prognostic/predictive factor for longer OS

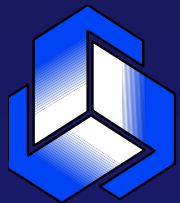
STS – Adjuvant CT Meta-Analysis



**Pts who benefit
the most of CT:**

- Man 30-60 yrs
- Extremity non leioS
- 5-10 cm
- Grade?

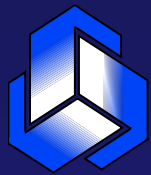
Sarcoma Meta-analysis.
Lancet 1997; 350: 1647



EORTC Adjuvant trials in STS

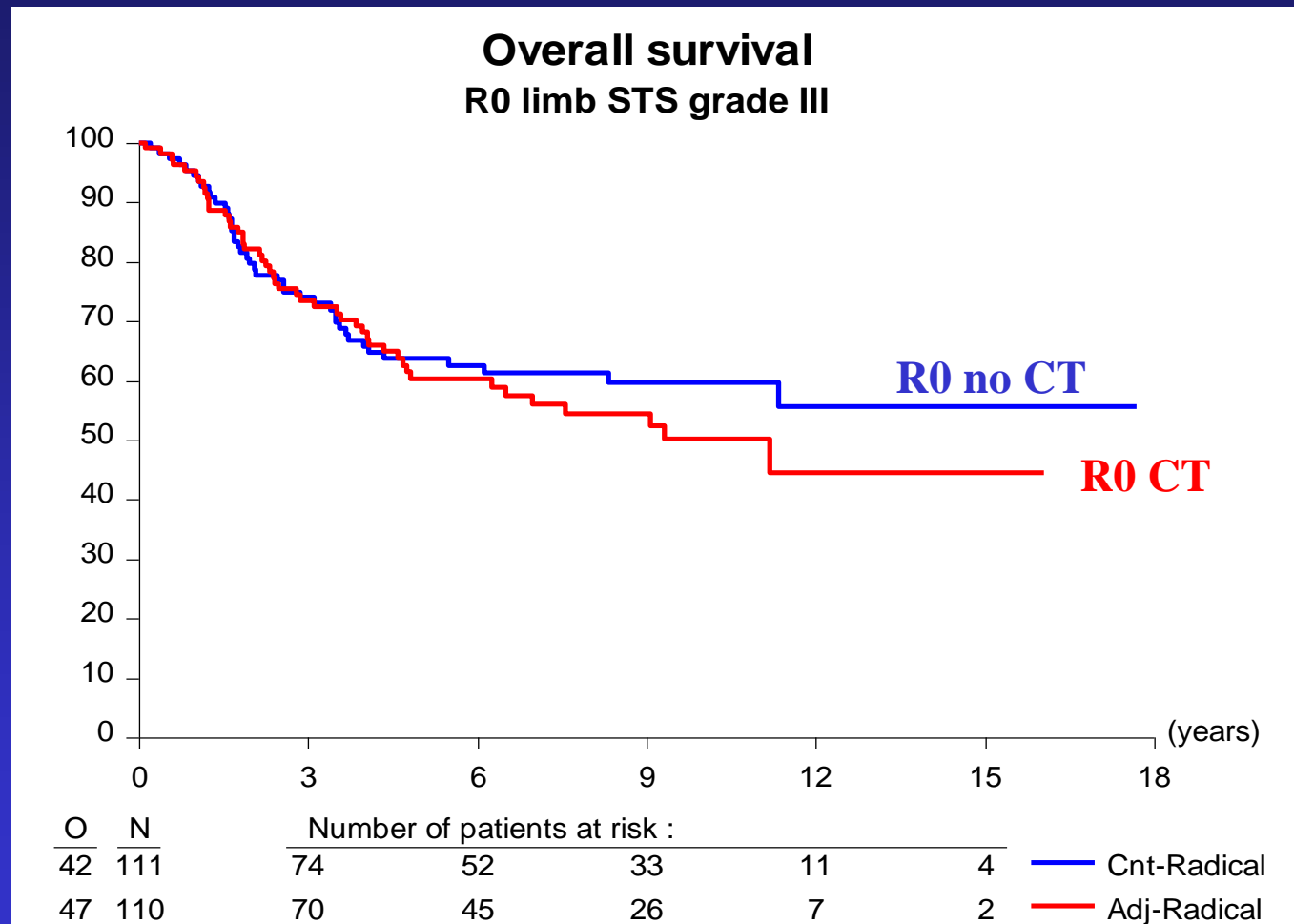
Predictive factors for OS and PFS

| | Interaction test | |
|-----------------------|------------------|---------------------------|
| | Overall survival | Progression free survival |
| Study | 0.9179 | 0.3119 |
| Sex | 0.0351 | 0.0357 |
| Age (40 yrs) | 0.0412 | 0.0561 |
| Tumor size (7 cm) | 0.6401 | 0.7746 |
| Local recurrence | 0.2513 | 0.6853 |
| Radical resection | 0.0391 | 0.1595 |
| Grade (I-II vs III) | 0.0860 | 0.7155 |
| Leiomyosarcoma | 0.5056 | 0.4055 |
| Liposarcoma | 0.4907 | 0.9203 |
| Synovial | 0.8574 | 0.7670 |
| Limb | 0.4953 | 0.5336 |
| Trunc – Head and neck | 0.5034 | 0.5933 |
| Central | 0.4732 | 0.4707 |
| Uterus | 0.2041 | 0.1438 |



EORTC Adjuvant trials in STS

Quality of resection required in first



No impact of size and histological subtype



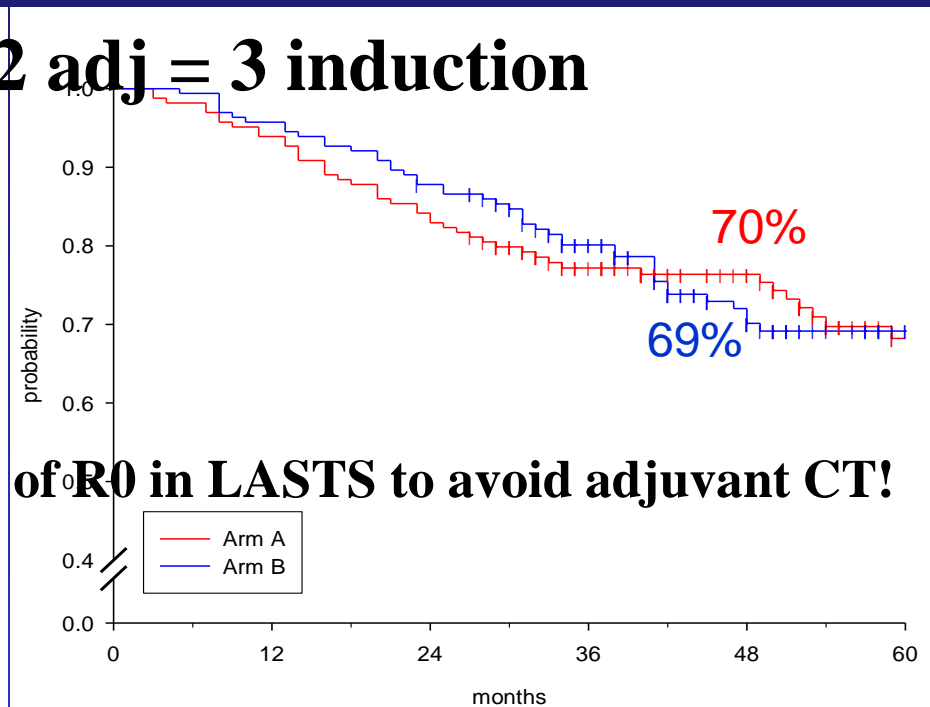
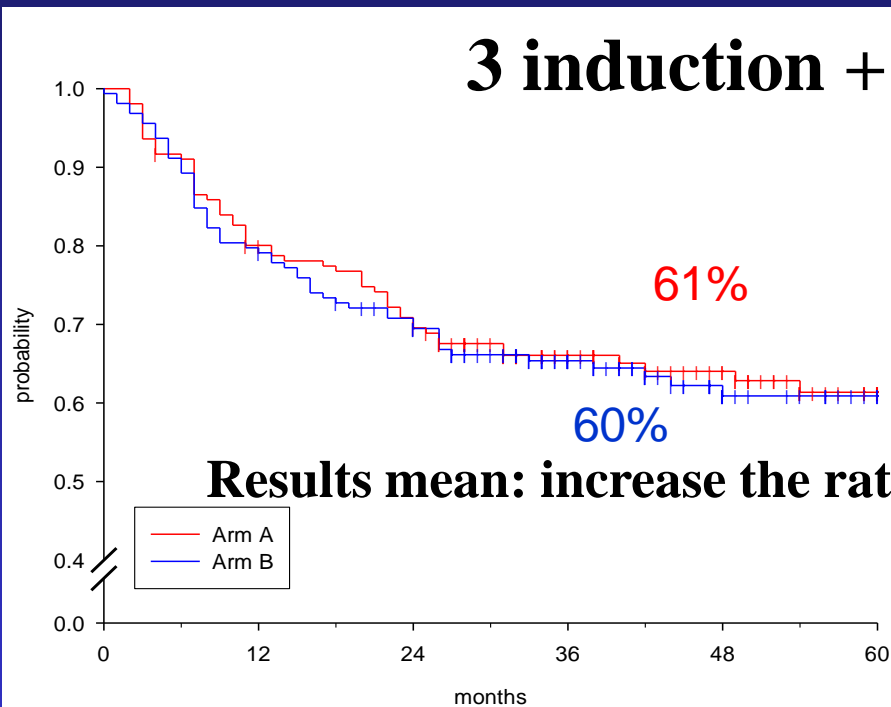
«Adjuvant» CT in localized STS

PFS and OS by study arm

PFS

OS

3 induction + 2 adj = 3 induction



clinical practice guidelines

Annals of Oncology 25 (Supplement 3): i1102–i1112, 2014
doi:10.1093/annonc/mdu254

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

The ESMO/European Sarcoma Network Working Group*

If the decision is made to use CT as upfront treatment, it may well be used preoperatively, at least in part. A local benefit may be gained, **facilitating surgery**

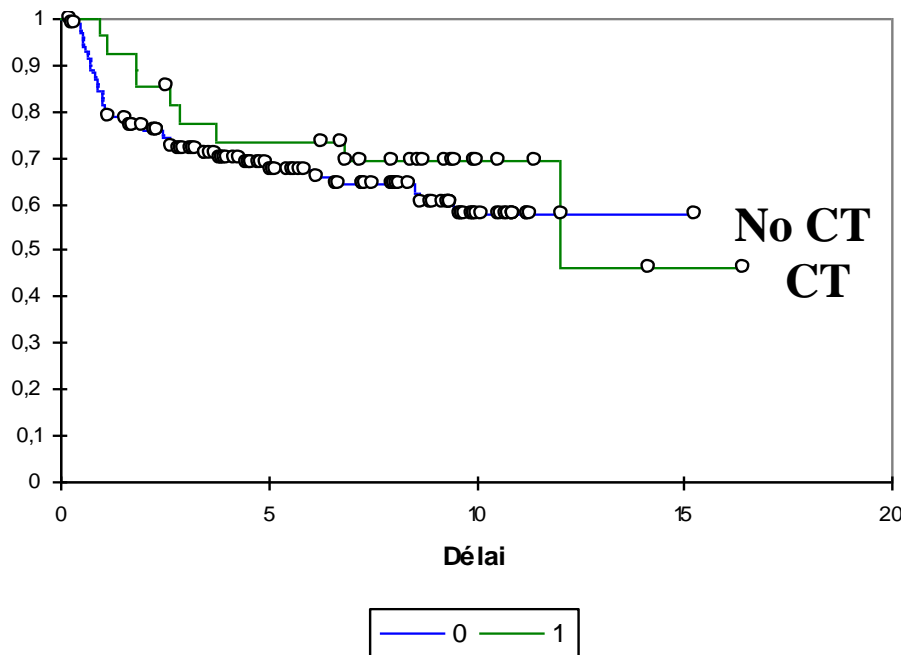
Palassini et al, JCO 2015

Adjuvant future randomized trials according to surgeon?

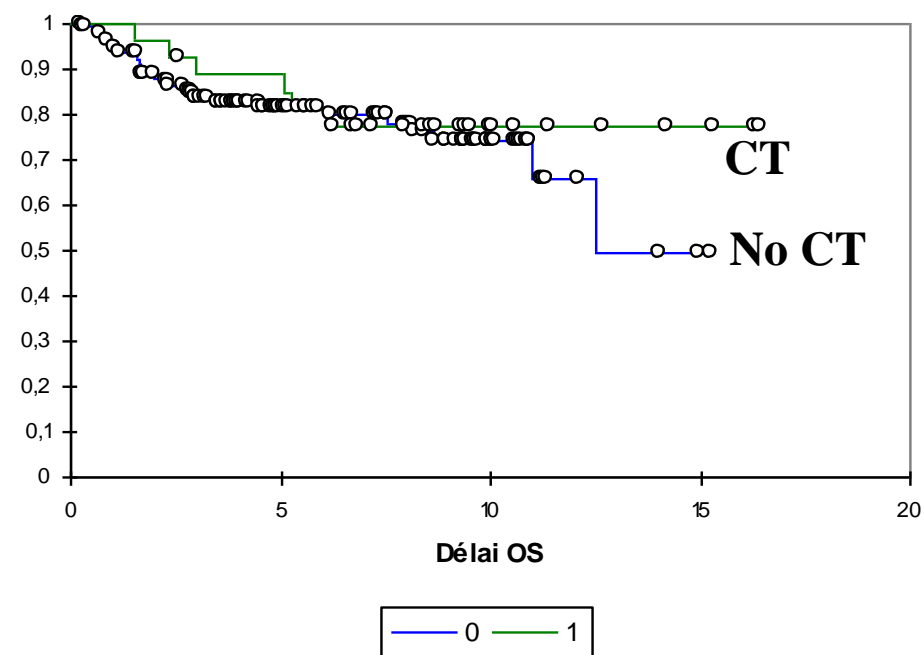
N = 160 extremity STS

Patients: Gustave Roussy
Surgeon: Sylvie Bonvalot

PFS selon Ctadj; p=0,4



OS selon Ctadj, p=0,5



No benefit of adjuvant chemotherapy if surgery is adapted!!

STS is a localized disease in 90% of cases at diagnosis

Metastases could be positively influenced by inadequate surgical procedures...

STS – Adjuvant CT

ESMO CPGs / IGR algorithm (2016)

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): i102–i112, 2014
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It is unknown whether adjuvant CT may be particularly beneficial in specific subgroups or even detrimental in others. Therefore, adjuvant CT is not standard treatment in adult-type STS. It can be proposed as an option to the high-risk individual patient for a shared decision-making with the patient

Adjuvant CT

R1 resection (even after salvage surgery) grade 3
specially in males. Discussion if margins unknown

No adjuvant CT

R0 resection, male/female grade 2-3
R1 resection, grade 2. All grade 1
Superficial STS, all grade, all age
All retroperitoneal sarcomas
All STS > 70 yrs

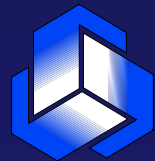
Induction CT

R2, R1 fragmentated resection before salvage surgery

Adjuvant systemic treatments in STS

An out-of date issue?

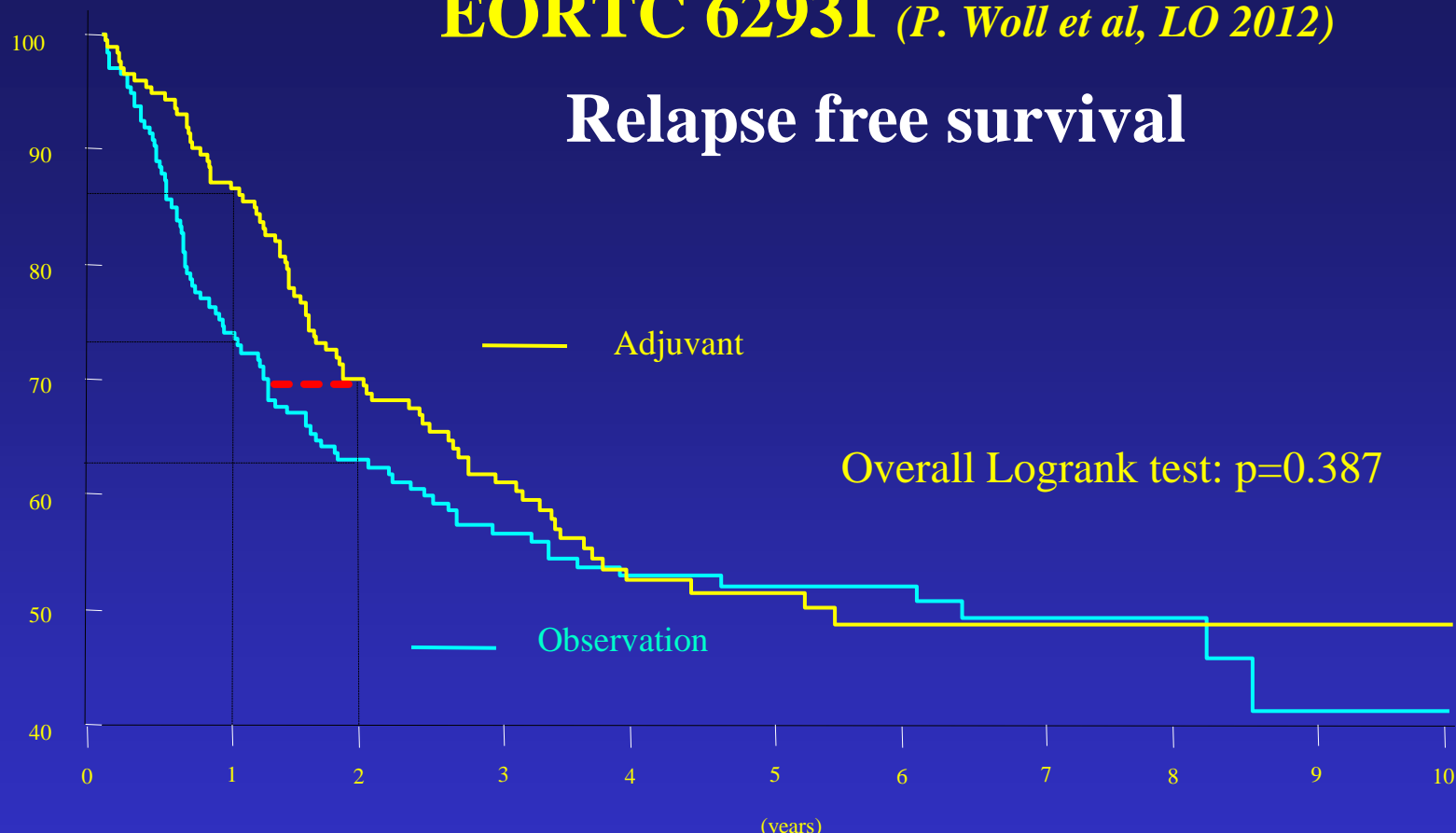
No, a new era has started!



STS – Adjuvant CT

EORTC 62931 (*P. Woll et al, LO 2012*)

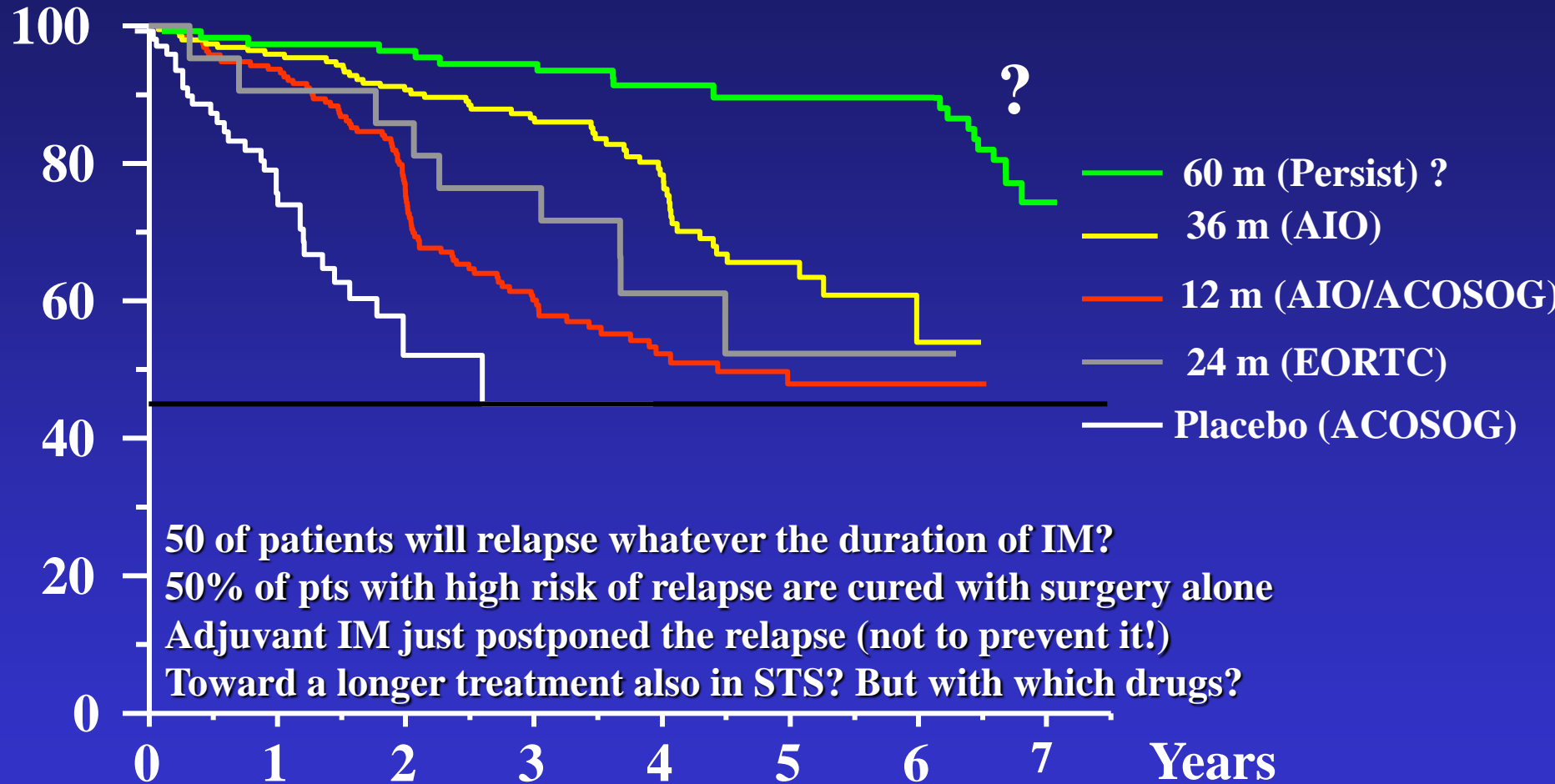
Relapse free survival



- 5 AI courses gives a PFS benefit of 6-9 months (as in advanced setting!)
- Pts not cured after resection of a local STS means synchronous infraclinical metastases at diagnosis
- 50% all pts with high grade STS are cured with surgery (+/- RT) alone!
Those with a true localized disease?

Adjuvant imatinib in GIST

PFS Evolution according to duration of TT



Future of adjuvant CT

four possible options

- 1. Randomized trial in selected groups**
- 2. Conventional CT in STS with molecular signature**
- 3. Selected regimen according to a pathway signature**
- 4. Targeted agents/anti-angiogenics**

Example of adjuvant trials in selected STS with conventional CT

Histological Sub-type

Trials

All sarcomas

Trabectedin vs nihil, Gem-Tax vs nihil

L-Sarcoma, Myxoid LPS

Trabectedin vs nihil

Leiomyosarcoma

Dox-DTIC vs nihil, Gem + DTIC vs nihil

Angiosarcoma

Taxol vs nihil

Synovial Sarcoma

Ifosfamide HD vs nihil

Duration of adjuvant CT has also to be tested (with no cumulative T drugs).....

Future of adjuvant CT

four possible options

- 1. Randomized trial in selected groups**
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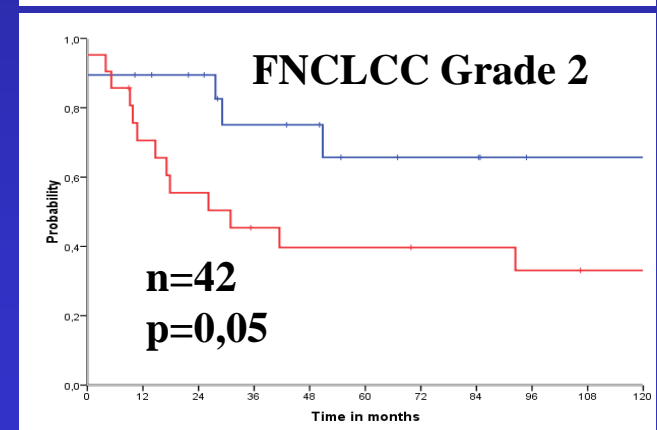
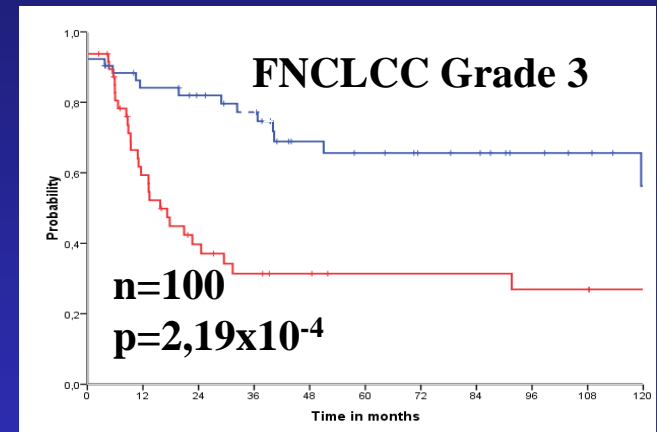
Non selected localized resectable STS

Conventional CT with « molecular signature »:

Adjuvant/induction
conventional CT
AI regimen

67 genes: Cinsarc signature

Chibon et al, Nat Med 2010

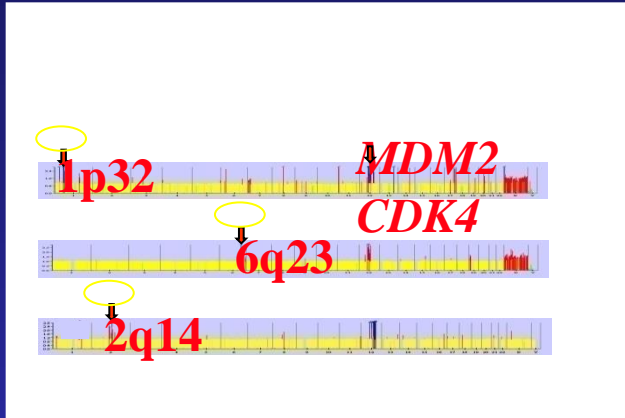


Future of adjuvant CT

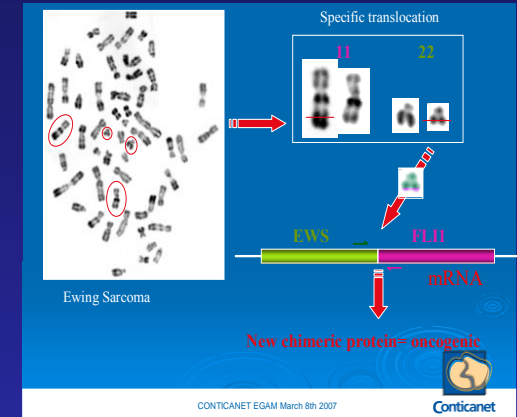
four possible options

1. **Randomized trials in selected groups**
2. **Conventional CT in STS with molecular signature**
3. **Selected regimen according to a « pathway » signature**
4. **Multi-targeted agents/anti-angiogenics**

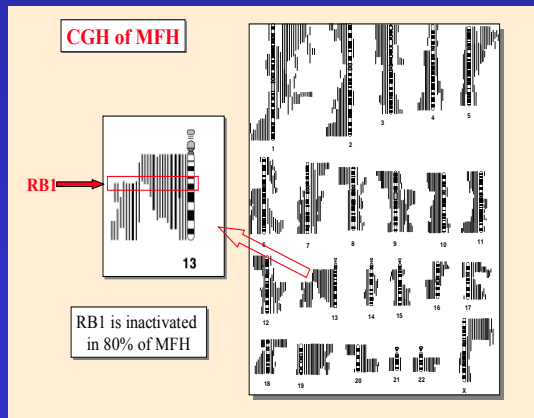
STS: at least 5 molecular subtypes



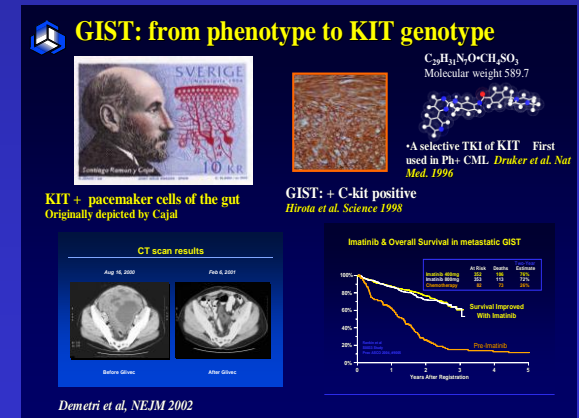
Gene amplification: WD/DDLPs



Gene translocation: 20%



Gene inactivation
INI1 loss:
Rhabdoid tumors
TSG loss, NF1, TSC1-2:
MPNST, PEComas



Complex gene alteration: LMS, UPS

Gene mutation: GIST/desmoids

Proof of concept in mesenchymal tumors

Toward selective adjuvant trials?

| Histology | Targets | Agents |
|--------------------------|-----------------------|----------------------|
| GIST | KIT/PDGFR | Imatinib |
| DermatoFSP | t(17-22) PDGFR | Imatinib |
| PECOMAS | mTor/TSC1,2 | Rapamycin inhibitors |
| Giant Cell Tumor | Rank/RankL | Denosumab |
| Pigmentitis VNS | t(1-2) CSF1 | Anti-CSF1 |
| Inflam. Myofi. T. | ALK alteration | Crizotinib |
| Alveolar STS | VEGFR? | Anti-VEGFR agents |

The collection of fresh/frozen tissue and tumour imprints is encouraged (plus blood samples), because new molecular pathology assessments could be made at a later stage in the patient's interest. Patients had to be included in clinical trials in referral centers .

Future of adjuvant CT

four possible options

- 1. Randomized trials in selected groups**
- 2. Conventional CT in STS with molecular signature**
- 3. Selected regimen according to a pathway signature**
- 4. Targeted agents/anti-angiogenics**

Advanced STS

« non targeted » oral anti-angiogenic drugs

| Histology | Targets | Agents |
|--------------------|-------------|---------------------|
| All except lipoS | VEGFR/PDGFR | Pazopanib |
| ASTS t(X-17) | VEGFR? | Cediranib/Sunitinib |
| Solitary Fibrous T | target? | Sunitinib |

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/ndu254

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

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Up-to date, no impact of anti-angiogenic drugs in the adjuvant setting in all tumors



Thank you



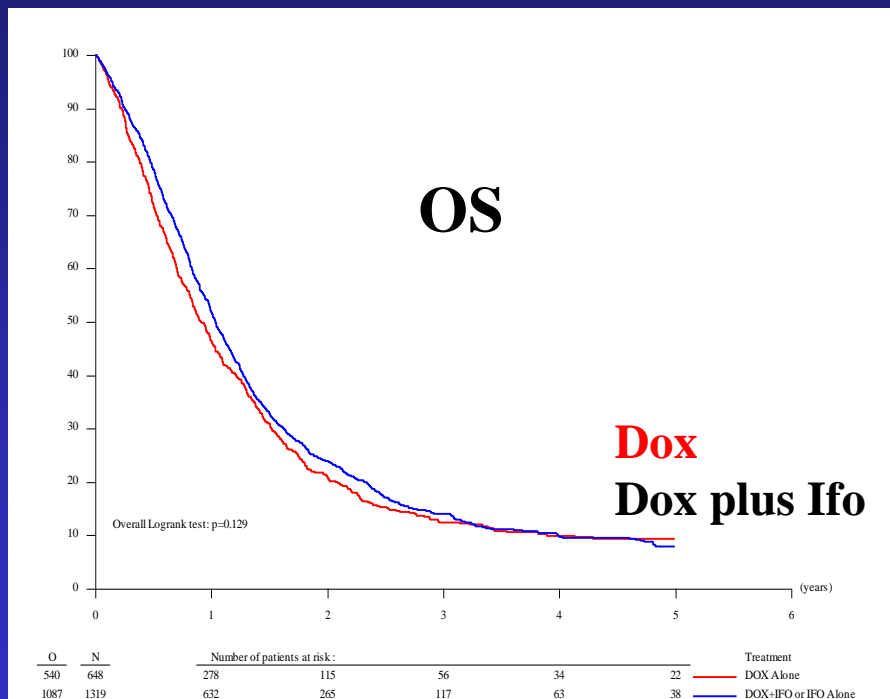


STS – advanced CT

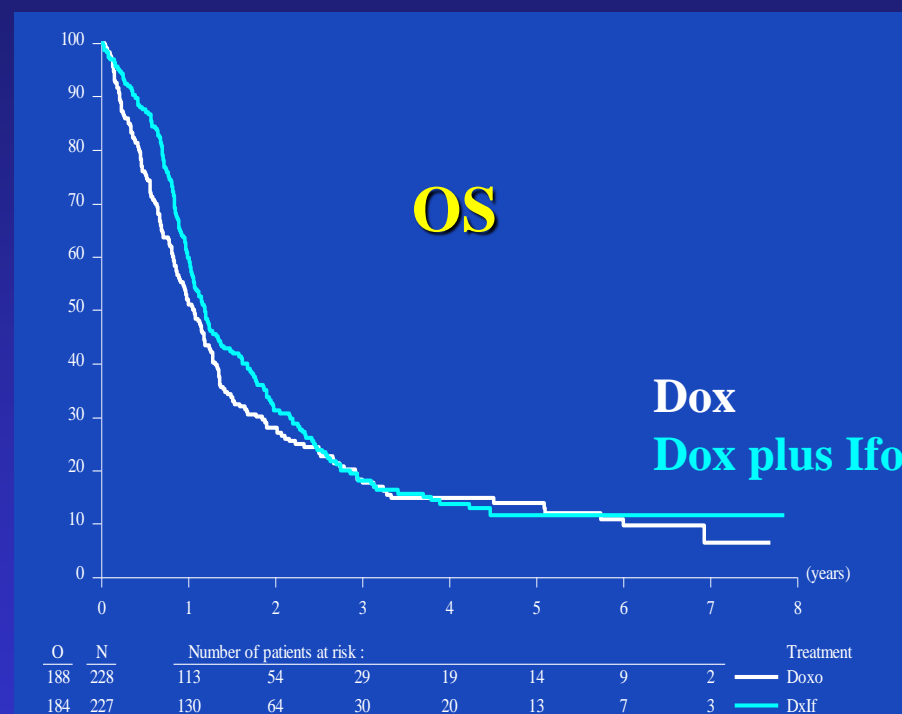
Impact of doxo-containing CT in adjuvant?

EORTC Database

EORTC 62012



S. Sleijfer et al, 2009



Judson et al, LO 2014

8% of patients alive at 5 years, Blay et al, EJC 2002