Molecular characterization should now be the determinant of modern cancer treatment in sarcoma

Poor

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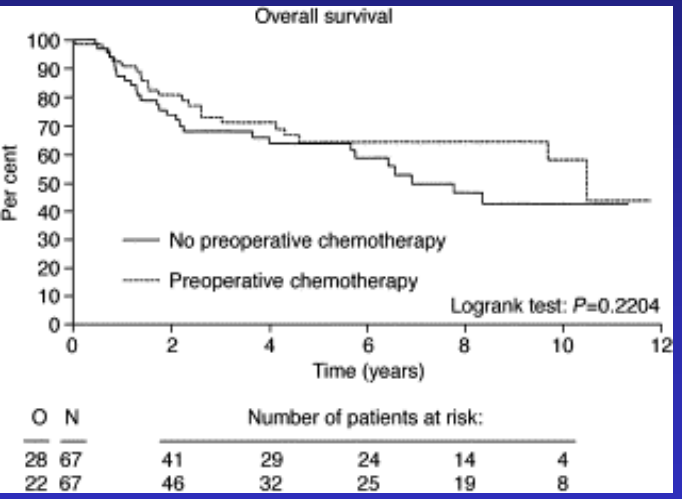
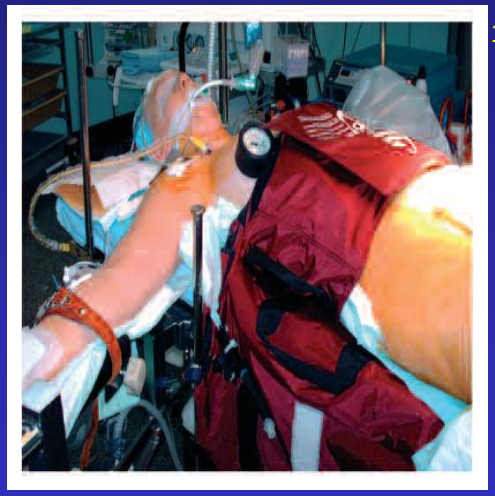
Académie de Médecine

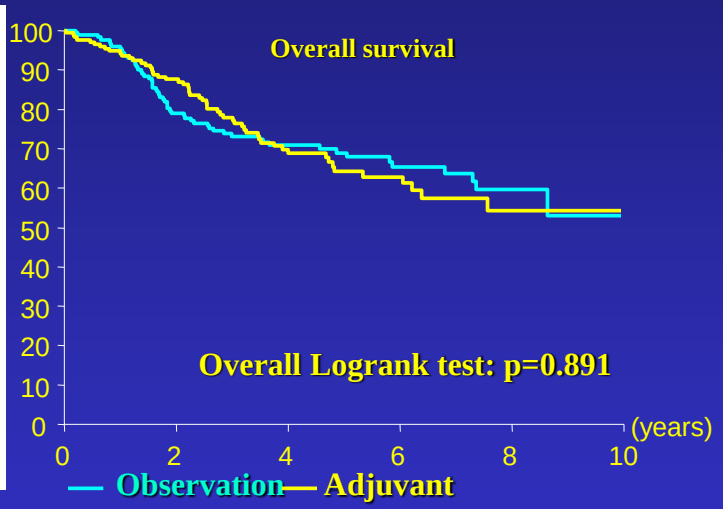
ESMO-ASIA, 19th of December 2015

Non selected localized resectable STS

Conventional CT: Adjuvant vs neo-adjuvant ?







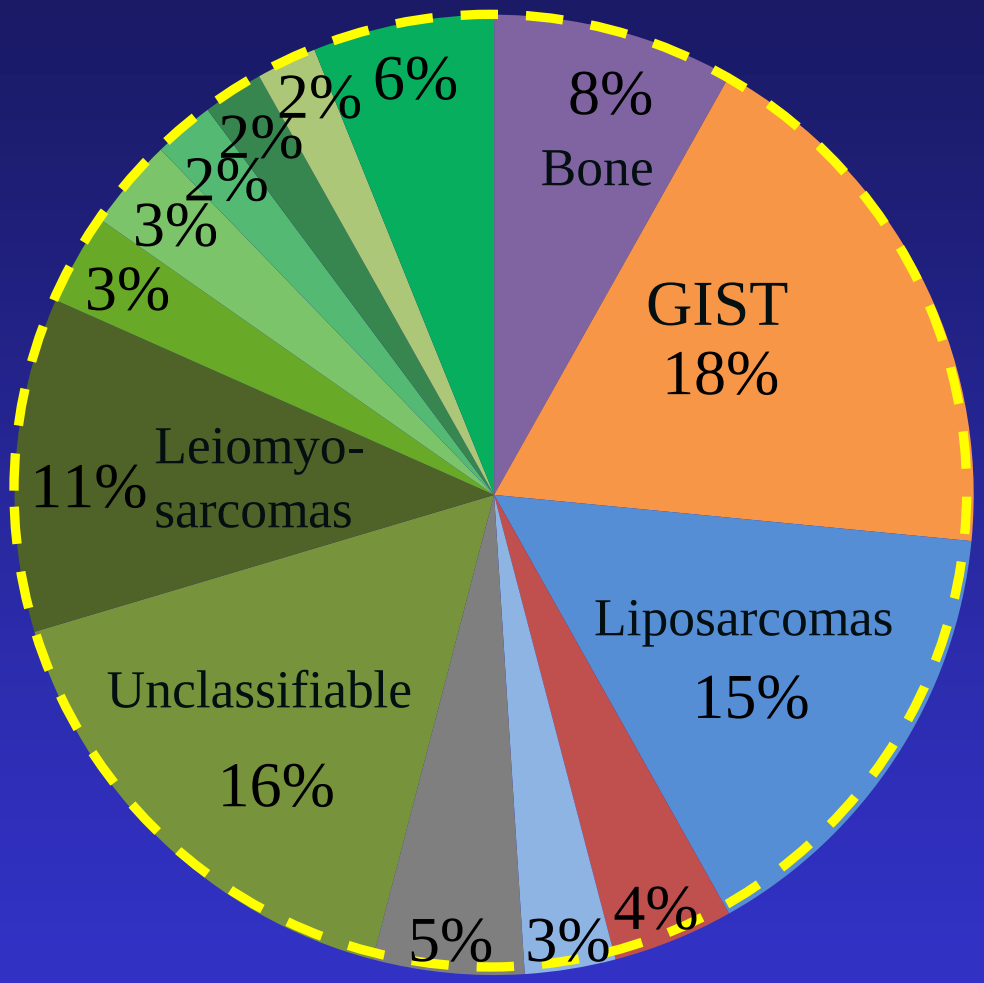
EORTC 62871
Gortzak EJC 2001

Impact on metastases unknown

EORTC 62031
Woll Lancet Oncol 2012

Impact on metastases unknown

Histological sub-type of Sarcoma



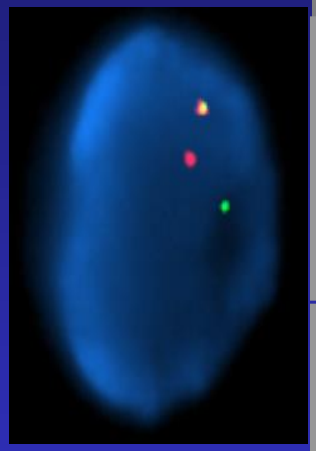
- Bone primary (osteosarcoma/ chondrosarcoma) (8%)
- GIST (18%)
- Liposarcoma (15%)
- Soft-tissue Ewing sarcoma/PNET (4%)
- Kaposi sarcoma (3%)
- Dermatofibrosarcoma (5%)
- Unclassified sarcoma (16%)
- Leiomyosarcoma (11%)
- Rhabdomyosarcoma (3%)
- Angiosarcoma (3%)
- Myxofibrosarcoma (2%)
- Synovial sarcoma (2%)
- Endometrial stromal sarcoma (2%)
- Other very rare subtypes (6%)

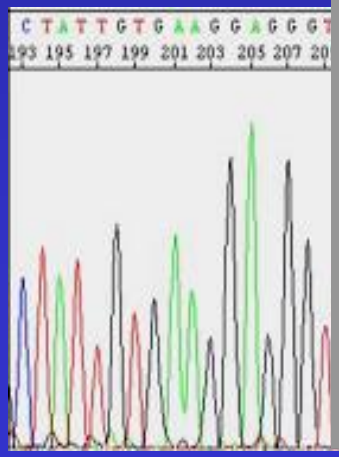
- **Considerable morphological overlap**
- **IHC not always helpful**
- **Entities differ widely in treatment and outcome**

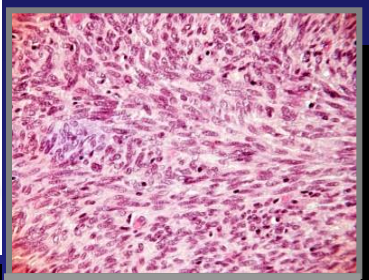
PNET, primitive neuroectodermal tumor.

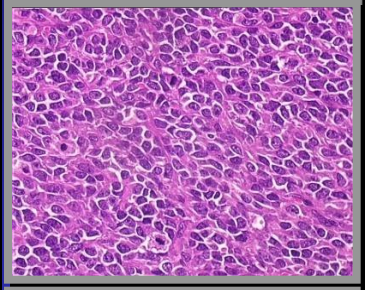
Ducimetiere F, et al. *PLoS ONE*. 2011;6(8):e20294.

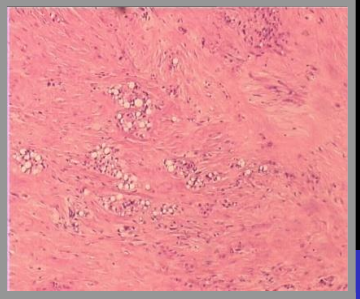
21st century: to understand our mistakes and sarcoma complexity

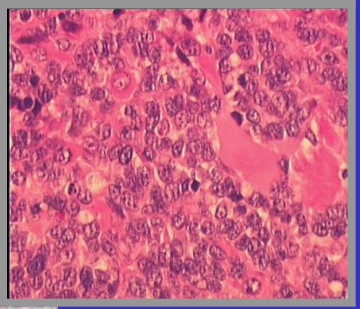


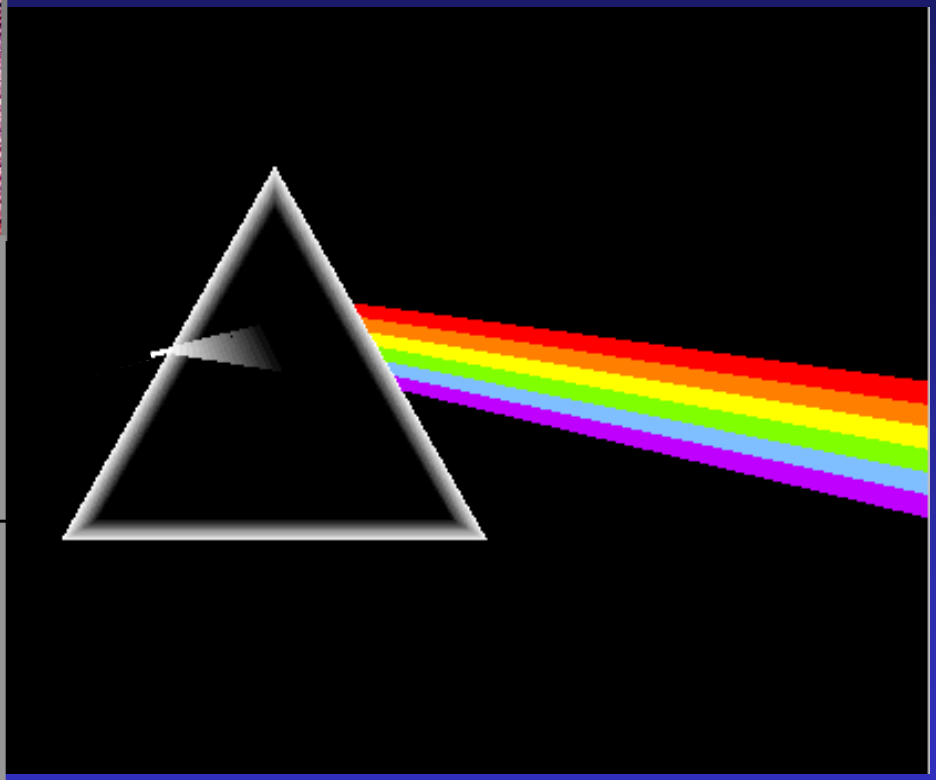












A

Rainbow

Of

Different

Sarcoma

Subtypes

In total 106 entities: Intermediate n=29
Malignant n=77

100 patients with advanced STS

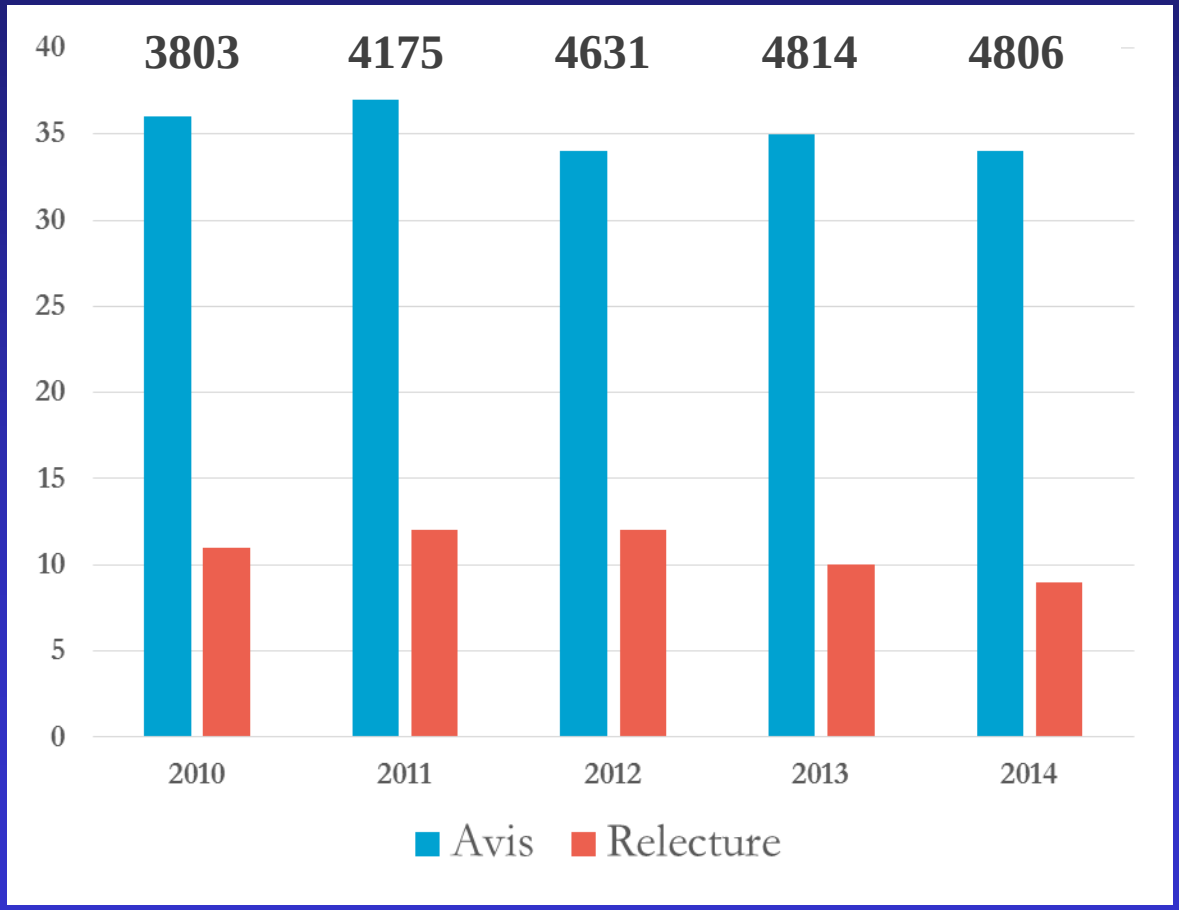
=

100 different diseases!!

Courtesy of G. Demetri

Rate of discrepancies for advice and reviewing (RRePS network)

% of tumor category change



RRePS Network 2010-14

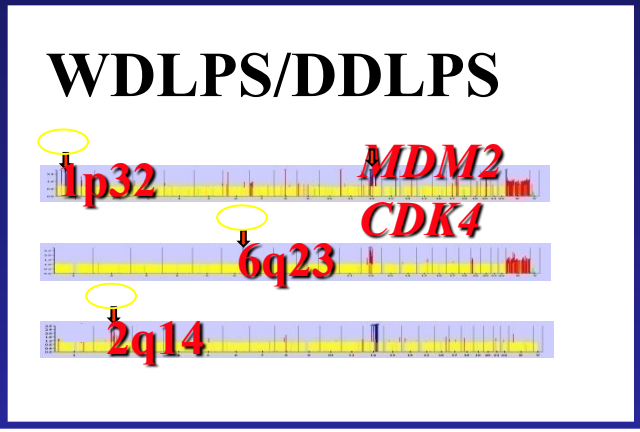
Cost of discordant diagnosis in mesenchymal neoplasms in France: Resultas from the RREPS Network

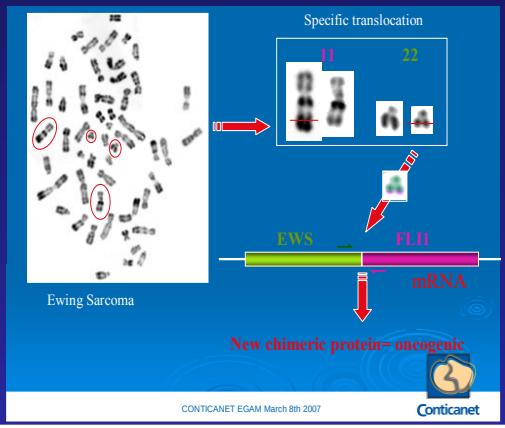
Inclusion criteria: pts with a discordant diagnosis identified after a histological review performed within the RRePS network in 2010 (22 French pathology centers)

- **2425 histological reviews out of 3414 patients registered**
- **341 major discordances (14%)**
- **Cost of the therapeutic strategies assessed for**
  - **The initial diagnosis: 2 186 816 €**
  - **The final diagnosis: 1 060 174 €**

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

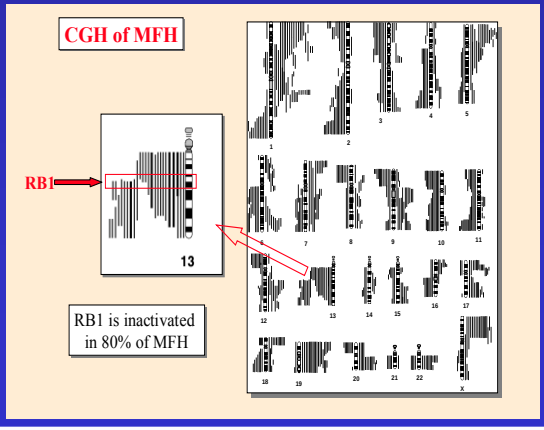
STS at least 5 molecular subtypes





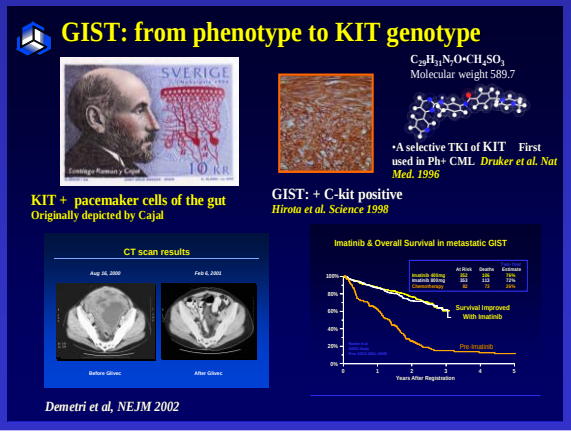
Gene amplification: LPS

Gene translocation: 20%



Gene inactivation

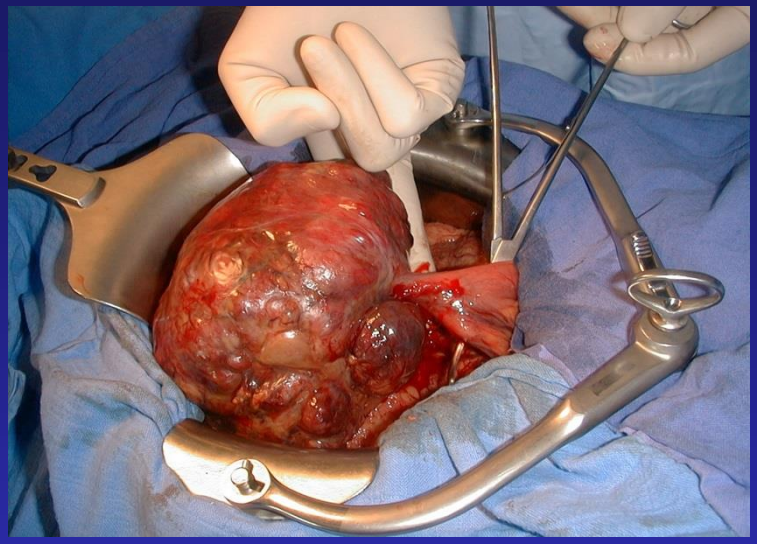
INI1 loss:
Rhabdoid tumors
TSG loss, NF1, TSC1-2:
MPNST, PEComas

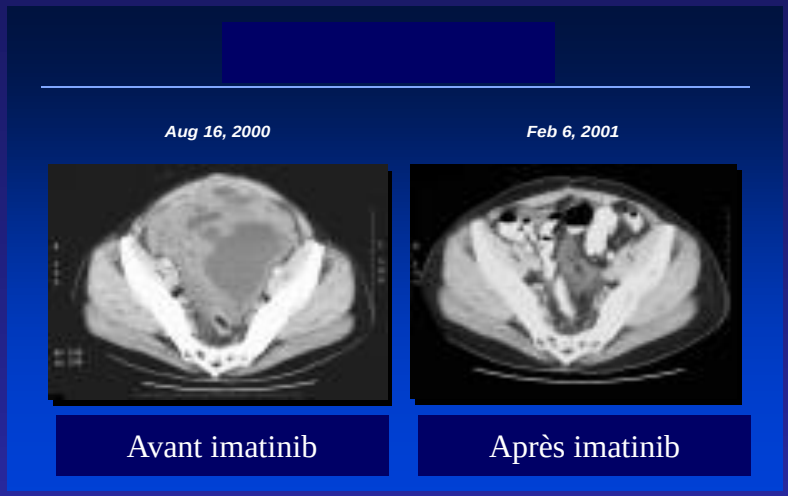


Complex gene alteration: LMS, UPS

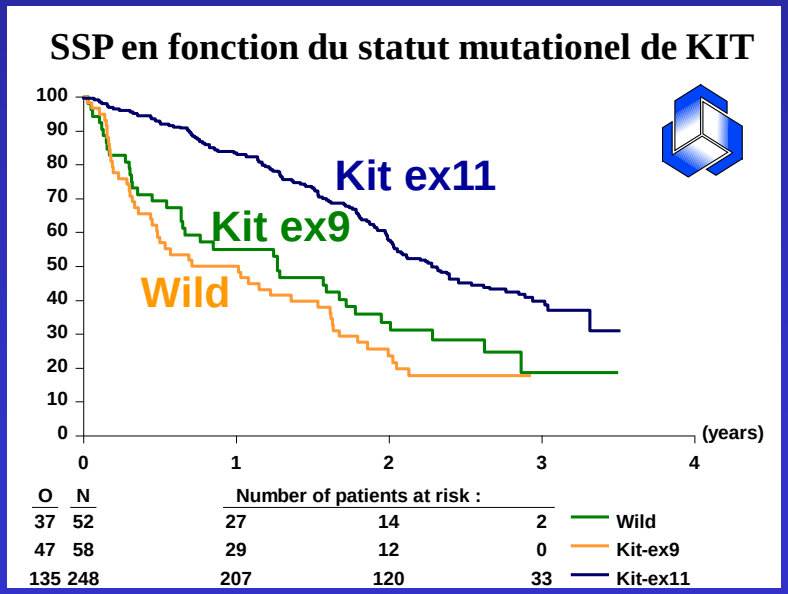
Gene mutation: GIST/desmoids

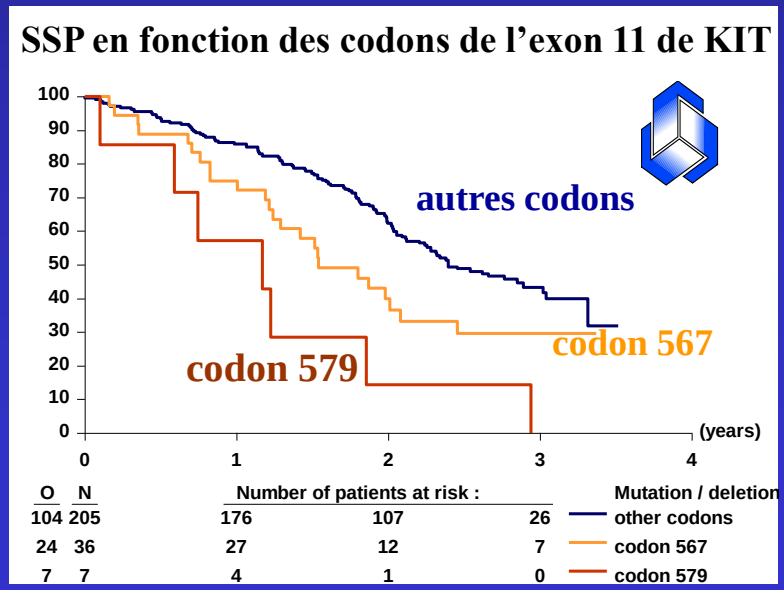
GIST: from phenotype to genotype
from 2000 to 2015





Demetri et al, NEJM 2002

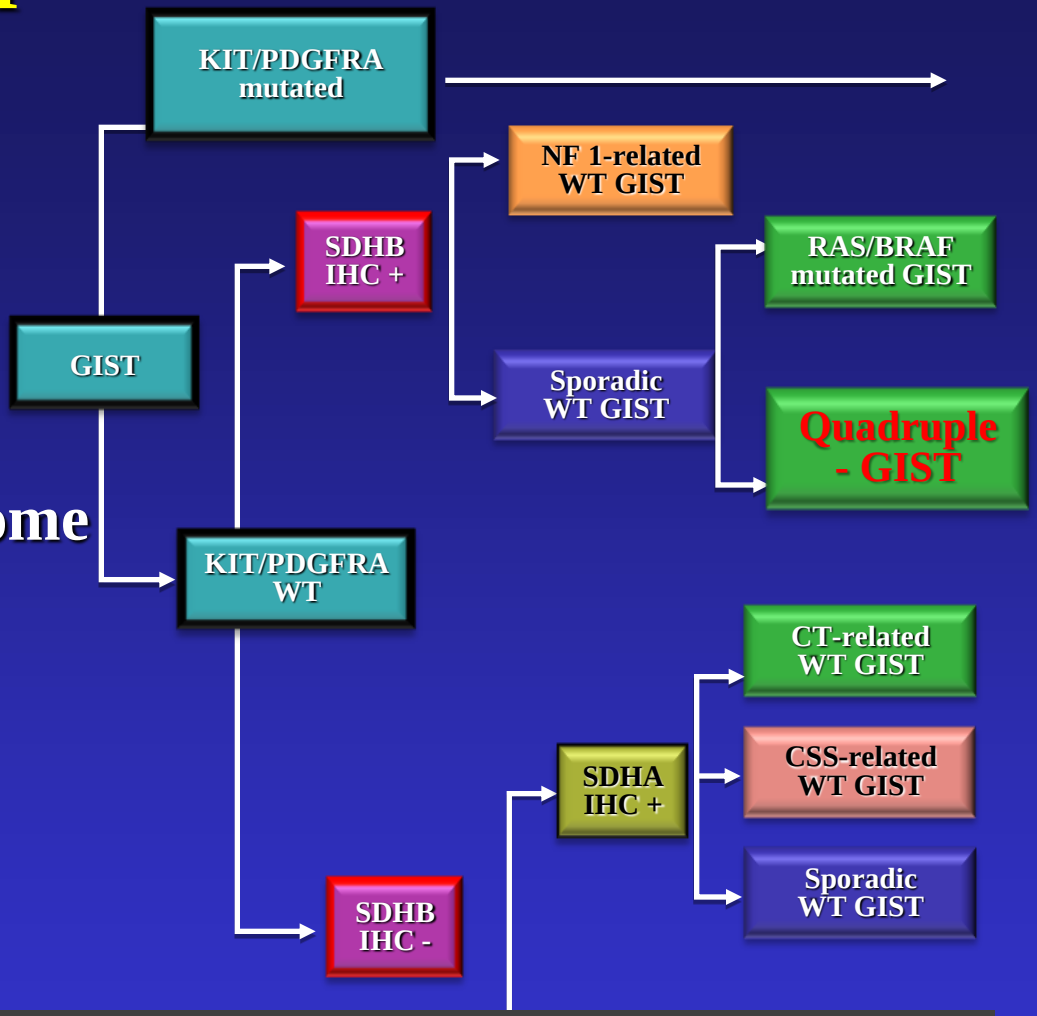




Maria Debiec-Rychter et al, EJC 2007

Wild-Type GIST

- **SDH Deficient GIST**
  - Paediatric GIST
  - Carney Triad:
    - "Leiomyosarcoma"/GIST
    - Pulmonary chondroma
    - Paraganglioma
  - Carney-Stratakis Syndrome
    - GIST
    - Paraganglioma
- **NF-1**
- **Non-Syndromic WT GIST**



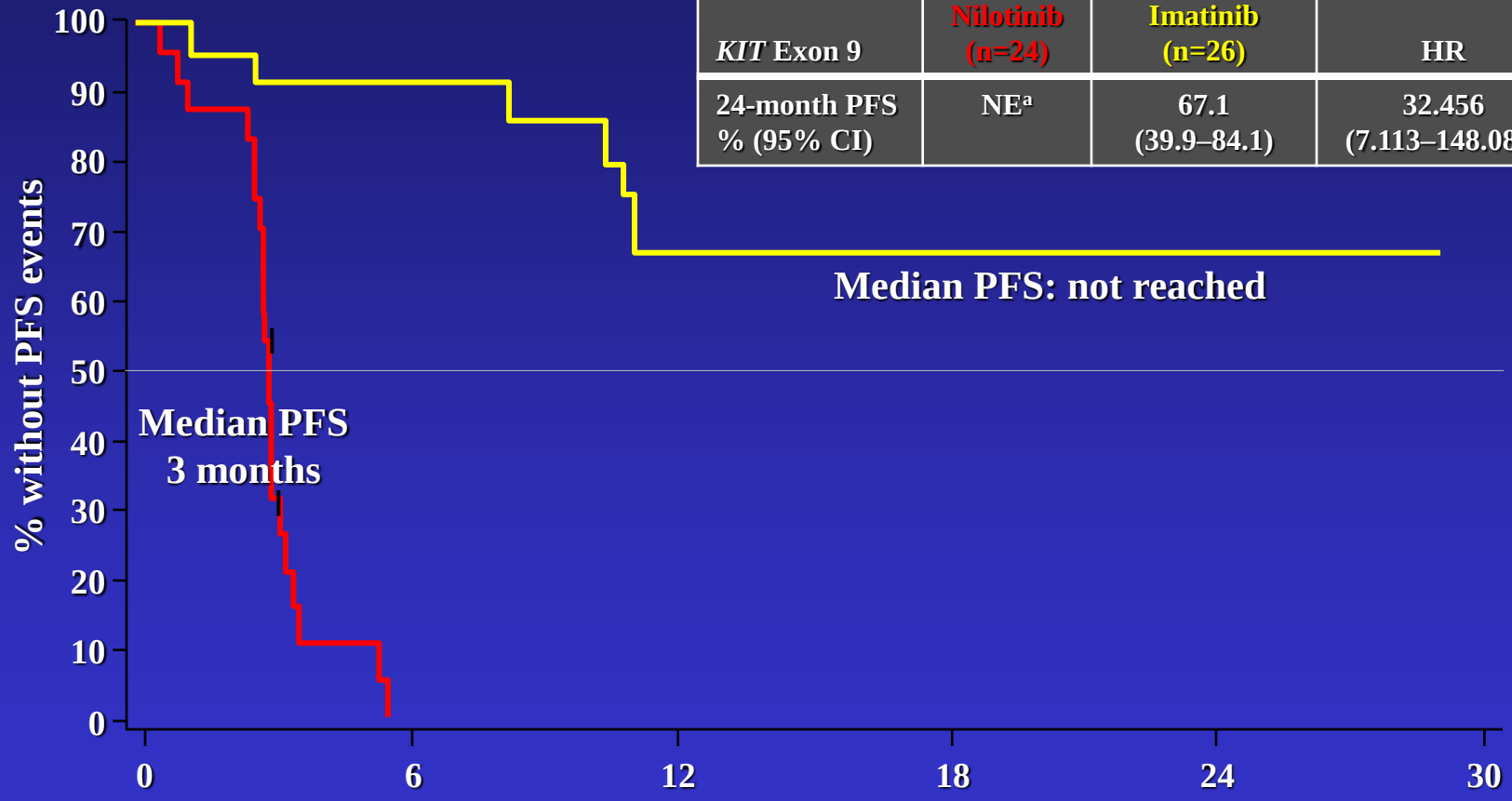
Identification of 14 HR GISTs with a D842V mutation (20% of gastric GIST) has represented a potential saving of > 1 million euros (3 yrs of imatinib)

Cost of molecular tests for STS in France: 800,000 euros/yr

Agnès Neuville et al, Am J Surg Pathol 2013; 37: 1259-68

ENESTg1 - PFS by Mutation Type: *KIT* Exon 9 Mutant

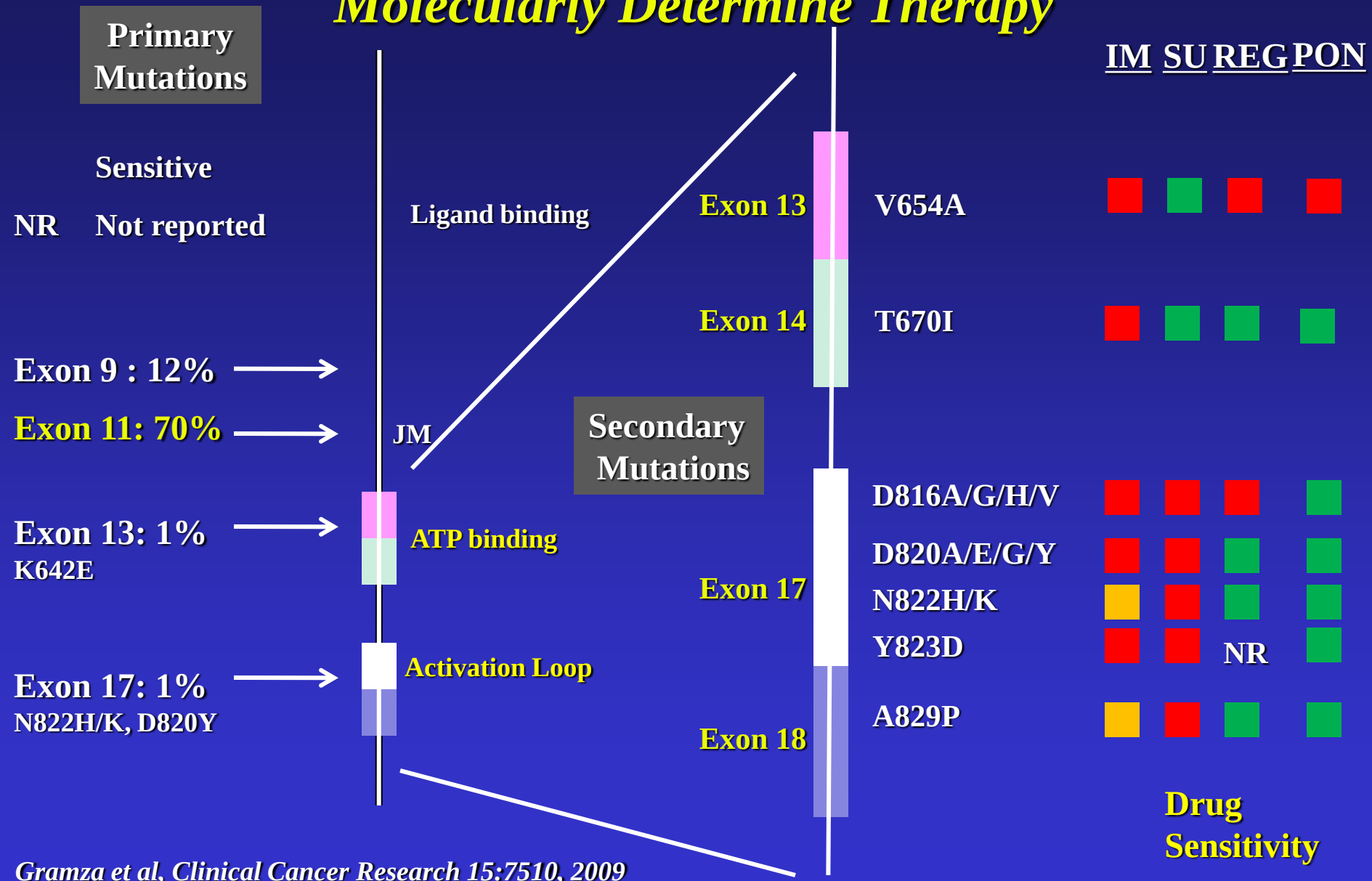
KIT Exon 9	Nilotinib (n=24)	Imatinib (n=26)	HR
24-month PFS % (95% CI)	NE[a]	67.1 (39.9–84.1)	32.456 (7.113–148.088)



JY Blay et al, Lancet Oncol, 2014

Future of GIST

Molecularly Determine Therapy

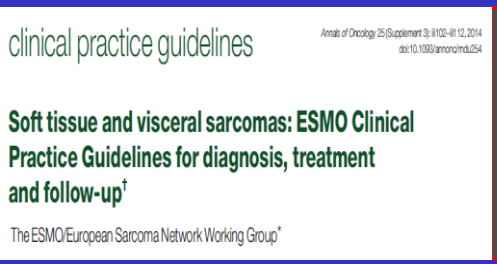


Gramza et al, Clinical Cancer Research 15:7510, 2009
Heinrich et al, ASCO 2013 Poster/Abstract 10509

Advanced STS/mesenchymal tumors

Targeted therapies: proof of concept

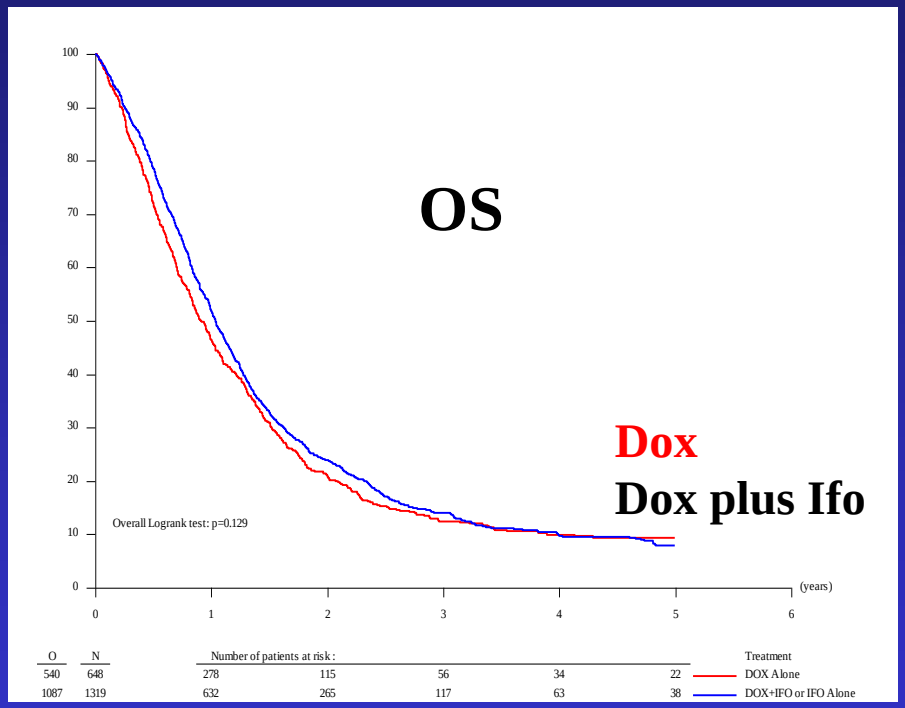
Histology	Targets	Agents
GIST	KIT/PDGFR	Imatinib
DermatoFSP	t(17-22) PDFGR	Imatinib
PECOMAS	mTor/TSC1,2	Rapamycin inhibitors
Giant Cell Tumor	Rank/RankL	Denosumab
Pigmentitis VNS	t(1-2) CSF1	Anti-CSF1
Inflam. Myofi. T.	ALK alteration	Crizotinib
Alveolar STS	VEGFR? Others?	Anti-VEGFR agents



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 .

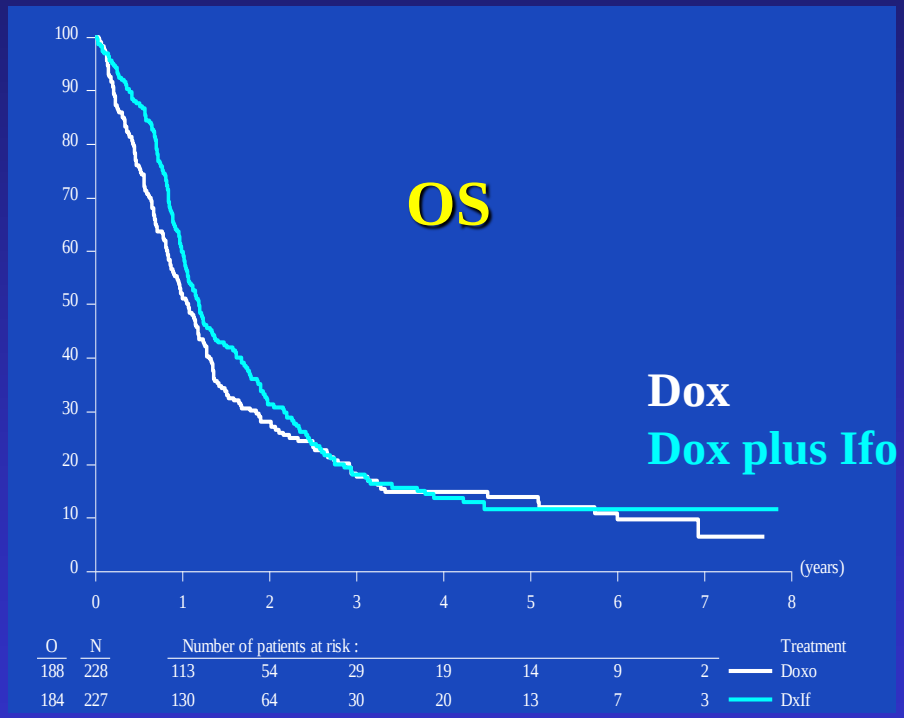
STS – advanced CT
Prehistorical era of STS

EORTC Database (1980-2000)



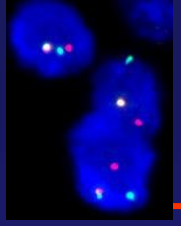
S. Sleijfer et al, 20th century

EORTC 62012 (2000-15)



Judson et al, 21st century

Without molecular biology, same results and curves in 22nd century…



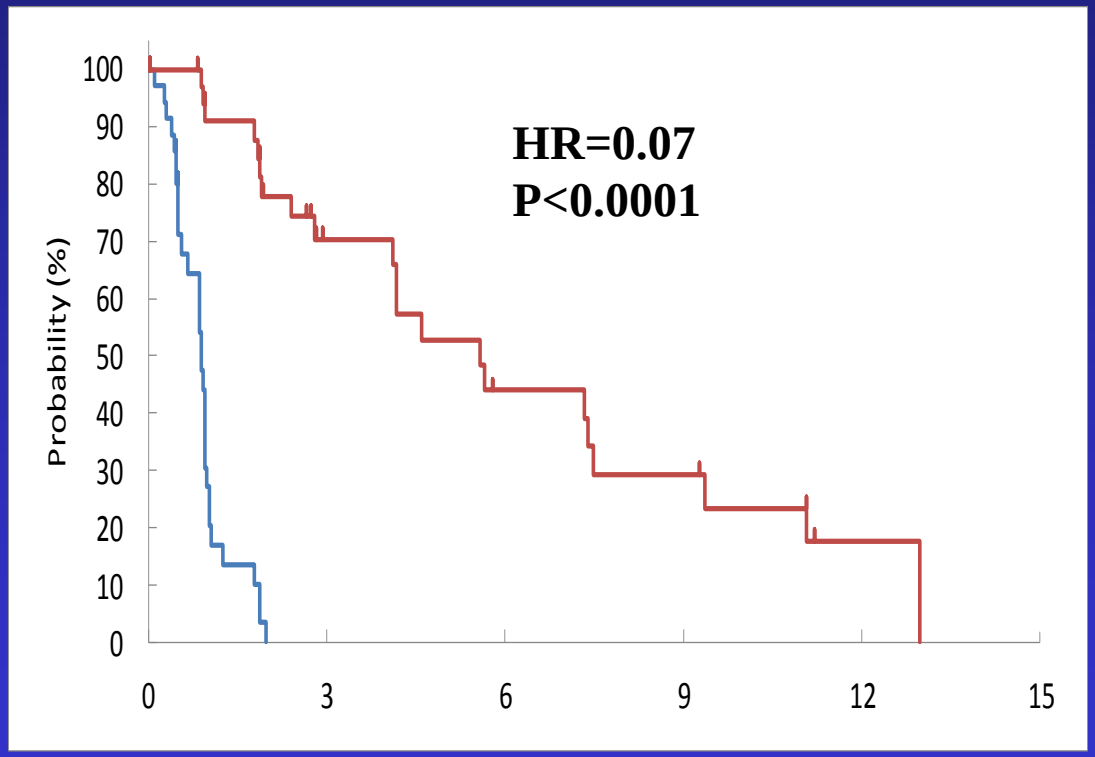
Sarcoma with “translocation” (20%)

Molecular diagnosis with FISH

Sarcoma type	Chromosomal transl.	Fusion gene
Ewing’s sarcoma	t(11;22)(q24;q12)	*EWS-FLI1*
	t(21;22)(q22;q12)	*EWS-ERG*
Clear cell sarcoma	t(12;22)(q13;q12)	*EWS-ATF1*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWS-WT1*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*EWS-CHN*
Myxoid liposarcoma	t(12;16)(q13;p11)	*TLS-CHOP*
	t(12;22)(q13;q12)	*EWS-CHOP*
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	*TLS-ATF1*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FKHR*
	t(1;13)(p36;q14)	*PAX7-FKHR*
Synovial sarcoma	t(X;18)(p11;q11)	*SYT-SSX1,2*
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	*COL1A1-PDGFB*
Congenital fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Inflammatory myofibroblastic tumor	t(2p23)	Various *ALK* fusions
Alveolar soft part sarcoma	t(X;17)(p11;q25)	*ASPL-TFE3*
Endometrial stromal sarcoma	t(7;17)(p15;q21)	*JAZF1-JJAZ1*
PVNS	t(1,2)	*COL6A3 et CSF1*

Impact of molecular biology in trial design

Randomized phase II study comparing trabectedin and BSC in pretreated translocation-related sarcomas



Kawai et al. Lancet Oncol 2015

T: 1.2 mg/m2

N subjects: 74

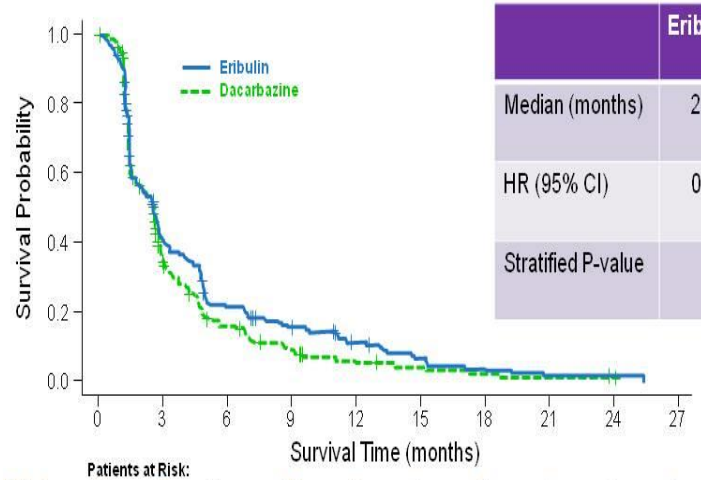
Significant difference in PFS
5.8 vs 0.9 months

And in OS
Not reached vs 8 months (p=0.025)

Impact of no molecular biology in trial design

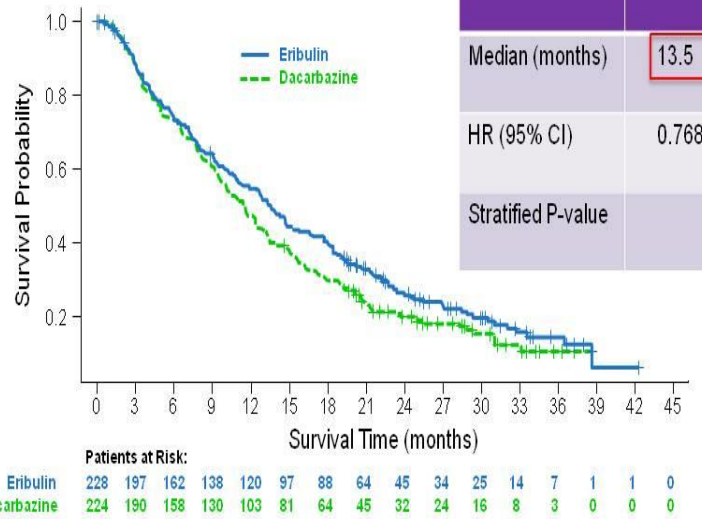
Eribuline vs dacarbazine in Lipo/leio-STS: A Phase III study (SAR 3007)

Secondary endpoint: PFS



	Eribulin	Dacarbazine
Median (months)	2.6	2.6
HR (95% CI)	0.877 (0.710, 1.085)	
Stratified P-value	0.2287	

Primary endpoint: OS



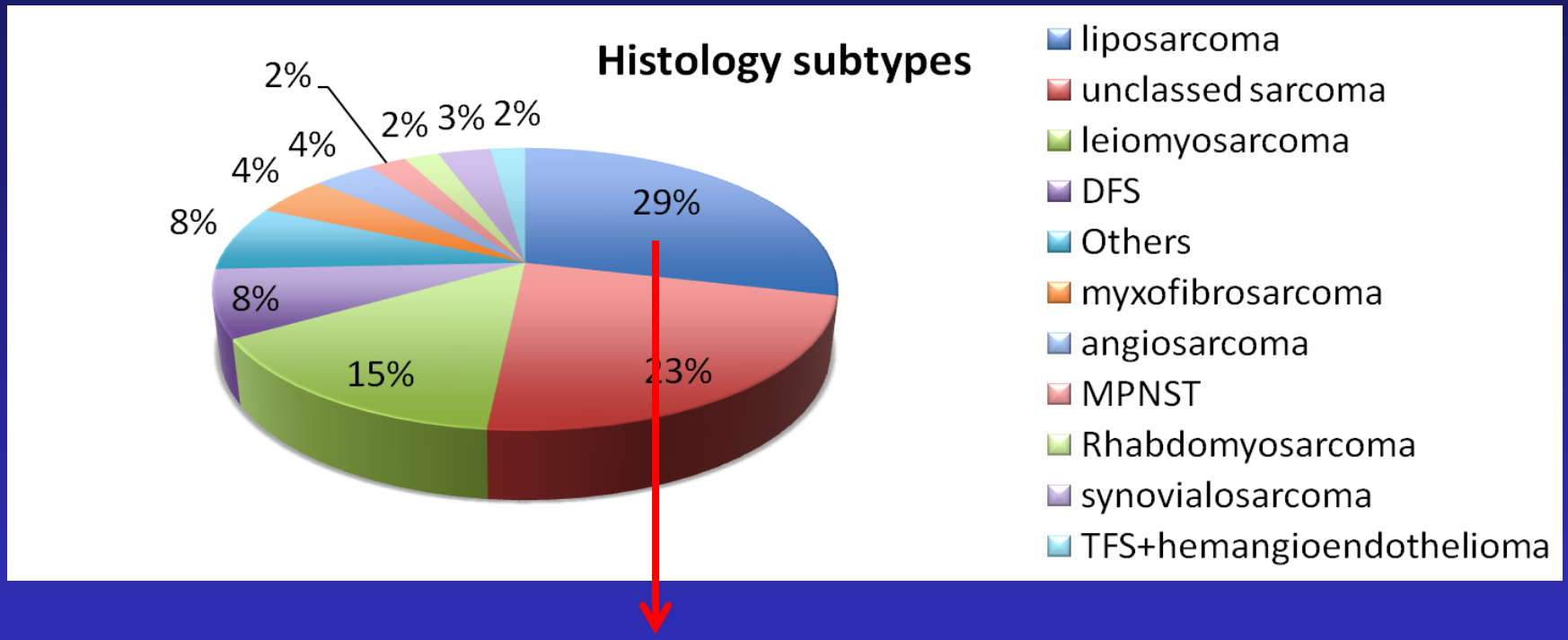
	Eribulin	Dacarbazine
Median (months)	13.5	11.5
HR (95% CI)	0.768 (0.618, 0.954)	
Stratified P-value	0.0169	

- The primary endpoint of OS was met, indicating a 2-month improvement in median OS with eribulin

CI, confidence interval

P. Schoffski et al. Lancet Oncology 2015 (accepted)

Molecular diagnosis of liposarcoma: mandatory!



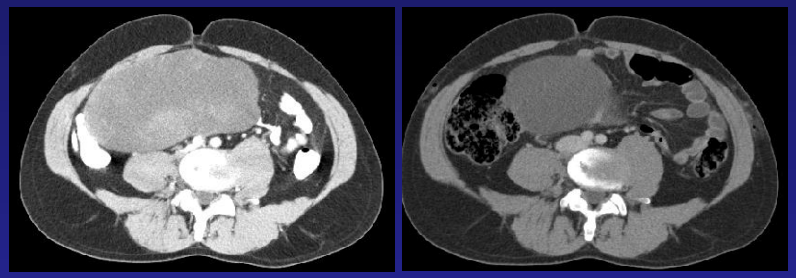
- **Specific translocations generating fusion genes (Myx LPS) 15%**
- **Amplifications chromosome 12 (MDM2+CDK4) 75-80%**
- **Complex genetic alterations (Pleo LPS, ...) 5-10%**

Ducimetière F et al. PLoS One 2011; 6: e20294.

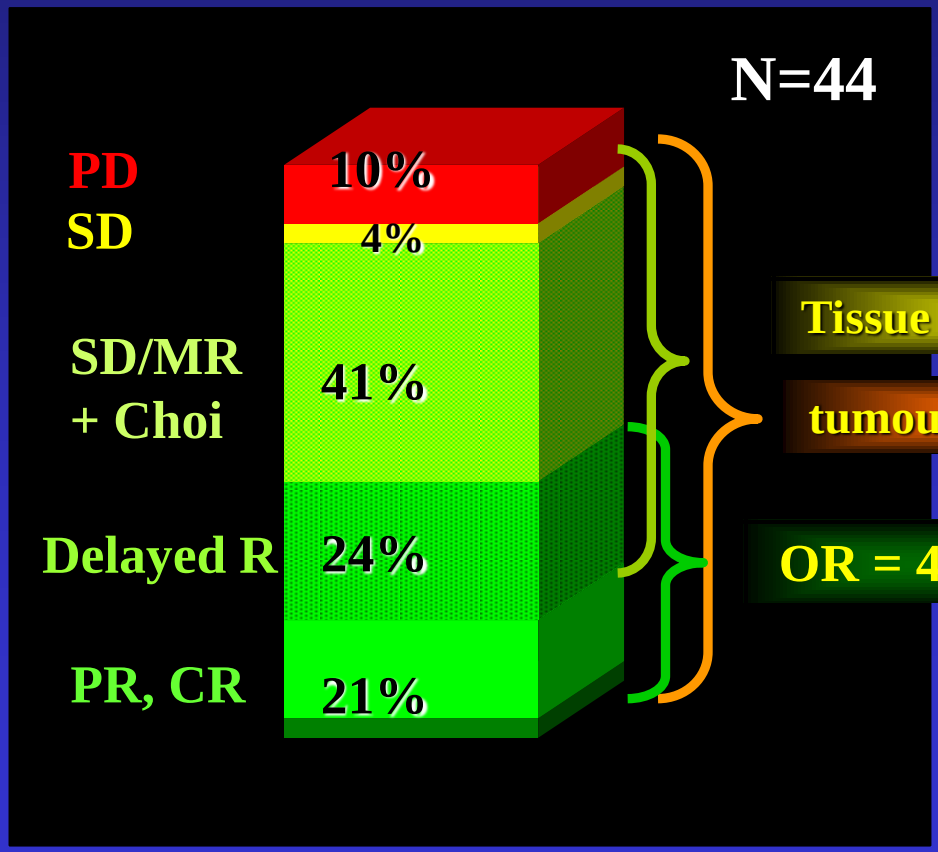
t(12;16)(q13;p11) MLPS

Trabectedin: The first targeted therapy in STS?

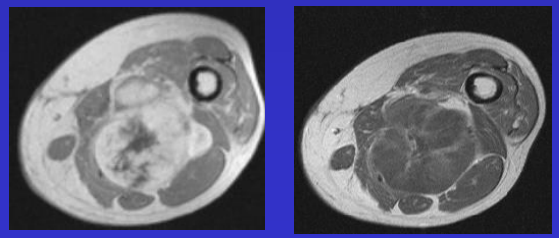
- Soft tissue 16 (43%)
- Abdominal cavity 14 (38%)
- Lung/pleura 11 (30%)
- Heart/pericardium/med 10 (27%)



Prior CT (Dox/ifo): 98%
Median courses: 9 (1-43)

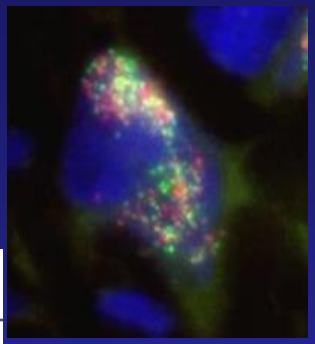


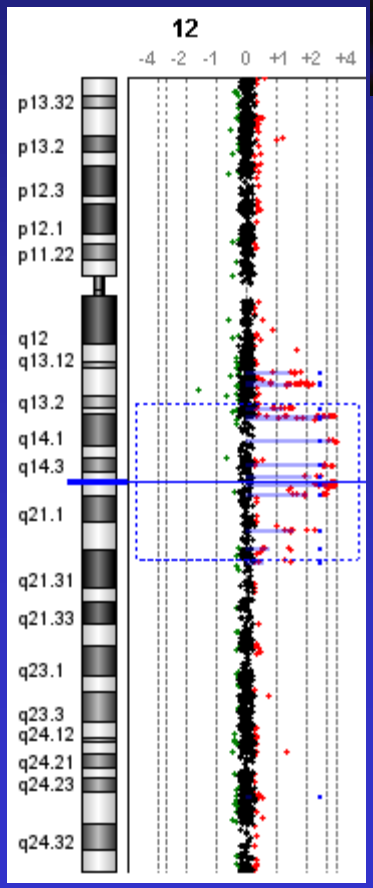
F. Grosso et al., Lancet Oncology, 2007

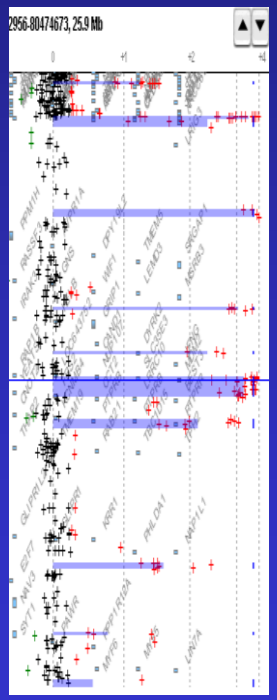


A. Gronchi et al, Annals of Oncol 2011

Adipocytic tumor: lipoma or liposarcoma?

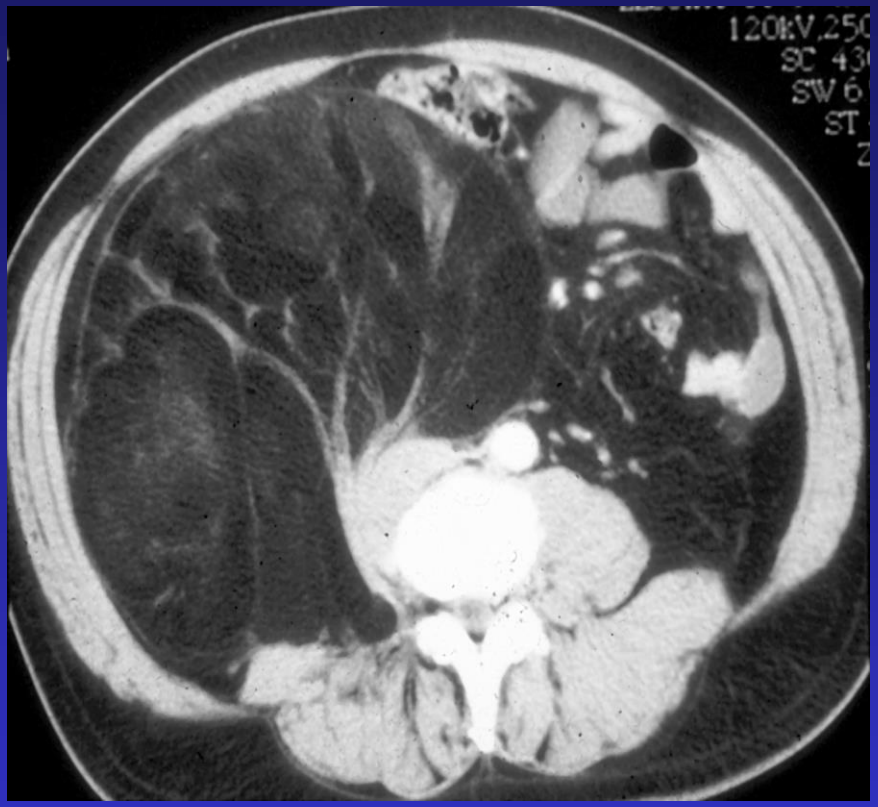






← CDK4

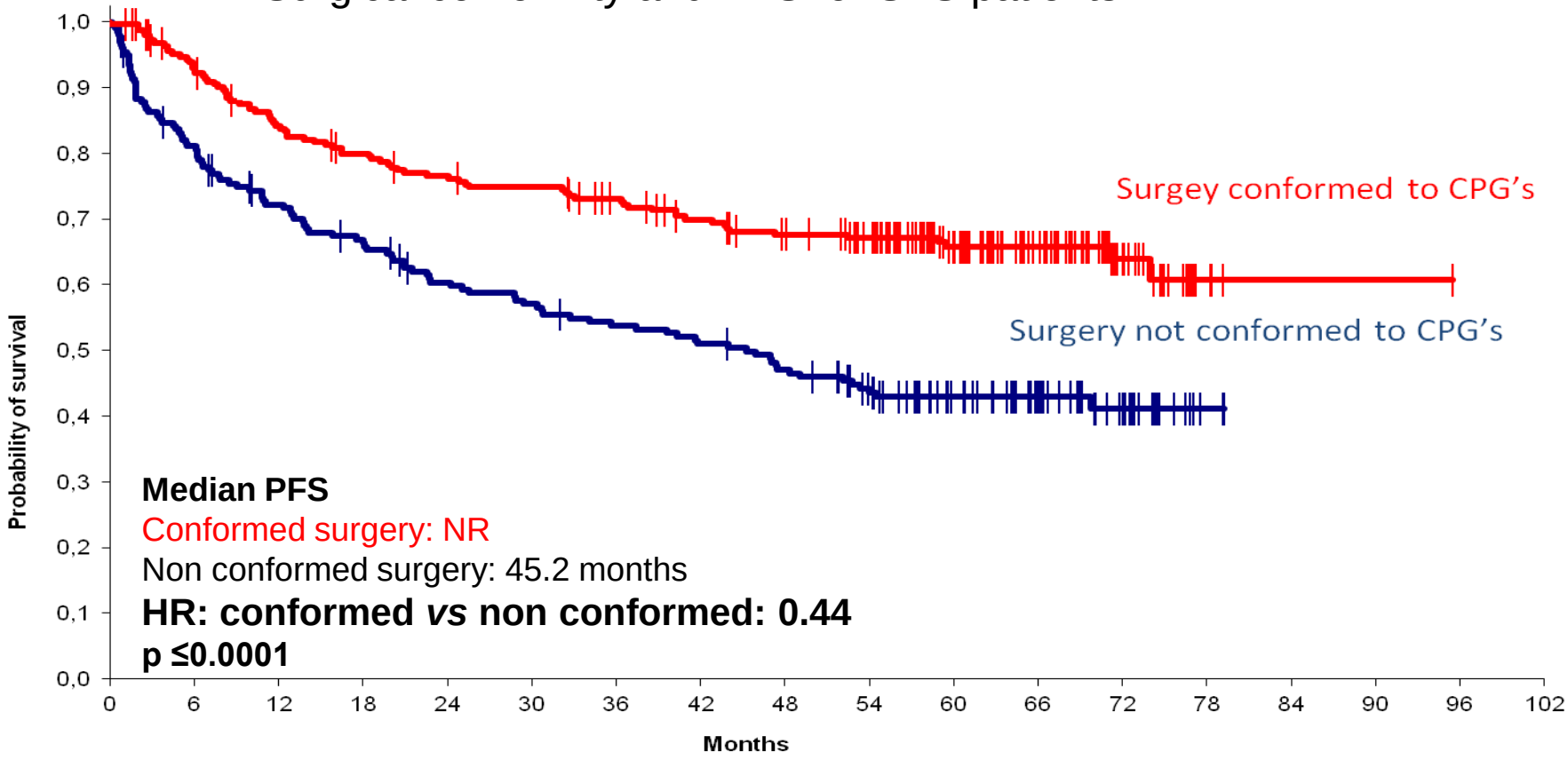
←MDM2



Major impact on surgery!!!

R1/R2 in lipoma ≠ R1/R2 in LPS!

PFS and surgical conformity for STS patients



Derbel et al, ESMO 2012 (submitted)

Future of sarcoma?

Which tumor, which target, which agent, which trial?

EORTC
European Organisation for Research and Treatment of Cancer

EORTC
Avenue E. Mounierlaan 83 / 11
Brussel 1200 Bruxelles
België - Belgique
Tel : +32 2 774 16 11
Fax : +32 2 772 35 45
E-mail : eortc@eortc.be
Web : http://www.eortc.be

EORTC Network of Core Institutions (NOCI)

Cross-tumoral phase 2 clinical trial exploring crizotinib (PF-02341066) in patients with advanced tumors induced by causal alterations of ALK and/or MET ("CREATE")

EORTC protocol 90101

(EudraCT number 2011-001988-52)
(NCT01524926)

Study Coordinator: Patrick Schöffski
Phone: +32 16 346900
Fax: +32 16 346901
E-mail: patrick.schoffski@uzleuven.be

Anaplastic large cell lymphoma (ALCL),
Inflammatory myofibroblastic tumor (IMFT)
Papillary renal cell carcinoma type (PRCC)
Alveolar soft part sarcoma (ASPS)
Clear cell sarcoma (CSC)
alveolar rhabdomyosarcoma (ARMS)

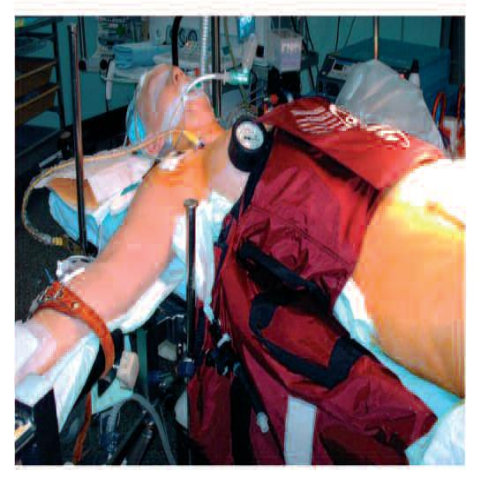
Non selected localized resectable STS

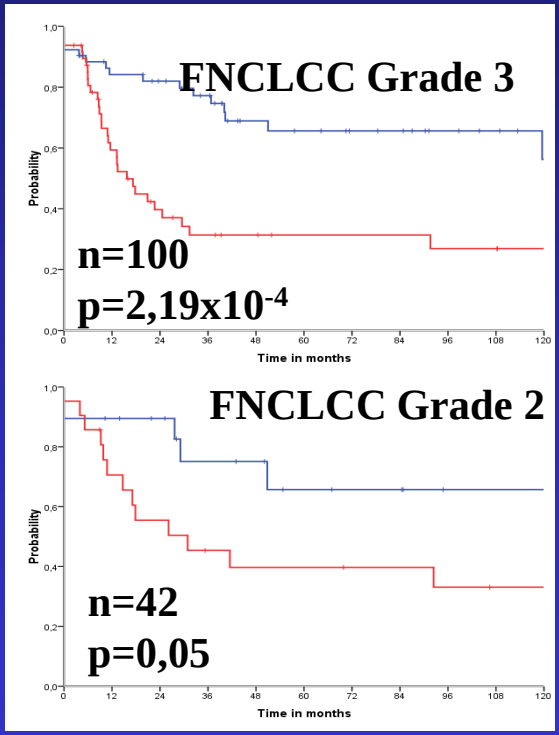
Conventional CT with « molecular signature »:

Induction conventional CT
AI regimen

67 genes: Cinsarc signature

Chibon et al, Nat Med 2010





Impact on metastases ?

Impact on metastases ?

Systemic treatment in STS 2000-2015

- Before 2000:
  - All sarcoma
    - Doxorubicin
    - Ifosfamide
    - DTIC?

- After 2000 (beside Dox/IFO/DTIC)
  - GIST: Imatinib, sunitinib, regorafenib
  - All: trabectedine, Gem+/-Tax
  - All but LPS: pazopanib
  - Myxoid LPS: trabectedin
  - LMS: PZB, trabectedin, Gem+/-Tax/DTIC
  - EWS: A,I,C,V,Ac, TopoI, IGF1R
  - A/E RMS: Topo inhibitors
  - ESS: Aromatase inhibitors
  - Pecomas: mTor inhibitots
  - SFT: sunitinib
  - AngioS: Paclitaxel, Gemcitabine
  - ASTS: anti-VEGFR
  - DFSP: Imatinib
  - PVNS: Imatinib, nilotinib, anti-CSF1
  - Desmoids: Imatinib, anti-VEGFR
  - Alveolar STS: VEGFR inhibitors
  - IMT: crizotinib

Currently, molecular characterization should now be the determinant of modern cancer treatment in sarcoma

Advantages of molecular tests:

1) A positive molecular test allows a reproducible and definitive diagnosis with the use of core-needle biopsy
2) Specific genomic abnormalities are becoming increasingly useful for treatment, and it will be mandatory for the selection of patients for the targeted agent directed against the mutated activated targets.
3) A positive result could be used as a medico-legal criterion by insurance companies
4) This strategy will help save money by a better selection of patients for appropriate treatment
5) This strategy gives the opportunity for pathologists to improve their histologic skills, much as IHC did 30 years ago

From the FSG: Agnès Neuville et al, Am J Surg Pathol 2013

Thank you!!!

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