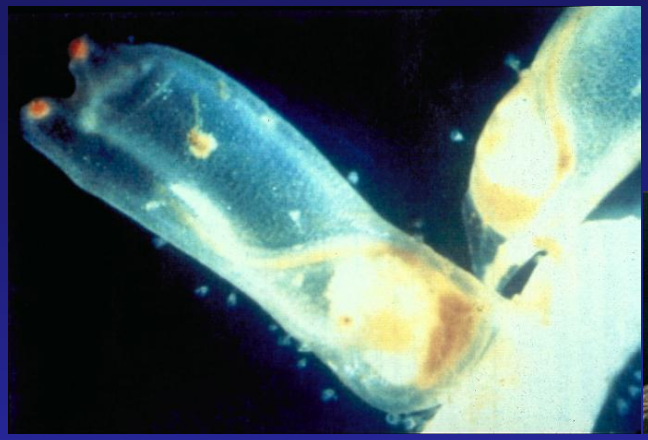
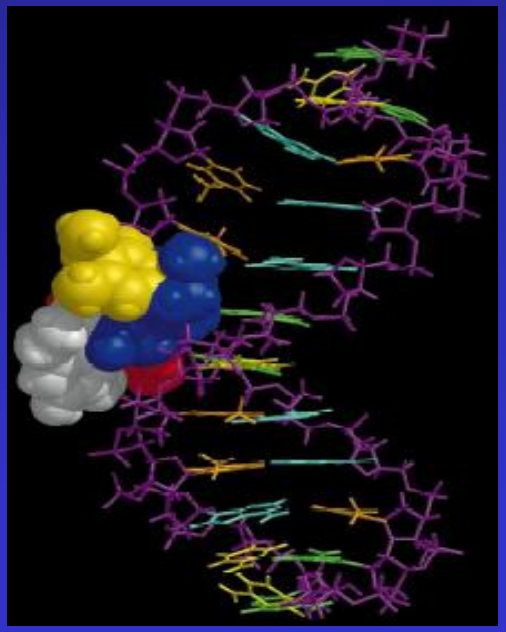
Place de la trabectedine (Yondelis®) dans la prise en charge des STM métastatiques

Mandelieu, SFPO, 16 oct 09

Trabectédine – Méchanismes d'action



Taxonomie: ***Ecteinascidia Turbinata***
Source: Caribbean Sea



- **Se fixe au petit sillon de l'ADN**
- **Interagit avec des facteurs de trancription de l'ADN**
- **Perturbe le cycle cellulaire: retarde S et bloque G2**
- **Activité indépendante de p-53**
- **interfère avec les mécanismes de réparation cellulaire (NER compétent pour son activité)**

Trabectedin: Phase II trials in STS

1.5 mg/m2 24 hours CI

STS 2d LINE
AFTER ≥1 PRIOR CT

195 PTS ENTERED

6 no treated

189 PTS TREATED

ET-743
1.5 mg/m^2 q3w (24h ci)

6 excluded (4 GIST, 2 ES)

183 PTS EVALUATED

ET-B-005-98 (EORTC)

ET-B-008-98 (FRANCE)

ET-B-017-99 (USA)

Trabectedin Activity: Phase II trials in STS

Phase II

Response	N=189	(%)	Median reduction	PFS med
CR	1	0.5%	100%	
PR	13	7%	67%	7 months
MR	11	6%	35%	7 months
SD	75	40%		
SD >6 months	32	17%		8 months
CR post surgery	7	4%		

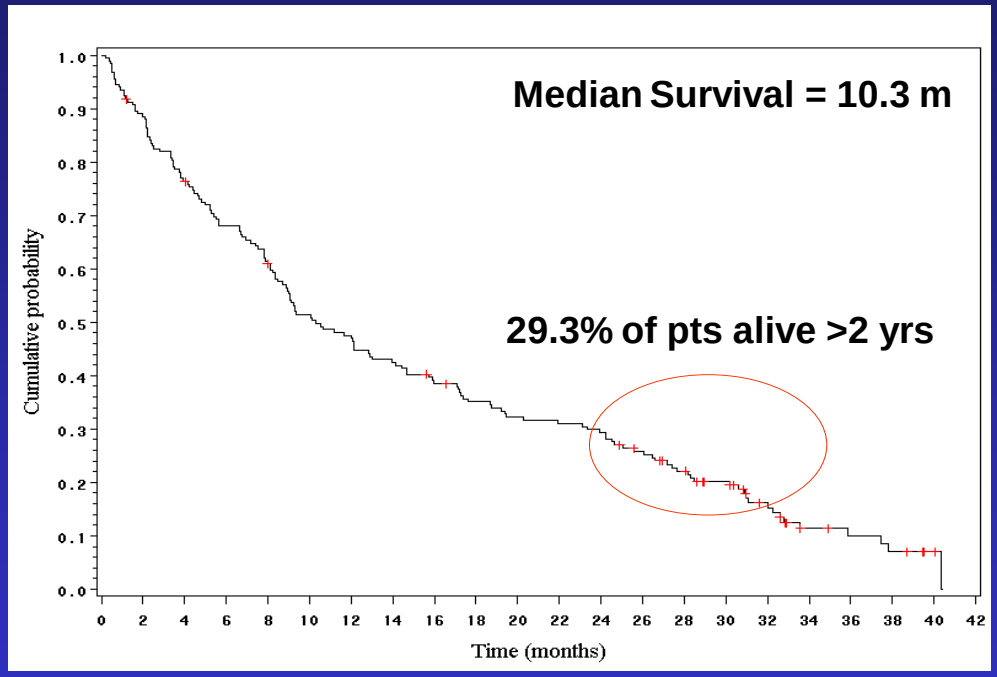
Clinical Benefiy / Tumor Control: PR+MR+SD 51.5%

Pooled Data A.Le Cesne et al JCO-05, A.Yovine et al JCO-04, R.G.Carbonero et al JCO-04 J.Jimeno et al Current.Op. Orthop 2003

Trabectedin, phase II

Promising survival outcome

...Despite an ORR < 10%…




VOLUME 22 · NUMBER 8 · APRIL 15 2004

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II and Pharmacokinetic Study of Ecteinascidin 743 in Patients With Progressive Sarcomas of Soft Tissues Refractory to Chemotherapy

R. Garcia-Carbonero, J.G. Supko, J. Manola, M.V. Seiden, D. Harmon, D.P. Ryan, M.T. Quigley, P. Merriam, J. Carvajal, G. Goss, U. Matulonis, R.G. Maki, T. Lopez, T.A. Puchalski, M.A. Sancho, J. Gomez, C. Guzman, J. Jimeno, and G.D. Demetri

VOLUME 23 · NUMBER 3 · JANUARY 20 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Study of ET-743 in Advanced Soft Tissue Sarcomas: A European Organisation for the Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group Trial

A. Le Cesne, J.Y. Blay, J. Judson, A. Van Oosterom, J. Verweij, J. Radford, P. Lorigan, S. Rodriguez, J. Ray-Coquard, S. Bonvalot, F. Collin, J. Forsyth, E. De Paoli, M. Van Glabbeke, and O.S. Nielsen

ABSTRACT

Purpose
This noncandomized multicenter phase II study was performed to evaluate the activity and safety of Ecteinascidin (ET-743) administered at a dose of 1.5 mg/m² as a 24-hour continuous infusion every 3 weeks in patients with pretreated advanced soft tissue sarcoma.

Patients and Methods
Patients with documentated progressive advanced soft tissue sarcoma received ET-743 as second- or third-line chemotherapy. Antitumor activity was evaluated every 6 weeks until progression, excessive toxicity, or patient refusal.

Results
One hundred four patients from eight European institutions were included in the study (March 1999 to November 2000). A total of 410 cycles were administered in 99 assessable patients. Toxicity mainly involved reversible grade 3 to 4 asymptomatic elevation of transaminases in 40% of patients, and grade 3 to 4 neutropenia was observed in 52% of patients. There were eight partial responses (PR; objective regression rate, 8%), 45 no change (NC; > 6 months in 26% of patients), and 39 progressive disease. A progression arrest rate (PR + NC) of 56% was observed in leiomyosarcoma and 61% in synovialosarcoma. The median duration of the time to progression was 105 days, and the 6-month progression-free survival was 29%. The median duration of survival was 9.2 months.

Conclusion
ET-743 seems to be a promising active agent in advanced soft tissue sarcoma, with no cumulative toxicities. The 6-months progression-free survival observed in advanced soft tissue sarcoma compares favorably with those obtained with other active drugs tested in second-line chemotherapy in previous European Organisation for the Research and Treatment of Cancer trials. The median overall survival was unusually long in these heavily pretreated patients mainly due to the high number of patients who benefit from the drug in terms of tumor control.

J Clin Oncol 23:576-584. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Results of first-line chemotherapy in adult advanced soft tissue sarcoma remain disappointing. Only two drugs, doxorubicin and ifosfamide, have demonstrated a relatively consistent single-agent activity yielding response rates of 10% to 25%.[1-4] Importantly, despite higher response rates achieved in some studies using combination chemotherapy, multidrug regimens have not demonstrated any advantage in terms of overall survival when compared with single-agent doxorubicin given at optimal doses.[1] In the

6-months PFS	**25%**
Pts alive at 1 year	**45%**
> 6 cycles	**28%**

STS-201

VOLUME 23 · NUMBER 3 · JANUARY 20 2005
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Study of ET-743 in Advanced Soft Tissue Sarcomas: A European Organisation for the Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group Trial

A. Le Cesne, J.Y. Blay, I. Judson, A. Van Oosterom, J. Verweij, J. Radford, P. Lorigan, S. Rodenhuis, I. Ray-Coquard, S. Bonvalot, F. Collin, J. Jimeno, E. Di Paola, M. Van Glabbeke, and O.S. Nielsen

Major impact (tumor control, 6-PFS) in:

- **Leiomyosarcoma 56%**
- **Liposarcoma 40%**

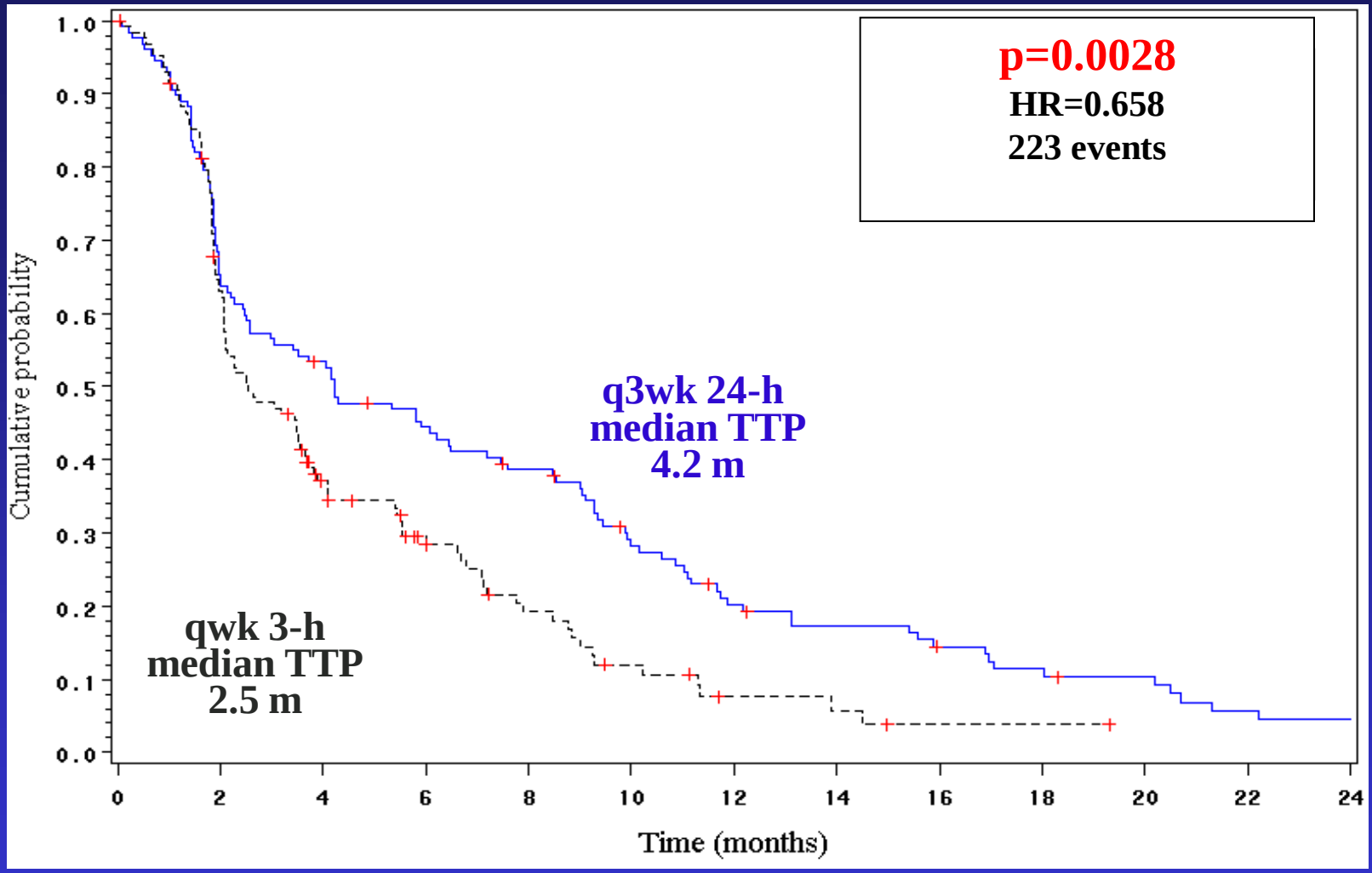
Advanced LipoS/LeioS ®

→ **Trabectedin: 1.5 mg/m2 24 h CI q3w**

→ **Trabectedin: 0.58 mg/m2 3h wkly 3wks/4**

- 270 patients randomized (260 treated)
- Baseline characteristics well balanced between both arms
- 66% leiomyosarcomas / 34% liposarcomas
- Prior chemotherapy: PD after anthracyclines and ifosfamide
  2/3 of pts received additional agents (Gem, 32%; docetaxel, 24%....)

STS-201: Updated TTP

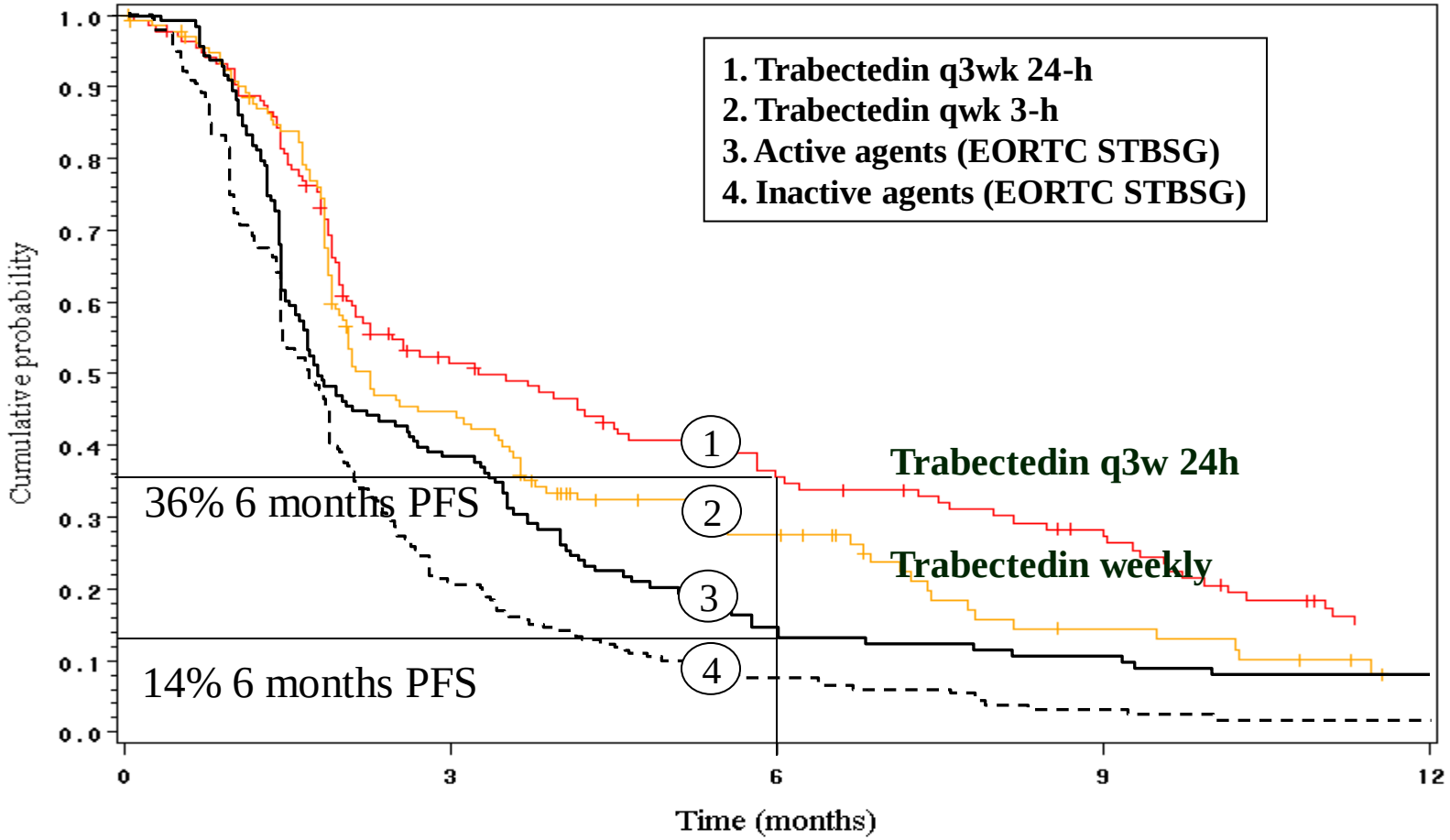


"Final survival data reinforce the internal consistency of efficacy endpoints showing better outcomes with trabectedin q3wk 24-h"

George D. Demetri et al, abstract 10509, ASCO 09

STS-201-Historical Context (EORTC)

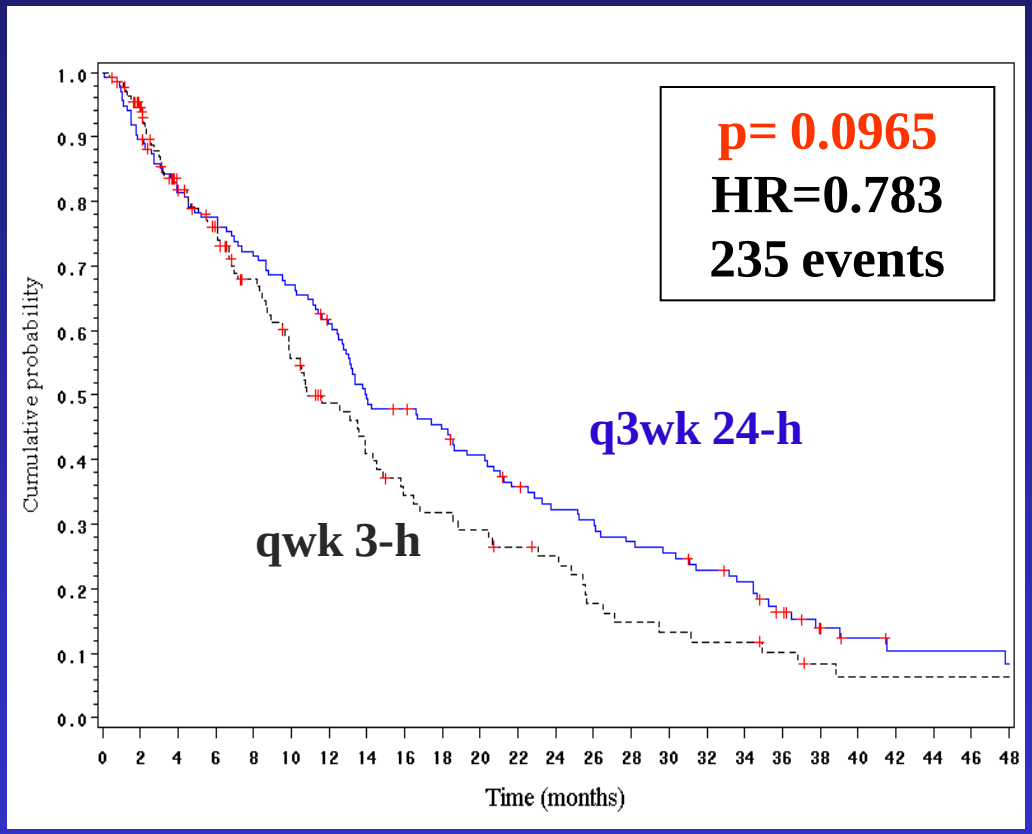
PFS in Sarcomas



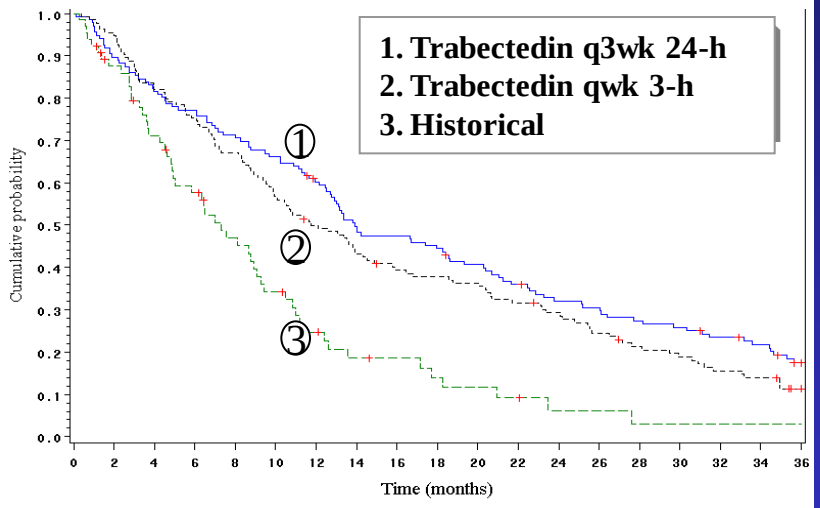
EMEA approval in september 07

STS-201 Overall survival

Censored at crossover



STS-201 *vs.* pooled EORTC trials in pretreated leiomyosarcoma/liposarcoma*



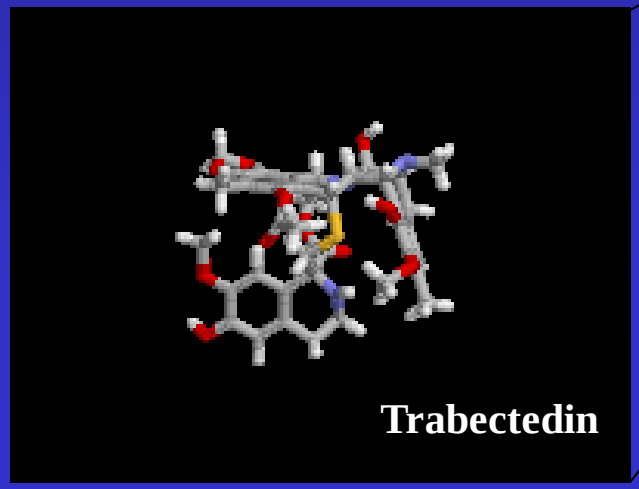
Acknowledging the limitations of historical comparisons, both trabectedin schedules showed substantially longer OS than other drugs in a similar setting

1-year survival:
61% *vs.* 49%, p=0.06

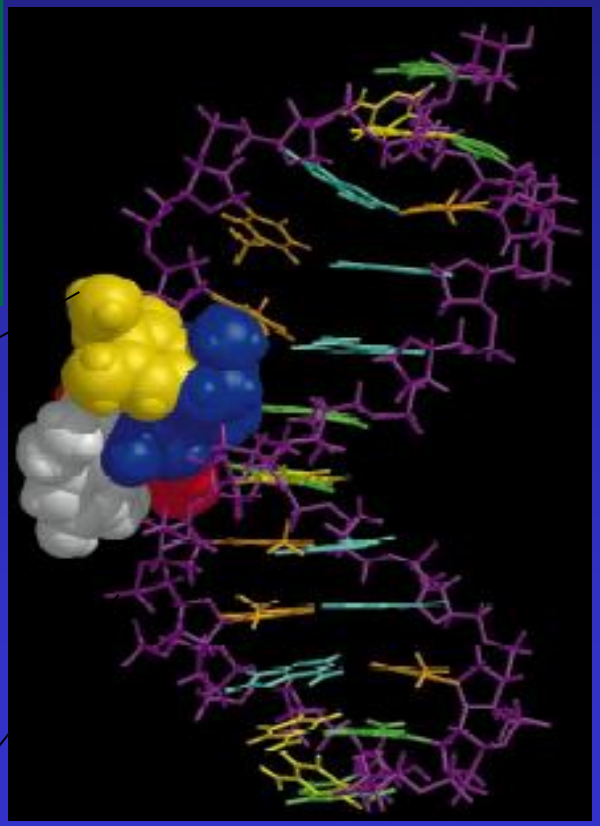
Yondelis® (trabectedin): European Label

A New Treatment Option for Sarcoma Patients Following European Commission approval on 20th September2007:

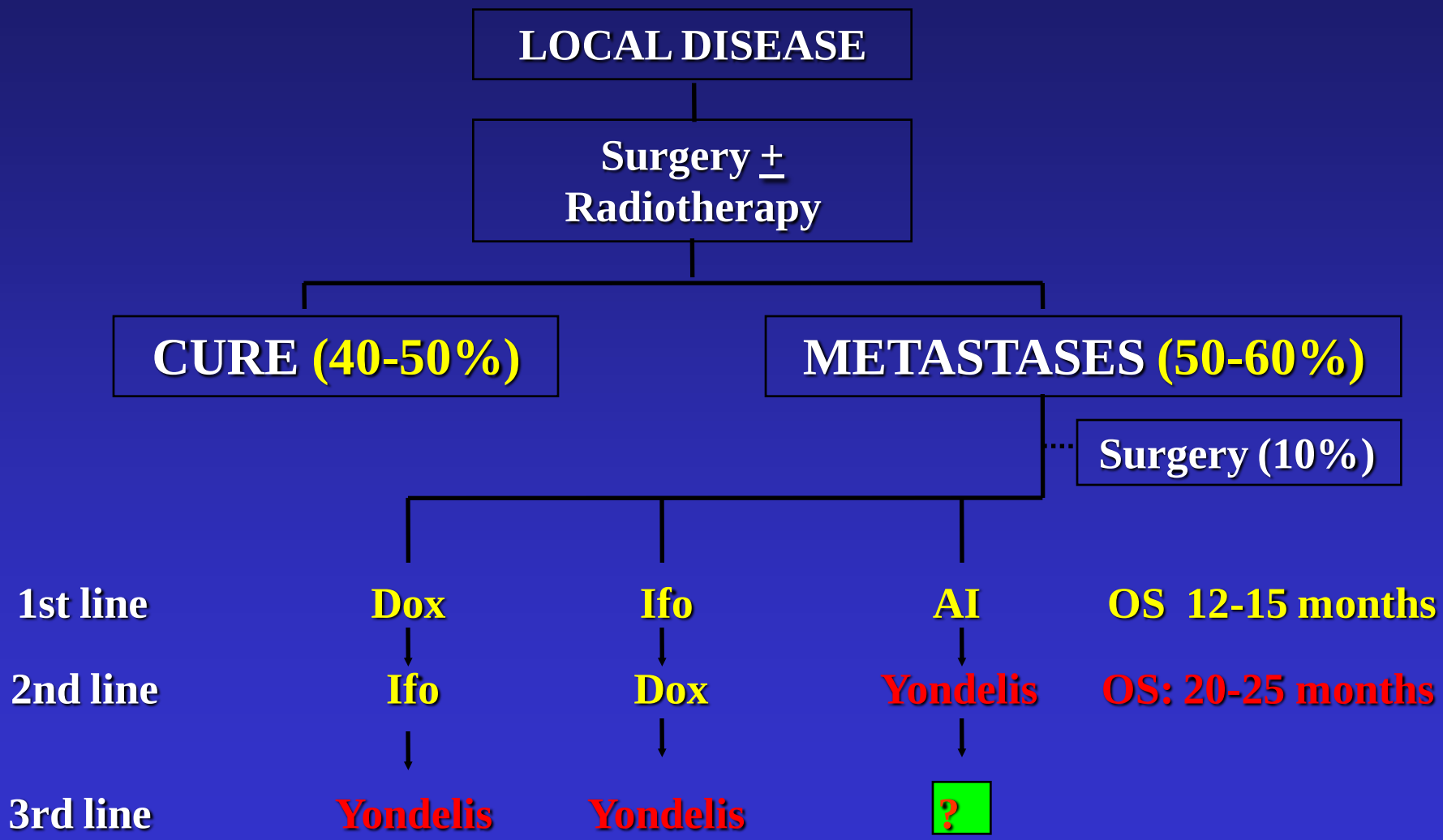
Yondelis® is indicated for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide or who are unsuitable to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.



Trabectedin



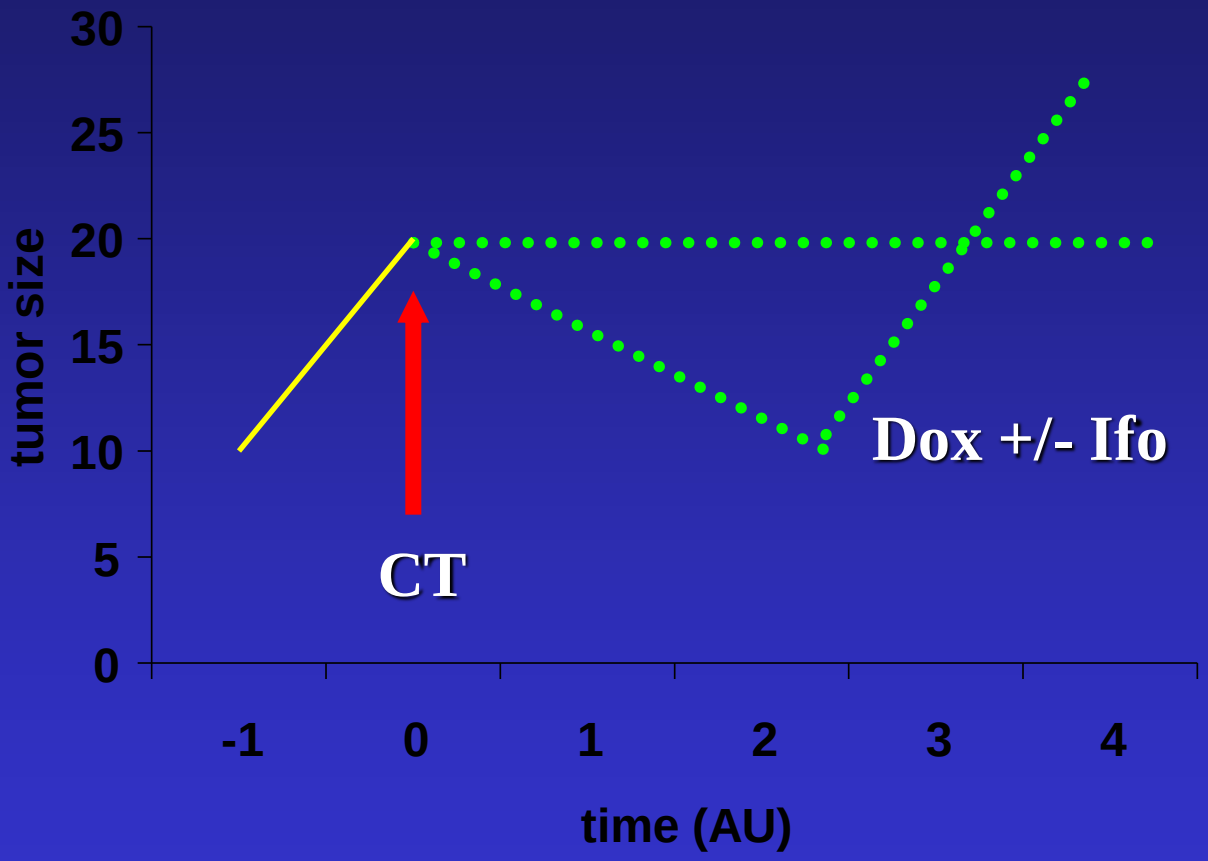
Soft Tissue Sarcomas: Treatment algorithm



Trabectédine: « take-home » messages en 2009

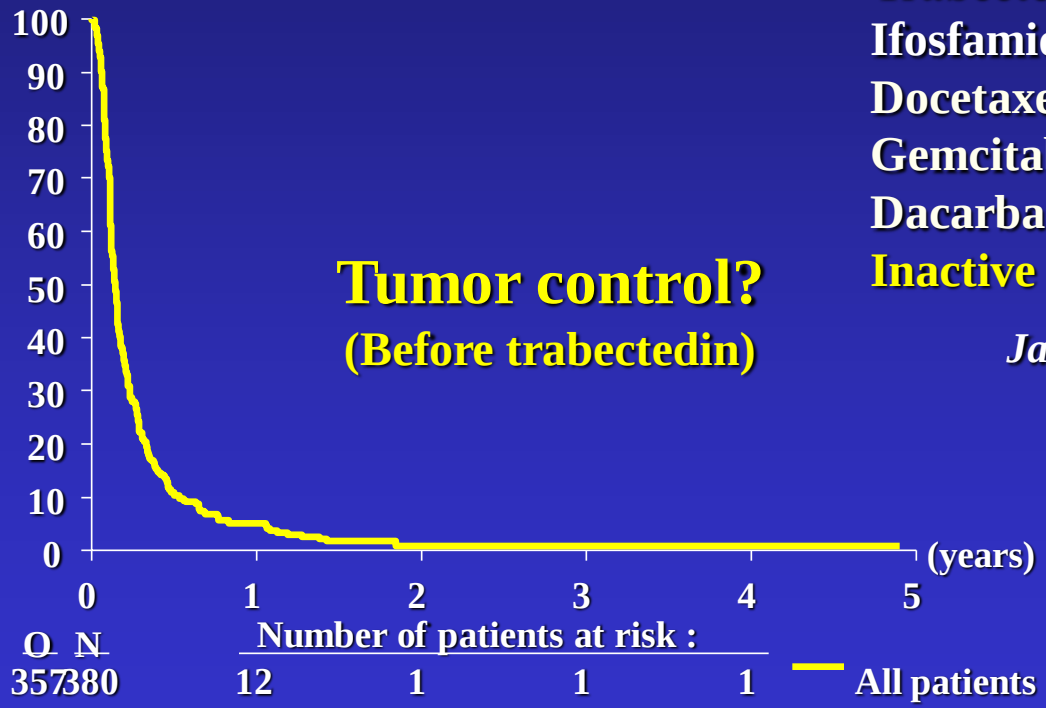
- Contrôle tumoral
- Critères RECIST
- Thérapeutique ciblée
- Signature moléculaire

Tumor evolution during treatment



Progression Free / Tumor control

2nd line treatment



Tumor control?
(Before trabectedin)

Drugs	N (>40)	PAR 2nd cycle
Trabectedin	123	54%
Ifosfamide	141	52%
Docetaxel	74	47%
Gemcitabine	95	39%
Dacarbazine	44	36%
Inactive agents		< 20%

Jaap Verweij, Educational book, ASCO 2003

Van Glabbeke et al, EJC 38:543-549,2002

Trabectedin, Phase II: Toxicity

Side effect	Doxorubicin (75mg/m^2)	Ifosfamide (≥10 gr/m^2)	Trabectedin (1.5 mg/m^2)
Neutropenia gr 3-4	85%	100%	52%
Neutropenic fever	29%	40%	5%
AST/ALT gr 3-4	NR	NR	51%
Cardiac toxicity	5-10%	-	-
Neurotoxicity	10%	30%	2%
Toxic deaths	0-4%	0-4%	1%
Alopecia	100%	100%	3%

No cumulative toxicity with trabectedin

* From: Verweij et al JCO 18:2081, 2000; Nielsen et al EJC 36:61, 2000; Judson et al EJC 37:870, 2001; Le Cesne et al JCO 13:1600, 1995 Demetri et al, ASCO 09

Drug Delivery (STS-201)

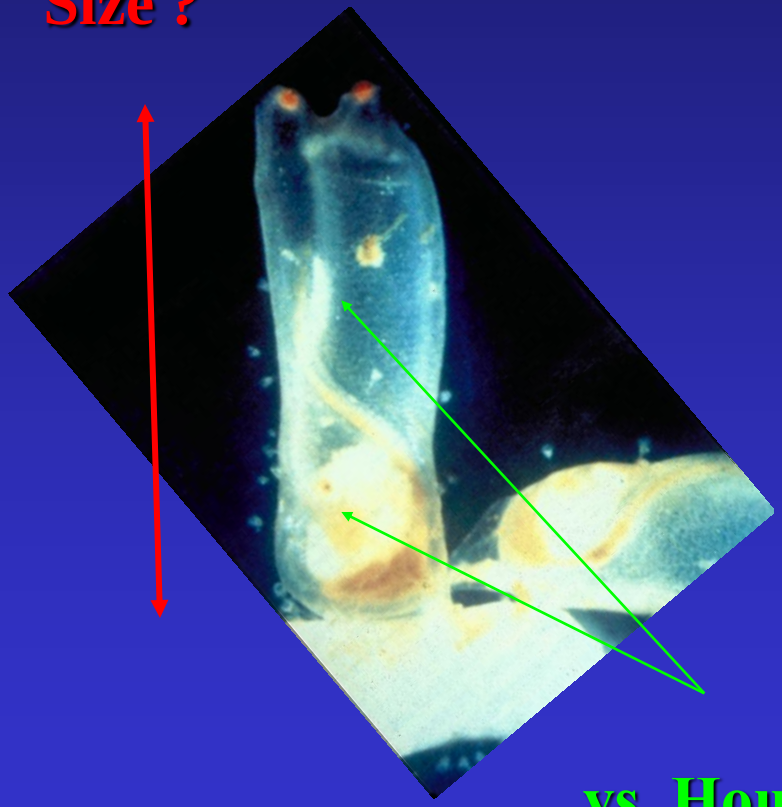
	qwk 3-h n=130	q3wk 24-h n=130
Median tt duration (weeks)	11.5	15.4
Median N° cycles (range)	2 (1 – 21)	5 (1 – 37)
Patients with 7 or more cycles	19%	38%
Median relative dose intensity	86%	81%

Trabectédine: « take-home » messages en 2009

- Contrôle tumoral
- Critères RECIST
- Thérapeutique ciblée
- Signature moléculaire

Trabectedin: the first « RECIST problem » in the evaluation of efficacy in STS?

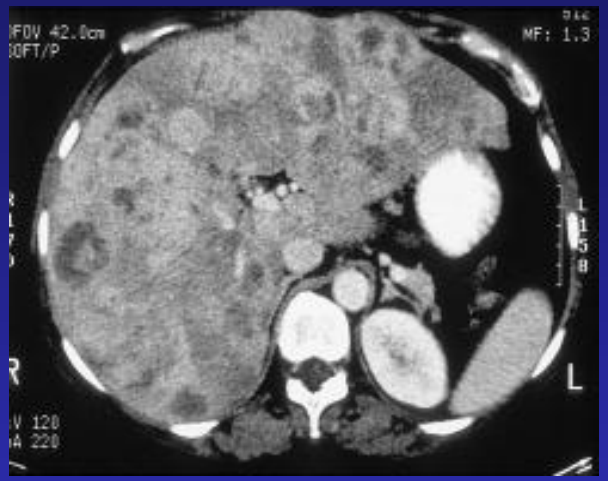
Size ?



- Tissue Response
- Choi criteria in STS?

…vs Hounsfield Unit?

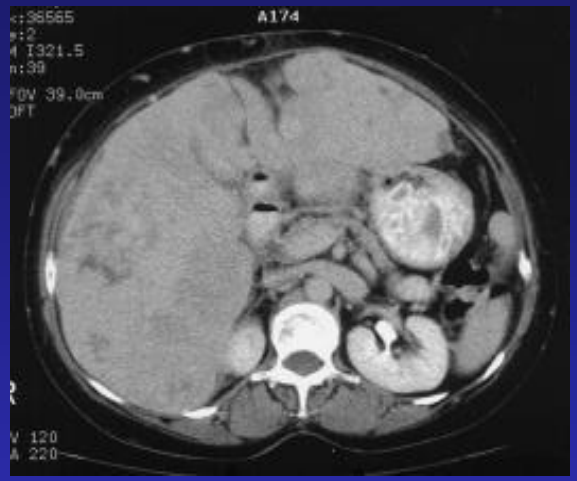
Trabectedin: Responses RECIST vs CHOI ?

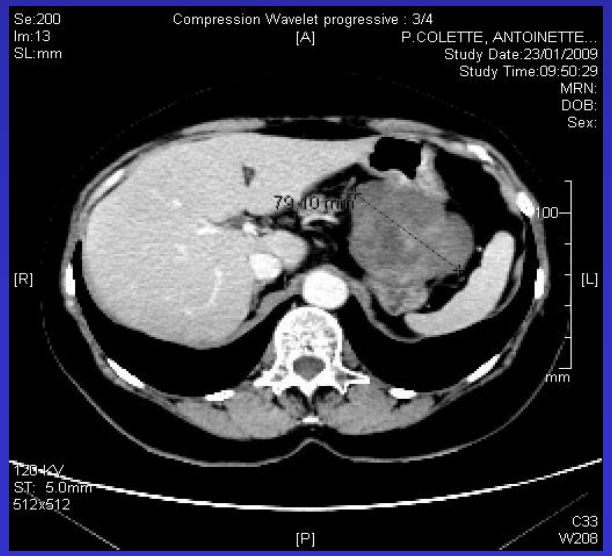


LMS

PR (RECIST)

9 cy



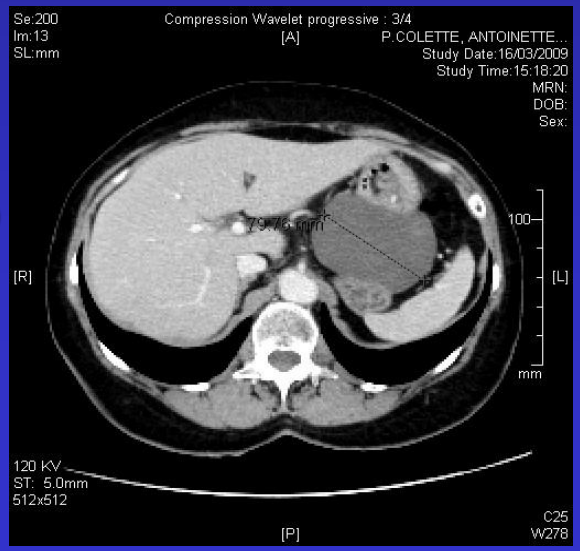


MLPS

SD (RECIST)

PR (CHOI)

15 cy

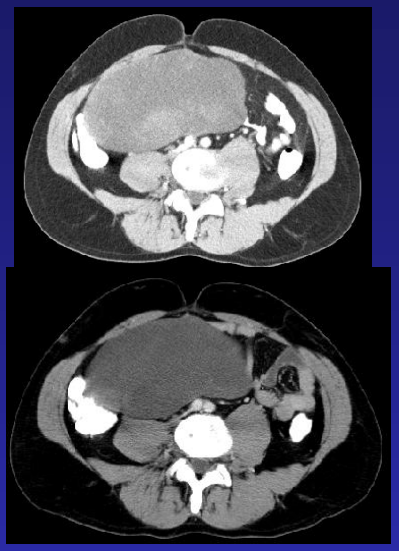


Trabectédine: « take-home » messages en 2009

- Contrôle tumoral
- Critères RECIST
- Thérapeutique ciblée
- Signature moléculaire

Trabectedin in MLPS /Responses

F. Grosso, Lancet Oncology, 2007



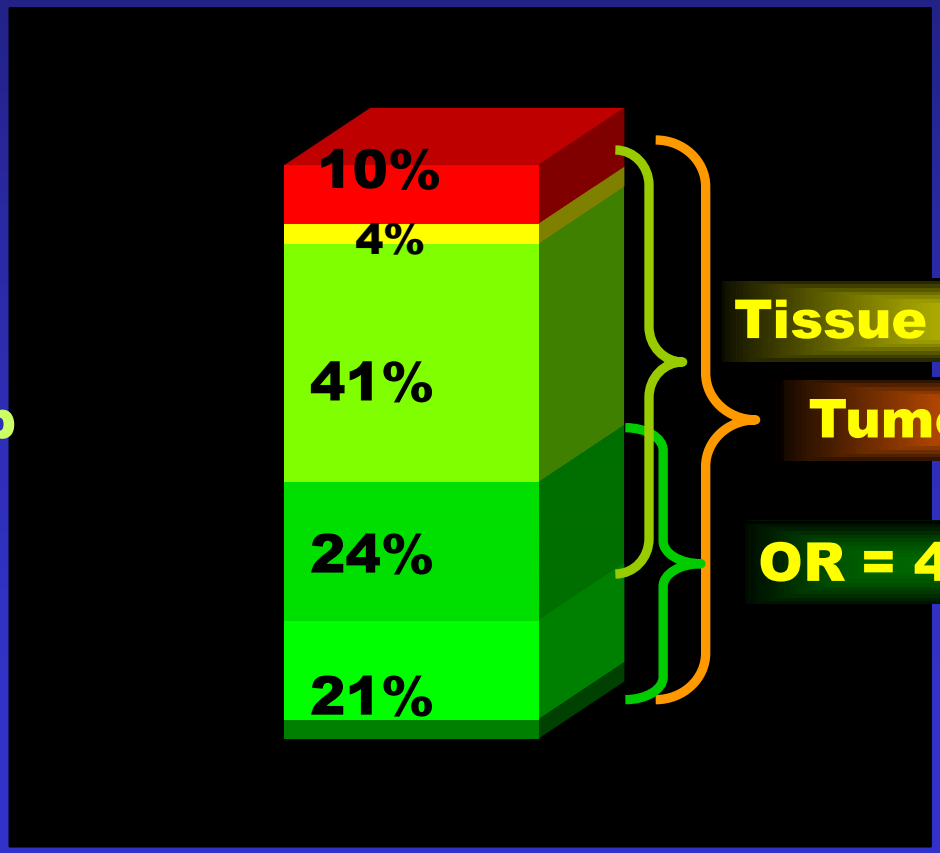
N=44

- PD
- SD

- SD/MR + tissue resp

- Delayed R

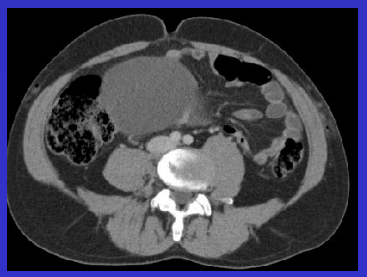
- PR, CR



Tissue response = 65%

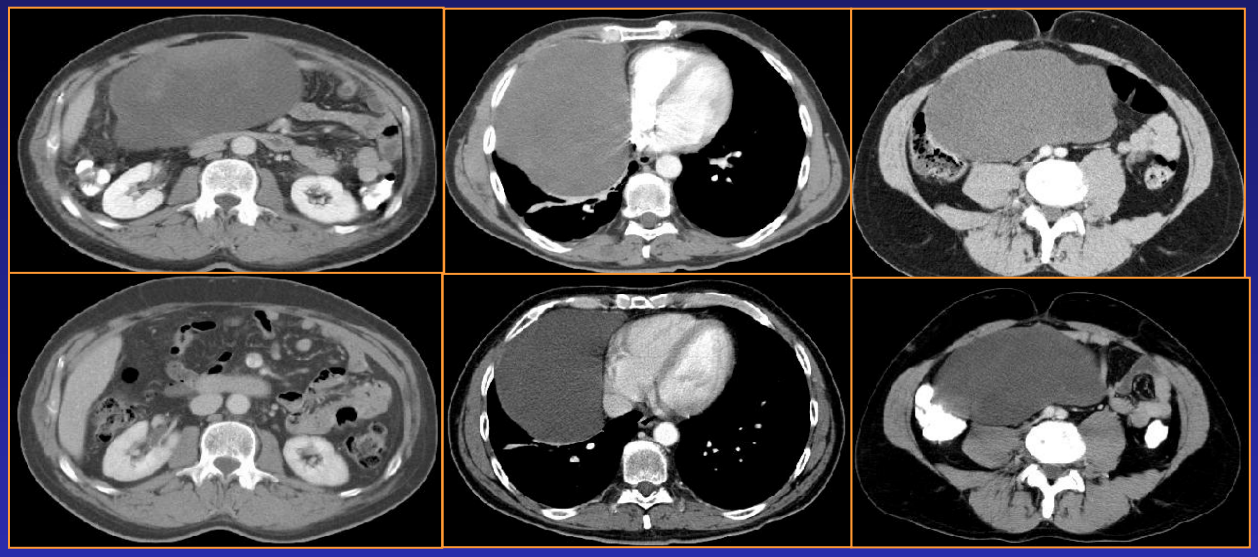
Tumor control = 90%

OR = 45%

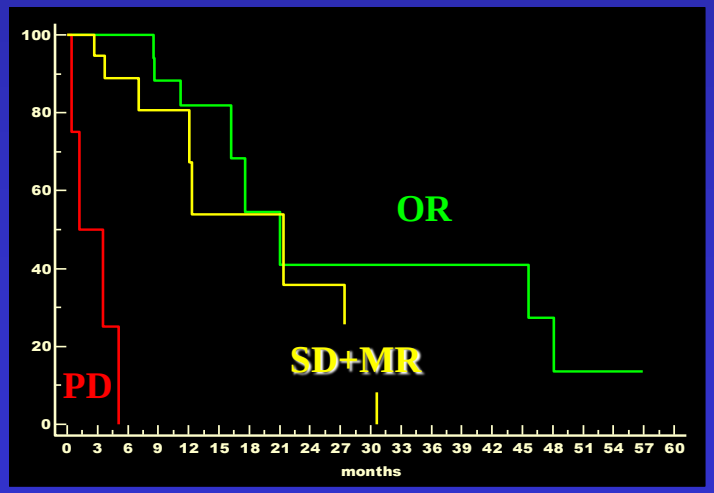


Trabectedin in MLPS : Targeted therapy?

CR/PR **MR** **NC-/+**



Responders to trabectedin (90%) = all type of responses…except PD!



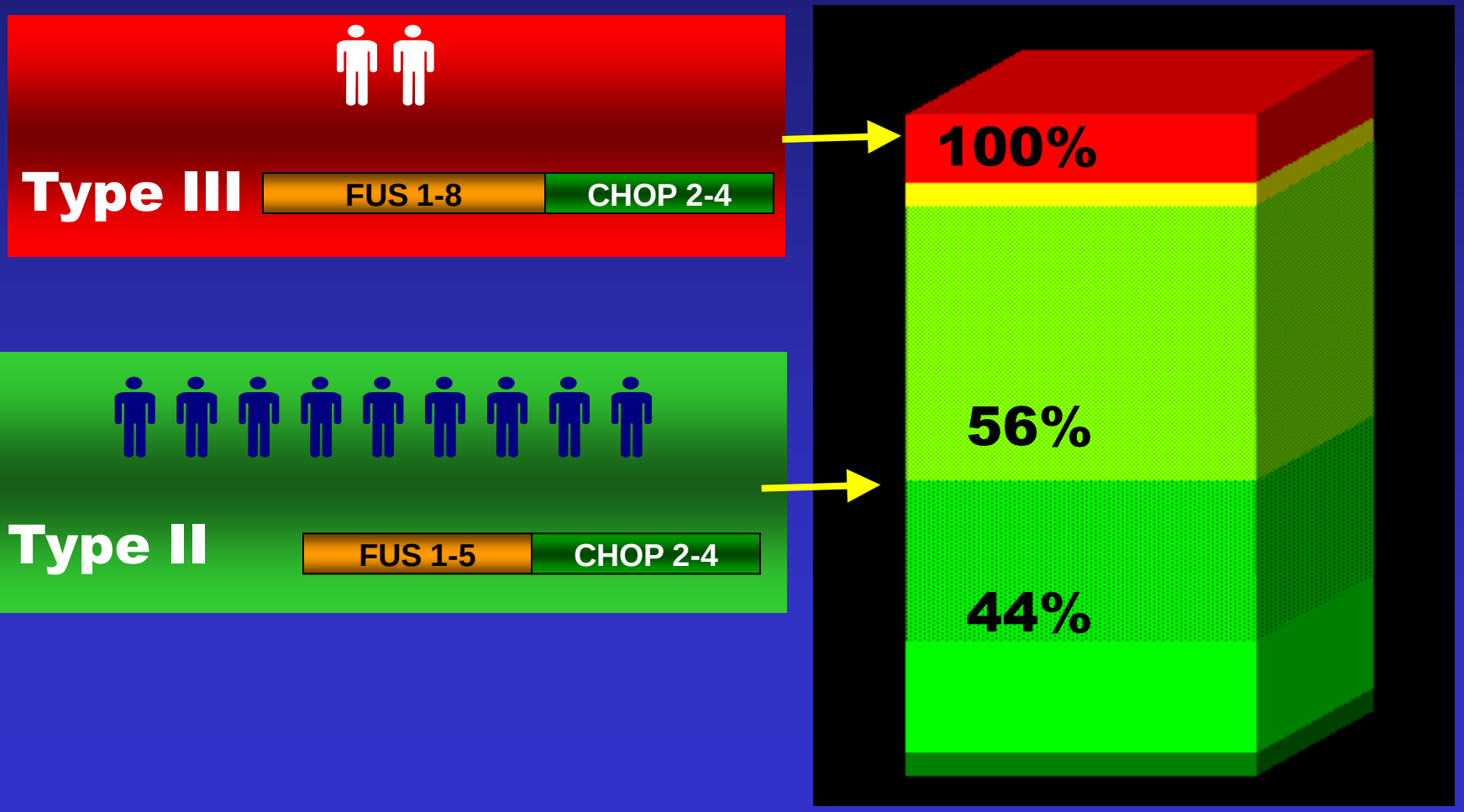
PFS according to tumor response

F. Grosso et al., Lancet Oncology, 2007

….as imatinib in GIST

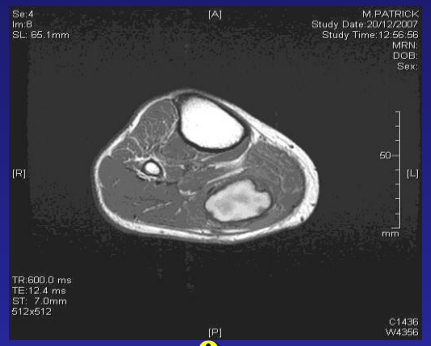
A.Le Cesne et al., JCO 2009

FUS-CHOP Fusion Transcript Molecular Variants → Response

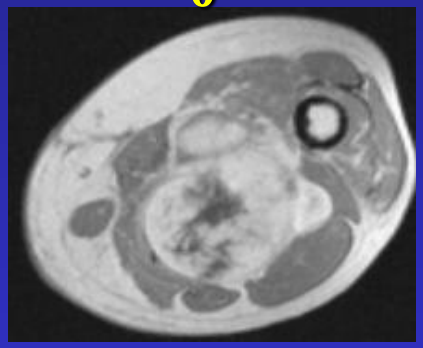


Trabectedin in MLPS : Induction CT in localized MLPS?

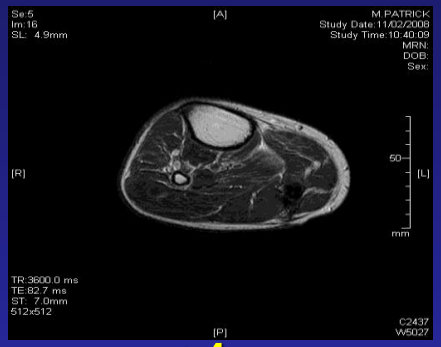
Multicenter Phase II (IGR/Milan/CLB/US)



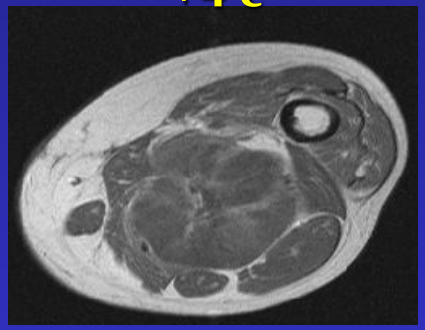
0



Analysis of fusion Transcripts/ Response



+4 c



N = 23:

4 to 6 cycles of trabectedin/Surgery/ RT
no PD, 26% of PR (Recist), 74% of SD
4 pCR, 10 pPR

A. Gronchi et al, ECCO 09

Indication in other histological subtypes of STS?

Translocation-Related Approach Trabectedin in Sarcoma

Sarcoma type	Chromosomal transl.	Fusion gene
Clear cell sarcoma	t(12;22)(q13;q12)	*EWS-ATF1*
Extraskeletal myxoid chondroS	t(9;22)(q22;q12)	*EWS-CHN*
Myxoid liposarcoma	t(12;16)(q13;p11)	*TLS/EWS-CHOP*
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	*TLS-ATF1*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3/7-FKHR*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWS-WT1*
Synovial sarcoma	t(X;18)(p11;q11)	*SYT-SSX1,2*
Inflammatory myofibroblastic T	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*

Randomized study
n = 80
Front-line therapy in TRS

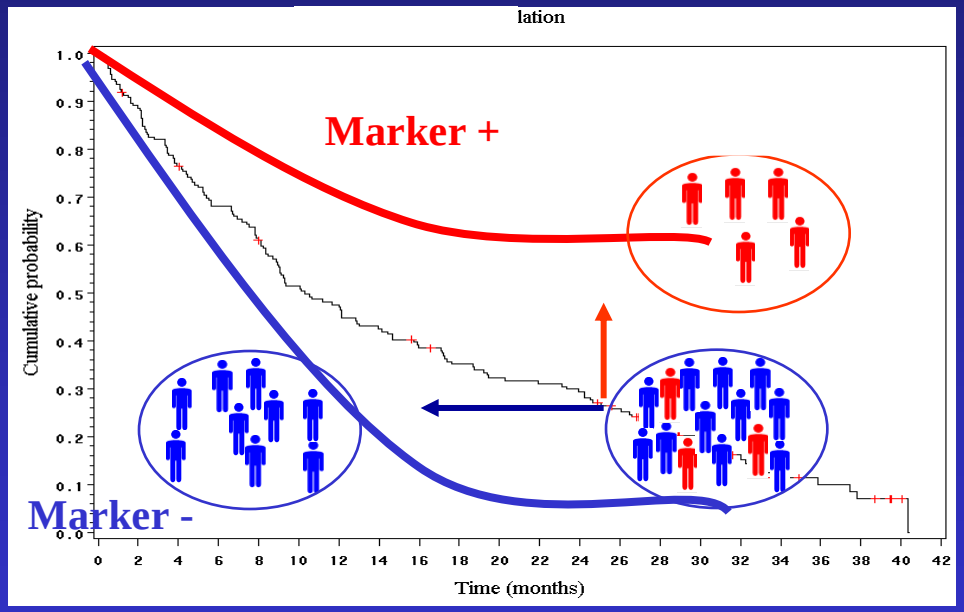
- **Trabectedin: 1.5 mg/m^2 24h q3w**
- **Doxorubicin-based CT q3w**

55% reduction in the relative risk of PD or death

Trabectédine: « take-home » messages en 2009

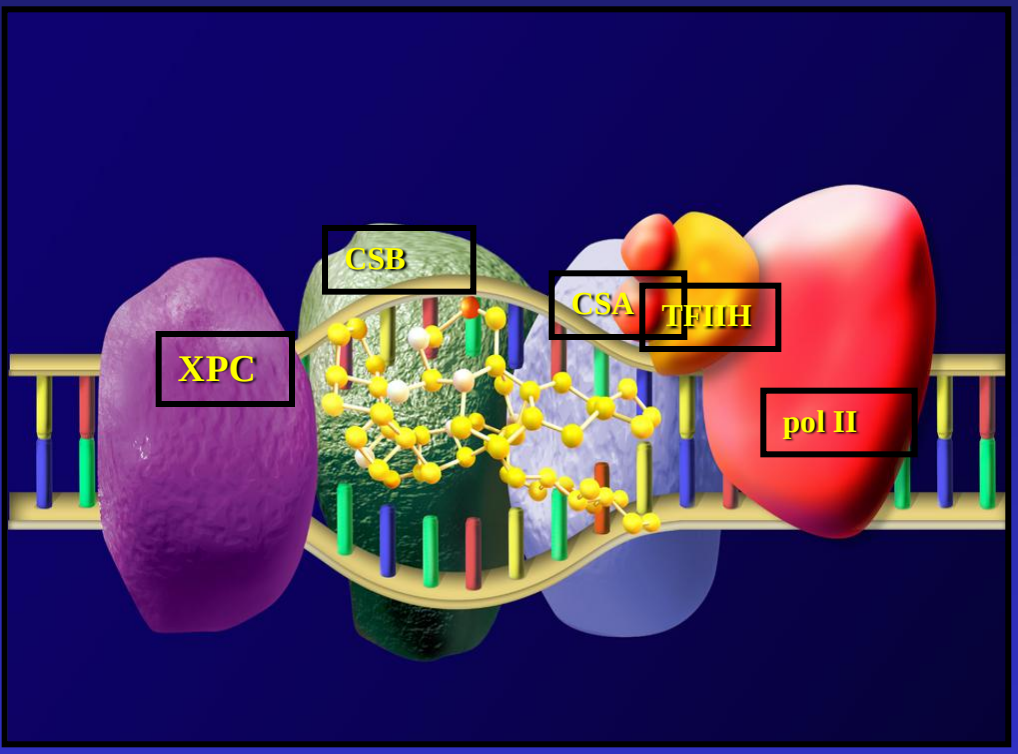
- Contrôle tumoral
- Critères RECIST
- Thérapeutique ciblée
- Signature moléculaire

Future of trabectedin in STS



Personalised treatment with surrogate biological markers

Transcription-Coupled Nucleotide Excision Repair

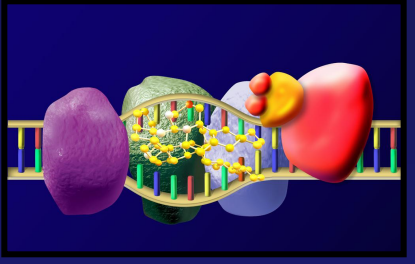


- ET-743 interacts with the NER system to induce cell death

- ERCC1, BRCA1 and XPG potential biomarkers of Yondelis efficacy

1) Proficient NER (high expression of ERCC1/XPG) is required for Yondelis cytotoxicity
2) In vitro low BRCA1 expression is associated with increased sensitivity to DNA damaging agents

→ Retrospective study to correlate mRNA expression levels of DNA repair related genes, in sarcoma patients treated with ET-743.



Transcription-Coupled NER

Outcome of patients treated with trabectedin

Parameter	BRCA1<3.26 + (ERCC1>4.99 or XPG>1.55)	Other	P-value
CR + PR	6/29 (21%)	7/61 (12%)	*0.3361*
CR+PR+MR+SD≥6	20/29 (69%)	18/61 (30%)	0.0006
PFS≥6 Months rate	17/31 (55%)	16/62 (26%)	0.0107
Median PFS (KM)	7.1 m	2.4 m	0.0015
PFS6 (KM)	60.2%	25.6%	0.0001
Median Survival (KM)	25.7 m	9.3 m	0.0107

MPLS

First data reported by P. Schöffski et al. AACR'07

Trabectedin in STS: Conclusions

Trabectedin:

1) Is the first cytotoxic drug approved in the field of STS since 20 yrs
2) Is the first active new drug highlighting the notion of prolonged tumor control in ASTS
3) RECIST not adequate to evaluate Yondelis efficacy in STS
4) Lacks cumulative T and is suitable for chronic administration
5) May suggest a targeted therapeutic approach in MLPS and in other translocation-related mesenchymal tumors
6) Identifies a STS patient subpopulation highly sensitive (expression of a low BRCA1 and high ERCC1) and could be used in adjuvant situation

Merci !!!!

Acknowledgments

Thanks to all of the patients worldwide, as well as to all Participating Investigators and Collaborating Teams

Demetri, G.D.
Chawla, S.
Schuetze, S.
Von Mehren, M.
Le Cesne, A.
Budd, G.
Casali, P.
Garin, A.
Hamm, J.
Manikhas, G.
Ritch, P.
Rushing, D.
Blay, J. Y.
Samuels, B.
Blackstein, M.
Kaiser, P.
Keohan, M. L.
Turner, R.
Verma, S.
Baker, L.
Hande, K.
Morris, D.
Ryan, C.
Elias, A.
Okuno, S.
Albritton, K.
Biakhov, M.
Butrynsk, J.
Mardynsky, Y.
Patterson, K.
Van Oosterom, A.
Gershanovich, M.
Judson, I.
Lopez, A.
Makhson, A.
Patel, S.
Pavlick, A.
Pliner, L.
Schutte, H.J.
Staddon, A.
Taub, R.
Buys, S.
Byrne, M.
Kopp, M.
Poveda, A.
Skubitz, K.
Ushakov, I.
Younus, J.
Reichardt, P.