# MOLECULAR CHARACTERIZATION SHOULD NOW BE DETERMINANT OF MODERN CANCER TREATMENT IN SARCOMA?

## NO

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# Disclosure

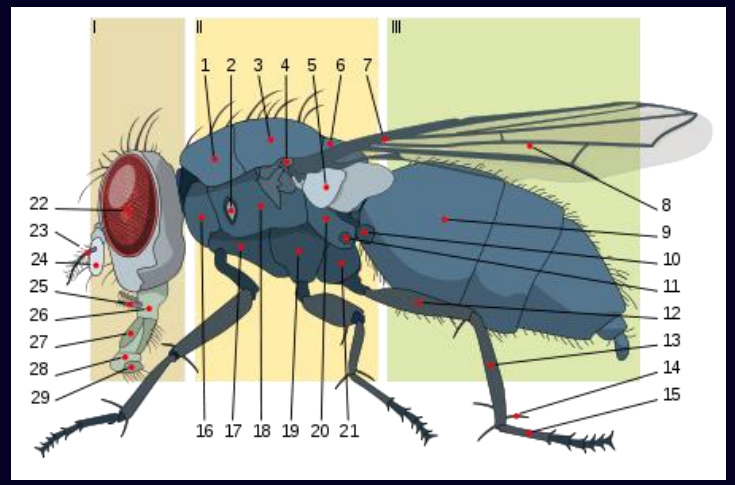
- **Consulting or Advisory Role**
  - ✓PharmaMar, GSK, Novartis, Amgen, Bayer
- **Speakers' Bureau**
  - ✓PharmaMar

# Treatment in sarcoma is NOT yet molecularly oriented

## Reasons for NO

- Chemotherapy standard in 1st, 2nd line & beyond in STS/OS/ES
- No predictive biomarkers for most frequent STS/OS/ES
- Negative prospective trials: predictive biomarker oriented
- Translocation related sarcomas: Difficult druggable diseases

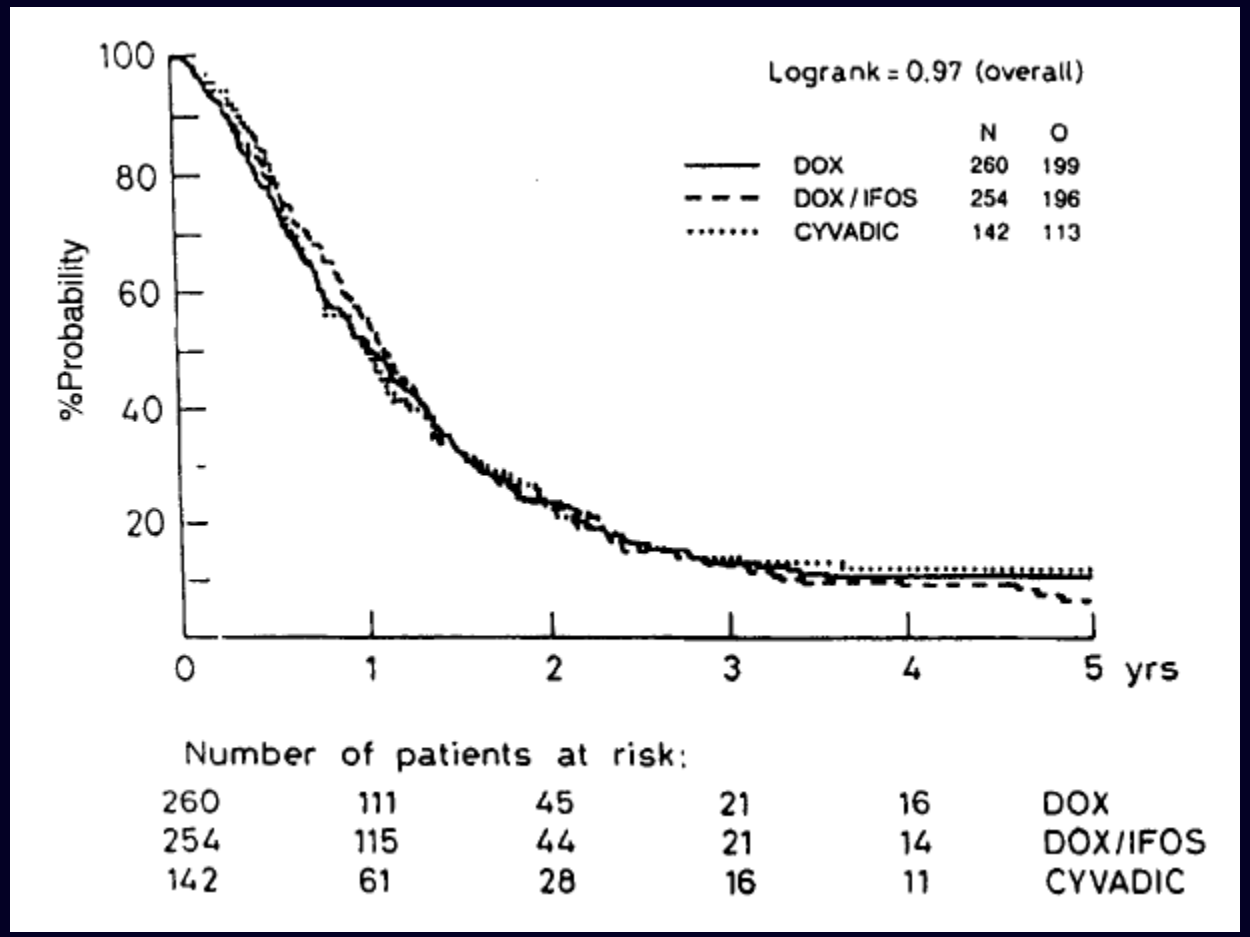
# CHEMOTHERAPY STANDARD SYSTEMIC TREATMENT IN STS and BS (1ST, 2ND & Beyond)



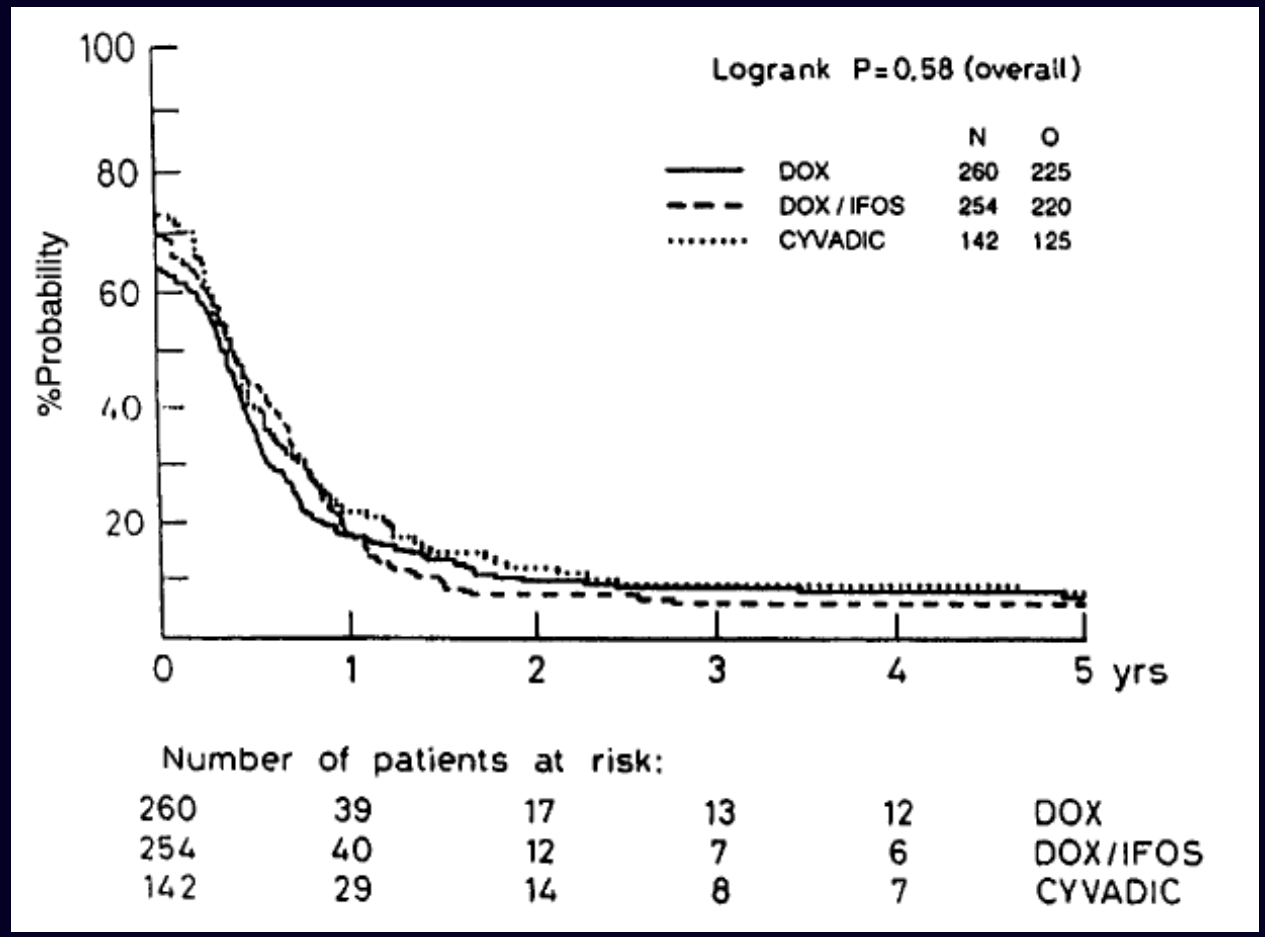

# Doxorubicin: Still Standard 1st line 20 y later

| Study | Drug | N | RR | Survival |
|---|---|---|---|---|
| ECOG | Doxorubicin | 93 | 19% | 8 mo |
| | Doxorubicin + DTIC | 95 | 13% | 8 mo |
| SWOG | Doxorubicin + DTIC | 79 | 32% | 9 mo |
| | Doxo + DTIC + cytoxan | 95 | 35% | 10.5 mo |
| ISSG | Doxorubicin + DTIC | 170 | 17% | 13 mo |
| | MAID | 166 | 32% | 12 mo |
| EORTC | Doxorubicin | 212 | 24% | 12 mo |
| | Doxorubicin + Ifosfamide | 202 | 27% | 12 mo |
| ECOG | Doxorubicin | 90 | 20% | 9 mo |
| | Doxorubicin + Ifosfamide | 88 | 34% | 12 mo |
| GEIS | Doxorubicin | 67 | 23% | 26w/pfs |
| | Doxorubicin + Ifosfamide | 65 | 24% | 24w/pfs |

# Doxorubicin: Still Standard 1st line 20 y later




Overall survival




Progression free survival

J Clin Oncol Vol 13, No 7 (July), 1995: pp 1537-1545

# The higher the dose the better the response

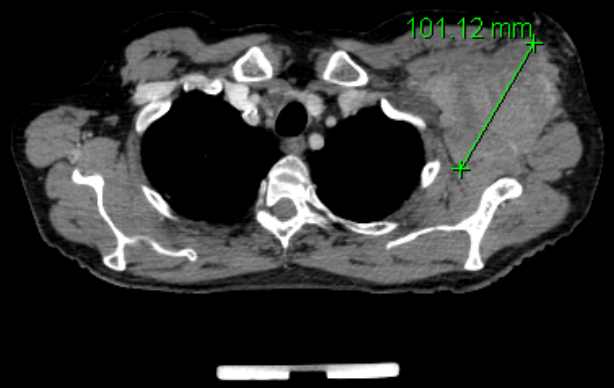
| Author | Ifos | D | DTIC | N | %CR | %RR |
|---|---|---|---|---|---|---|
| Kirchner | 7,5 | 65 | 0 | 14 | 7 | 43 |
| Elias | 7,5 | 60 | 900 | 97 | 11 | 51 |
| Antman | 7,5 | 60 | 900 | 23 | 13 | 57 |
| Hartlap | 7,5 | 50 | 0 | 21 | 14 | 57 |
| Loeher | 5 | 60 | 0 | 38 | 8 | 39 |
| Mansi | 5 | 60 | 0 | 22 | 14 | 41 |
| Bramwell | 5 | 50 | 850 | 40 | 5 | 25 |
| Schuete | 5 | 50 | 0 | 162 | 9 | 34 |
| Santoro | 5 | 50 | 0 | 144 | 6 | 25 |

Se:4
Im:111

[A]

8/10/2009

MRN:1259058




[R]

TORAX-ABD-PELVIS
CONTRAST

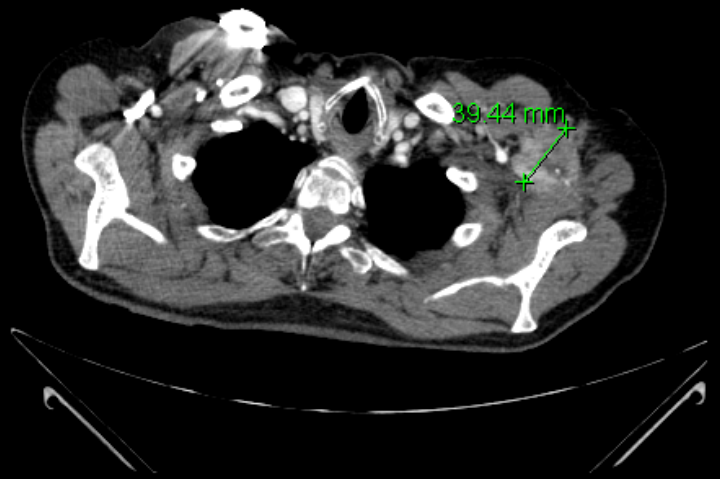
[P]

Se:2
Im:59

[A]

15/12/20

MRN:12



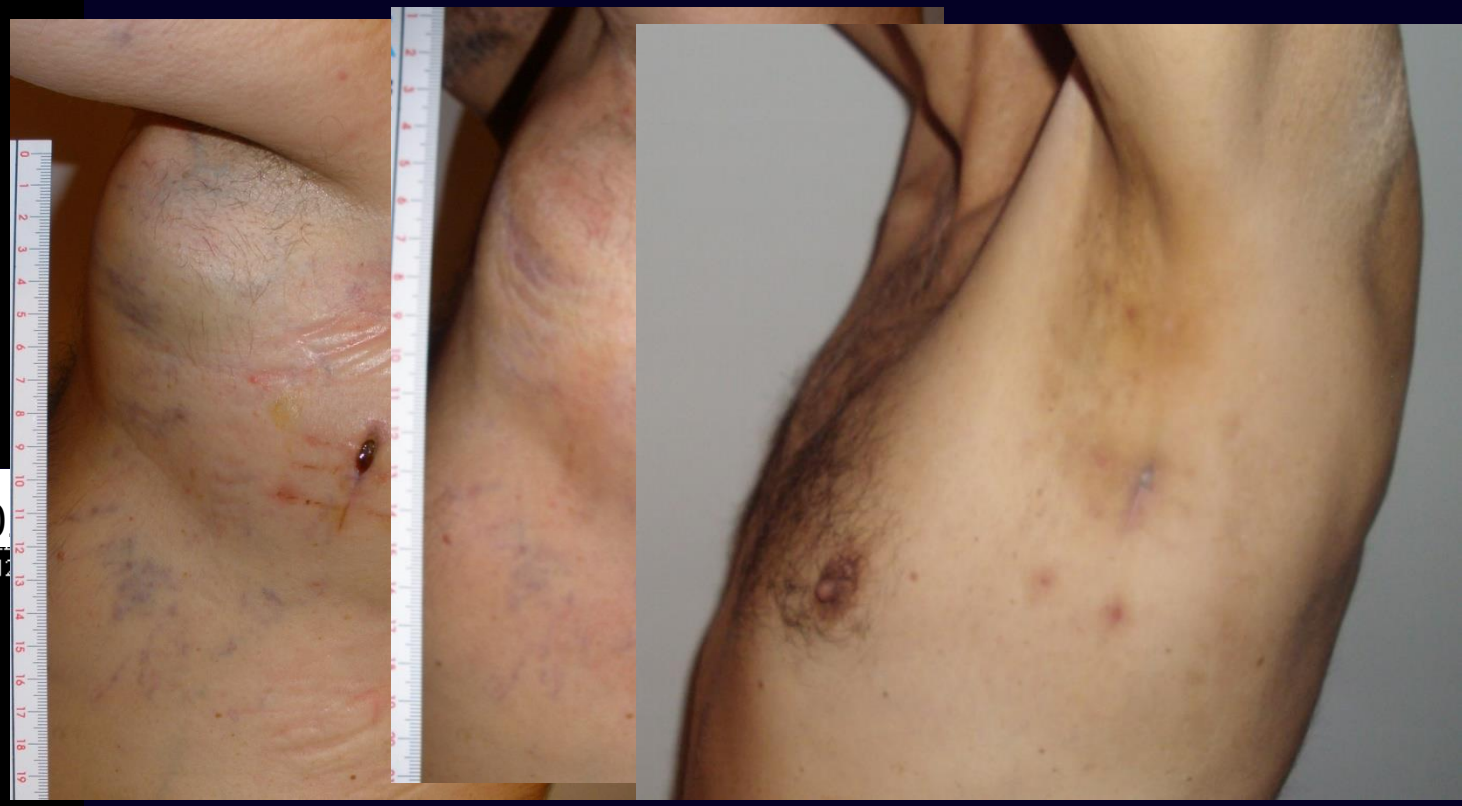

[R]

[L]

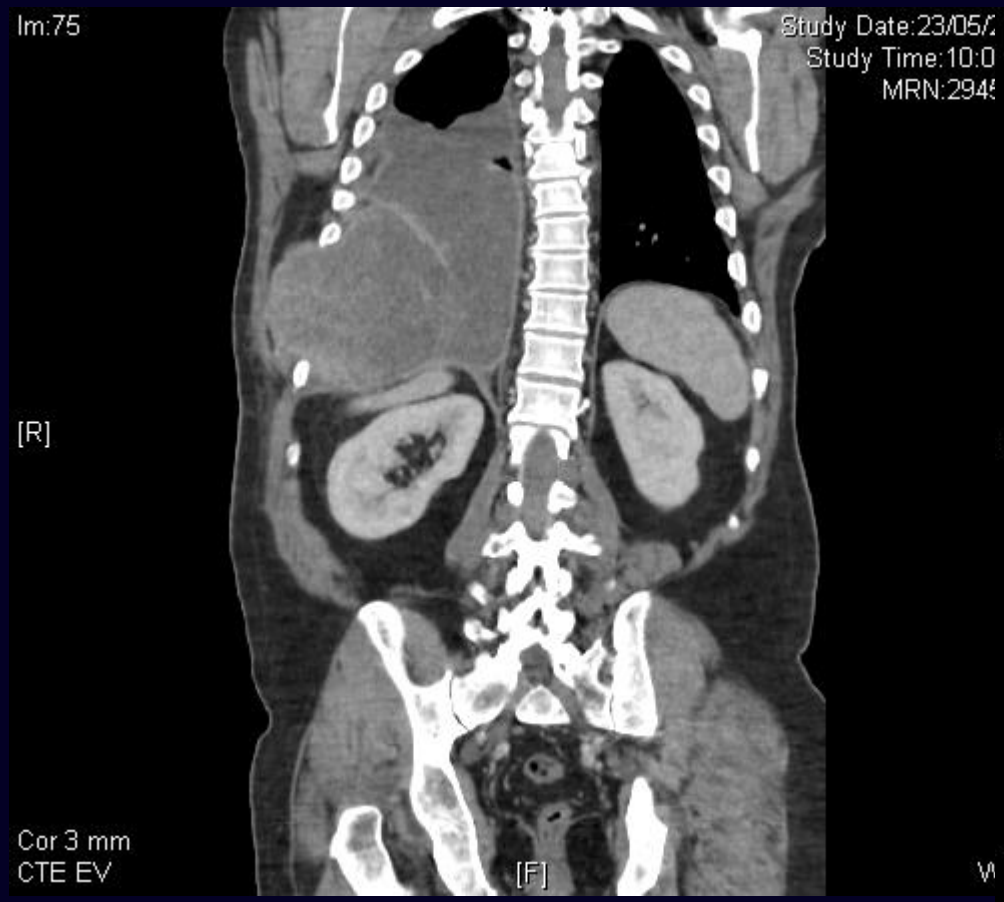
CONTRAST

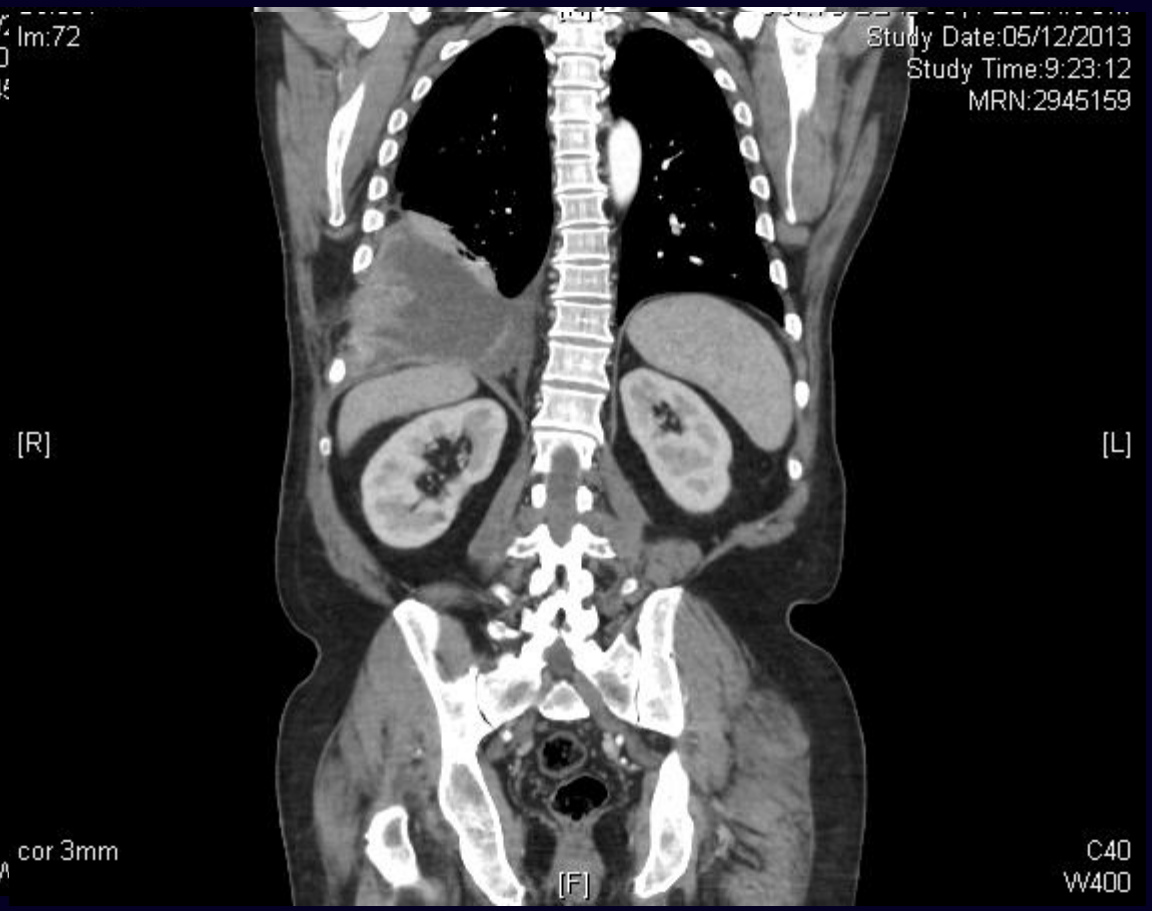
[P]

C60
W360

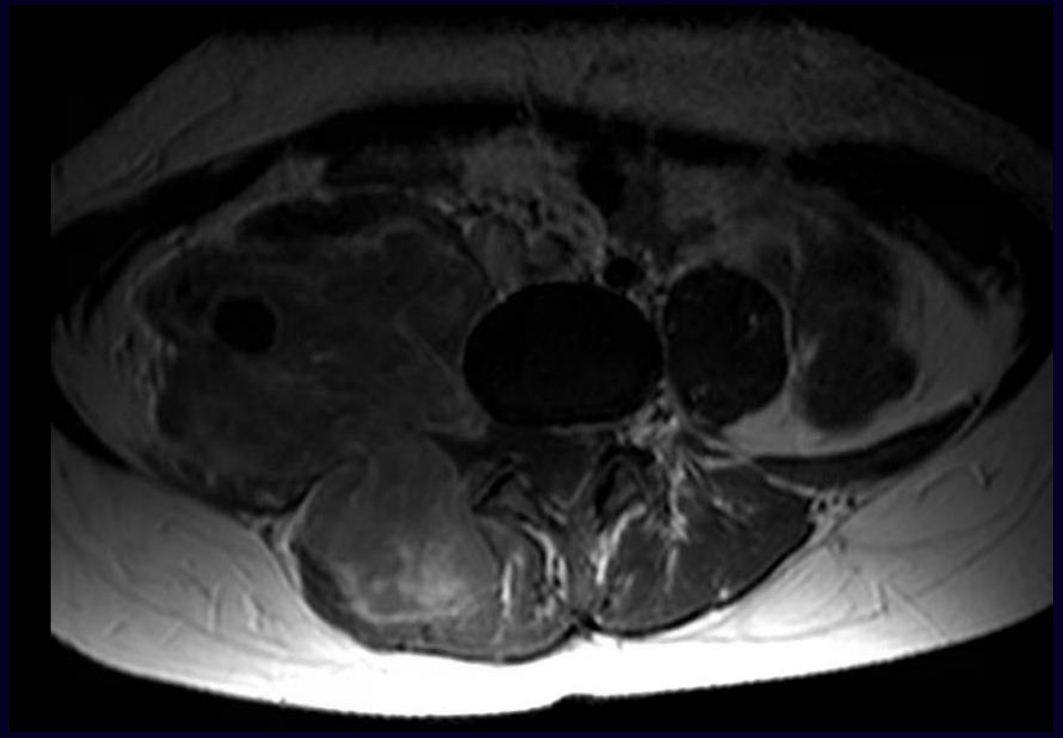


# SYNOVIAL SARCOMA

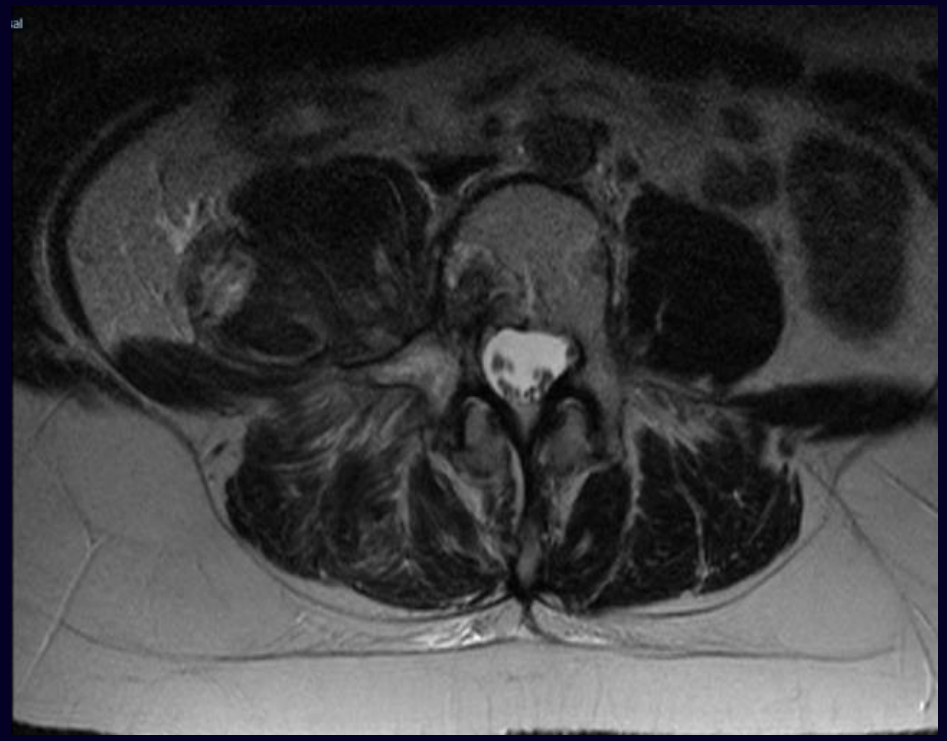


# High grade Sarcoma treated with Epirubicin-Ifosfamide



OCT 2014



JUNE 2015

# Synovial Sarcoma after 3 cycles of Epirubicin-Ifosfamide

18/9/2014

25/11/2014

# Clinical Guidelines

clinical practice guidelines

*Annals of Oncology* 25 (Supplement 3): iii102–iii112, 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*

1st line
- Anthracyclines based

2nd line
- Trabectedin
- Gemcitabine based
- Pazopanib

NCCN National Comprehensive Cancer Network®

Active drugs
- Anthracyclines
- Ifosfamide
- Epirubicin
- Dacarbazine
- Temozolomide
- Vinorelbine
- Pazopanib
- Eribulin

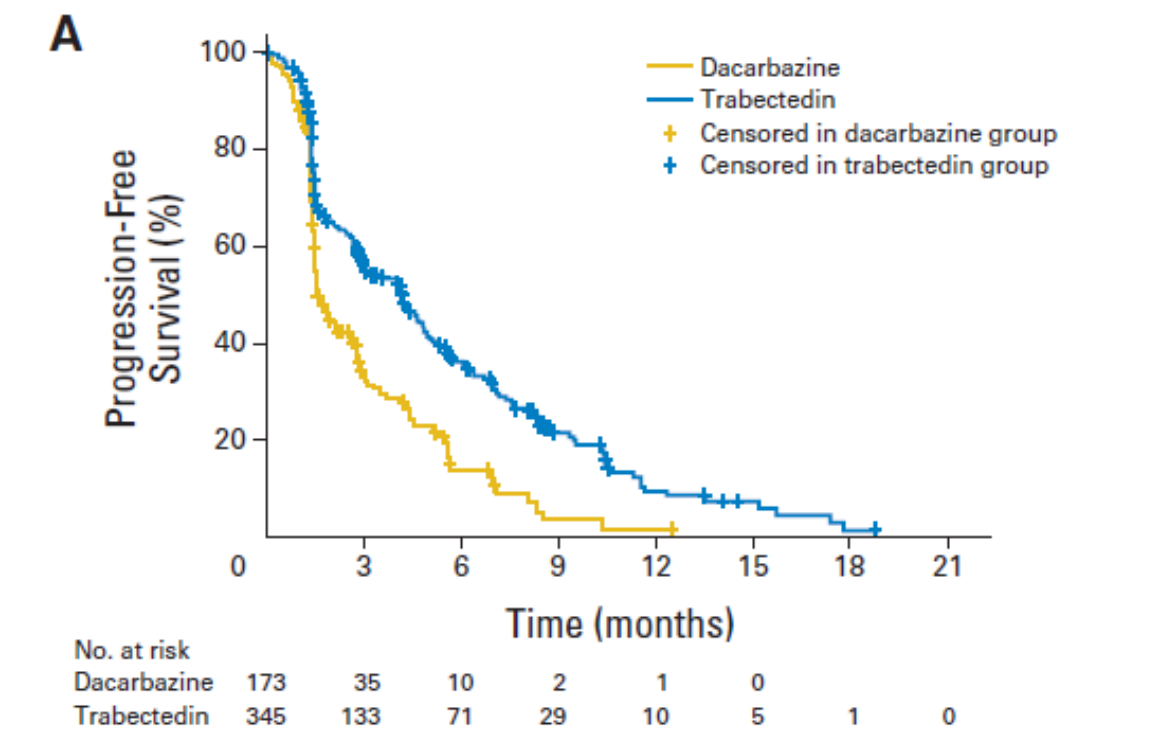
# In most frequent sarcoma subtypes chemotherapy still the systemic backbone

| | 1st line | 2nd line | |
|---|---|---|---|
| UPS | Anthracyclin based | Trabectedin, Pazopanib, Gemcitabine | |
| LMS | Anthracyclin based Doxo+DTIC? | Trabectedin, Pazopanib, Gemcitabine | Ifosfamide may be less active |
| Myxoid LPS | Anthracyclin based | Trabectedin | |
| MPNST | Anthracyclin based | Etoposide+Ifosfamide, Trabectedin, Pazopanib, Gemcitabine | Less chemosensitive subtype |
| Synovial | Anthracyclin based | HD Ifosfamide | Trabectedin, Pazopanib |
| DD Lipos | Anthracyclin based | Trabectedin, Eribulin | |

# Trabectedin

## Phase III : SAR 3007 (518 L-Sarcomas)

Significantly better PFS in Trabectedin arm (HR, 0,55; P<0,001) [1]



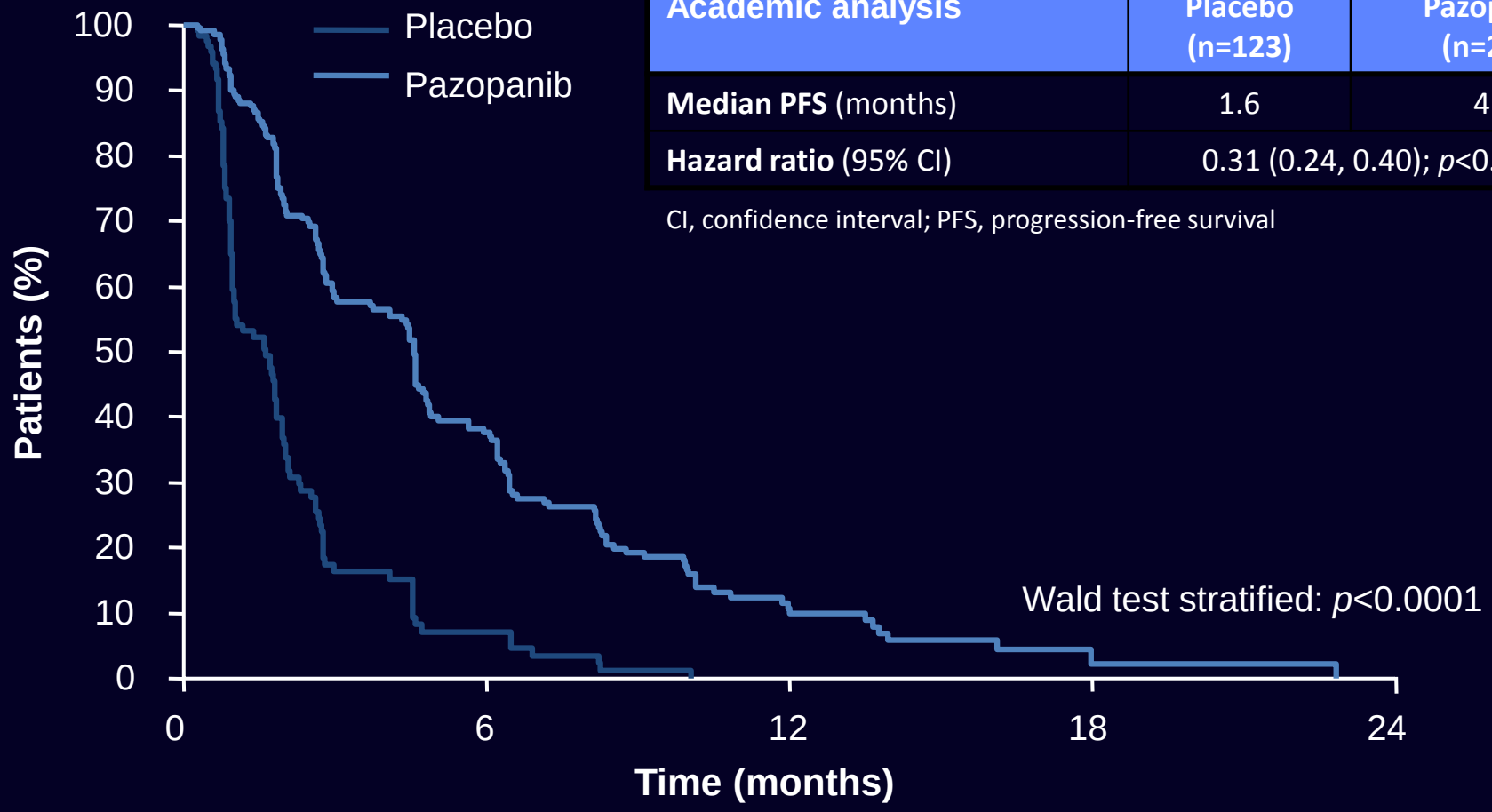

| | DTIC | Trabectedin |
|---|---|---|
| PFS* | 1,5 months | 4,2 months |
| PF RATE 3 M | 37% | 56% |
| PF RATE 6M | 14% | 34% |

*PFS reviewed according to independent radiological assessment.


1. Demetri GD et al. J Clin Oncol 2015 Sep 14 pii: JCO.2015624734 [Epub ahead of print])

# Pazopanib

## Phase III : Palette (No Adipocytic sarcomas)




| Academic analysis | Placebo (n=123) | Pazopanib (n=246) |
|---|---|---|
| **Median PFS** (months) | 1.6 | 4.6 |
| **Hazard ratio** (95% CI) | 0.31 (0.24, 0.40); *p*<0.0001 | |

CI, confidence interval; PFS, progression-free survival

Van Der Graaf W *et al. Lancet* 2012;379:1879

# Gemcitabine & DTIC

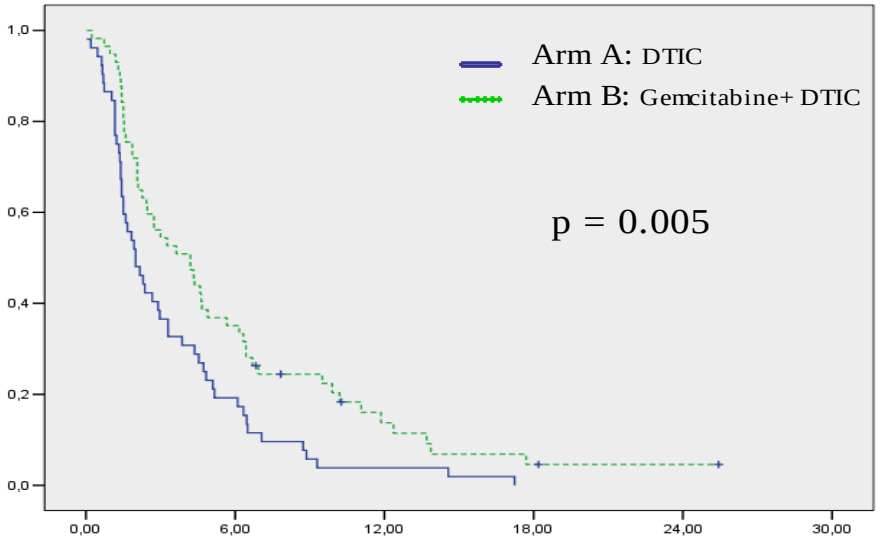
## Randomized Phase II : Most Frequent Sarcomas

Treatment Schedule: ARM A: DTIC 1200 mg/m$^2$ q 21 days

ARM B: Gemcitabine 1800 mg/m$^2$/min + DTIC 500 mg/m$^2$ q 14 days

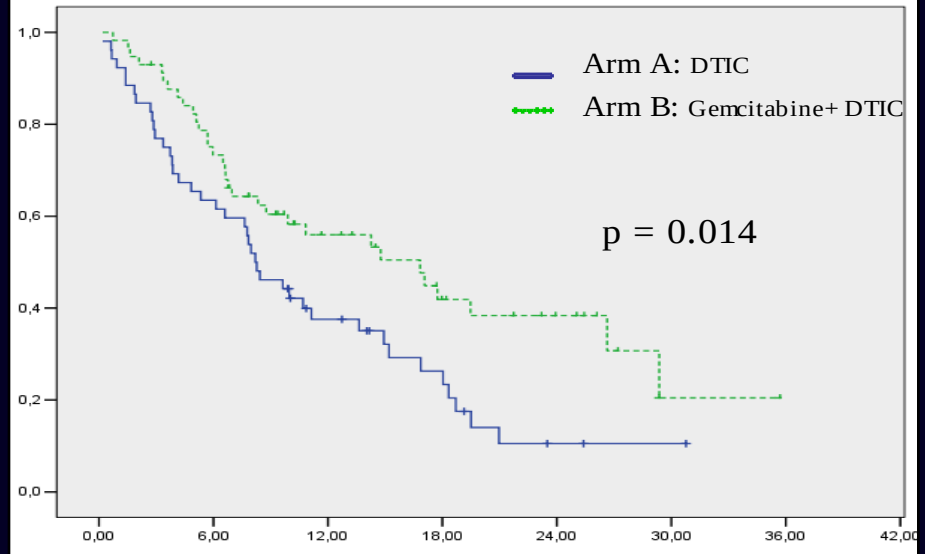
Study Design: 113 pts. Randomized phase II study. Endpoint: PFR at 3 months

PROGRESSION FREE SURVIVAL




| | PFS median | CI 95% | p value | HR | CI 95% |
|---|---|---|---|---|---|
| Arm A | 2 m. | [1.25 - 2.75] | 0.005 | Ź1 | |
| Arm B | 4.2 m. | [2.47 - 5.9] | | 0.579 | [0.39 - 0.856] |

OVERALL SURVIVAL



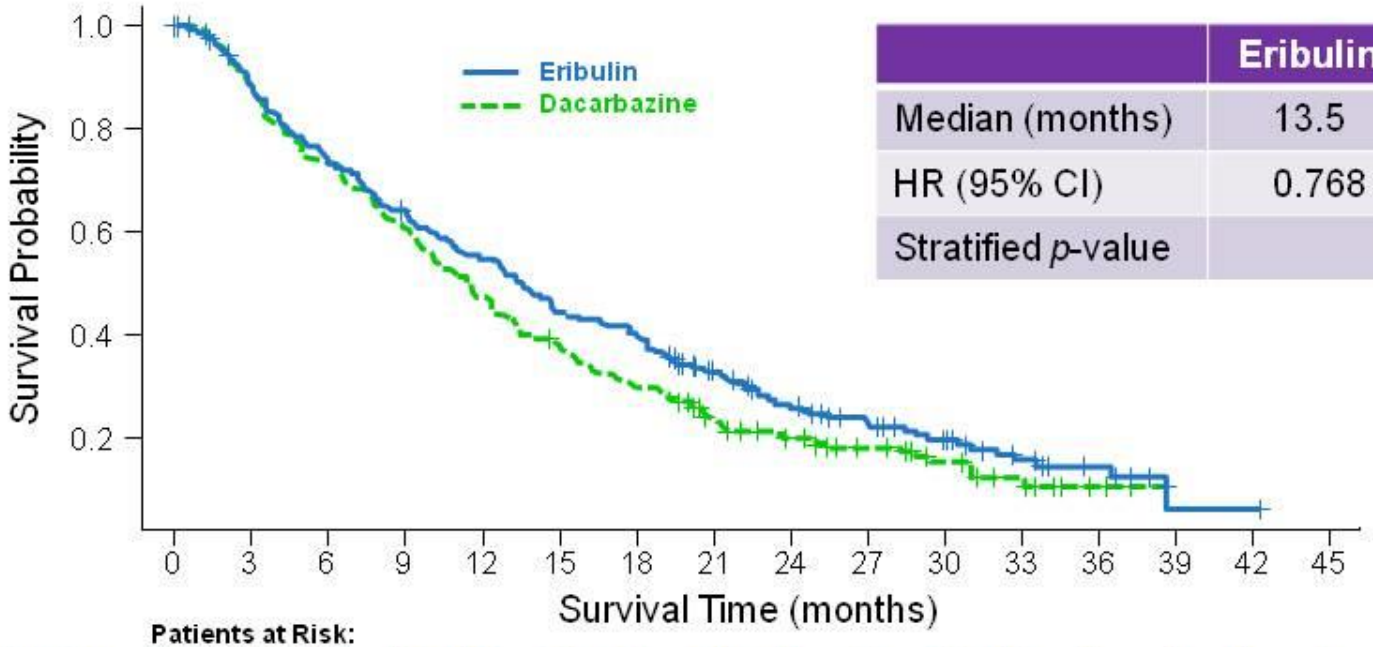

| | OS median | CI 95% | p value | HR | CI 95% |
|---|---|---|---|---|---|
| Arm A | 8.2 m. | [6 Š 10.4] | 0.014 | Ź1 | |
| Arm B | 16.8 m. | [8.78 Š 24.88] | | 0.563 | [0.35 - 0.897] |

J Clin Oncol 2011 Jun 20;29(18):2528-33

# Eribulin

## Phase III : L-Sarcomas

### 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 | |

**Patients at Risk:**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Eribulin | 228 | 197 | 162 | 138 | 120 | 97 | 88 | 64 | 45 | 34 | 25 | 14 | 7 | 1 | 1 | 0 |
| Dacarbazine | 224 | 190 | 158 | 130 | 103 | 81 | 64 | 45 | 32 | 24 | 16 | 8 | 3 | 0 | 0 | 0 |

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

CI, confidence interval.



PRESENTED AT: ASCO Annual '15 Meeting

J Clin Oncol Vol 33, No 18_suppl (June 20 Supplement), 2015: LBA10502

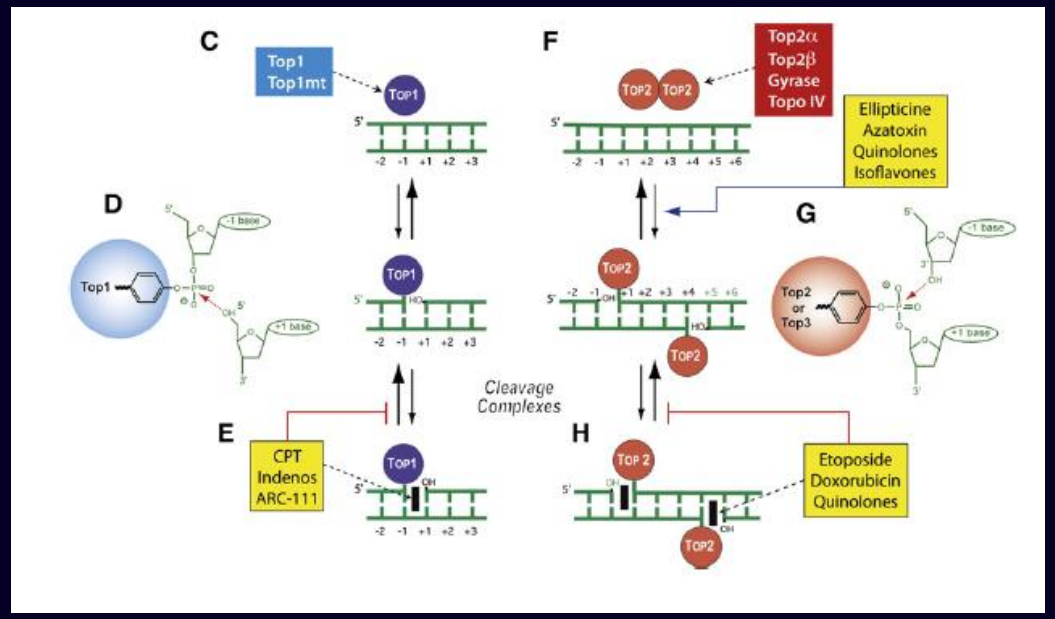
# Predictive biomarkers in most of STS?

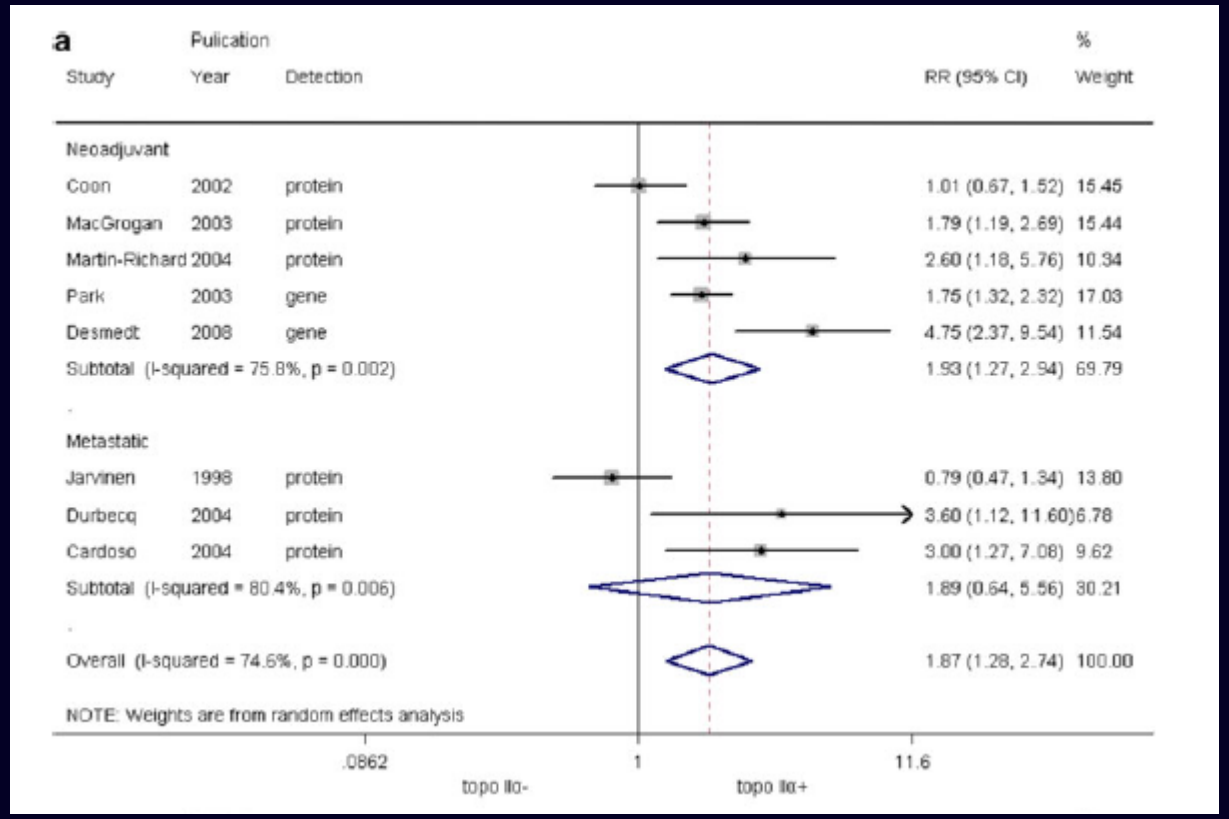
## Not yet

| | AGENT | COMMENTS |
|---|---|---|
| Localized advanced STS | Anthracyclin based | Better pathologic response if High IHC for TOP2A (1) |
| Localized High risk STS | Anthracyclin & Ifosfamide based | MRP1 could be a biomarker for Resistance (2) |
| Advanced STS | Trabectedin | High levels of NER machinery genes (XPG, ERCC1) and low of BRACA1 could predict Trabectedin efficacy (3) |
| STS | Gemcitabine | Not yet established relationship with RRM1 |
| STS | Pazopanib | Not yet established relationship with angiogenic factors |

Eur J Cancer. 2011;47: 1319-1327 (1)
Mol Cancer Ther 2014 Jan;13(1):249-59 (2)
Cancer. 2011 Aug 1;117(15):3445-56 (3)

# Meta-analysis for the value of TOP2A in Breast Cancer

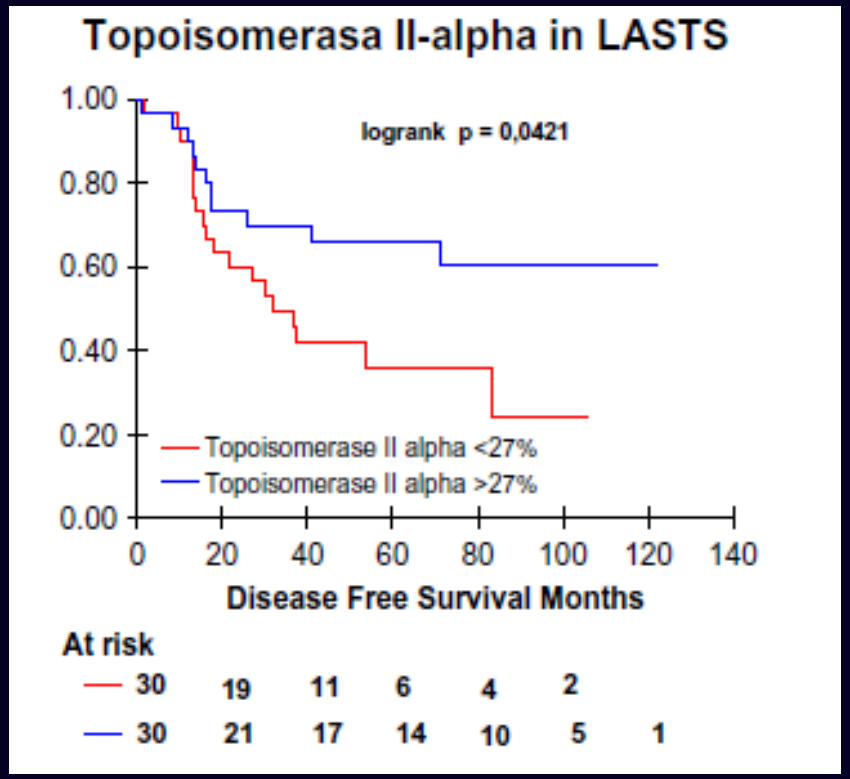


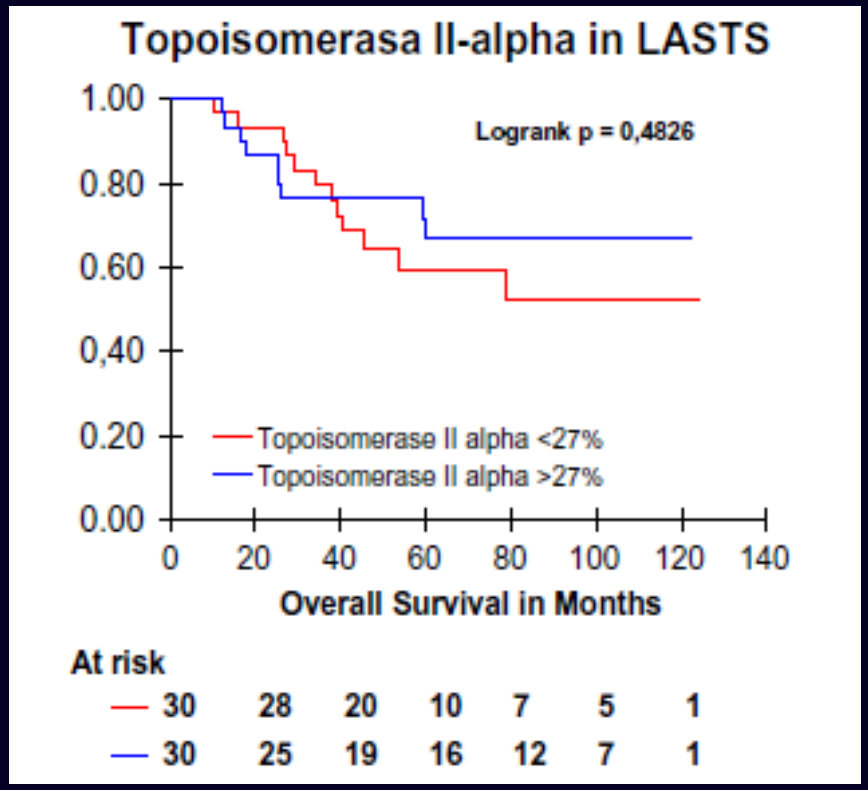

Breast Cancer Res Treat (2011) 129:839–848

# Retrospective analysis: TOP2A in STS

N = 78 Locally advanced STS treated with anthracyclines



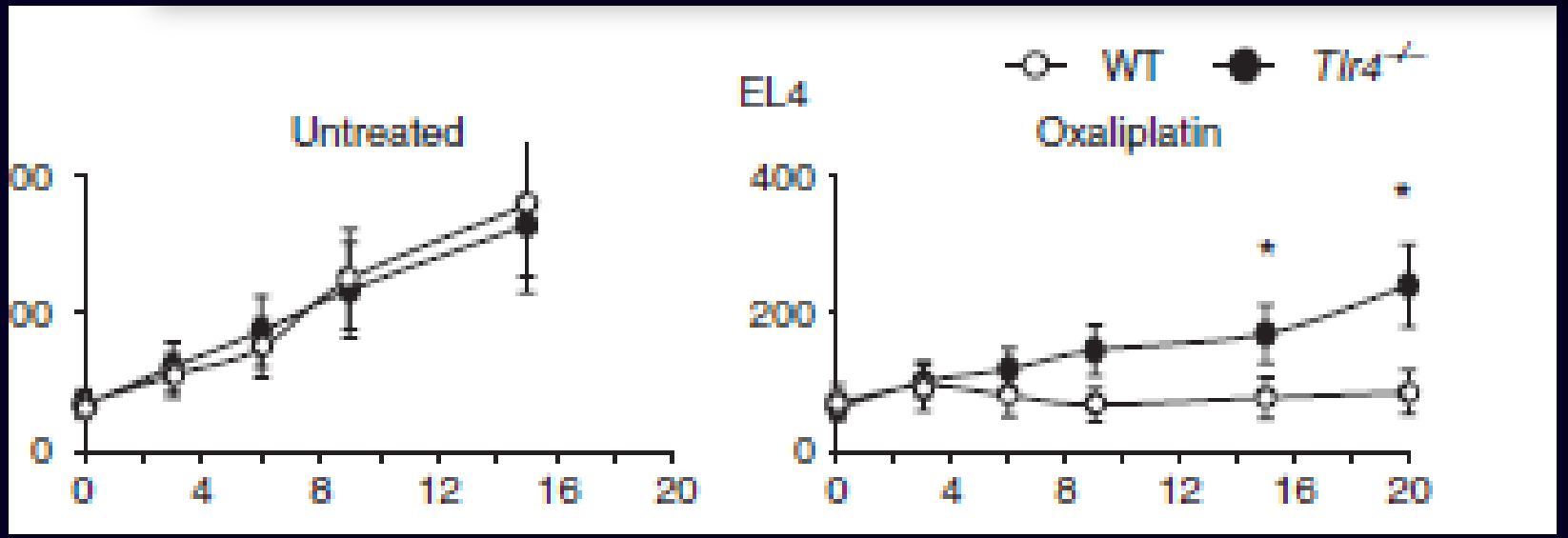

DFS

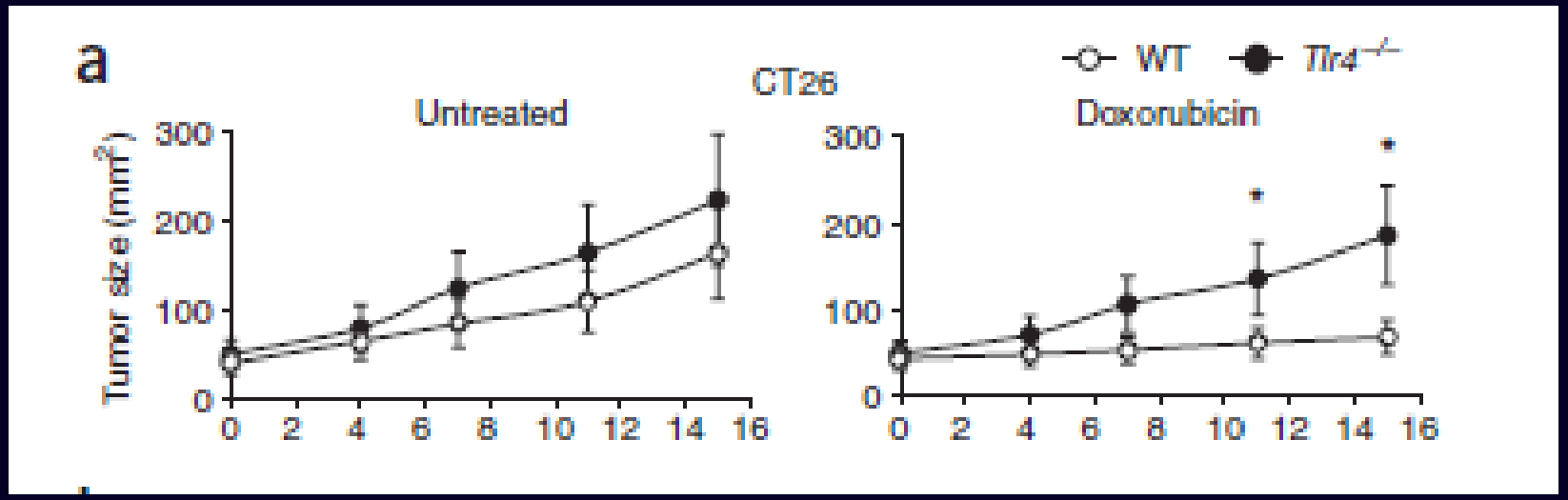



OS

EUR J CANCER 47 (2011) 1319–1327

# Relevance of HMGB1 & TLR4

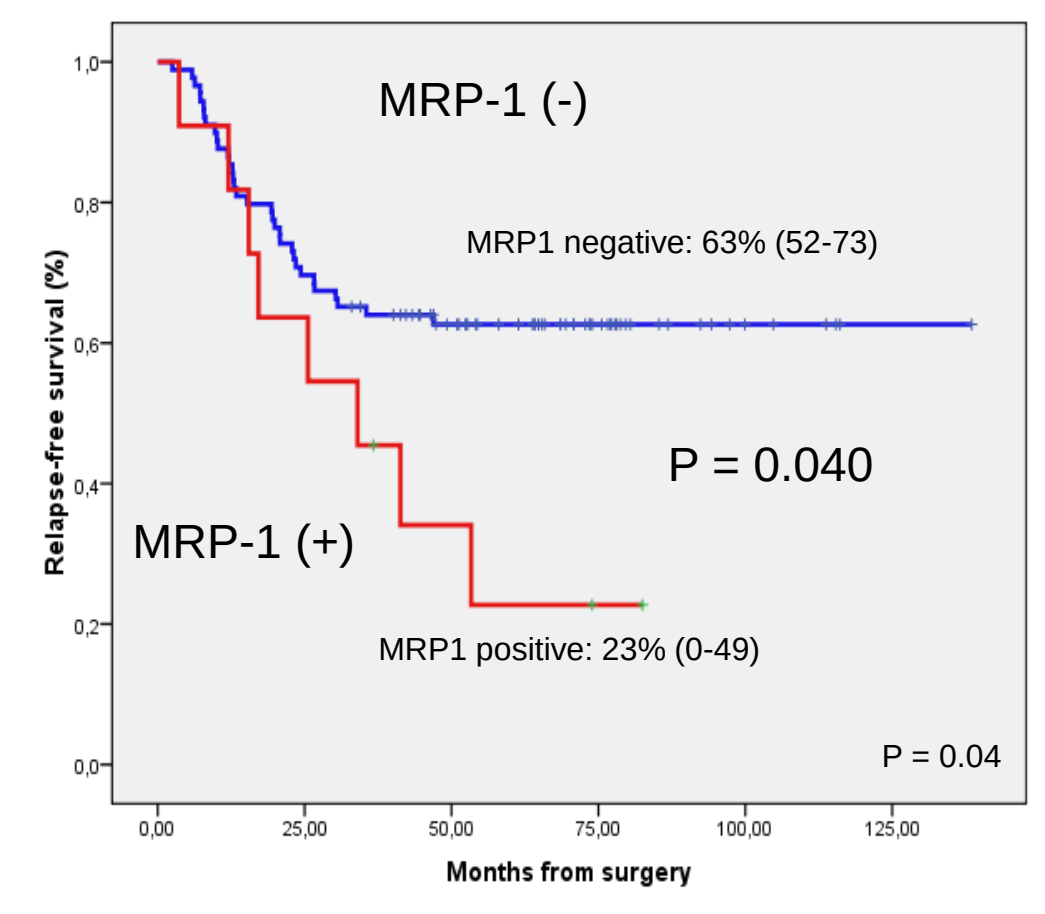


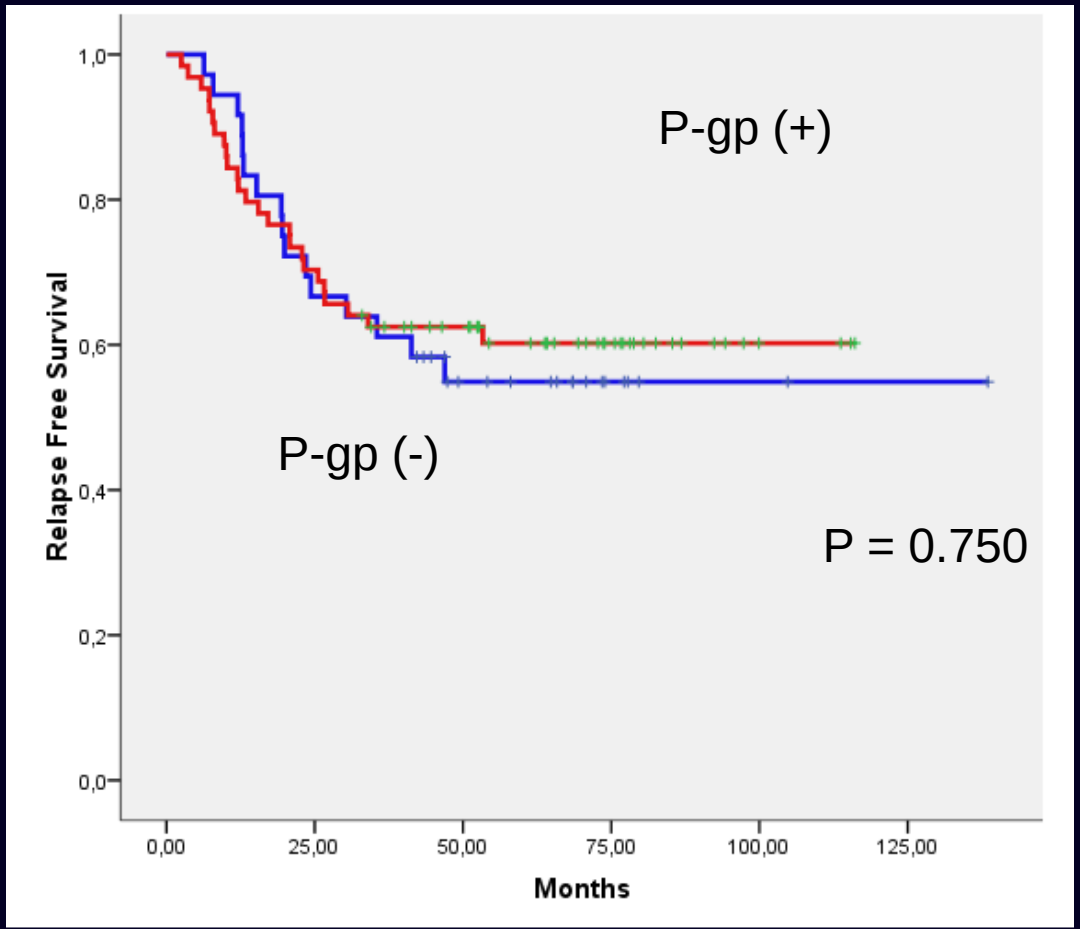




Apetoh et al. Nat Med. 2007

# Resistant mechanisms: MRP1

N = 98 Locally advanced STS treated with Epirubicin&Ifosfamide

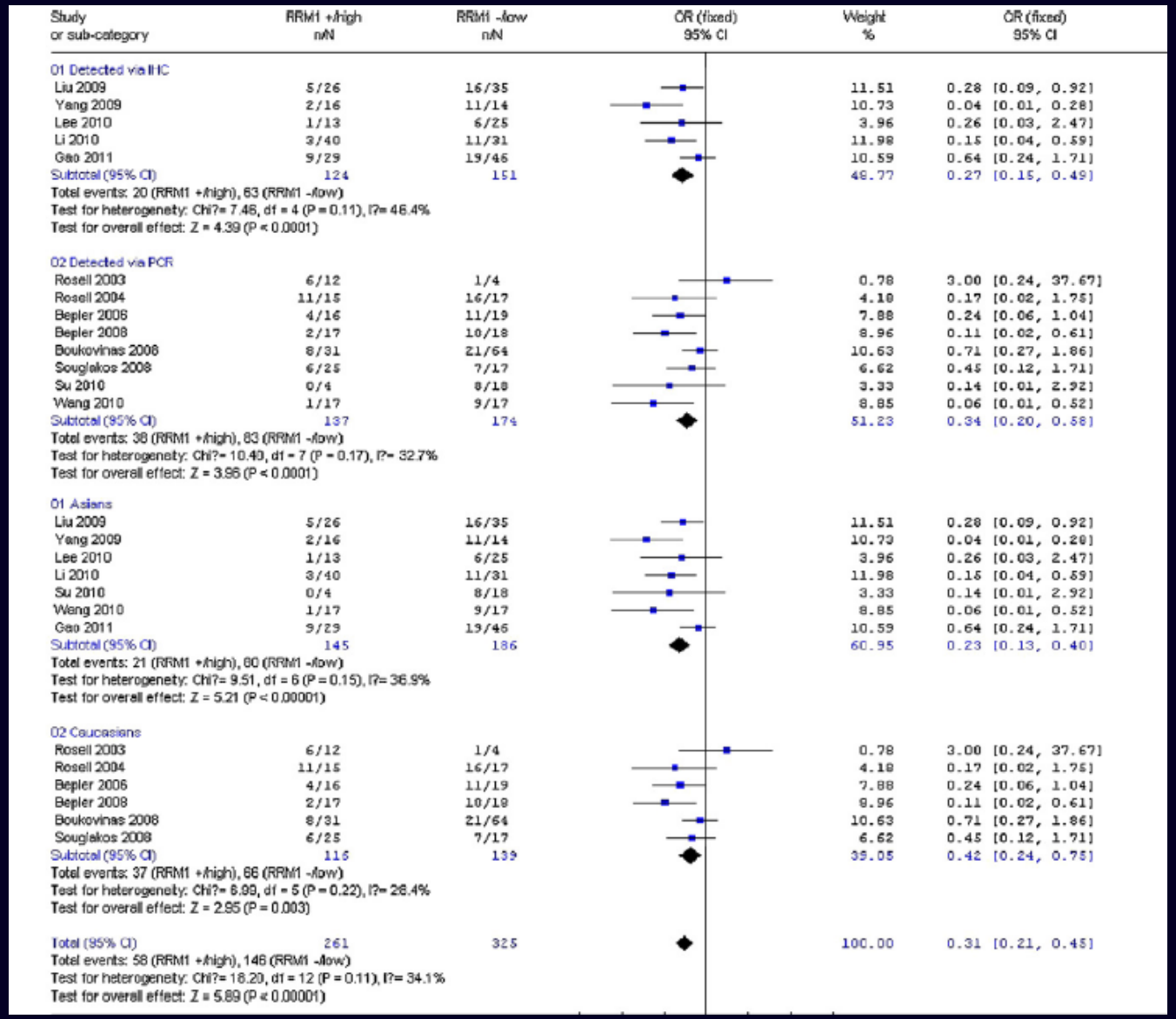



Mol Cancer Therapeutic 2014 Jan;13(1):249-59

# Retrospective Meta-analysis: RRM1 in NSCLC

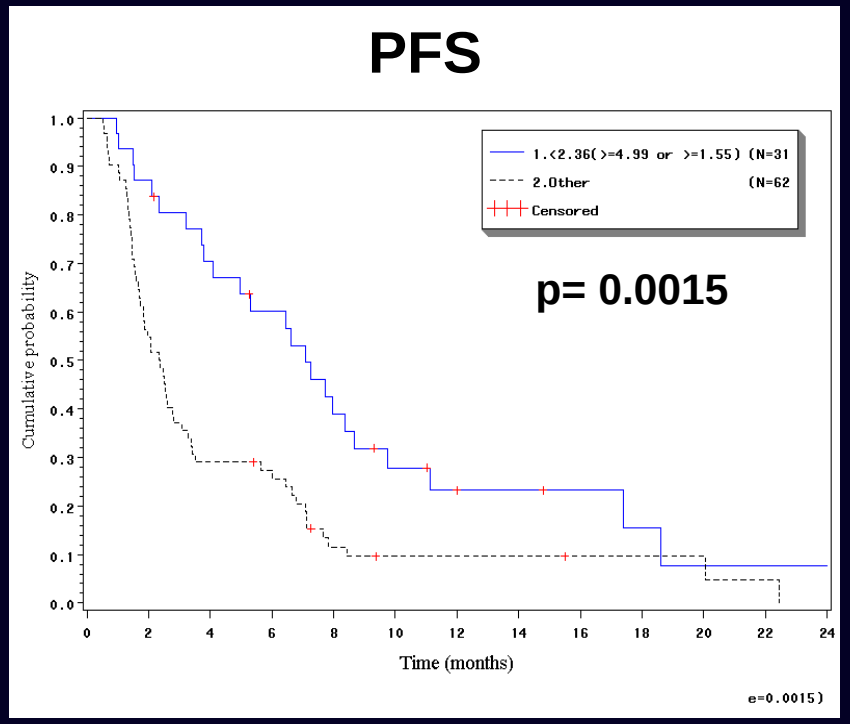
## Gemcitabine based regimens

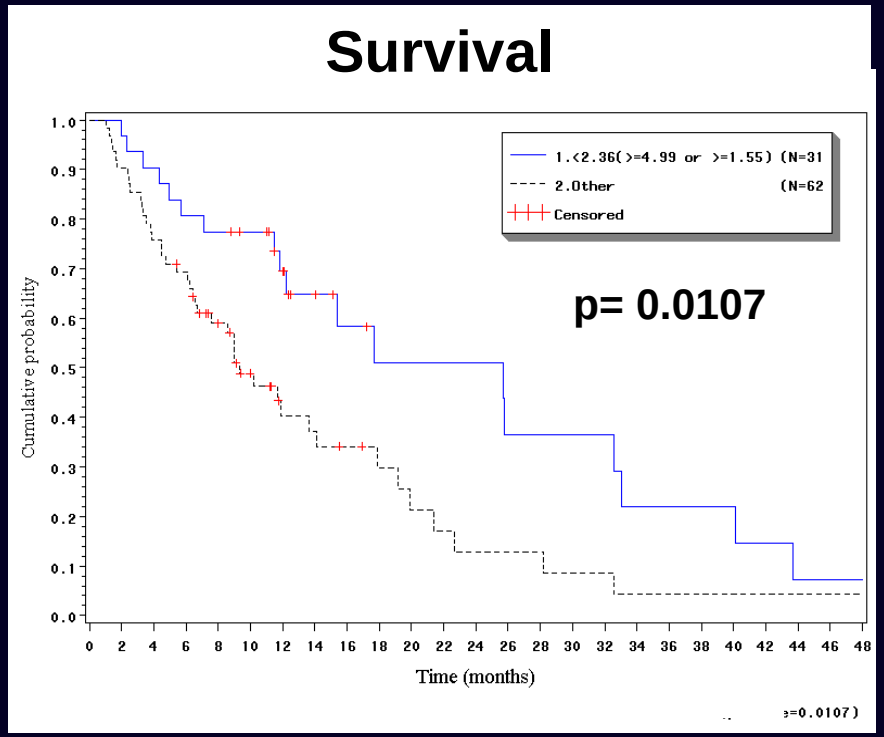


| Study or sub-category | RRM1 +/high n/N | RRM1 -/low n/N | OR (fixed) 95% CI | Weight % | OR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Detected via IHC | | | | | |
| Liu 2009 | 5/26 | 16/35 | | 11.51 | 0.28 [0.09, 0.92] |
| Yang 2009 | 2/16 | 11/14 | | 10.73 | 0.04 [0.01, 0.28] |
| Lee 2010 | 1/13 | 6/25 | | 3.96 | 0.26 [0.03, 2.47] |
| Li 2010 | 3/40 | 11/31 | | 11.98 | 0.15 [0.04, 0.59] |
| Gao 2011 | 9/29 | 19/46 | | 10.59 | 0.64 [0.24, 1.71] |
| Subtotal (95% CI) | 124 | 151 | | 48.77 | 0.27 [0.15, 0.49] |
| Total events: 20 (RRM1 +/high), 63 (RRM1 -/low) | | | | | |
| Test for heterogeneity: Chi?= 7.46, df = 4 (P = 0.11), I?= 46.4% | | | | | |
| Test for overall effect: Z = 4.39 (P < 0.0001) | | | | | |
| 02 Detected via PCR | | | | | |
| Rosell 2003 | 6/12 | 1/4 | | 0.78 | 3.00 [0.24, 37.67] |
| Rosell 2004 | 11/15 | 16/17 | | 4.18 | 0.17 [0.02, 1.75] |
| Bepler 2006 | 4/16 | 11/19 | | 7.88 | 0.24 [0.06, 1.04] |
| Bepler 2008 | 2/17 | 10/18 | | 8.96 | 0.11 [0.02, 0.61] |
| Boukovinas 2008 | 8/31 | 21/64 | | 10.63 | 0.71 [0.27, 1.86] |
| Souglakos 2008 | 6/25 | 7/17 | | 6.62 | 0.45 [0.12, 1.71] |
| Su 2010 | 0/4 | 8/18 | | 3.33 | 0.14 [0.01, 2.92] |
| Wang 2010 | 1/17 | 9/17 | | 8.85 | 0.06 [0.01, 0.52] |
| Subtotal (95% CI) | 137 | 174 | | 51.23 | 0.34 [0.20, 0.58] |
| Total events: 38 (RRM1 +/high), 83 (RRM1 -/low) | | | | | |
| Test for heterogeneity: Chi?= 10.40, df = 7 (P = 0.17), I?= 32.7% | | | | | |
| Test for overall effect: Z = 3.96 (P < 0.0001) | | | | | |
| 01 Asians | | | | | |
| Liu 2009 | 5/26 | 16/35 | | 11.51 | 0.28 [0.09, 0.92] |
| Yang 2009 | 2/16 | 11/14 | | 10.73 | 0.04 [0.01, 0.28] |
| Lee 2010 | 1/13 | 6/25 | | 3.96 | 0.26 [0.03, 2.47] |
| Li 2010 | 3/40 | 11/31 | | 11.98 | 0.15 [0.04, 0.59] |
| Su 2010 | 0/4 | 8/18 | | 3.33 | 0.14 [0.01, 2.92] |
| Wang 2010 | 1/17 | 9/17 | | 8.85 | 0.06 [0.01, 0.52] |
| Gao 2011 | 9/29 | 19/46 | | 10.59 | 0.64 [0.24, 1.71] |
| Subtotal (95% CI) | 145 | 186 | | 60.95 | 0.23 [0.13, 0.40] |
| Total events: 21 (RRM1 +/high), 80 (RRM1 -/low) | | | | | |
| Test for heterogeneity: Chi?= 9.51, df = 6 (P = 0.15), I?= 36.9% | | | | | |
| Test for overall effect: Z = 5.21 (P < 0.00001) | | | | | |
| 02 Caucasians | | | | | |
| Rosell 2003 | 6/12 | 1/4 | | 0.78 | 3.00 [0.24, 37.67] |
| Rosell 2004 | 11/15 | 16/17 | | 4.18 | 0.17 [0.02, 1.75] |
| Bepler 2006 | 4/16 | 11/19 | | 7.88 | 0.24 [0.06, 1.04] |
| Bepler 2008 | 2/17 | 10/18 | | 8.96 | 0.11 [0.02, 0.61] |
| Boukovinas 2008 | 8/31 | 21/64 | | 10.63 | 0.71 [0.27, 1.86] |
| Souglakos 2008 | 6/25 | 7/17 | | 6.62 | 0.45 [0.12, 1.71] |
| Subtotal (95% CI) | 116 | 139 | | 39.05 | 0.42 [0.24, 0.75] |
| Total events: 37 (RRM1 +/high), 66 (RRM1 -/low) | | | | | |
| Test for heterogeneity: Chi?= 6.99, df = 5 (P = 0.22), I?= 28.4% | | | | | |
| Test for overall effect: Z = 2.95 (P = 0.003) | | | | | |
| Total (95% CI) | 261 | 325 | | 100.00 | 0.31 [0.21, 0.45] |
| Total events: 58 (RRM1 +/high), 146 (RRM1 -/low) | | | | | |
| Test for heterogeneity: Chi?= 16.20, df = 12 (P = 0.11), I?= 34.1% | | | | | |
| Test for overall effect: Z = 5.89 (P < 0.00001) | | | | | |

Lung Cancer 75 (2012) 374– 380

# Impact of combined Low BRCA1 + High (ERCC1 or XPG) mRNA expression in the outcome of sarcoma patients treated with trabectedin




**Favorable subpopulation: low BRCA1 + high (XPG or ERCC1)**

**Remaining STS patients**

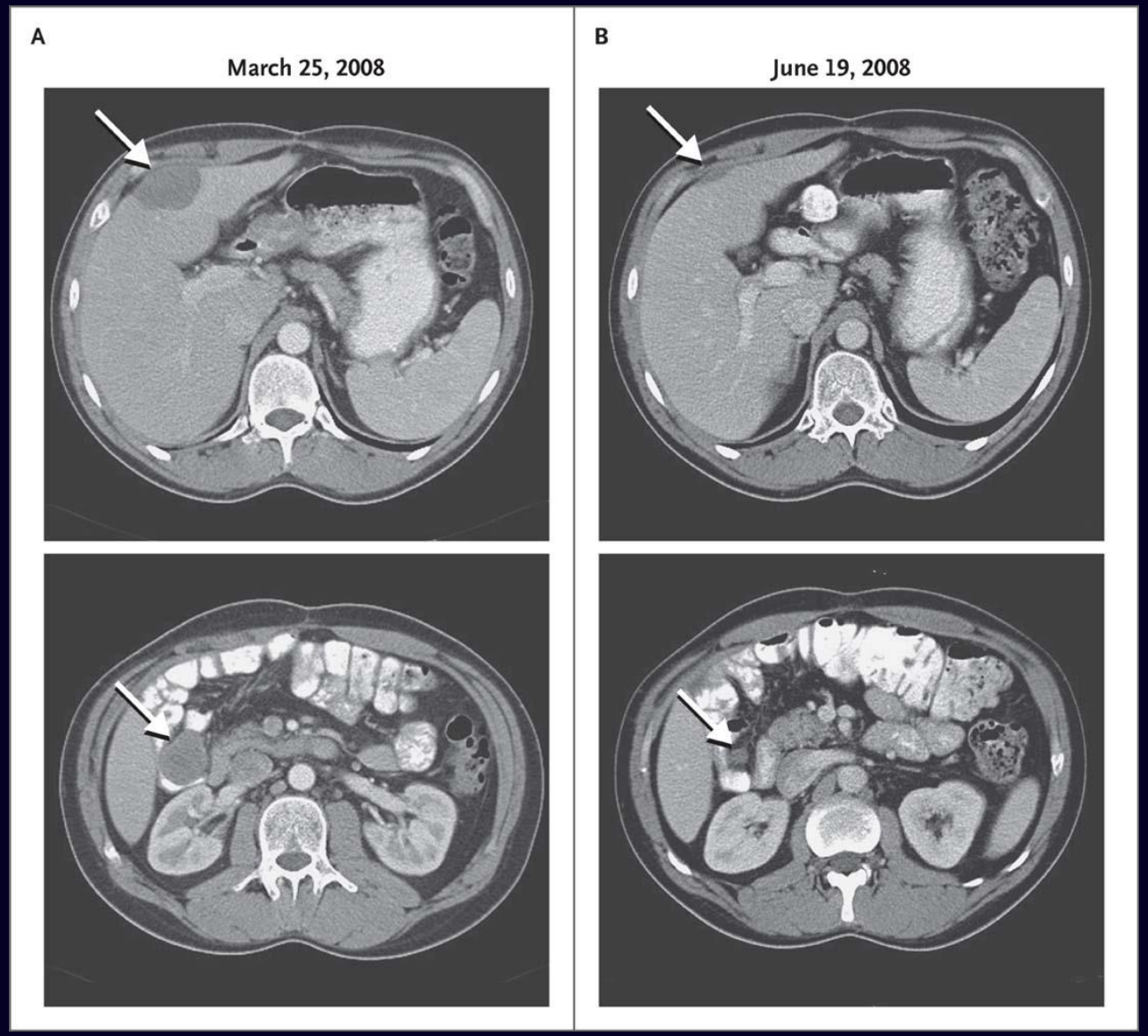
Eur J Cancer. 2011 May;47(7):1006-12

# Predictive biomarkers very scarce in STS?

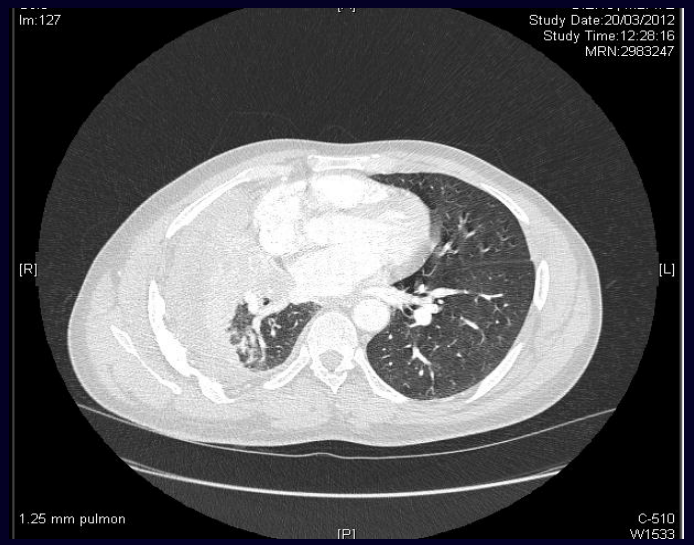
| Sarcoma Subtype | Predictive biomarker |
|---|---|
| Inflammatory Miofibroblastic Tumor | Crizotinib efficacy related to ALK rearrangement (1) |
| DFSP | Imatinib efficacy related to t(17;22) (2) |
| GIST | KIT/PDGFRa Important correlations but not in STS |
| GCTB | RANKL relevant but not predictive |

N Engl J Med 2010;363:1727-33(1)
J Clin Oncol 2005;23:866-73 (2)

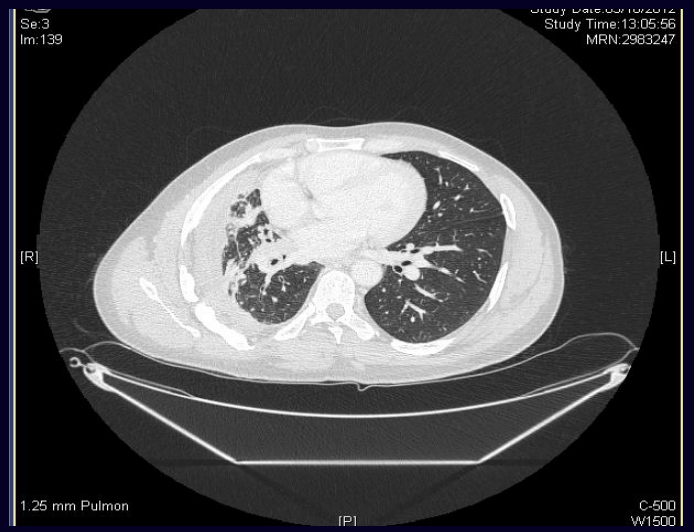
# IMT: ALK & Crizotinib




Butrynski JE et al. N Engl J Med 2010;363:1727-1733



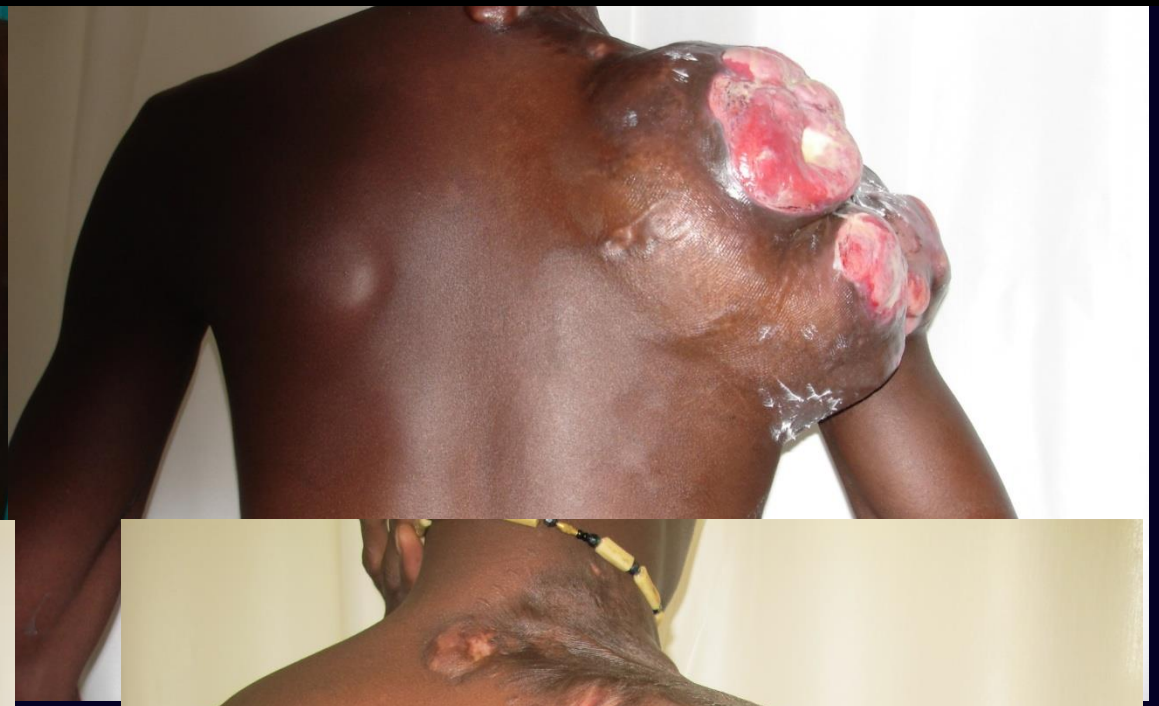

MARCH 2012

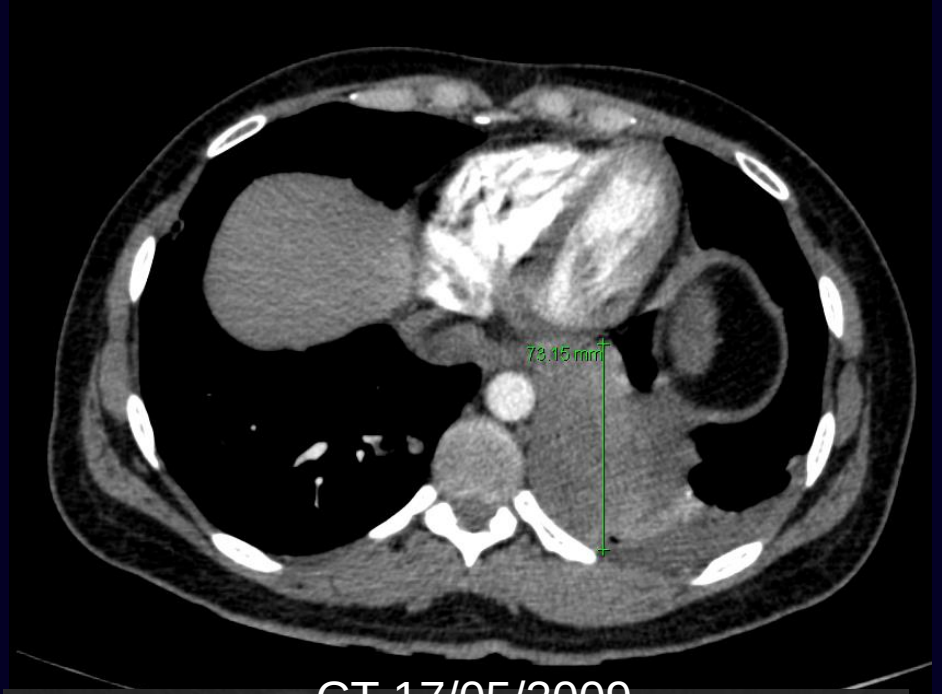



OCTOBER 2012

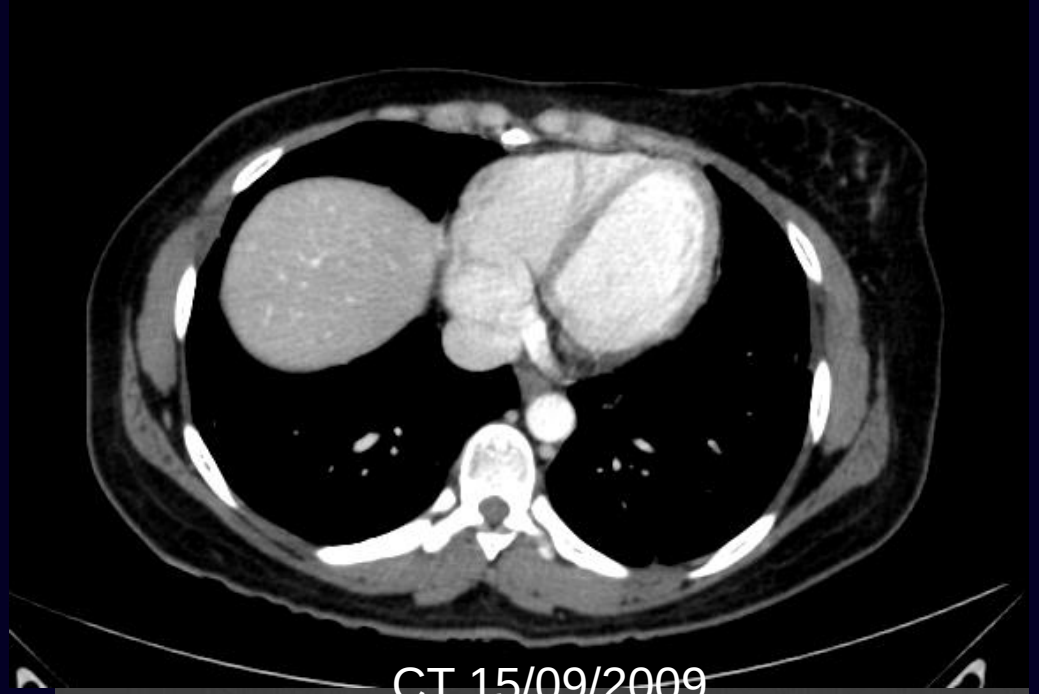
Personal case

# DFSP: PDGFB rearrangement & Imatinib

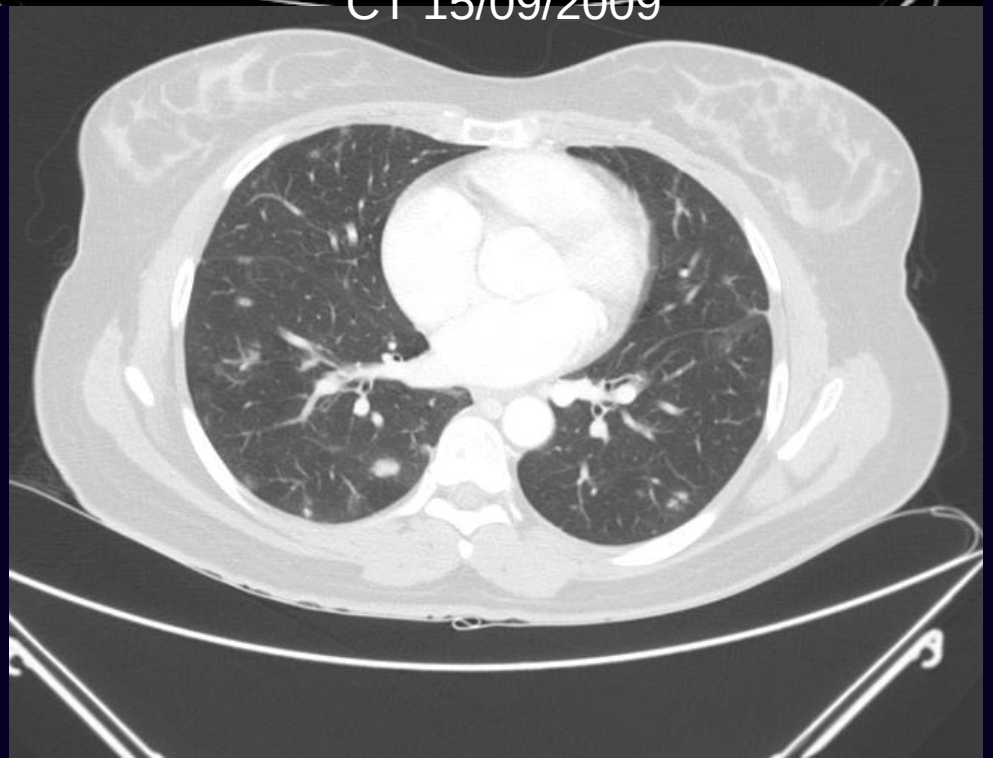





CT 17/05/2009



CT 15/09/2009



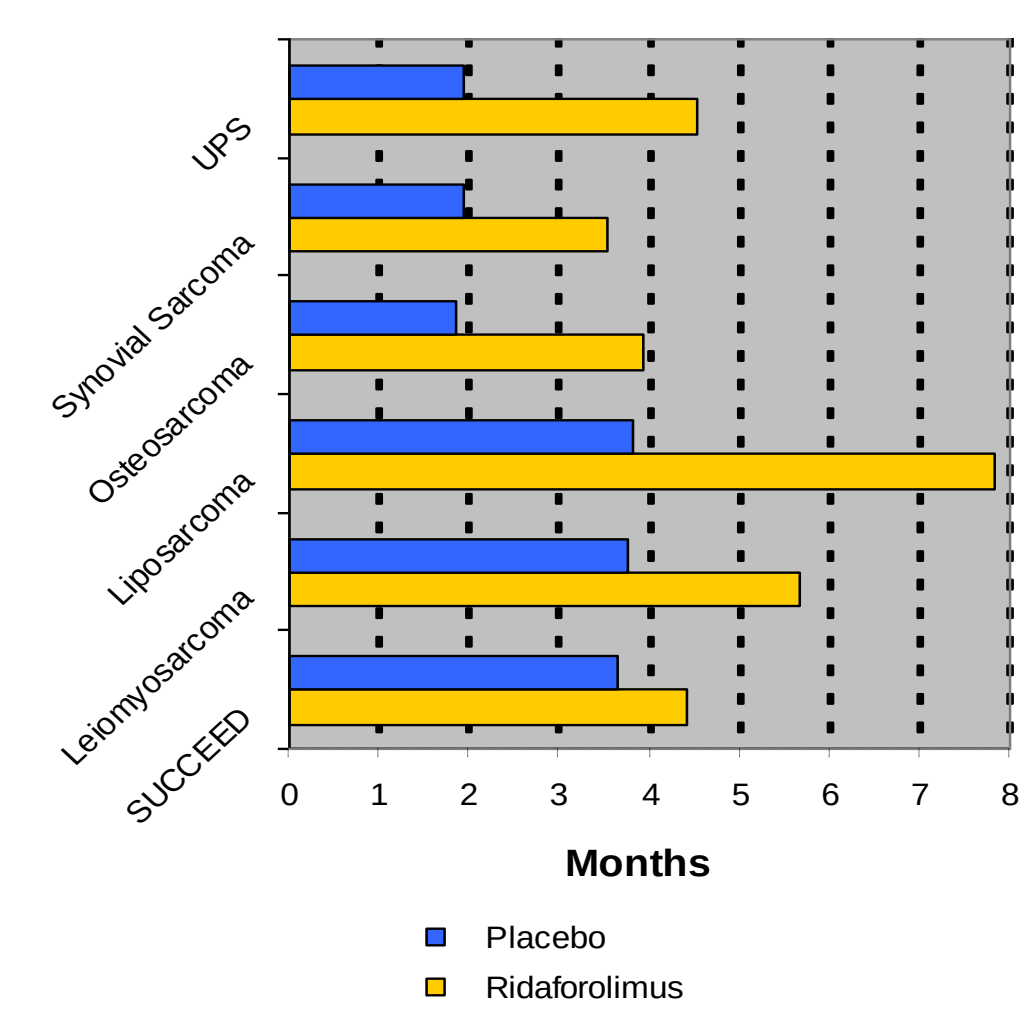
# TARGETED THERAPIES IN SARCOMA (NON-GIST)

It accounts for less than 15% of STS

| | |
|---|---|
| ✓ IMATINIB: | DFSP; CHORDOMA; PVNS |
| ✓ SUNITINIB | Solitary fibrous tumor |
| ✓ CRIZOTINIB | Inflammatory miofibroblastic tumor |
| ✓ M-TOR INH | PEComas; Leiomyomatosis |
| ✓ PAZOPANIB | Several |
| ✓ TRABECTEDIN | LPS MIXOIDE; Synovial Sarcoma |
| ✓ PARP INH | S EWING (ONGOING) |
| ✓ NUTLINS | WD/DD LIPOSARCOMA |
| ✓ WNT | TBD |
| ✓ HEDGHOG/NOTCH | TBD |
| ✓ DENOSUMAB | TCG ÓSEO |
| ✓ Anti CSF1 | PVNS |

# SUCCEED trial did not SUCCEED

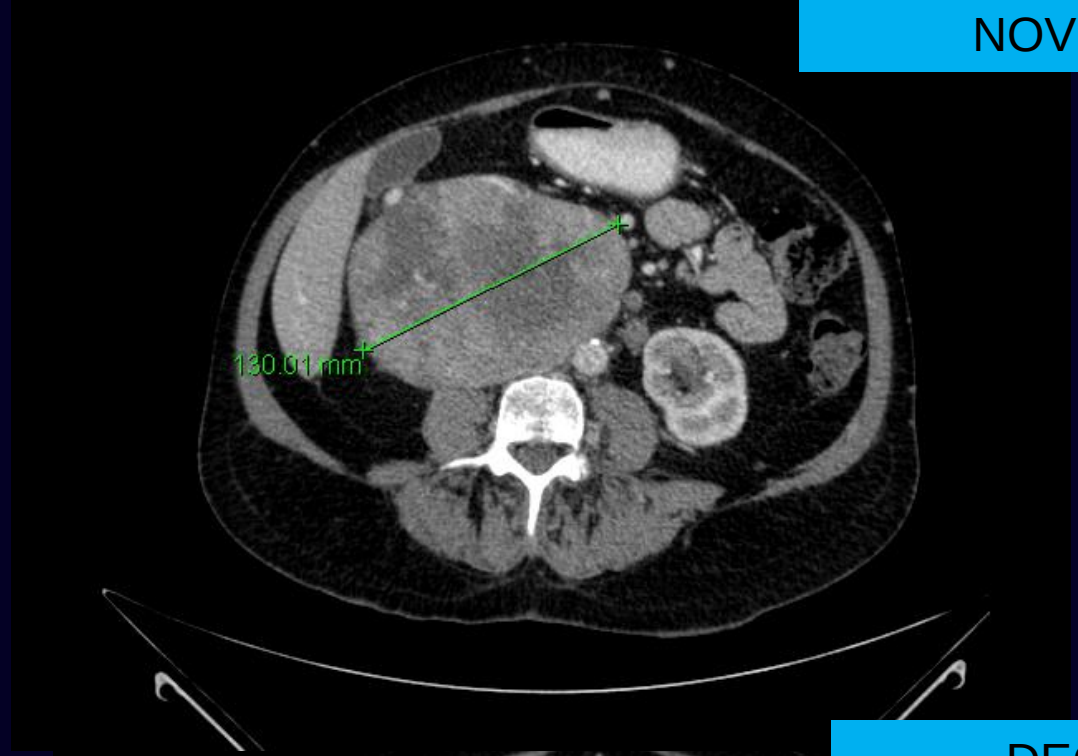
## PFS by pathologic subgroup

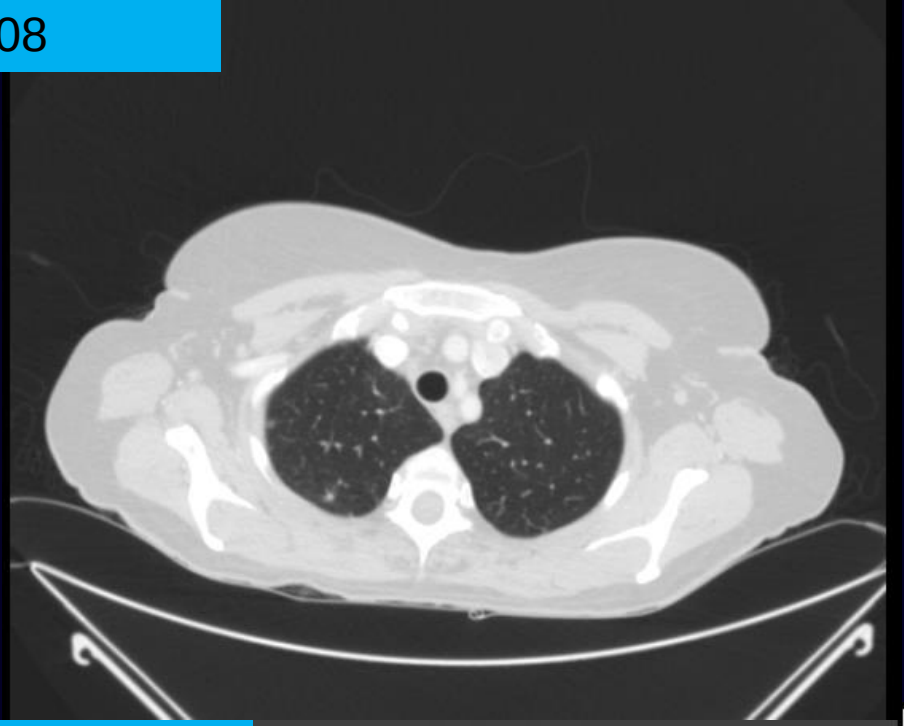



| Difference | % imp | P-value |
|---|---|---|
| 10.4 weeks* | 135.1 % | |
| 6.4 weeks* | 83.1 % | |
| 8.3 weeks* | 112.1 % | |
| 16 weeks* | 104.6 % | |
| 7.7 weeks | 51.3 % | p=0.0001 |
| 3.1 weeks | 21.2 % | p=0.0001 |

* Differences not statistically significant

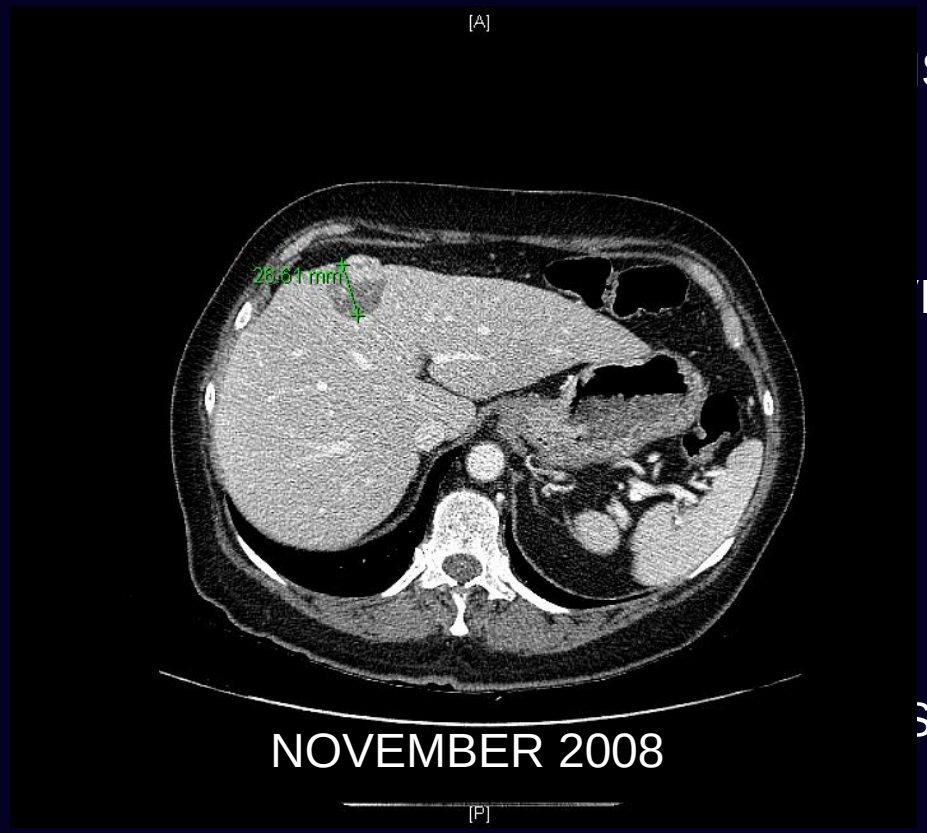
NOVEMBER 2008



DECEMBER 2009


SD

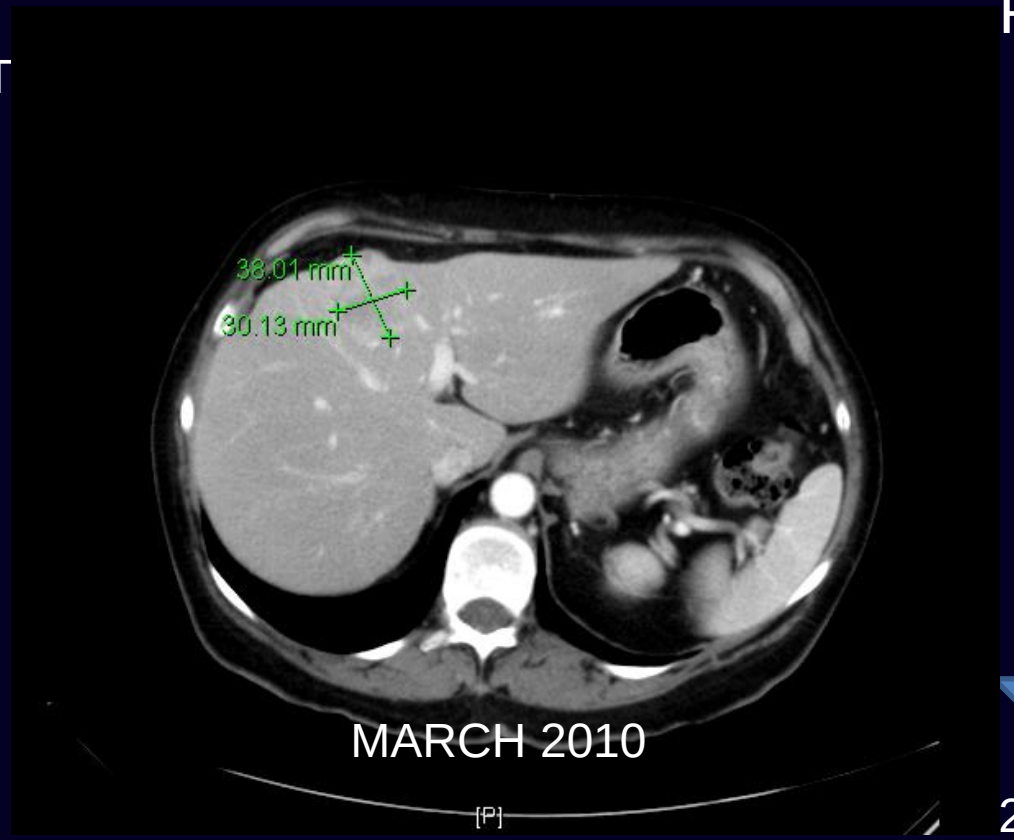



NOVEMBER 2008

S T

IC

SE




MARCH 2010

NEW TRABECDETIN RECHALLENGE

NOVEMBER 2010

PROGRESSION DISEASE

AUGUST 2012

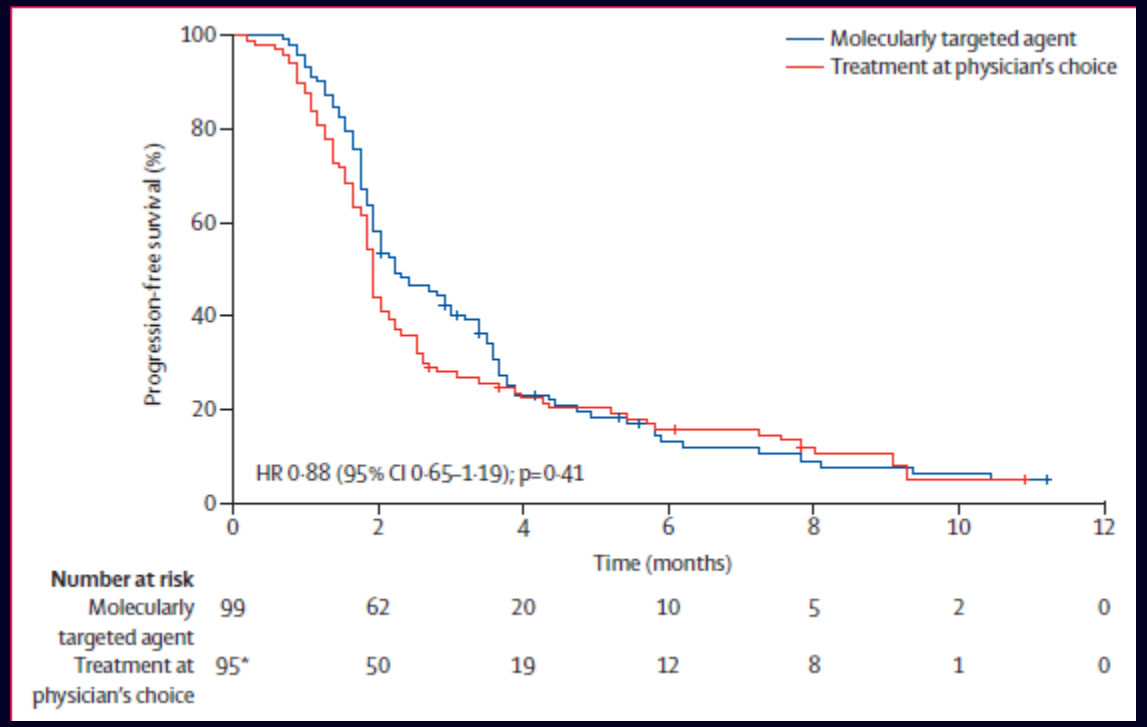
PFS

OS

22 M

+ 52 M

# Studies exploring molecularly targeted therapy: SHIVA TRIAL: 197 R´




PFS: NO significant differences

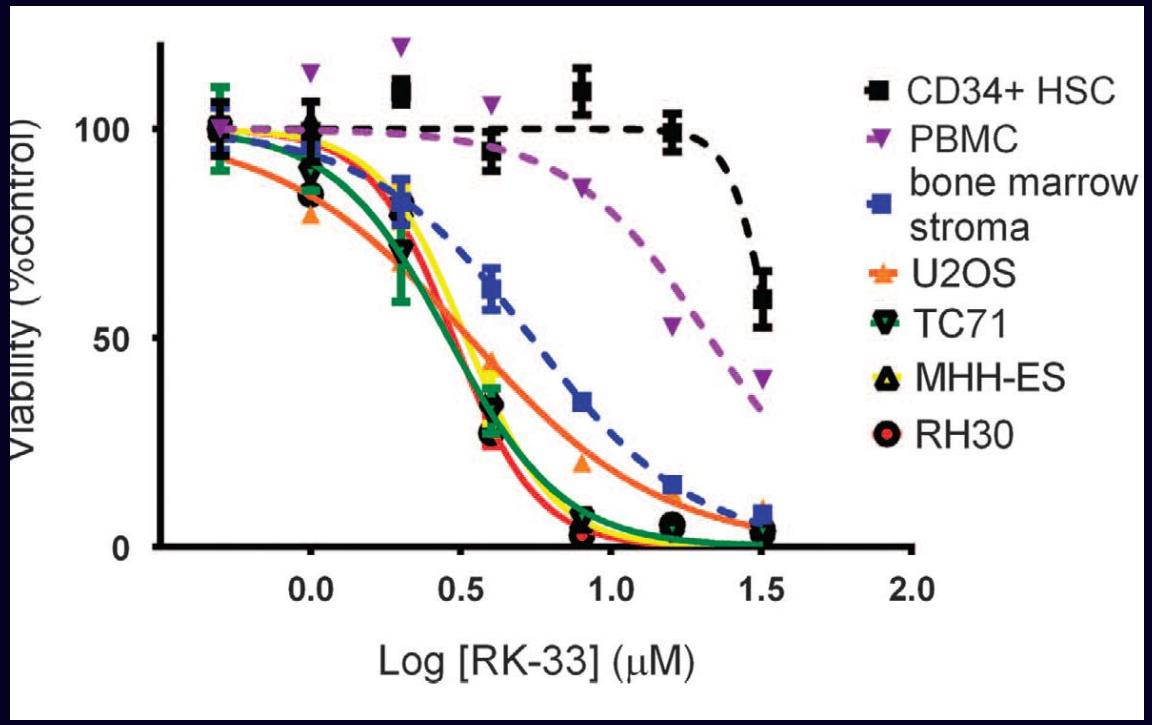
| | Patients who received molecularly targeted agents (n=100*) | | | Patients who received cytotoxic chemotherapy (n=91†) | | |
|---|---|---|---|---|---|---|
| | Grade 2 necessitating drug interruption or delay‡ | Grade 3 | Grade 4 | Grade 2 necessitating drug interruption or delay | Grade 3 | Grade 4 |
| Any event§ | 12 (12%) | 36 (36%) | 7 (7%) | 9 (10%) | 28 (31%) | 4 (4%) |
| Neutropenia | 0 | 1 (1%) | 0 | 0 | 5 (5%) | 2 (2%) |
| Febrile neutropenia | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Anaemia | 0 | 5 (5%) | 0 | 2 (2%) | 4 (4%) | 0 |
| Thrombocytopenia | 1 (1%) | 1 (1%) | 1 (1%) | 0 | 0 | 1 (1%) |
| Loss of appetite | 2 (2%) | 0 | 1 (1%) | 0 | 2 (2%) | 0 |
| Asthenia | 0 | 2 (2%) | 3 (3%) | 2 (2%) | 2 (2%) | 0 |
| Nausea | 2 (2%) | 2 (2%) | 0 | 1 (1%) | 0 | 0 |
| Vomiting | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Mucositis | 0 | 1 (1%) | 0 | 0 | 1 (1%) | 0 |
| Constipation | 0 | 0 | 0 | 0 | 1 (1%) | 0 |
| Abdominal pain | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Weight loss | 1 (1%) | 0 | 0 | 0 | 0 | 0 |
| Weight gain | 0 | 0 | 0 | 1 (1%) | 0 | 0 |
| Dyspnoea | 1 (1%) | 6 (6%) | 0 | 0 | 2 (2%) | 0 |
| Skin reactions | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 0 |
| Cardiac ischaemia | 0 | 0 | 0 | 0 | 1 (1%) | 0 |
| Arrhythmia | 0 | 0 | 0 | 0 | 1 (1%) | 0 |
| Arthralgia | 0 | 2 (2%) | 0 | 0 | 0 | 0 |
| Peripheral neuropathy | 0 | 1 (1%) | 0 | 0 | 1 (1%) | 0 |
| Aspartate aminotransferase increase | 0 | 2 (2%) | 0 | 0 | 0 | 0 |
| Creatinine increase | 0 | 0 | 0 | 0 | 1 (1%) | 0 |
| Other | 2 (2%) | 9 (9%) | 5 (5%) | 3 (3%) | 6 (7%) | 1 (1%) |

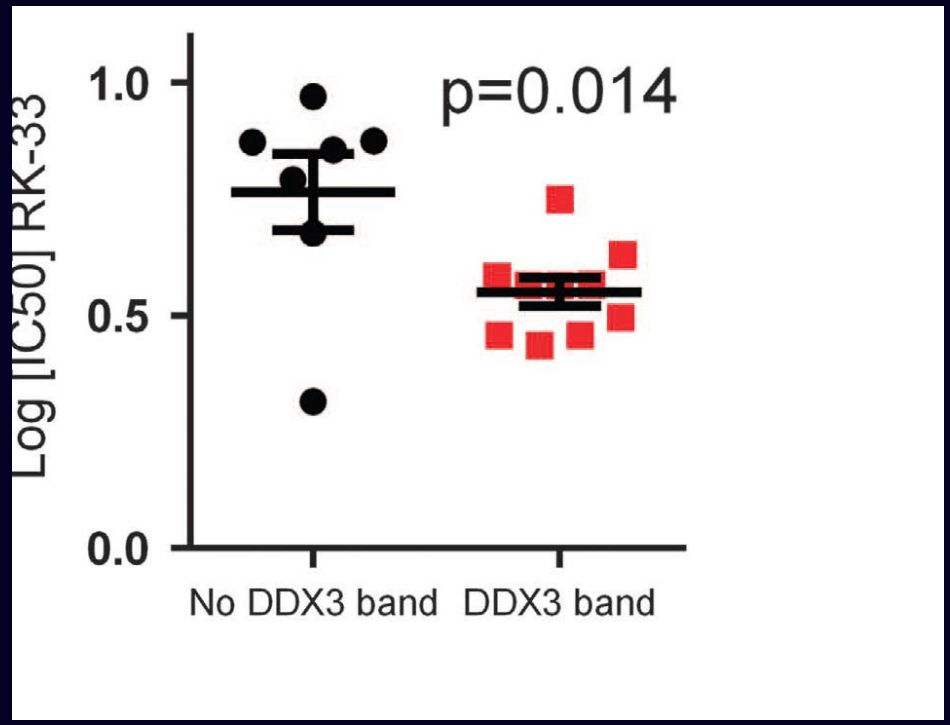
AEs: Molecuraly targeted more toxic

***Lancet Oncol* 2015; 16: 1324–34**

# RNA helicase DDX3: target in Ewing

Role for DDX3 inhibitor: RK-33




Wilky A, et al. Oncogene (2015), 1–10

# REMARKS

- Chemotherapy is the standard approach in 1st, and for most of 2nd line & beyond in STS and BS
- No predictive biomarkers for most frequent sarcomas
- Expectations of molecularly addressed therapies are coming from most uncommon subtypes.
- Traslocation- related sarcomas are poor “Druggable” entities so far

# THANKS

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