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ONCOLOGY

# How does biology guide the treatment of soft tissue sarcoma (STS)?

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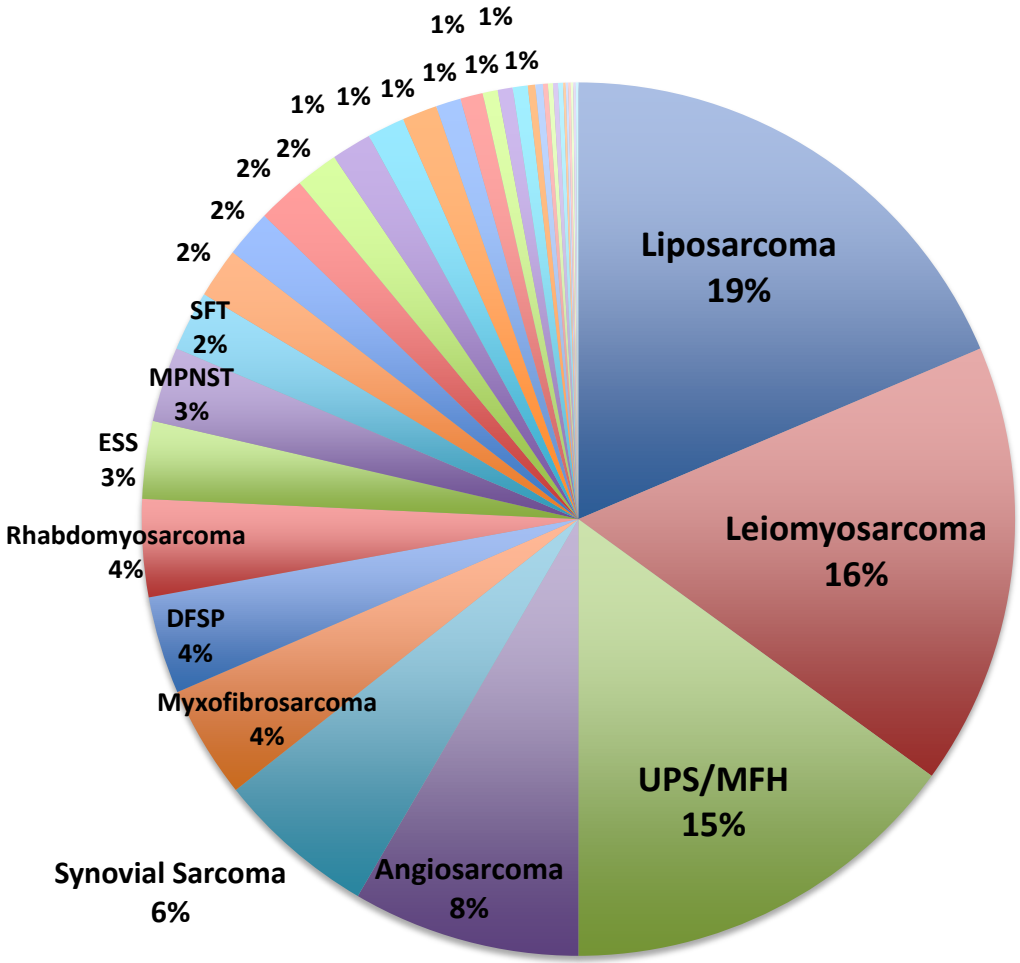
# Disclosure slide

- Research and education funding
  - Novartis, Bayer, JNJ, Pfizer
- Consulting or advisory role
  - Novartis, Merck
- Travel Grants
  - Novartis, Roche

# Soft Tissue Sarcoma

- Clinically and molecularly heterogeneous disease sharing a mesenchymal origin
- Made up of >40 distinct subtypes
- Historically looked upon as one single disease entity and treated with cytotoxic chemotherapy with limited benefit

# National Cancer Centre Singapore
# Soft Tissue Sarcoma Database (n=1080)

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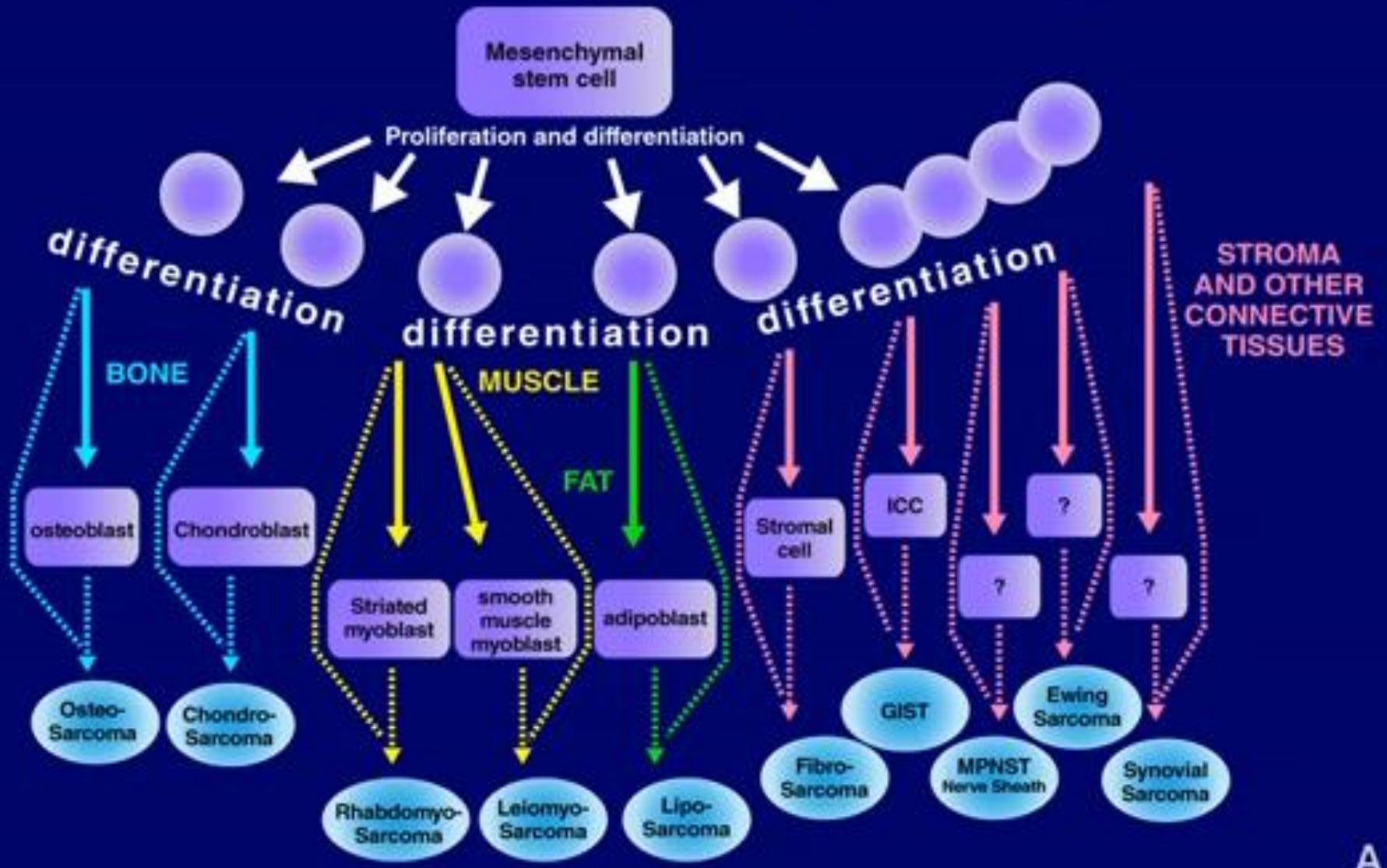
# Sarcomas Are Uncommon Cancers Linked by Mesenchymal Origin



# Molecular Classification of STS

| | Molecular biology | Genes/ chromosomes | STS sub-type |
|---|---|---|---|
| 1 | Recurrent translocation | t(1,2)<br>t(12;16); t(12;22) | Pigmented villonodular synovitis (PVNS)<br>Myxoid Liposarcoma |
| 2 | Kinase/ gene mutation | *KIT, PDGFRA*<br>*TSC* 1/2 | GIST<br>PECOMA |
| 3 | Simple genetic alterations | *MDM2/ CDK4* amplification | Well diff/ de-diff Liposarcoma |
| 4 | Gene inactivation | Loss of INI1 | Epitheloid sarcoma |
| 5 | Complex cytogenetics | | Leiomyosarcoma<br>Angiosarcoma<br>Undifferentiated pleomorphic sarcoma |

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# Recurrent Translocation

# Soft tissue sarcoma (STS) with recurrent translocation

| | Histology | Translocation | Treatment |
|---|---|---|---|
| 1 | Myxoid LPS | t(12;16); t(12;22) | Trabectedin |
| 2 | Translocation related STS | various | 2nd line Trabectedin |
| 3 | Pigmented villonodular synovitis (PVNS) | t(1,2) | CSF-1 inhibitor |
| 4 | ALK + Inflammatory myofibroblastic tumor | ALK rearrangement | ALK inhibitors |
| 5 | Alveolar soft part sarcoma (ASPS) | t(X,17)(p11;q25) | Anti-VEGF |

# 1. Myxoid Liposarcoma (LPS)

## Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study

Federica Grosso, Robin L Jones, George D Demetri, Ian R Judson, Jean-Yves Blay, Axel Le Cesne, Roberta Sanfilippo, Paola Casieri, Paola Collini, Palma Dileo, Carlo Spreafico, Silvia Stacchiotti, Elena Tamborini, Juan Carlos Tercero, Josè Jimeno, Maurizio D'Incalci, Alessandro Gronchi, Jonathan A Fletcher, Silvana Pilotti, Paolo G Casali

- Myxoid LPS is a distinct subtype within the liposarcoma family of tumors
- Associated with translocations t(12;16)(q13;p11) or t(12;22)(q13;q12)
- Resulting in formation of DDIT3-FUS or DDIT3-EWSR1 fusion proteins
- Trabectedin is a chemotherapy derived from the marine sea squirt
- Binds to DNA minor groove
- Interferes with binding of fusion proteins to DNA promoters

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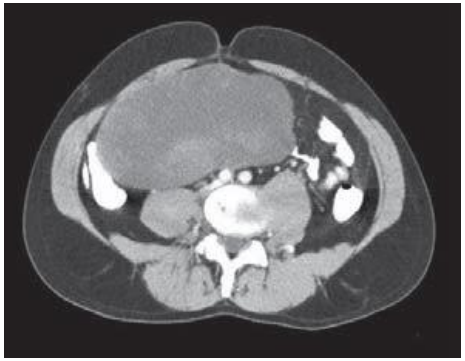
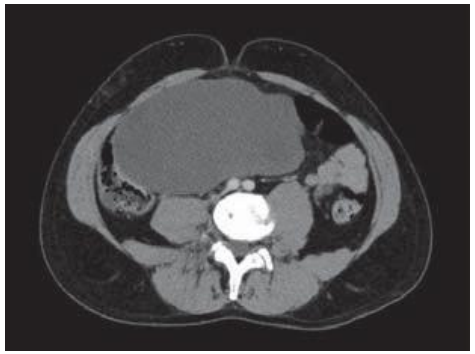
Lancet Oncol 2007; 8: 595–602

# Myxoid Liposarcoma (LPS)

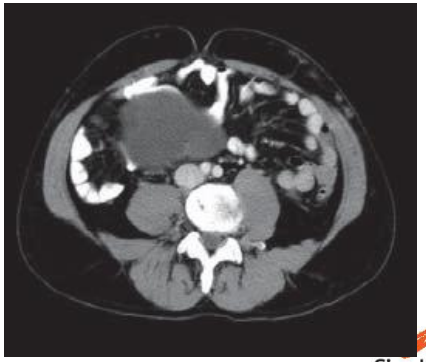
- Retrospective study of 51 pts with pre-treated myxoid LPS
- Median of 2 prior lines of chemo
- Response rate 51%
- Median progression free survival 14 months



Baseline



#1 cycle



#11 cycle

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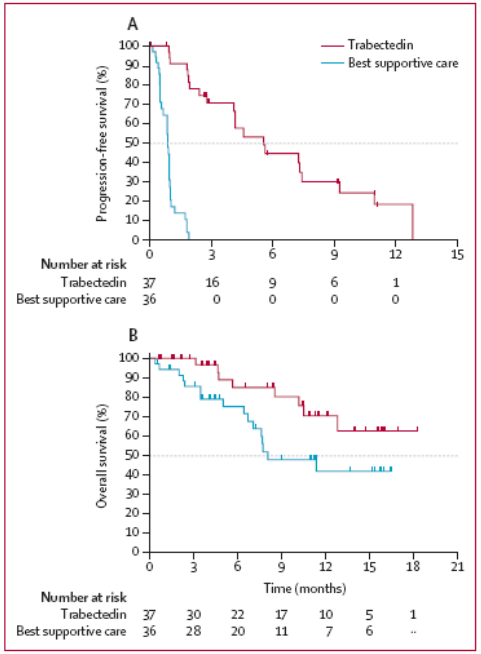
# 2. Translocation related STS

## Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study

*Akira Kawai, Nobuhito Araki, Hideshi Sugiura, Takafumi Ueda, Tsukasa Yonemoto, Mitsuru Takahashi, Hideo Morioka, Hiroaki Hiraga, Toru Hiruma, Toshiyuki Kunisada, Akihiko Matsumine, Takanori Tanase, Tadashi Hasegawa, Shunji Takahashi*

- Randomized phase II
- N= 76 failed or intolerant to chemotherapy
- Trabectedin vs BSC in pts with translocation related sarcoma
- Median PFS 5·6mth (T) vs 0·9mth (BSC)
  (HR 0·07 p<0·0001)





Lancet Oncol 2015; 16: 406–16

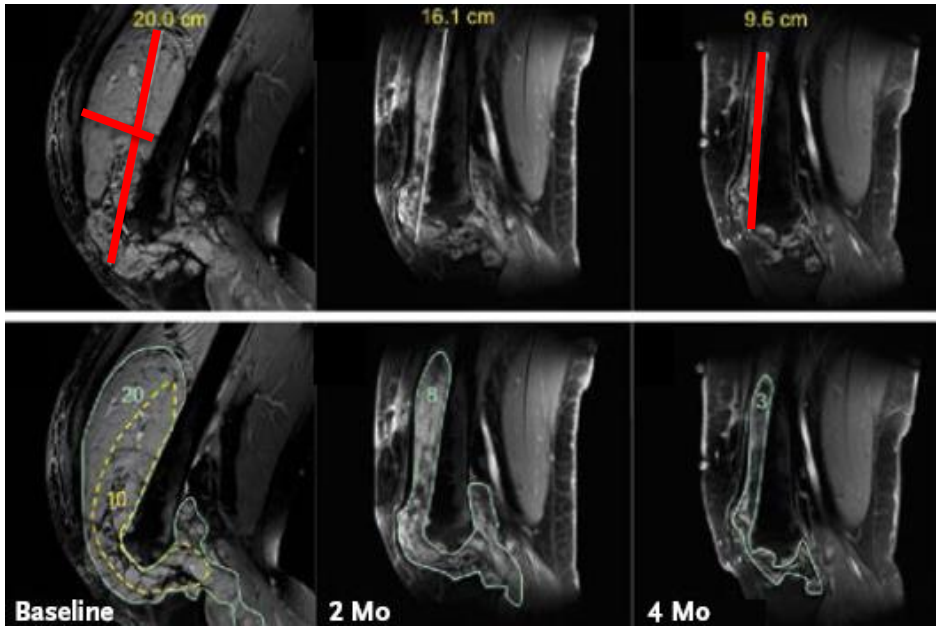
# 3. Pigmented villonodular synovitis (PVNS)

- Disease characterized by t(1,2): *CSF1* fused to *COL6A3*
- Resulting in over-expression of CSF1 by small fraction of neoplastic cells attracting large population of NON-neoplastic cells
- "Landscape" effect[1]
- Surgery mainstay of treatment
- Imatinib and nilotinib (ORR 5%) have reported activity[2,3]

1 PNAS. 2006;103(3):690–695
2 Annals of Oncology. 2008;19:821–826
3 J Clin Oncol 31, 2013 (suppl; abstr 10516)

# CSF 1 inhibition in PVNS

- **PLX3397** an oral CSF1 inhibitor
- 23 pts with progressive PVNS were enrolled in the extension study
- Response rate 52% (12/23 pts)
- Median duration of response >8mth





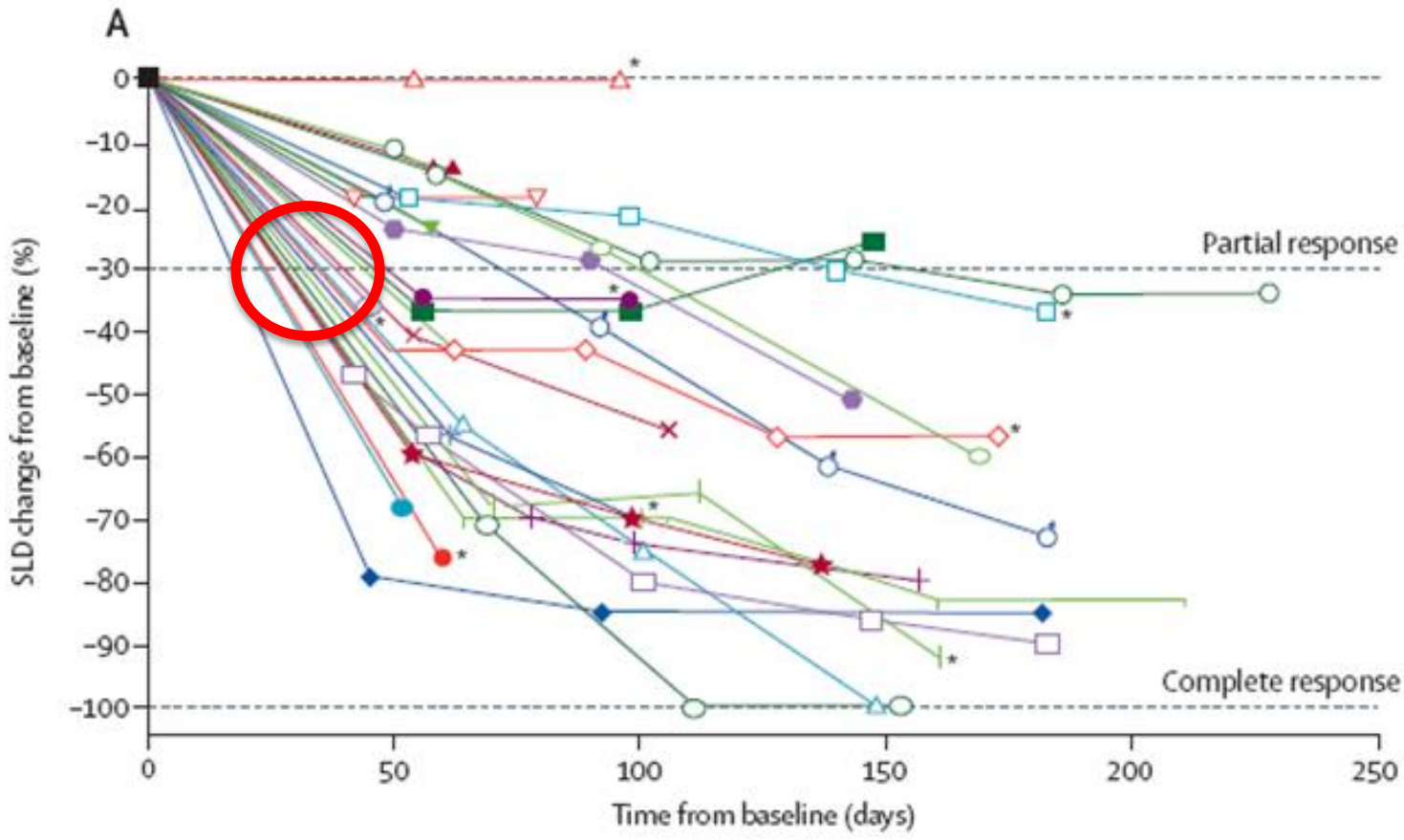
N Engl J Med 2015;373:428-37

# CSF 1 inhibition in PVNS

- **Emactuzumab (RG7155)** is novel monoclonal antibody that inhibits CSF1R activation
- 28pts PVNS pts were enrolled in dose escalation and dose extension phase
- 28% had seen prior imatinib
- Response rate 86% (including complete response of 7%)


Lancet Oncol 2015; 16: 949–56

# Emactuzumab (RG7155) in PVNS




**68% PR within 6 weeks**

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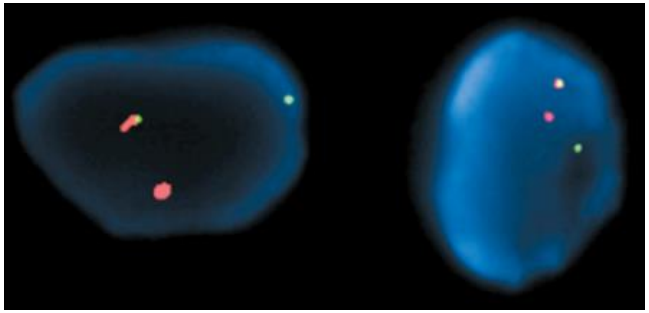
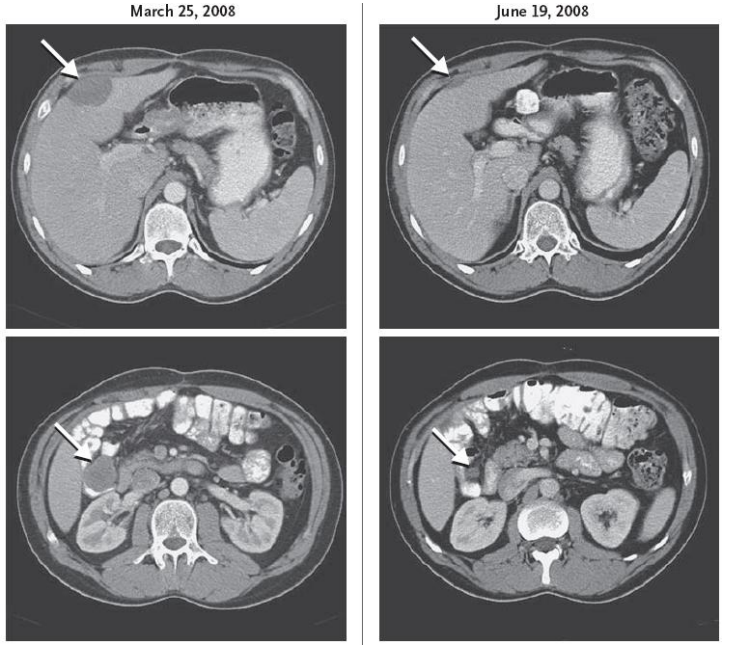
# 4. Inflammatory Myofibroblastic Tumor (IMT)

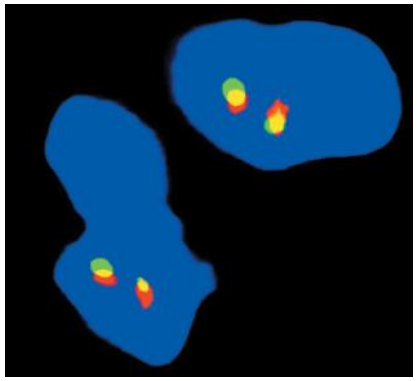
- Half of cases of IMT carry ALK gene (2p23) rearrangement causing aberrant ALK expression
- Crizotinib is an ALK inhibitor

**Patient 1**






**Patient 2**



**No response**


N Engl J Med 2010;363:1727-33

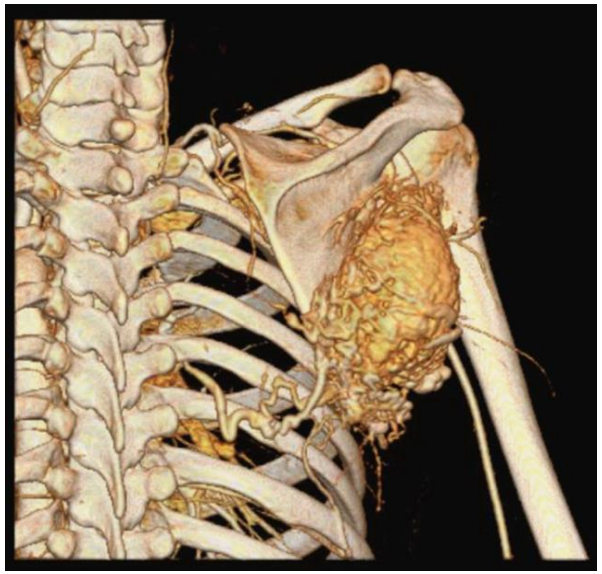
# 5. Alveolar soft part sarcoma (ASPS)

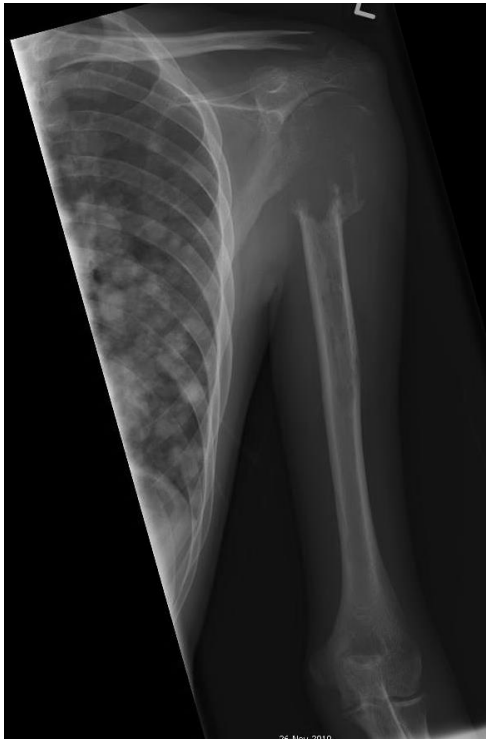
- Rare sarcoma characterized by presence of t(X,17)(p11;q25)
- Resulting in formation of ASPL-TFE3 transcription factor
- Associated with enhanced MET signaling
- ASPS is a vascular tumor and gene expression profile studies demonstrate upregulation of several transcripts associated with angiogenesis, proliferation and metastasis [1,2]

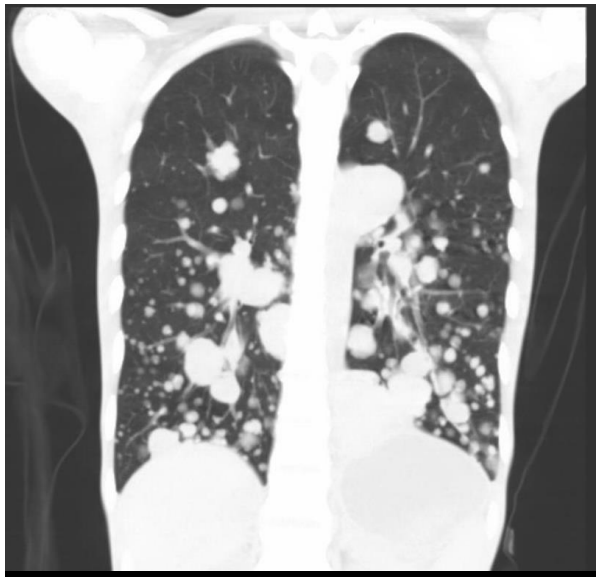
1 BMC Cancer. 2009;9:22
2 Clin Cancer Res. 2007;13:7314-7321

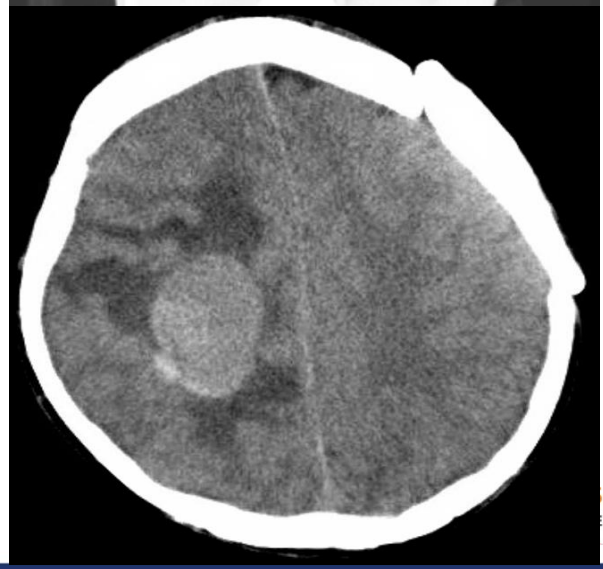
# 5. Alveolar soft part sarcoma (ASPS)

- Cytotoxic chemo ineffective
- Response rates 7% [1]
- 5 year survival 20% [2]







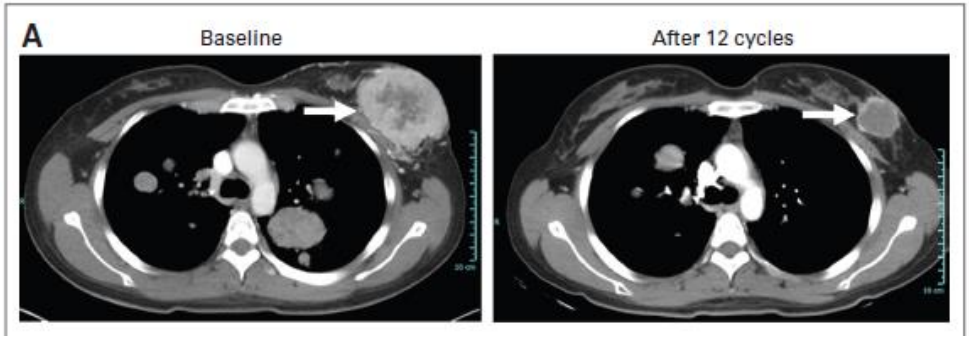


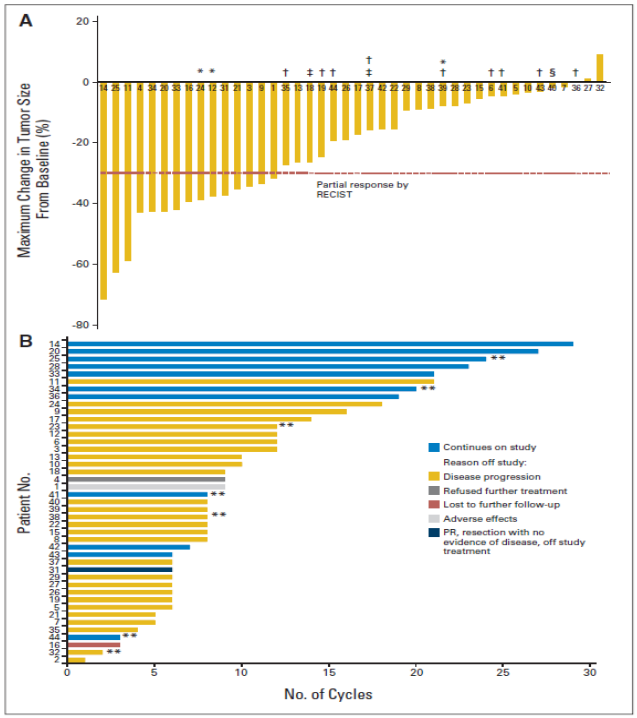


1 Eur J Cancer. 2003;39(11):1511-6 2 Cancer. 1989;63:1-13

# 5. Alveolar soft part sarcoma (ASPS)

- Cediranib is a small molecule tyrosine kinase inhibitor with activity against VEGR-1/ 2/ 3
- Phase 2 (n=43 evaluable) [1]
- Response rates: 35%
- Microanalysis on paired samples showed down-regulation of genes related to angiogenesis





1 Clin Oncol. 2013;31:2296-2302

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# Kinase/ Gene mutation

## PECOMA

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# Perivascular epithelioid cell tumor (PECOMA)

- PECOMA family of tumors consist of related mesenchymal neoplasms
  - **Lymphangio-leiomyomatosis** (LAM)
  - **Angiomyolipoma**; and
  - **PEComa**, an epithelioid malignancy typically arising in the gastrointestinal tract, retroperitoneum, uterus, or somatic soft tissues
- No effective therapy for PECOMA
- LAM and AML seen in high frequency in patients with Tuberous Sclerosis

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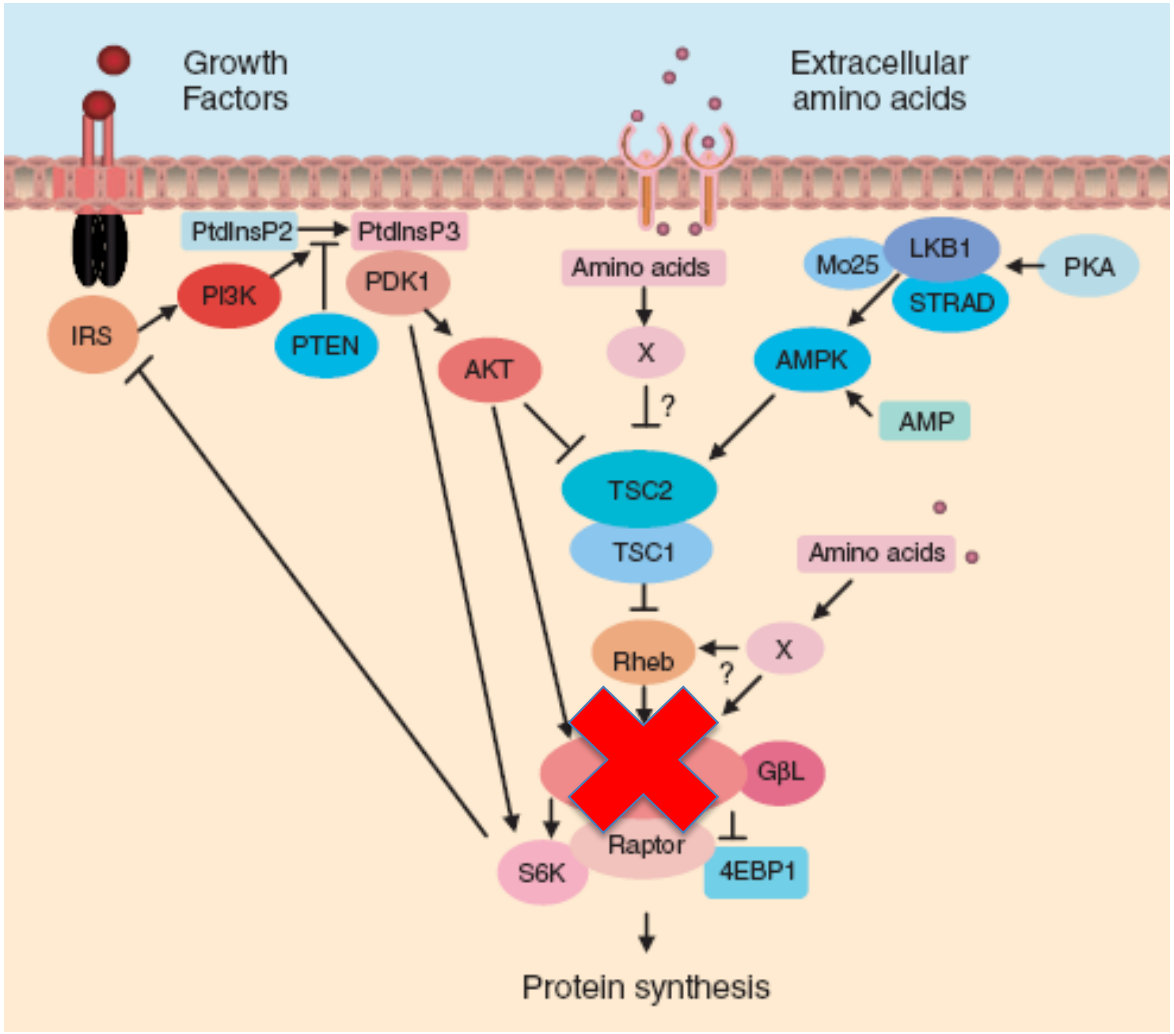
J Clin Oncol. 2010;28:835-840

# TSC/ mTOR pathways

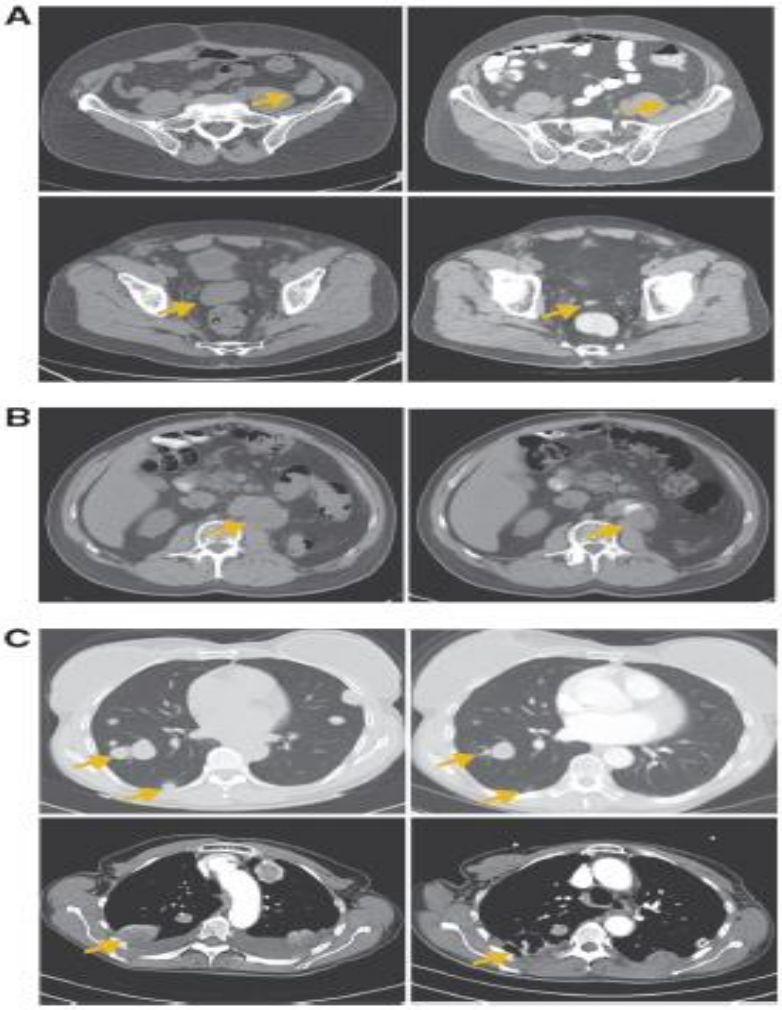




Nature Genetics 37, 19 - 24 (2005)

# Oral Sirolimus in PECOMA

- PEComas demonstrated
  - Loss of TSC2 protein expression
  - Baseline mTORC1 activation
  - Homozygous loss of *TSC1* was identified in one PEComa
- 3 consecutive pts treated with oral sirolimus
- All responded radiologically





J Clin Oncol. 2010;28:835-840

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# Simple genetic alterations

***MDM2* & *CDK4* amplification in well-differentiated/de-differentiated liposarcoma**

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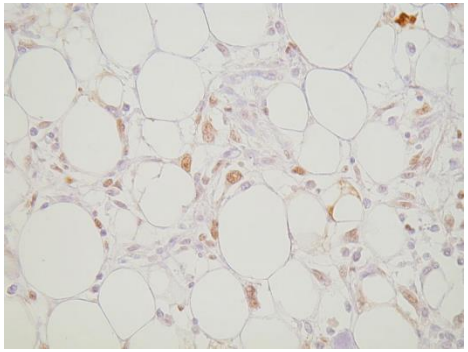
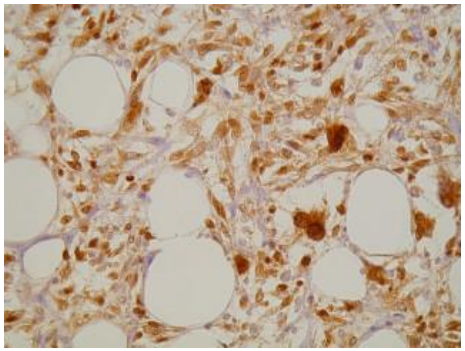
# Well-diff/ De-differentiated Liposarcoma (WD/DD LPS)

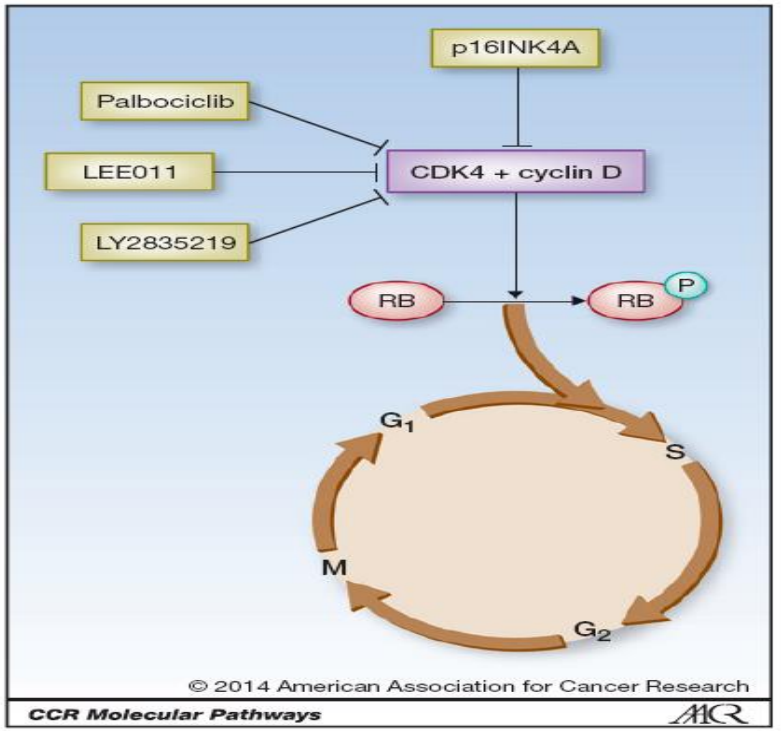
- WD/ DD LPS characterized by *MDM2* and *CDK4* upregulation



**MDM2 staining**



**CDK4 staining**






Clin Cancer Res 2014; 20(13); 3379–83

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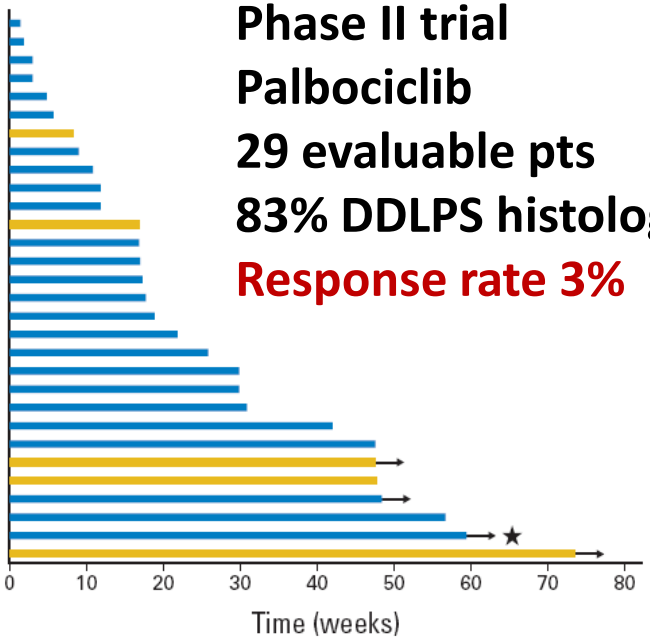
JOURNAL OF CLINICAL ONCOLOGY

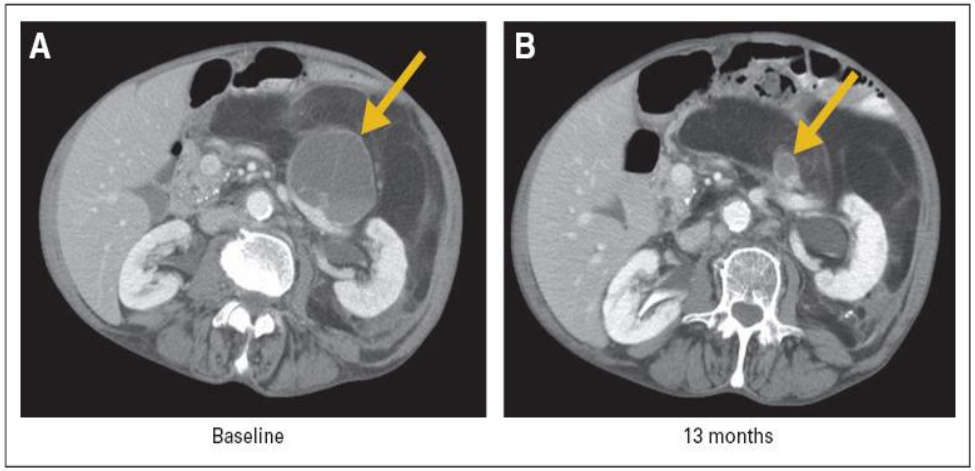
ORIGINAL REPORT

# Phase II Trial of the CDK4 Inhibitor PD0332991 in Patients With Advanced *CDK4*-Amplified Well-Differentiated or Dedifferentiated Liposarcoma

*Mark A. Dickson, William D. Tap, Mary Louise Keohan, Sandra P. D'Angelo, Mrinal M. Gounder, Cristina R. Antonescu, Jonathan Landa, Li-Xuan Qin, Dustin D. Rathbone, Mercedes M. Condy, Yelena Ustoyev, Aimee M. Crago, Samuel Singer, and Gary K. Schwartz*




**Phase II trial**
**Palbociclib**
**29 evaluable pts**
**83% DDLPS histology**
**Response rate 3%**

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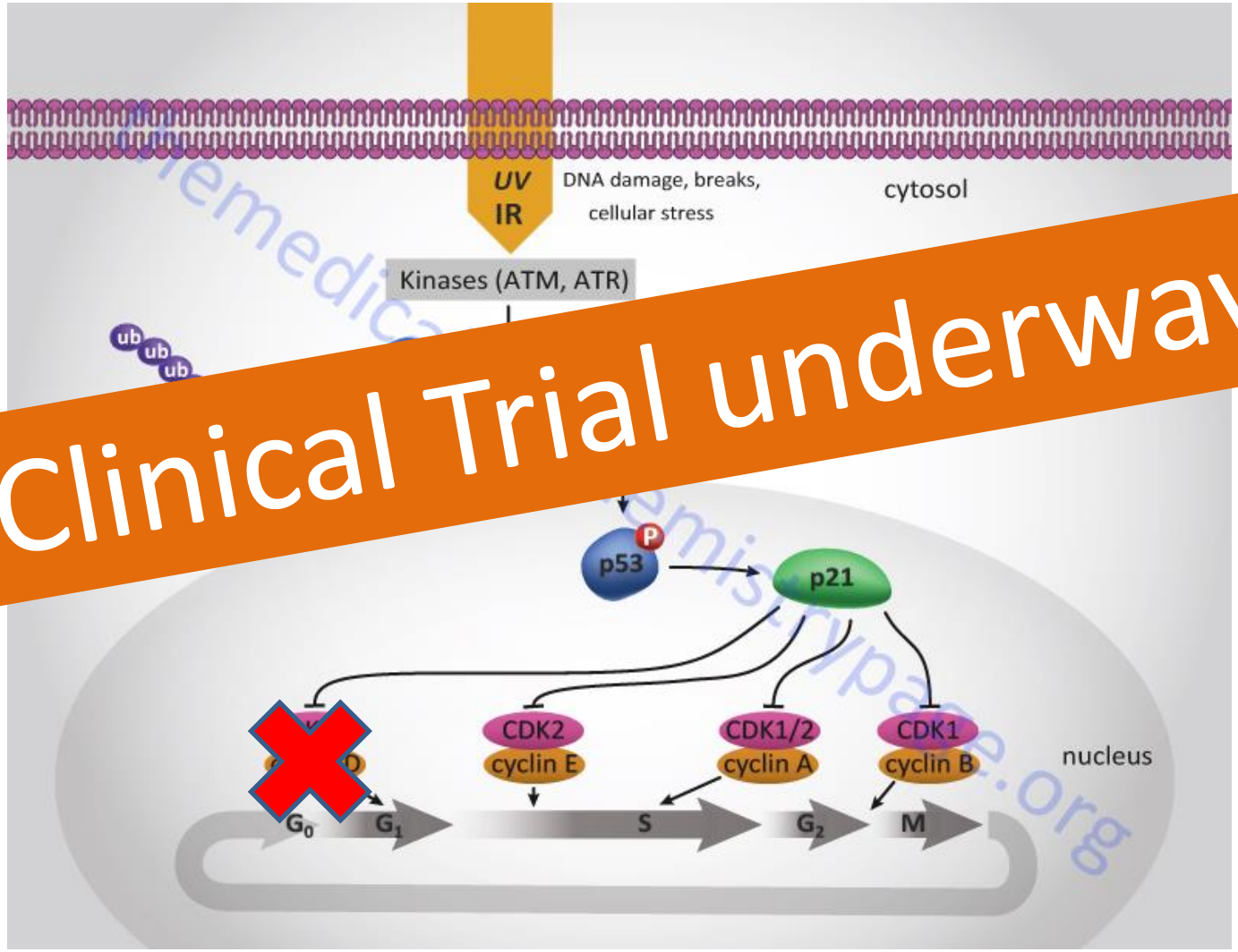
J Clin Oncol 2013; 31:2024-2028

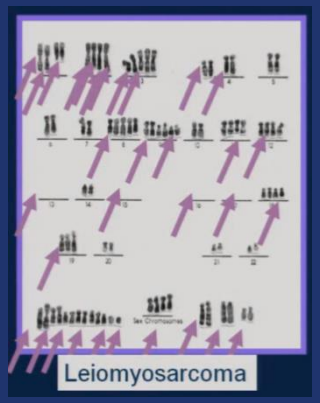
# Dual *MDM2* & *CDK4* inhibition in Liposarcoma




Clinical Trial underway

# Complex cytogenetics

**e.g. Leiomyosarcoma**
**Angiosarcoma**
**Undifferentiated pleomorphic sarcoma (UPS)**


Leiomyosarcoma

# FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) system

- Divides sarcomas in 3 distinct grades
- Correlated with clinical behavior
- Cytotoxics remains an option in STS with complex cytogenetics

| | |
|---|---|
| **Tumour differentiation** | |
| Score 1: | sarcomas closely resembling normal adult mesenchymal tissue (e.g., low grade leiomyosarcoma). |
| Score 2: | sarcomas for which histological typing is certain (e.g., myxoid liposarcoma). |
| Score 3: | embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, osteosarcomas, PNET. |
| **Mitotic count** | |
| Score 1: | 0-9 mitoses per 10 HPF* |
| Score 2: | 10-19 mitoses per 10 HPF |
| Score 3: | ≥20 mitoses per 10 HPF |
| **Tumour necrosis** | |
| Score 0: | no necrosis |
| Score 1: | <50% tumour necrosis |
| Score 2: | ≥50% tumour necrosis |
| **Histological grade** | |
| Grade 1: | total score 2,3 |
| Grade 2: | total score 4,5 |
| Grade 3: | total score 6, 7, 8 |

Modified from Trojani et al. {2131}.
PNET: primitive neuroectodermal tumour
*A high power field (HPF) measures 0.1734 $mm^2$

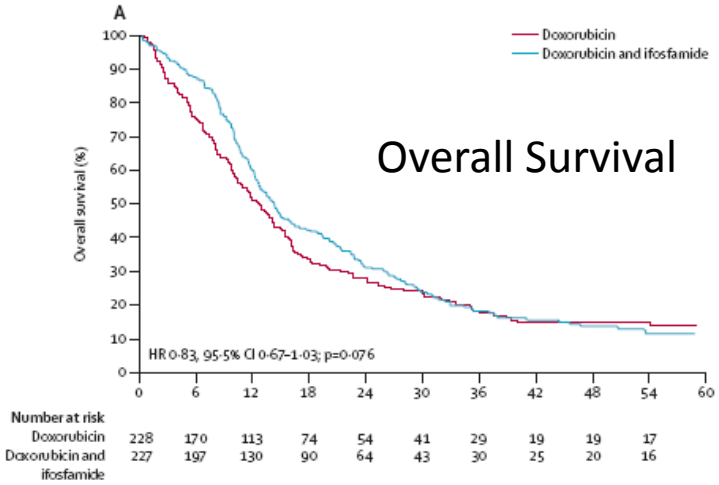
# 1st Line Cytotoxic chemotherapy

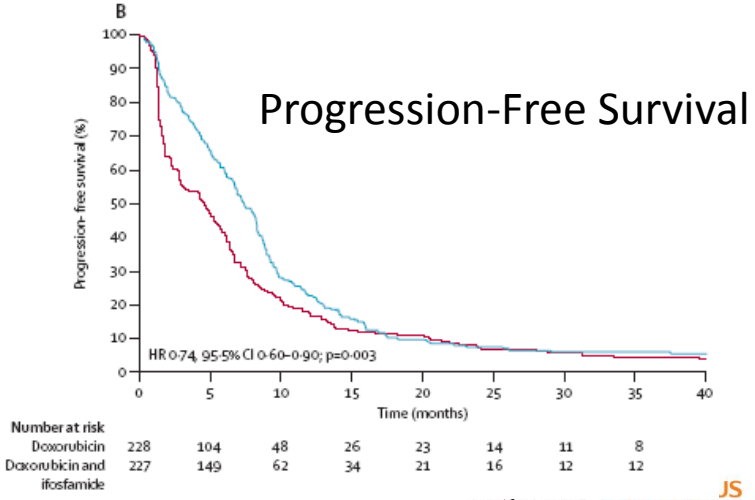
- **EORTC 62012**
- Phase III randomised study
- Metastatic high grade STS
- Doxorubicin (75mg/m2) vs
  doxorubicin plus ifosfamide (10grams/m2)
- N=228 pts enrolled

# Results of EORTC 62012

**Combination Doxo-Ifosfamide**

- Improves response rate from 14% to **26%** (p<0.0006)
- Improves progression free survival from 4.6mth to **7.4mth** (p<0.003)
- But no overall survival benefit

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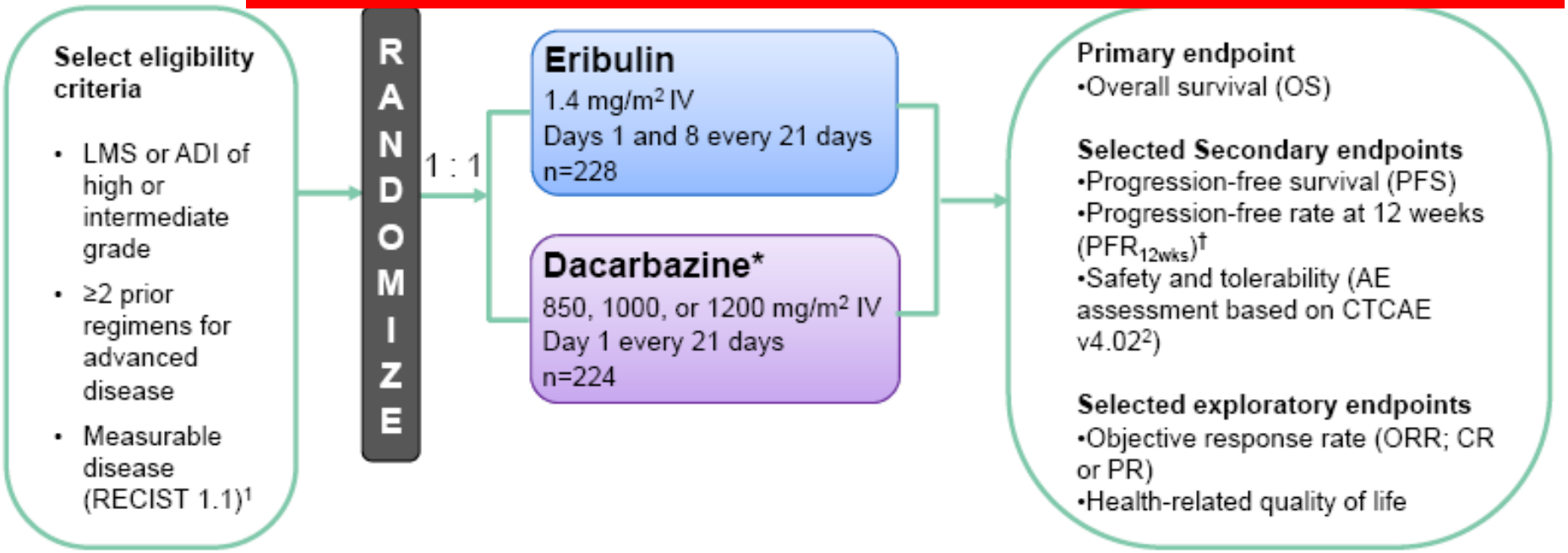
# Chemotherapy in Pre-treated pts

**2/3 had Leiomyosarcoma**

## Study d




*Starting dose selected by the local investigator at study initiation; †$PFR_{12wks}$, proportion of patients who were still alive without disease progression at 12 weeks from randomization.

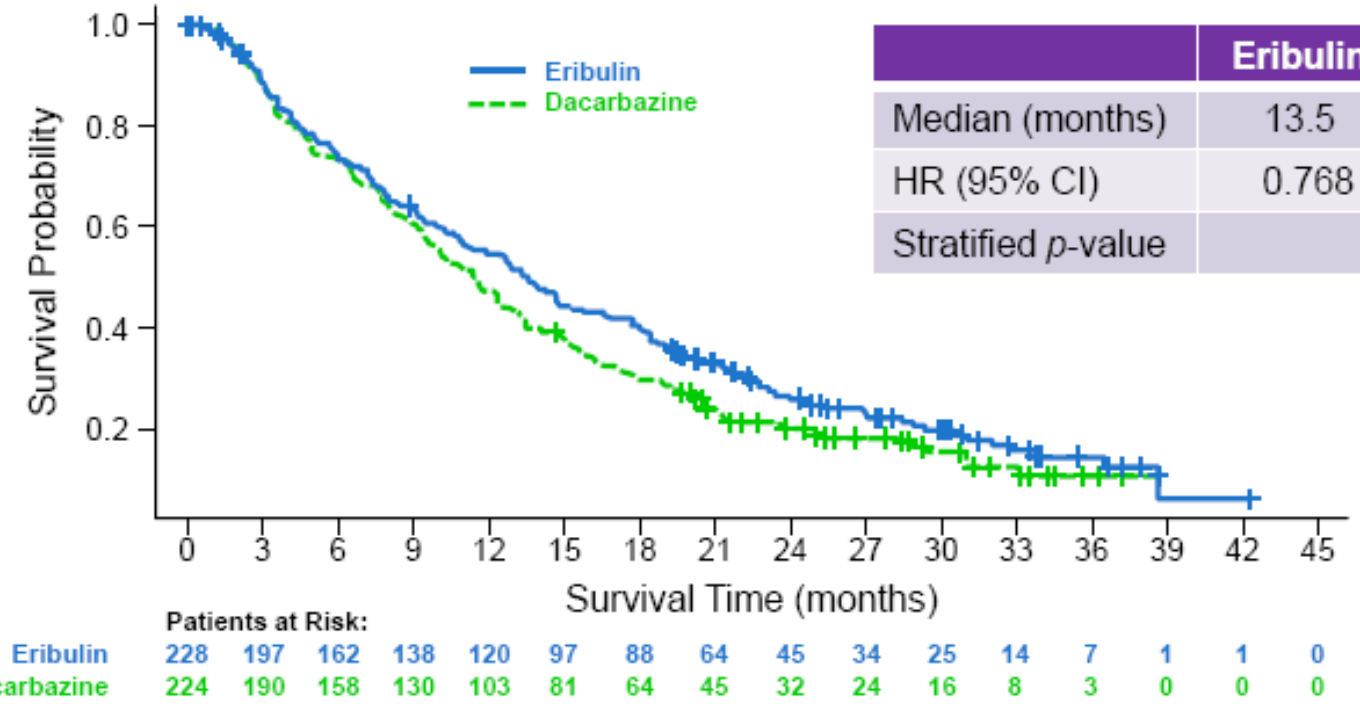
CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; OS, overall survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Eisenhauer et al. *Eur J Cancer* 2009; 2. CTCAE v4.02 available at http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf; accessed May 6, 2015.



PRESENTED AT: ASCO Annual '15 Meeting

# 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.





J Clin Oncol 33, 2015 (suppl; abstr LBA10502)

# Conclusion

- Soft tissue sarcoma is clinically and molecularly heterogeneous
- Range of treatment is diverse and constantly evolving
- Understanding biology of disease is crucial in the management of soft tissue sarcoma

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# Thank you