MADRID 2014 ESMO congress

How clinical trials could have been done, and were not, in rare cancers

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LUMC

Rare Cancers

- <6/100.000 per year
- histology/molecular subtyping increases the number of rare cancers
- Example STS 4/100.000 : 50 = 0.08/100.000

Classical systemic treatment STS studies

- Case reports
- Retrospective analysis of case series
  - Not often practice changing
- Retrospective analysis of trials
  - PFR at 3 and 6 months benchmarks(van Glabbeke EJC 2002, 543-9)
  - Analysis of subtypes
- Typically few phase III studies

And what do we want

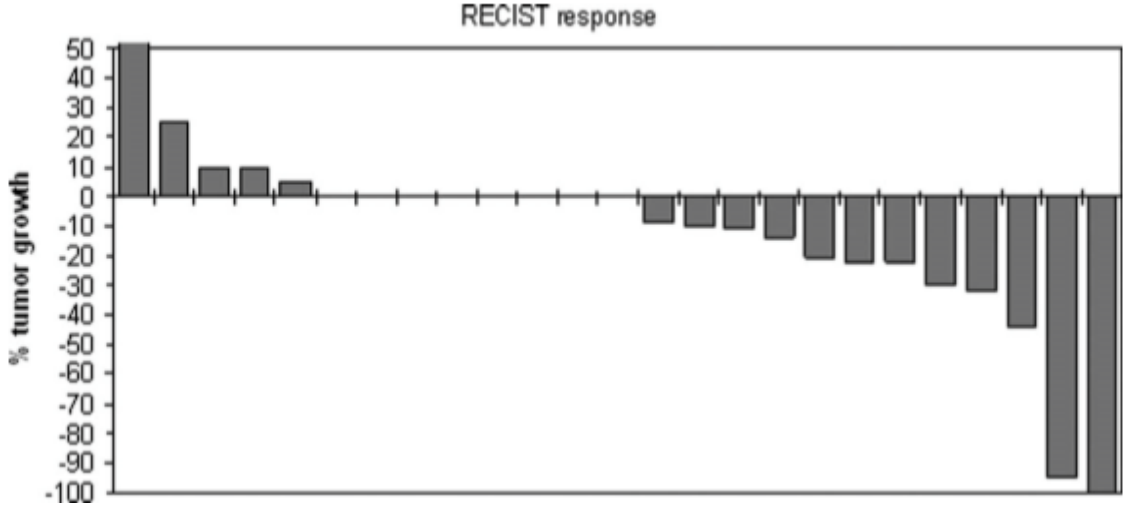
- Progress beyond dox and ifos
  - E.g. paclitaxel for angiosarcoma, gemcitabine plus docetaxel for leiomyosarcoma and UPS and ifosfamide for synovial sarcoma and less so for leiomyosarcoma, recently pazopanib and trabectedin
- Improve (quality of) life for our patients
- A convincing level of evidence

First histotype directed STS study -The perfect example-

- GIST
  - Clear mechanism of action
  - High activity of drug in phase I/II
  - No-activity in non-GIST STS
  - The perfect phase III studies
    - Parallel accross the ocean
    - Inclusion after pathology review
    - Optimal biological dose

Efficacy of Imatinib Mesylate for the Treatment of Locally Advanced and/or Metastatic Tenosynovial Giant Cell Tumor/ Pigmented Villonodular Synovitis

Philippe A. Cassier, MD[1]; Hans Gelderblom, MD[2]; Silvia Stacchiotti, MD[3]; David Thomas, MD[4]; Robert G. Maki, MD[5]; Judith R. Kroep, MD[2]; Winette T. van der Graaf, MD[6]; Antoine Italiano, MD[7]; Beatrice Seddon, MD[8]; Julien Dômont, MD[9]; Emanuelle Bompas, MD[10]; Andrew J. Wagner, MD[11]; and Jean-Yves Blay, MD[1,12]



Cancer 2012, 1649-55

Variable	No. of Patients (%) All Grades	Grade 3-4
Adverse event		
Edema/fluid retention	12 (41)	1 (3)
Fatigue	7 (24)	1 (3)
Nausea	5 (17)	0 (0)
Skin rash/dermatitis	3 (10)	1 (3)
Other	4 (14)	2 (7)[a]
Treatment status		
Continued on IM	12 (41)	
Stopped IM	17 (59)	
Reason for stopping		
Progression	3 (10)	
Toxicity	6 (21)	
Surgery	4 (14)	
Patient's choice	4 (14)	

Active.....

But.....

How could we have done better?

- Active but (surprise?) poor compliance?
- Do we need other approach in benign/borderline tumours?
- Next step shorter treatment with more active drugs, specific CSF-1 inh
- There are enough patients → patient involvement

Phase II Study of Imatinib in Advanced Chordoma

Silvia Stacchiotti, Alessandra Longhi, Virginia Ferraresi, Giovanni Grignani, Alessandro Comandone, Roger Stupp, Alexia Bertuzzi, Elena Tamborini, Silvana Pilotti, Antonella Messina, Carlo Spreafico, Alessandro Gronchi, Paola Amore, Vincenza Vinaccia, and Paolo Giovanni Casali

JCO 2012, 914-20

- First prospective chordoma trial in 20 years!
- But primary endpoint ORR by RECIST (1/56)
- How to do better?
  - Growth modulation index? Secondary endpoints well done
  - European chordoma registry with a.o. PROMS
  - Adaptive licensing or through guidelines

Imatinib Mesylate in Advanced Dermatofibrosarcoma Protuberans: Pooled Analysis of Two Phase II Clinical Trials

Piotr Rutkowski, Martine Van Glabbeke, Cathryn J. Rankin, Wlodzimierz Ruka, Brian P. Rubin, Maria Debiec-Rychter, Alexander Lazar, Hans Gelderblom, Raf Sciot, Dolores Lopez-Terrada, Peter Hohenberger, Allan T. van Oosterom, and Scott M. Schuetze

JCO 2010, 1772-79

- Clear mech action
- 2 unfinished studies
- 2 different endpoints
- 2 different doses
- Despite slow study→ registration

Could we have done better?

Table 3. DFSP Best Response by Subtype

DFSP Subtype	No. of Patients					
	PR		SD		PD	
	Imatinib 400 mg/d	Imatinib 800 mg/d	Imatinib 400 mg/d	Imatinib 800 mg/d	Imatinib 400 mg/d	Imatinib 800 mg/d
DFSP classic	2	4	3	2		
DFSP fibrosarcomatous	2	3		1		2
DFSP pigmented						1
Not DFSP					1	

Abbreviations: DFSP, dermatofibrosarcoma protuberans; PR, partial response; SD, stable disease; PD, progressive disease.

11/24 PR

JCO 2010 1772-79

Efficacy and Safety of Trabectedin in Patients With Advanced or Metastatic Liposarcoma or Leiomyosarcoma After Failure of Prior Anthracyclines and Ifosfamide: Results of a Randomized Phase II Study of Two Different Schedules

George D. Demetri, Sant P. Chawla, Margaret von Mehren, Paul Ritch, Laurence H. Baker, Jean Y. Blay, Kenneth R. Hande, Mary L. Keohan, Brian L. Samuels, Scott Schuetze, Claudia Lebedinsky, Yusri A. Elsayed, Miguel A. Izquierdo, Javier Gómez, Youn C. Park, and Axel Le Cesne

JCO 2009, 4188-96

- Median TTP 3.7 months vs 2.2 months
- Thousands of patients in studies
- Hard to convince regulatory
- How should we have done better?
- Answer: A randomised study!

Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial

Penella J Woll, Peter Reichardt, Axel Le Cesne, Sylvie Bonvalot, Alberto Azzarelli†, Harald J Hoekstra, Michael Leahy, Frits Van Coevorden, Jaap Verweij, Pancras C W Hogendoorn, Monia Ouali, Sandrine Marreaud, Vivien H C Bramwell, Peter Hohenberger, for the EORTC Soft Tissue an Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee

Lancet Oncology 2012, 1045-1054

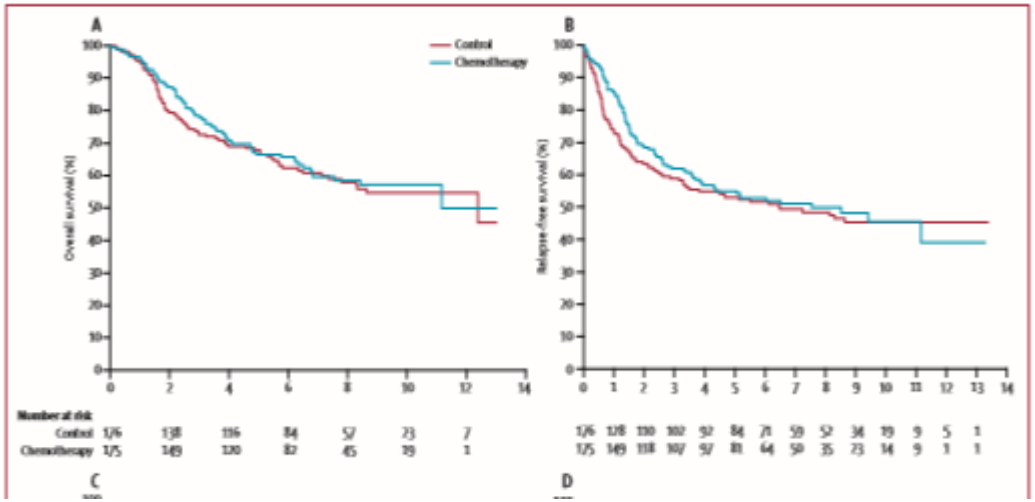
	Control (n=176)	Chemotherapy (n=175)
Age (years)		
Median (range)	49·1 (17·5–71·4)	49·2 (17·3–68·5)
Sex		
Male	98 (56%)	96 (55%)
Performance status		
0	114 (65%)	124 (71%)
1	62 (35%)	51 (29%)
Tumour site		
Extremity	118 (67%)	116 (66%)
Limb girdle	24 (14%)	20 (11%)
Central*	34 (19%)	39 (22%)
Tumour size (cm)		
Median (range)	8·6 (0·3–35)	7·5 (1·2–38)

Data are number of patients (%) unless otherwise indicated. *Central includes head and neck and other.

Table 1: Patient characteristics

	Local diagnosis		Review diagnosis	
	Control (n=176)	Chemotherapy (n=175)	Control (n=136)	Chemotherapy (n=145)
Histological type				
MFH	51 (29%)	33 (19%)	25 (18%)	15 (10%)
Liposarcoma*	35 (20%)	24 (14%)	25 (18%)	20 (14%)
Leiomyosarcoma	22 (12%)	36 (21%)	23 (17%)	32 (22%)
Synovial sarcoma	22 (12%)	28 (16%)	18 (13%)	22 (15%)
Other	46 (26%)	54 (31%)	45 (33%)	56 (39%)
Trojani grade				
Grade I	0	0	7 (5%)	10 (7%)
Grade II	69 (39%)	72 (41%)	64 (47%)	70 (49%)
Grade III	107 (61%)	103 (59%)	66 (48%)	64 (44%)

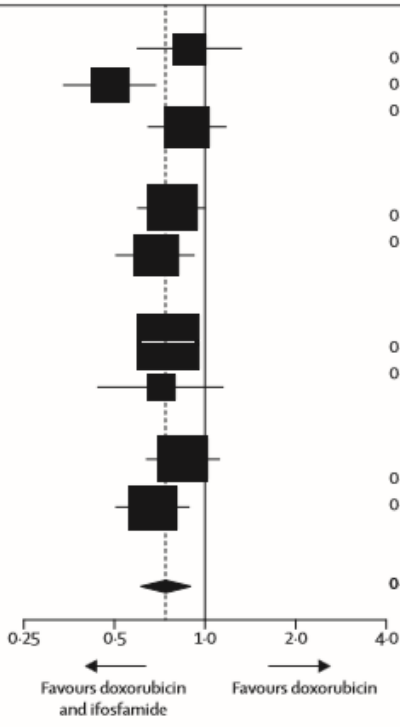
Data are number of patients (%). 281 tumours were submitted for central pathological review. MFH=malignant fibrous histiocytoma (undifferentiated pleomorphic sarcoma). *Includes pleomorphic, myxoid, and dedifferentiated subtypes.



Primary endpoint neg

Many variables

	Events/patients		Observed–expected	Variance	HR (95% CI)
	Doxorubicin and ifosfamide	Doxorubicin			
Age (years)					
<40	54/60	48/52	–3	24·6	0·88 (0·60–1·31)
40–49	66/70	75/78	–22·9	31·3	0·48 (0·34–0·68)
≥50	90/97	92/98	–6·1	44·9	0·87 (0·65–1·17)
Heterogeneity test (df=2) p=0·020					
WHO performance status					
0	112/123	120/131	–14·6	56·9	0·77 (0·60–1·00)
1	98/104	95/97	–17·2	45	0·68 (0·51–0·91)
Heterogeneity test (df=1) p=0·528					
Liver metastases					
No	175/190	179/192	–24·3	86	0·75 (0·61–0·93)
Yes	35/37	36/36	–5·8	16·9	0·71 (0·44–1·14)
Heterogeneity test (df=1) p=0·826					
Tumour grade					
Intermediate	104/113	105/111	–8·6	51	0·84 (0·64–1·11)
High	106/114	110/117	–20·6	51·3	0·67 (0·51–0·88)
Heterogeneity test (df=1) p=0·238					
Total	**210/227 (92·5%)**	**215/228 (94·3%)**	**–30·7**	**103·1**	**0·74 (0·61–0·90)**



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Controversy remains

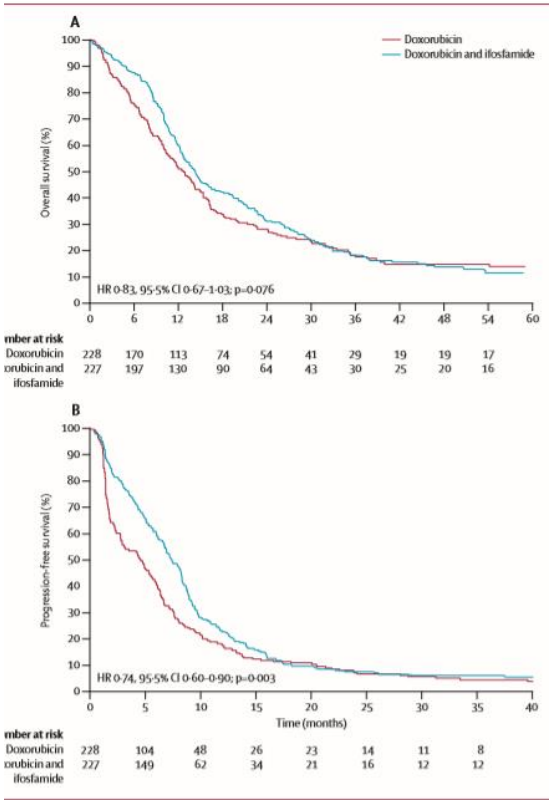
- Did we select the right patients?
- Meta analysis vs individual trials
- Histotype driven adjuvant studies?

Histotype	Standard chemotherapy	Administered histology-driven therapy
Leiomyosarcoma	EPIRUBICIN + IFOSFAMIDE	GEMCITABINE + DACARBAZINE
Myxoid Liposarcoma with hypercellularity	EPIRUBICIN + IFOSFAMIDE	ADRIAMYCIN
Synovial Sarcoma	EPIRUBICIN + IFOSFAMIDE	HIGH-DOSE + IFOSFAMIDE
Malignant Peripheral Nerve Sheath Tumour (MPNST)	EPIRUBICIN + IFOSFAMIDE	IFOSFAMIDE + ETOPOSIDE
eserved Undifferentiated Pleomorphic Sarcoma	EPIRUBICIN + IFOSFAMIDE	GEMCITABINE + DOCETAXEL

Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial

*Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarsky, Jeremy Whelan, Peter Hohenberger, Anders Krarup-Hansen, Thierry Alcindor, Sandrine Marreaud, Saskia Litière, Catherine Hermans, Cyril Fisher, Pancras C W Hogendoorn, A Paolo dei Tos, Winette T A van der Graaf, for the European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group**

Lancet Oncology 2014 415-424



	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
Complete response	1 (<1%)	4 (2%)
Partial response	30 (13%)	56 (25%)
Stable disease	105 (46%)	114 (50%)
Progressive disease	74 (32%)	30 (13%)
Early death (progression)	4 (2%)	5 (2%)
Early death (other cause)	3 (1%)	2 (1%)
Not evaluable	11 (5%)	16 (7%)

Higher response rate and PFS with combo,

...but febrile neutropenia 13 vs 46%

Dox vs dox/ifos

- Everyone continues to do what he did..
- Could we have done better?
  - Larger study with more subtypes and QOL, but who pays?
  - Collection of post study treatments? But none proved OS benefit
  - Include shared decision making models in the future?
  - Cultural differences? ..impossible

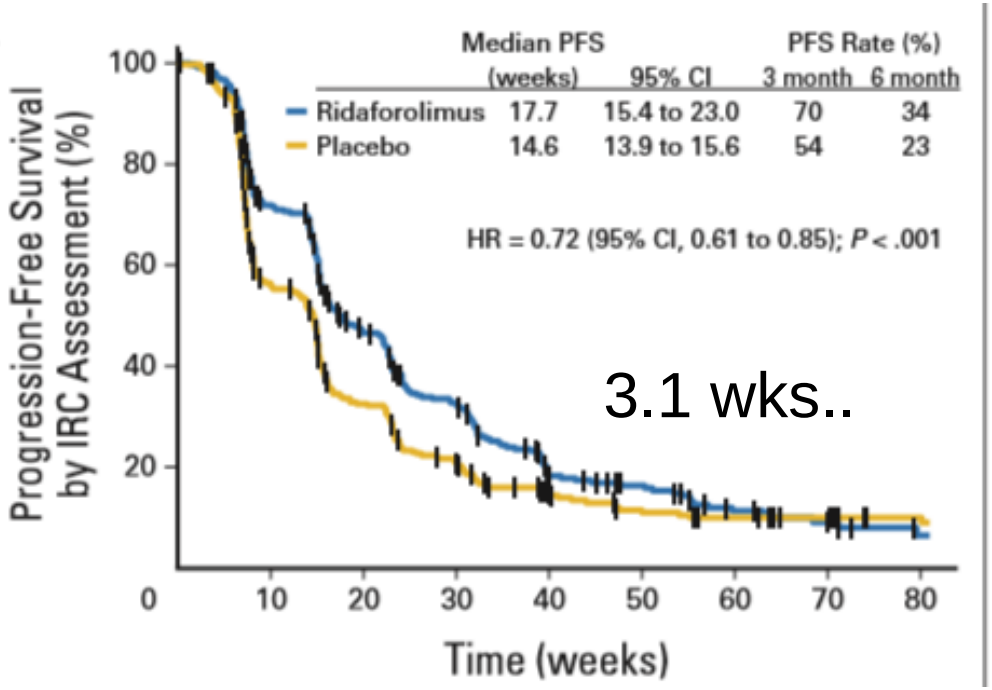
Results of an International Randomized Phase III Trial of the Mammalian Target of Rapamycin Inhibitor Ridaforolimus Versus Placebo to Control Metastatic Sarcomas in Patients After Benefit From Prior Chemotherapy

George D. Demetri, Sant P. Chawla, Isabelle Ray-Coquard, Axel Le Cesne, Arthur P. Staddon, Mohammed M. Milhem, Nicolas Penel, Richard F. Riedel, Binh Bui-Nguyen, Lee D. Cranmer, Peter Reichardt, Emmanuelle Bompas, Thierry Alcindor, Daniel Rushing, Yang Song, Ruey-min Lee, Scot Ebbinghaus, Joseph E. Eid, John W. Loewy, Frank G. Haluska, Pierre F. Dodion, and Jean-Yves Blay

JCO 2013
2485-92

Mix of tumours
Mix of grades
Mix of lines of therapy
Many, many sites
No biomarker

→ R.I.P. Ridaforolimus



Statistical significance vs clinical relevance

How clinical trials in sarcoma should have been done

1. Proper selection of patients (path review), trial design, and endpoints
2. Consensus on possible biomarkers, and do it
3. Centralized treatment (EORTC database)
4. Patient empowerment (accrual, design, regulatory)
5. Registries with full clinical and genomic data
6. Negotiation with regulatory agencies (flexible "graduation rules"), put findings in guidelines!