Universität Zürich

UniversitätsSpital Zürich

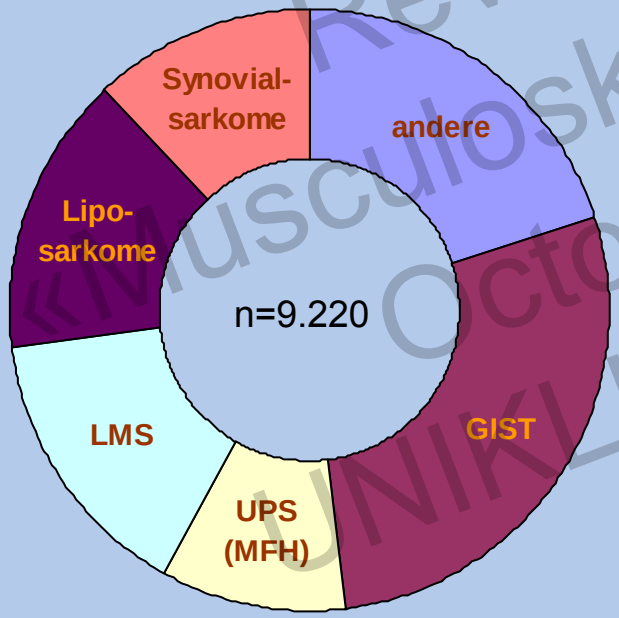
Uniklinik Balgrist, 6.10.2011

„Chemotherapeutische Konzepte bei Knochen und Weichteilsarkomen“

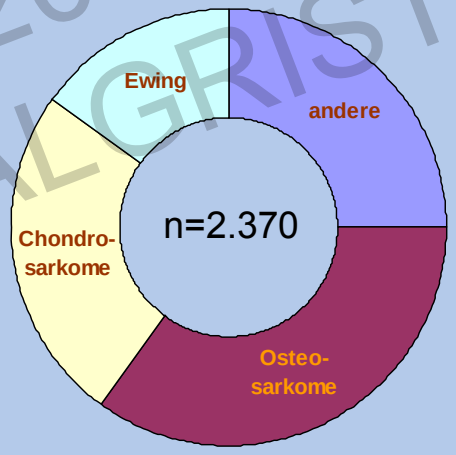
Frank Stenner-Liewen
Klinik und Poliklinik für Onkologie,
UniversitätsSpital Zürich

Sarkome der Erwachsenen

Weichteilsarkome



Knochensarkome



3.560 Todesfälle/Jahr US 1.330

Weichteilsarkome (STS)

Schweiz: weniger als 200 Neuerkrankungen pro Jahr (ohne GIST)

~1% der Tumoren der Erwachsenen

~8% der kindlichen Tumoren

Weichteilsarkome sind alters- und lokalisationsunabhängig

Biologie der Weichteilsarkome (STS)

Translokationsassoziierte Sarkome - definierte Karyotypen

Nicht translokationsassoziierte Sarkome ☞ **65%**

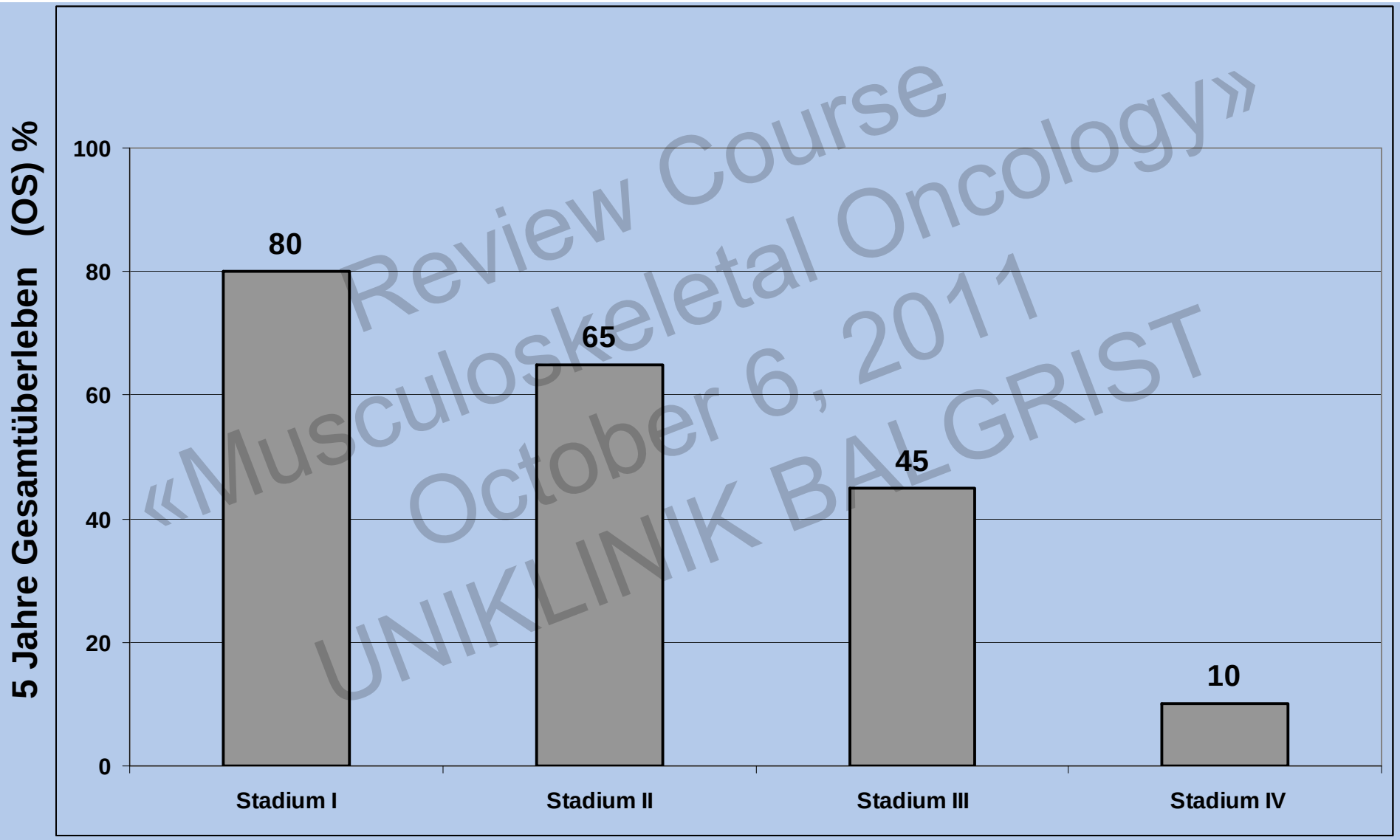
p53-Mutationen/Deletionen
CDKN2A-Deletionen
MDM2-Amplifikationen
Telomer-Dysfunktionen

---

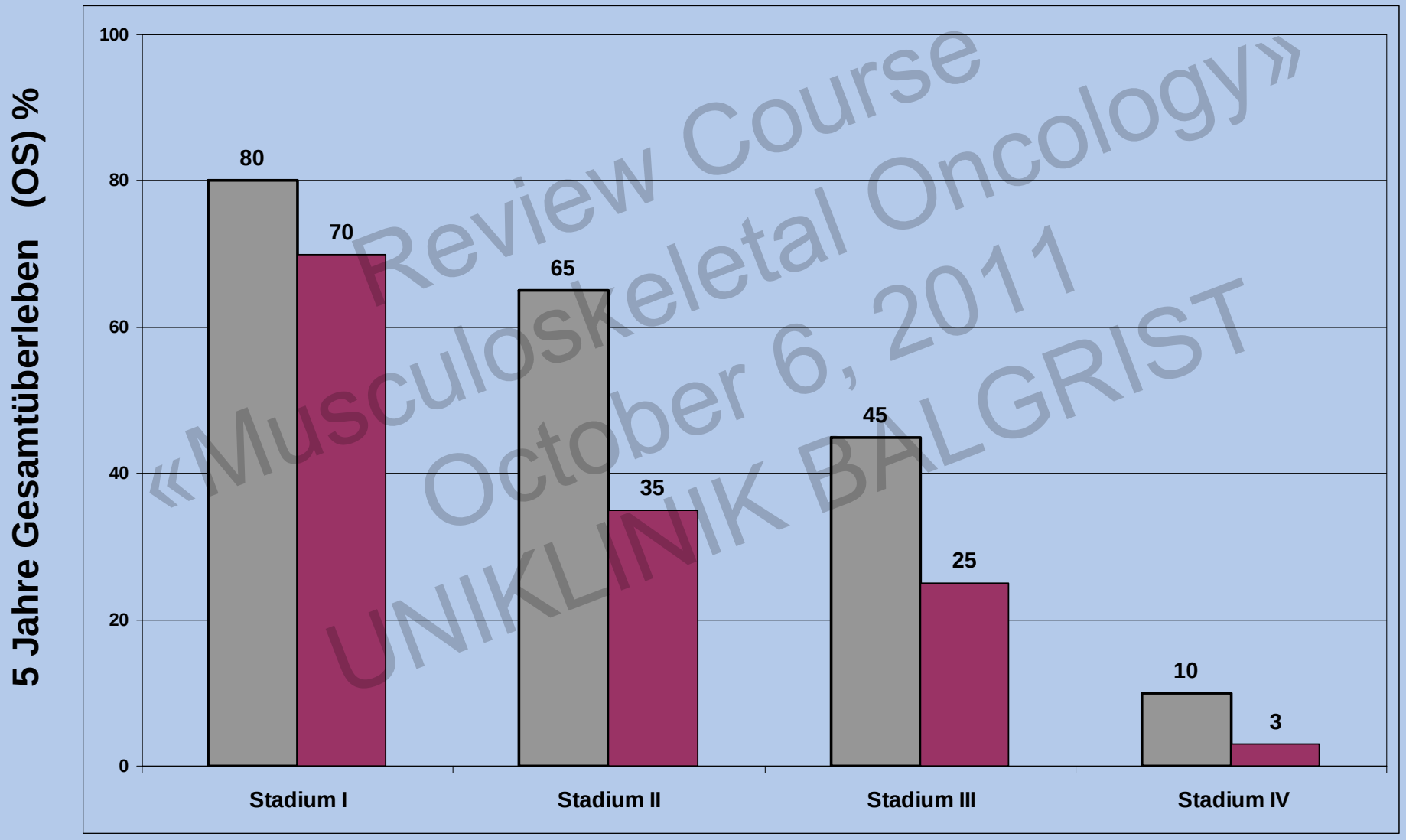
mutierte Onkogene **(GIST: *c-KIT*, *PDGFRA*)**

komplexe Karyotypen **(Leiomyosarkome/ UPS MFH)** ☞ **30%**

Weichteilsarkome 5 Jahres ÜLR ist stadienabhängig



Weichteilsarkome 5 JÜLR Vergleich mit NSCLC



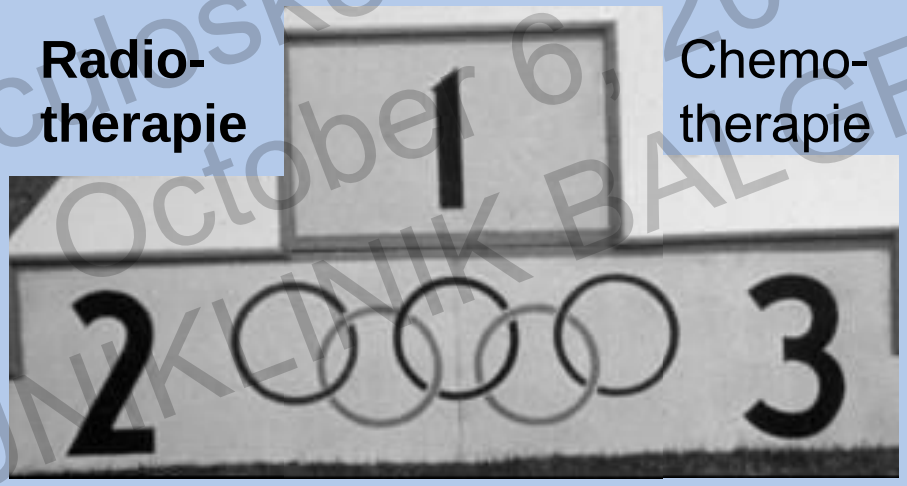
Weichteilsarkome (STS)
Therapiemodalitäten - Stellenwert

Chirurgie

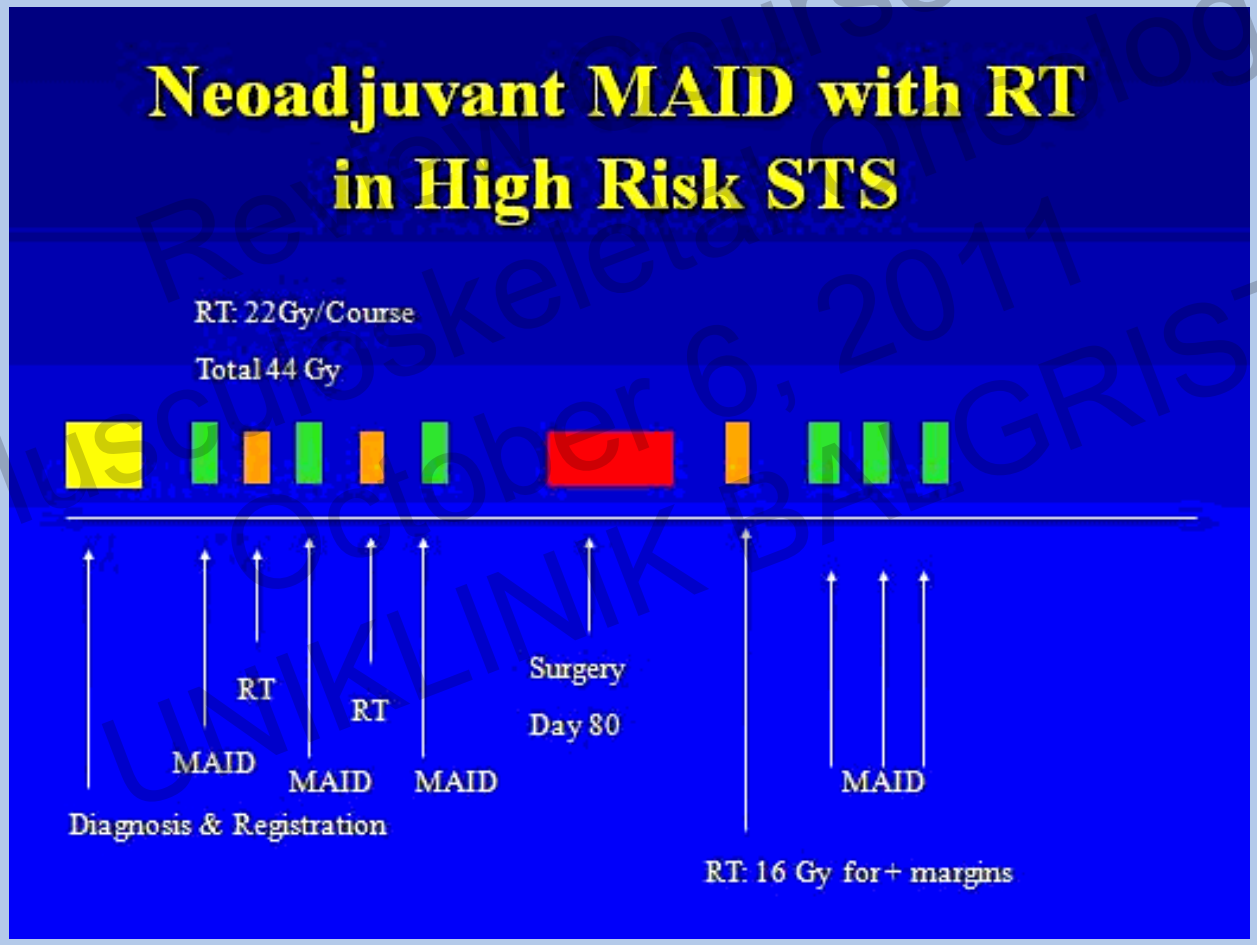
Radio-therapie

Chemo-therapie

+Hyperthermie?!

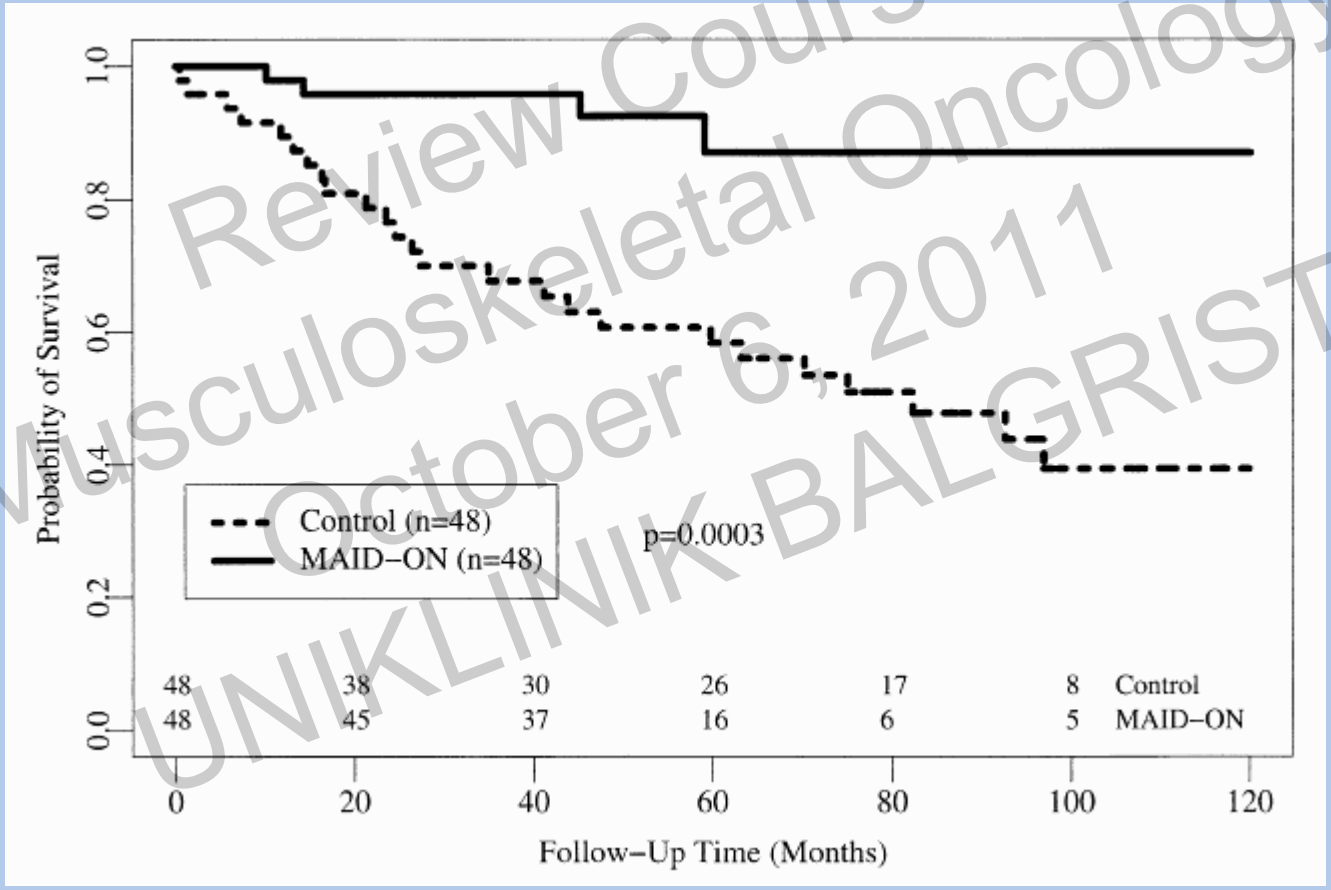


Weichteilsarkome – Neoadjuvante Radiochemotherapie?



I. J. Radiation Oncology Volume 56, Number 4, 2003 Neoadjuvant chemoradiation for large sarcomas ● T. F. DELANEY *et al*

Weichteilsarkome – neoadjuvante Radiochemotherapie?



I. J. Radiation Oncology Volume 56, Number 4, 2003 Neoadjuvant chemoradiation for large sarcomas ● T. F. DELANEY *et al*

Weichteilsarkome
- neoadjuvante Radiochemotherapie?

Toxizität !

	Grade 3		Grade 4		Grade 5	
	No.	%	No.	%	No.	%
Hematologic	8	13	50	78	2	3
Hematologic (general)	10		21		2	
Hemoglobin	29		6		0	
WBC	7		47		0	
Platelets	17		25		0	
Neutrophils	4		46		0	
Hematocrit	2		0		0	
Nonhematologic	31	48	12	19	1	2
Infection	17		4		1	
Worst overall	6	9	53	83	3	5

I. J. Radiation Oncology Volume 56, Number 4, 2003 Neoadjuvant chemoradiation for large sarcomas ● T. F. DELANEY *et al*

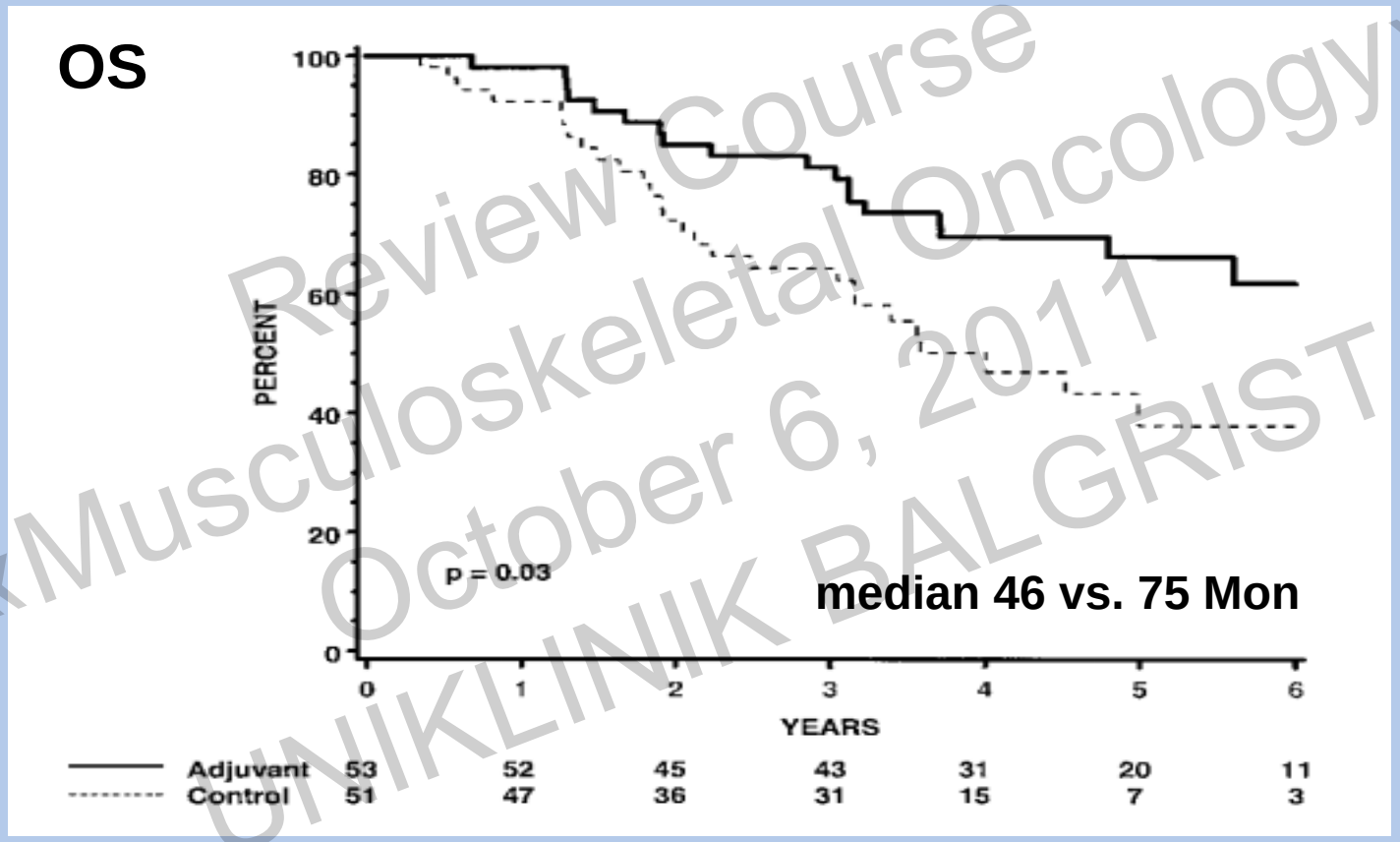
Weichteilsarkome
- neoadjuvante Radiochemotherapie?

Neoadjuvant Chemoradiation for Extremity/Truncal Sarcomas

- Eilber et al. UCLA protocols: Local control ~90%
  - Initially IA, then IV adriamycin 30 mg/day + concurrent XRT 17.5-35 Gy (28 Gy)
  - Similar results from other institutions
- MGH: Interdigitated MAID (#3) + 44 Gy → S →MAID(#3) +/-XRT
  - ↓ DM and improved DFS/OS vs. historical control
- RTOG: MAID (#3) + 44 Gy → S →MAID(#3) +/-XRT
  - 26% delayed wound healing; 93% complete pre-op Rx
  - 66% grade 4 neutropenia

T. F. Delaney ASCO 08

Weichteilsarkome - adjuvante Chemotherapie?

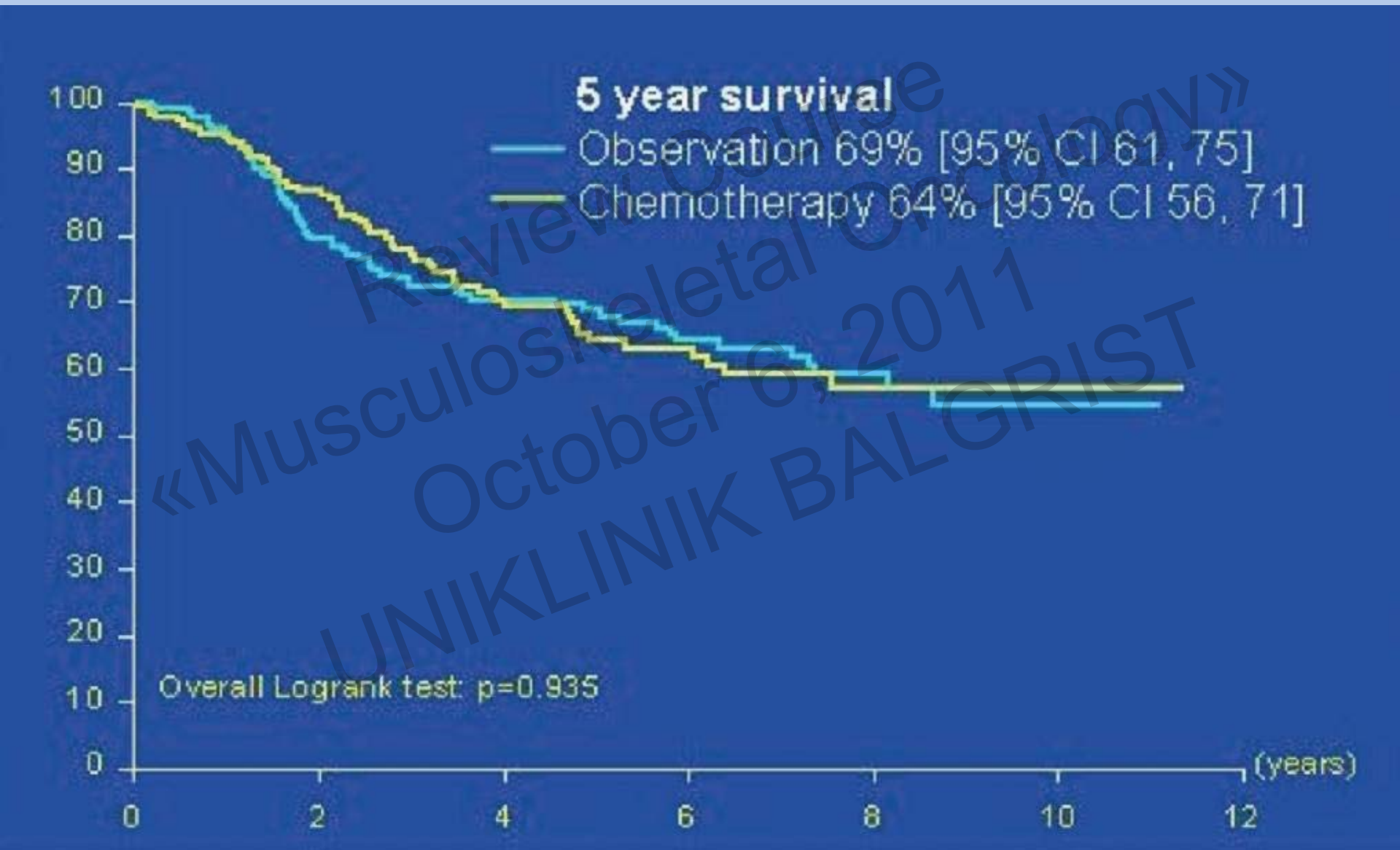


35% °IV Neutropenie,
13% Neutropenes Fieber !

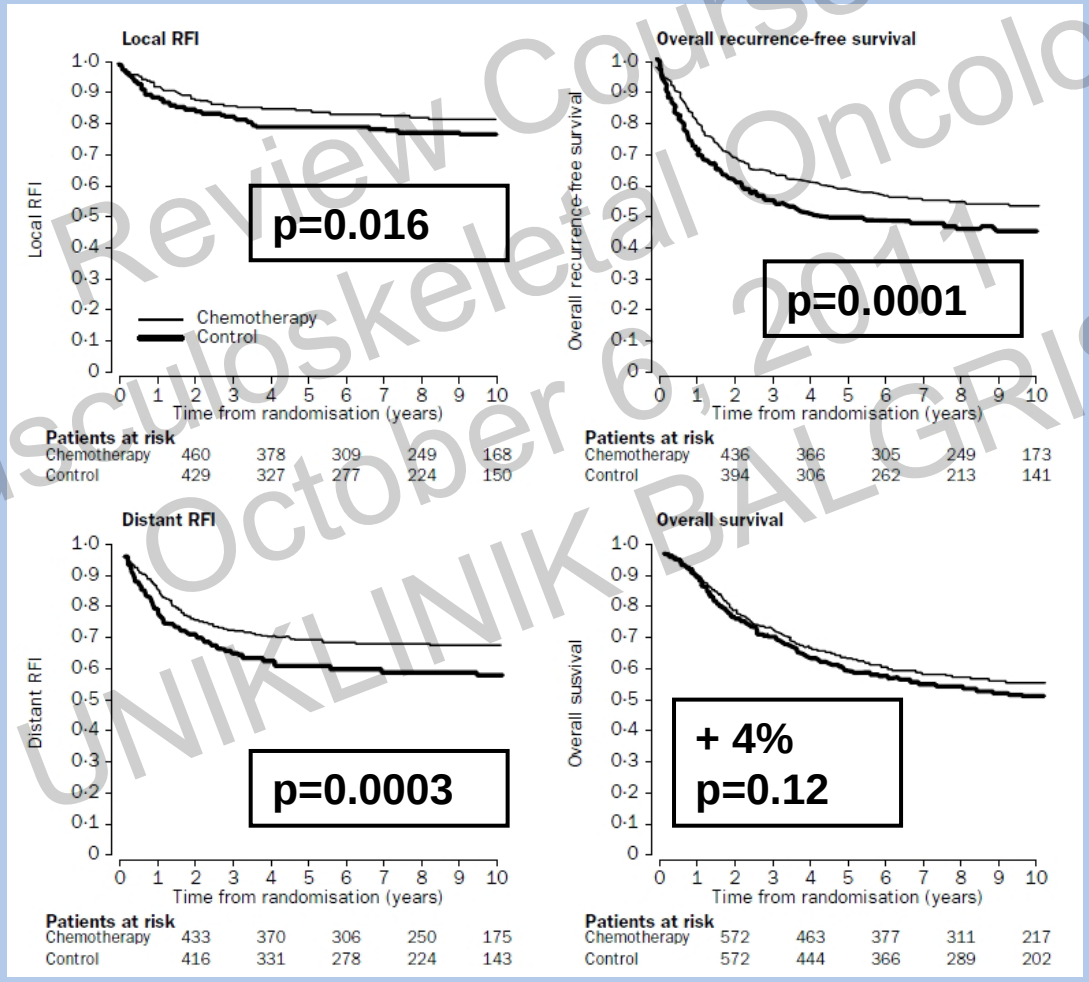
Among patients with lesions of the extremities, the hazard ratio was 0. 80 (*p* 0.029) equivalent to a 7% absolute benefit at 10 years

Sergio Frustaci, Franco Gherlinzoni, et al. JCO 19,5,2001,1238-

STS - Adjuvante Chemotherapie ?
Studie EORTC 62931



STS - Adjuvante Chemotherapie ?
Sarcoma Meta-Analysis Collaboration (SMAC)



THE LANCET
Vol 350 • December 6, 1997

STS - Adjuvante Chemotherapie?

Pervaiz N. et al CANCER August 1, 2008, Vol113, N3: 573-

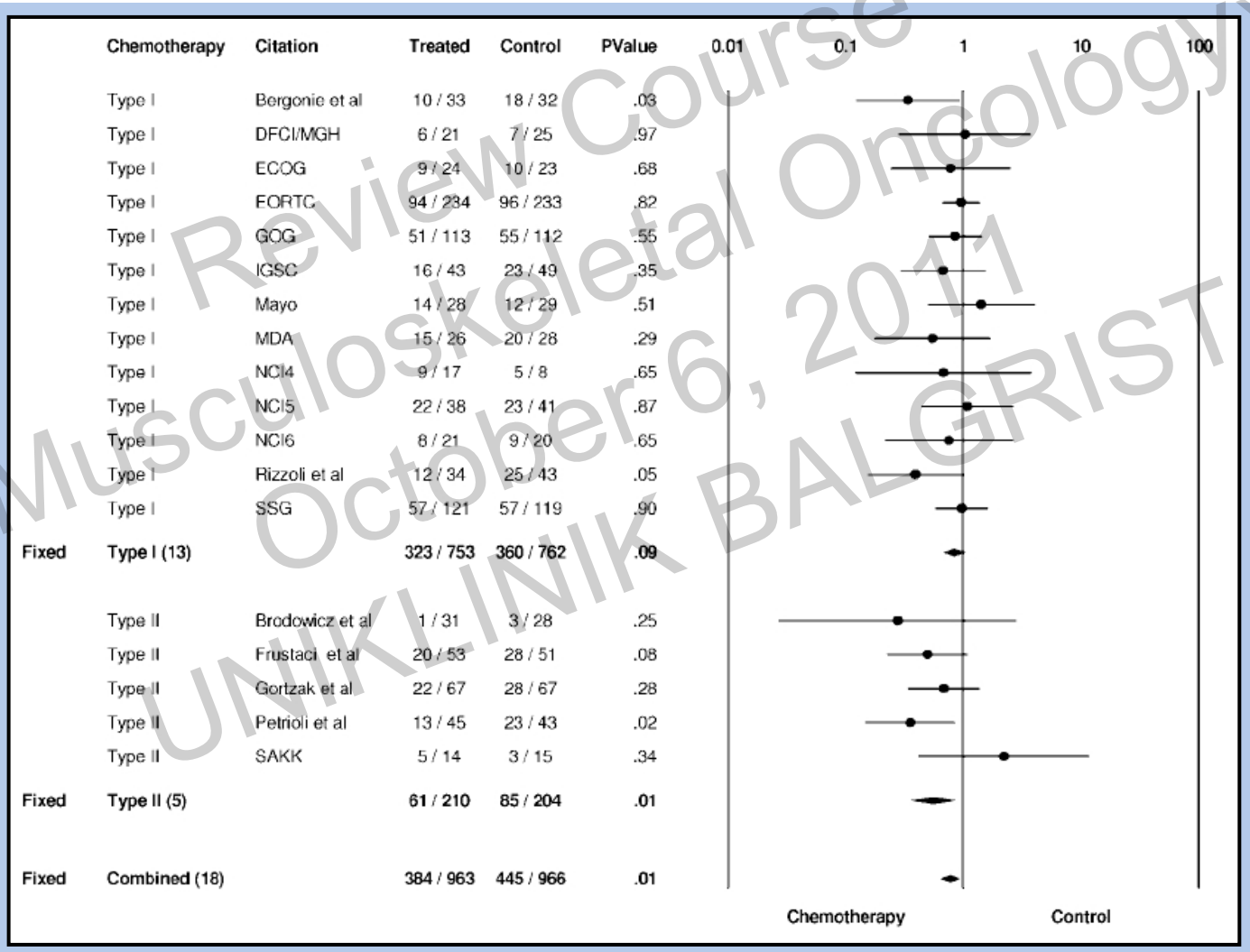
A Systematic Meta-Analysis of Randomized Controlled Trials of Adjuvant Chemotherapy for Localized Resectable Soft-Tissue Sarcoma

Absolute Risk Reductions and 95% Confidence Intervals for Local Recurrence, Distant Recurrence, Overall Recurrence, and Survival

	Local recurrence		Distant recurrence		Overall recurrence		Survival	
Treatment	ARR	95% CI	ARR	95% CI	ARR	95% CI	ARR	95% CI
Doxorubicin	3%	1%-7%	9%	4%-14%	9%	4%-14%	5%	6%-21%
Doxorubicin with ifosfamide	5%	1%-12%	10%	1%-19%	12%	3%-21%	11%	3%-19%
Combined	4%	0%-7%	9%	5%-14%	10%	5%-15%	6%	2%-11%

STS - Adjuvante Chemotherapie

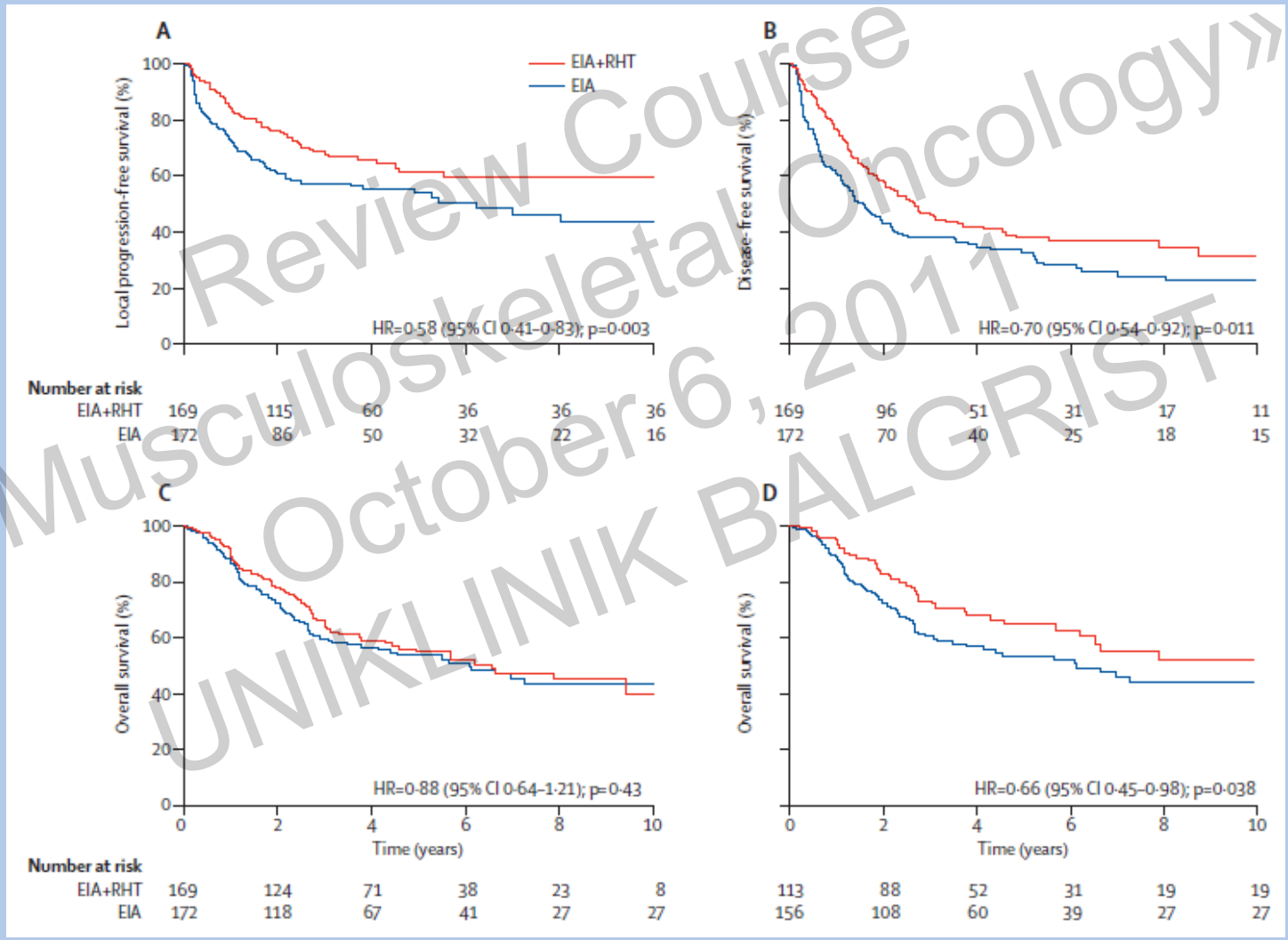
Pervaiz N. et al CANCER August 1, 2008, Vol113, N3: 573-



	Chemotherapy	Citation	Treated	Control	PValue
	Type I	Bergonie et al	10 / 33	18 / 32	.03
	Type I	DFCI/MGH	6 / 21	7 / 25	.97
	Type I	ECOG	9 / 24	10 / 23	.68
	Type I	EORTC	94 / 234	96 / 233	.82
	Type I	GOG	51 / 113	55 / 112	.55
	Type I	IGSC	16 / 43	23 / 49	.35
	Type I	Mayo	14 / 28	12 / 29	.51
	Type I	MDA	15 / 26	20 / 28	.29
	Type I	NCI4	9 / 17	5 / 8	.65
	Type I	NCI5	22 / 38	23 / 41	.87
	Type I	NCI6	8 / 21	9 / 20	.65
	Type I	Rizzoli et al	12 / 34	25 / 43	.05
	Type I	SSG	57 / 121	57 / 119	.90
Fixed	**Type I (13)**		**323 / 753**	**360 / 762**	**.09**
	Type II	Brodowicz et al	1 / 31	3 / 28	.25
	Type II	Frustaci et al	20 / 53	28 / 51	.08
	Type II	Gortzak et al	22 / 67	28 / 67	.28
	Type II	Petrioli et al	13 / 45	23 / 43	.02
	Type II	SAKK	5 / 14	3 / 15	.34
Fixed	**Type II (5)**		**61 / 210**	**85 / 204**	**.01**
Fixed	**Combined (18)**		**384 / 963**	**445 / 966**	**.01**

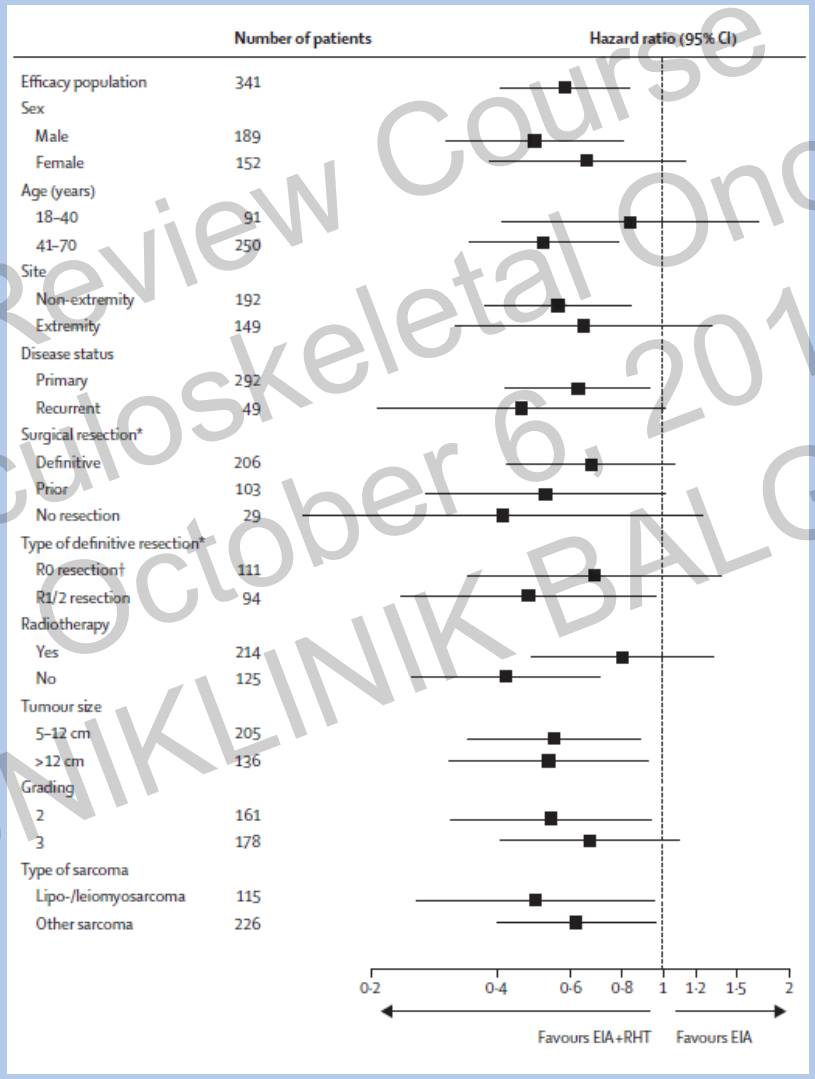
Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study

Rolf D Issels, Lars H Lindner*, Jaap Verweij, Peter Wust, Peter Reichardt, Baard-Christian Schem, Sultan Abdel-Rahman, Soeren Daugaard, Christoph Salat, Clemens-Martin Wendtner, Zeljko Vujaskovic, Rüdiger Wessalowski, Karl-Walter Jauch, Hans Roland Dürr, Ferdinand Ploner, Andrea Baur-Melnyk, Ulrich Mansmann, Wolfgang Hiddemann, Jean-Yves Blay, Peter Hohenberger, for the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) and the European Society for Hyperthermic Oncology (ESHO)*



Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study

Rolf D Issels, Lars H Lindner*, Jaap Verweij, Peter Wust, Peter Reichardt, Baard-Christian Schem, Sultan Abdel-Rahman, Soeren Daugaard, Christoph Salat, Clemens-Martin Wendtner, Zeljko Vujaskovic, Rüdiger Wessalowski, Karl-Walter Jauch, Hans Roland Dürr, Ferdinand Ploner, Andrea Baur-Melnyk, Ulrich Mansmann, Wolfgang Hiddemann, Jean-Yves Blay, Peter Hohenberger, for the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) and the European Society for Hyperthermic Oncology (ESHO)*



Zusammenfassung
Konzepte für lokalisierte STS
(Stadium III; - T2B, NO/NX,M0)

• Neoadjuvant T. (interessantes Konzept + Hyperthermie) **besser** als adjuvant

Für adjuvante Chemotherapie gibt es heute *noch* keinen „standard of care“
falls dann Typ II (+ Ifosphamide) Therapie

Individualisierte Entscheidung - interdisziplinär (Tumorboards!)

• Für individualisierte Patientenselektion wichtig:

Tumor > 5cm, hohes Grading (FNCLCC), extrakompartimentaler Sitz,

Rezidiv, Alter

Five-year results from a Scandinavian Sarcoma Group Study (SSG XIII) on adjuvant chemotherapy combined with accelerated radiotherapy in high-risk soft tissue sarcoma of the extremities and trunk wall

Nina L. Jansen, M.D.[1], Øyvind S. Bruland, M.D., Ph.D.[2], Mikael Eriksson, M.D., Ph.D.[3], Jacob Engellau, M.D., Ph.D.[4], Ingela Turesson, M.D., Ph.D.[5], Anders Follin, M.D.[6], Clement S. Trovik, M.D., Ph.D.[7], and Kirsten Sundby Hall, M.D., Ph.D.[8]

VI=RF!

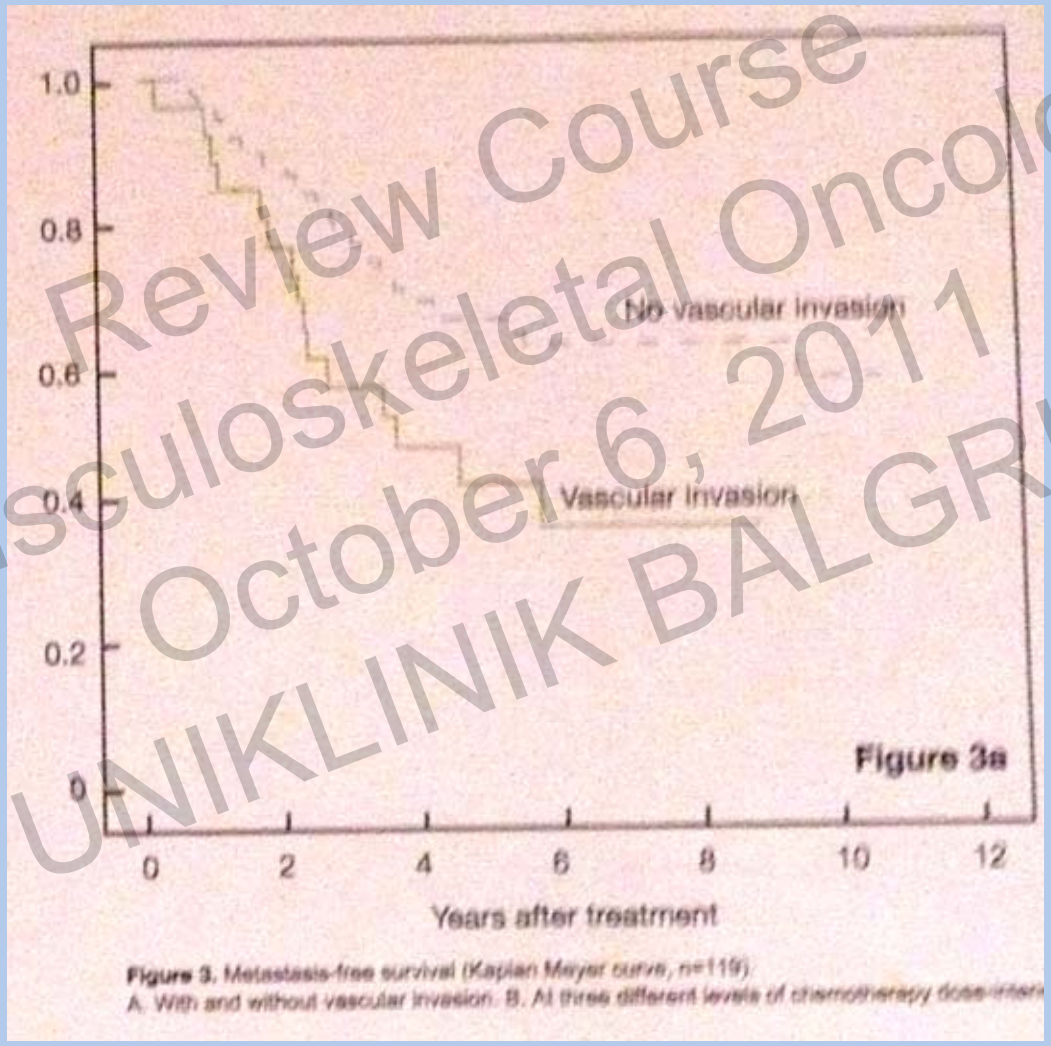


Figure 3a

Figure 3. Metastasis-free survival (Kaplan Meyer curve, n=119).
A. With and without vascular invasion. B. At three different levels of chemotherapy dose-inten

Zusammenfassung
Konzepte für lokalisierte STS
(Stadium III; - T2B, NO/NX,M0)

•Behandlung in Zentren (mit Tumorboards = centers of experience)

(Skandinavische Philosophie: Überweisung vor Biopsie)

-> Lokalrezidivrate: 55% vs. 21% (ausserhalb vs. in einem Sarkom Zentrum)

•Wenn immer möglich Therapie innerhalb von Studien

Factors Predicting Local Recurrence of Deep High-Grade Soft Tissue Sarcomas

Sawamura, C. Ae, K. Tanizawa, T. Shimoji, T. Matsumoto, S.
Orthopaedics, Cancer Institute Hospital for Japanese Foundation for Cancer Research, Tokyo, Japan

Evaluate patient characteristics associated with development of local recurrence for deep, high-grade soft tissue sarcomas

- Previous treatments before referral
  - Unplanned excision
  - Local recurrence before referral
- Adjuvant treatment effects (Radiation, Chemotherapy)
- Risk factors for local recurrence

Fig4. Treatments and metastasis before referral

77 patients (18%) had unplanned excision
79 patients (18%) had local recurrence before referral
54 patients (12%) had metastasis at diagnosis

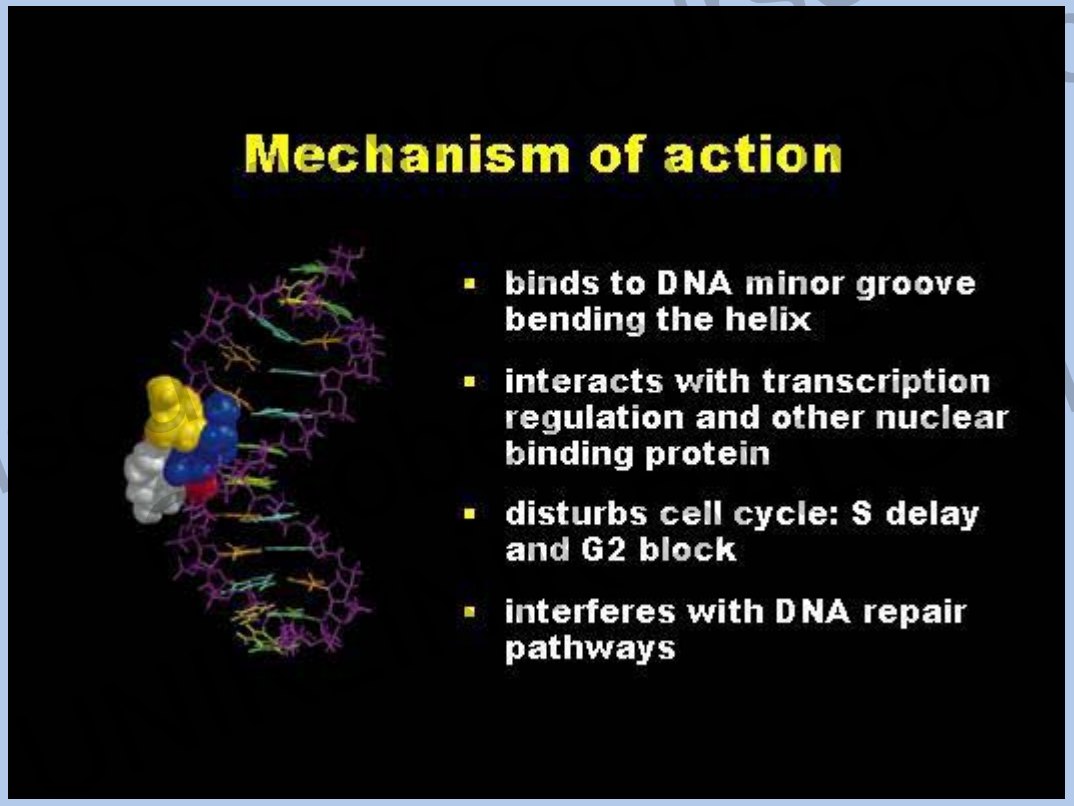
Risk Factors	Rate Ratio	Univariate P	Multivariate P
Unplanned excision	0.8	0.114	0.71
Local rec before referral	1.6	<0.001	0.008
Metastasis at Diagnosis	2.8	<0.001	0.004
Positive Margin	5.4	<0.001	<0.001
Post-op radiation	1.1	<0.001	0.79
Limb salvage	2.0	0.007	0.11

STS - Stadium IV
palliative Chemotherapie

	Response Rate	OS (Monate)
Doxorubicin (1,2)	**9-12 %**	**7.2-12**
Pegyl. liposom D. (2)	**10%**	**10.7**
Ifosphamide (1,3)	**5.5-25% (*2nd* 7%)**	**12 (*2nd* 10.5)**
Doxo / Ifo (4-5)	**18-25%**	**13**

1. Longan et al. JCO 2007,25:3144-
2. Judson et al. Eur J Cancer 2001,37:870-
3. Van Oosterom et al. Eur J Cancer 2002,38:2397-
4. Le Cesne et al. JCO 2000, 18:2676-
5. Worden et al. JCO 2005, 23:106-

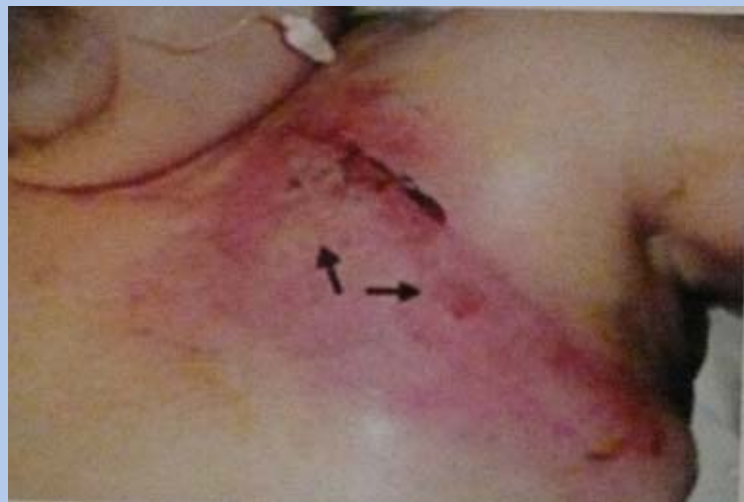
STS - Stadium IV
Trabectedin



Trabectedin Toxizitäten

- **Grad 3/4 Myelosuppession**
- **Transaminasenanstieg**

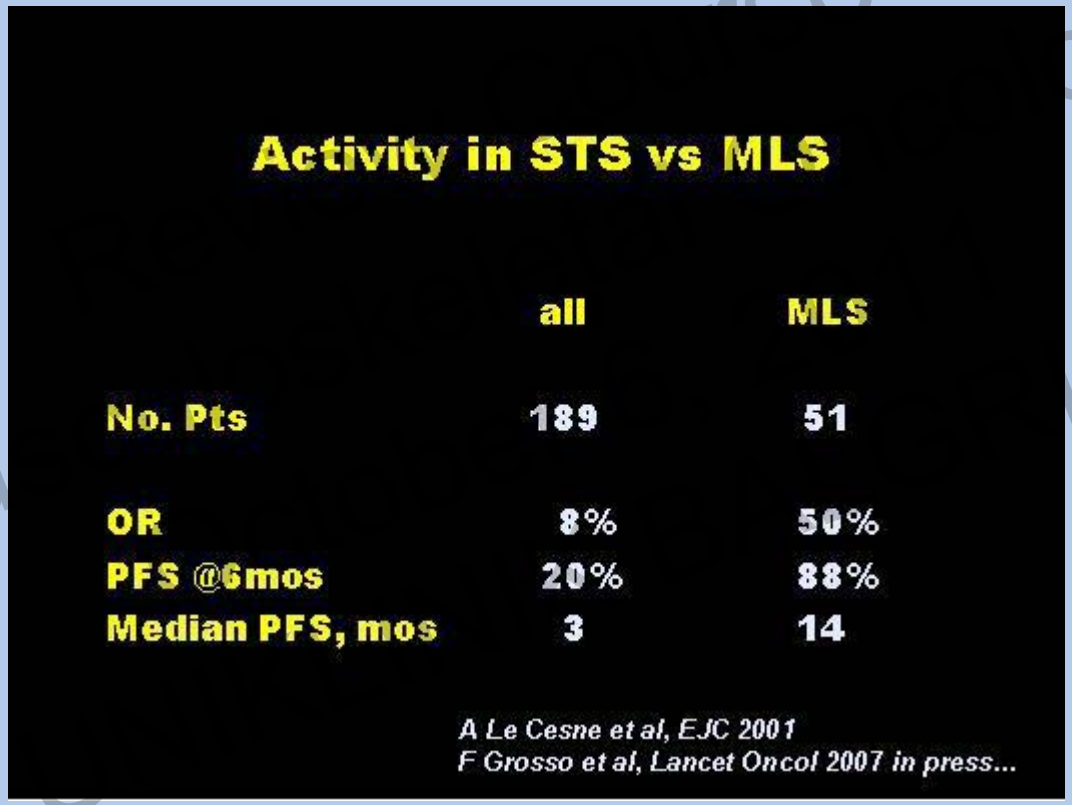
*** KEINE Kardio- oder Nephrotoxizität**
*** selten Alopezie**



Trabectedin Zulassung

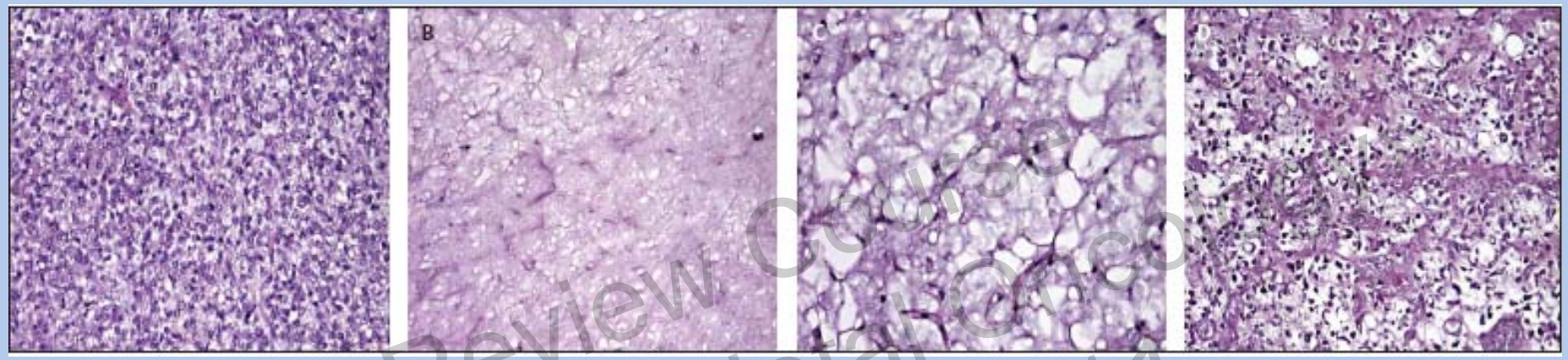
EMEA Zulassung:
„Yondelis® (q3wk 24hrs) ist indiziert für die Behandlung von Patienten mit fortgeschrittenen Weichteiltumoren nach dem Versagen von Anthrazyklinen und Ifosfamid oder von Patienten, die diese Substanzen nicht erhalten dürfen“.

Trabectedin
bei Myxoidem Liposarkom

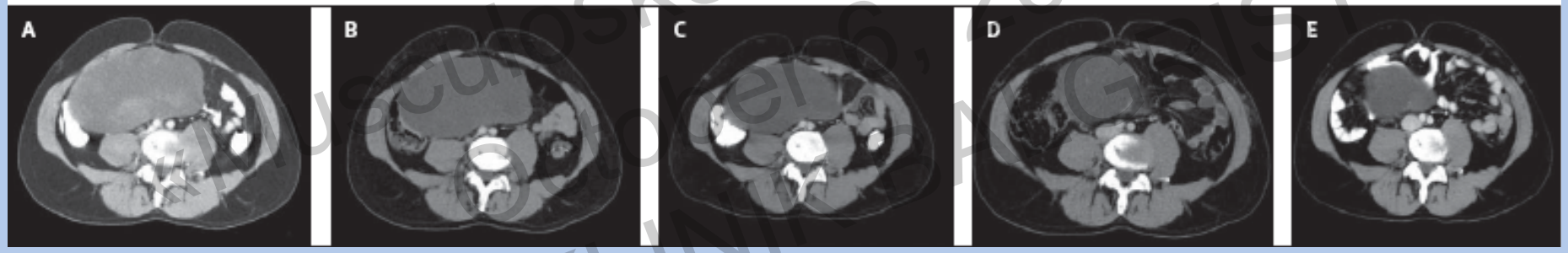


Rationale

Trabectedin 1.1-1.5 mg/m^2 as 3h or 24h infusion q3wks



Histology before (1st left) and after treatment: cell depletion, mature fibroblasts and necrosis

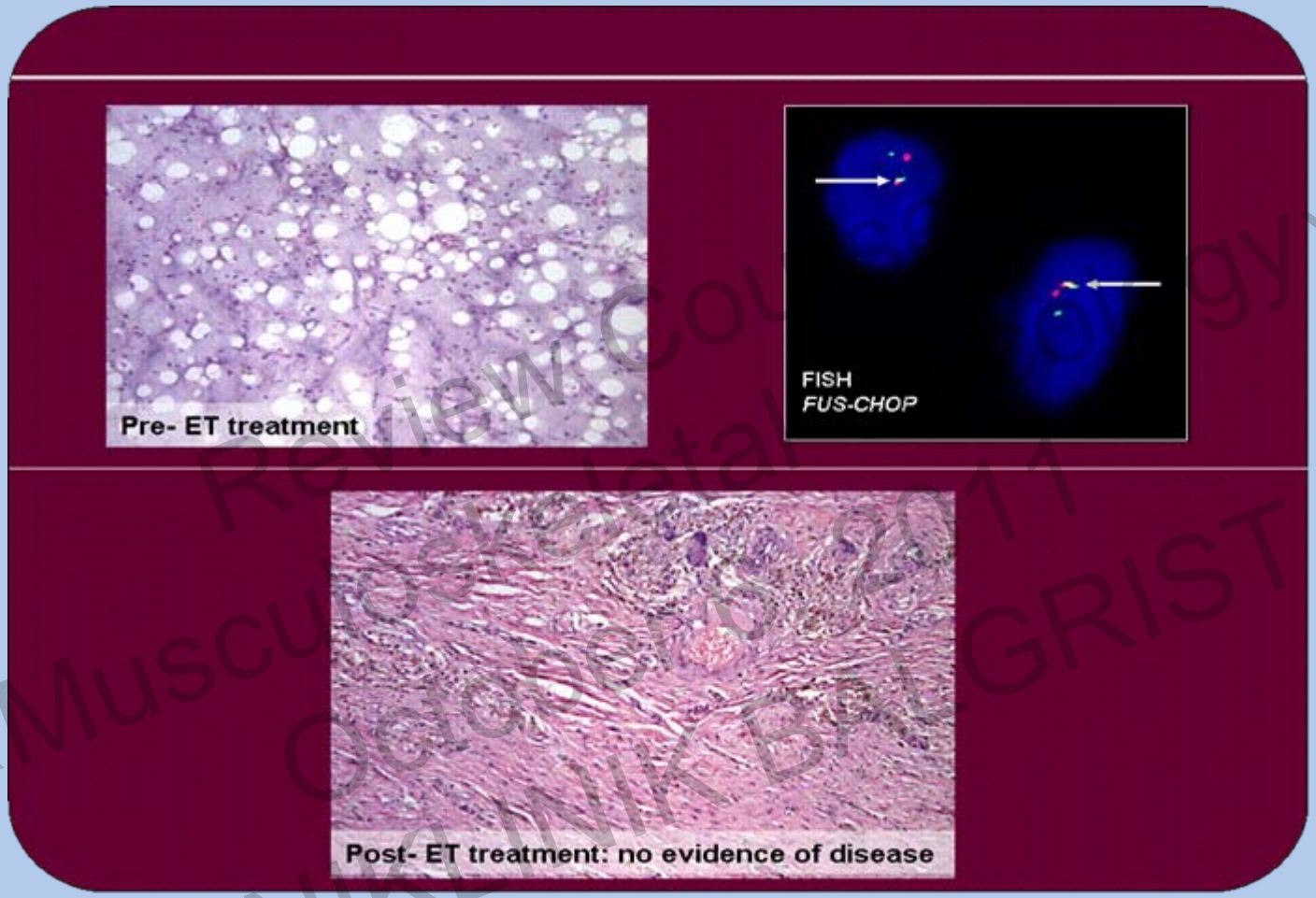


Sequential CT scans of abdominal tumour in the same patient. Change in tumour density followed by tumour size decrease after 5, 8 and 11 courses of trabectedin

(Grosso F, Jones RL, Demetri GD, et al. Lancet Oncol 2007)

- From A Phase II neoadjuvant trial in MRCL

Complete Pathological Response



Pre-treatment: myxoid liposarcoma. FISH positive for FUS-CHOP.

Post-treatment: no evidence of residual tumour. Presence of fibrosis, mono and multinucleated hystiocytes and hemosiderin deposits.

(Response by RECIST: PR)

Pathological and Radiological Response. Patients Evaluable for Efficacy (N=23)

Response	N (%)
Pathological Response*	
Complete pathological response (Absence of residual tumour tissue)	4 (17.4)
Post treatment tumour regression (cellular and vascular component)	
• High • Moderate • Low • No changes	1 (4.3) 9 (39.1) 5 (21.7) 1 (4.3)
Radiological Response (RECIST)	
• Partial response • Stable disease	6 (26) 17 (34)

* Central pathological review not yet available for 3 patients

Trabectedin 1st line?
EORTC 62091

Doxorubicin mono 75mg/m2 (q3w x6)
vs
Trabectidin (until progression)

Differentialtherapie der Weichteilsarkome 2011

Angiosarkom, Kaposi Sarkom	**Taxane, Gemcitabin, liposomales Doxorubicin Sorafenib, VEGF(R)-Inhibitoren?**
Synovialsarkom	**Ifosfamid**
Leiomyosarkom	**Trabectidin, Temozolomid, Gemcitabin, Gemcitabin + Docetaxel**
Liposarkom (myxoid/andere)	**Trabectidin, Gemcitabin**
RMS	**Vincristin, Vinorelbine, Irinotecan, Topotecan**
Chordoma	**Imatinib 800**
Alveolar cell	**Trabectidin ?**
Aggressive Fibromatose	**Imatinib**
Dermatofibrosarcoma Protruberans	**Imatinib 800**
Giant Cell Tumor	**Denosumab**

modifiziert nach Hartmann, Patel, Drugs 2005

Zusammenfassung
Konzepte für metastasierte Weichteilsarkome (Stadium IV)

- Mono vs. Kombinationstherapie (Doxorubicin +/- IFO)? -> weitere Studien
- 2nd line Trabectidin
- Differentialtherapie wo immer möglich (GIST, DFSP)
- In der Palliation bei Symptomatik immer Einbezug aller Modalitäten

Osteosarkome

Euro-BOSS ältere (>40)

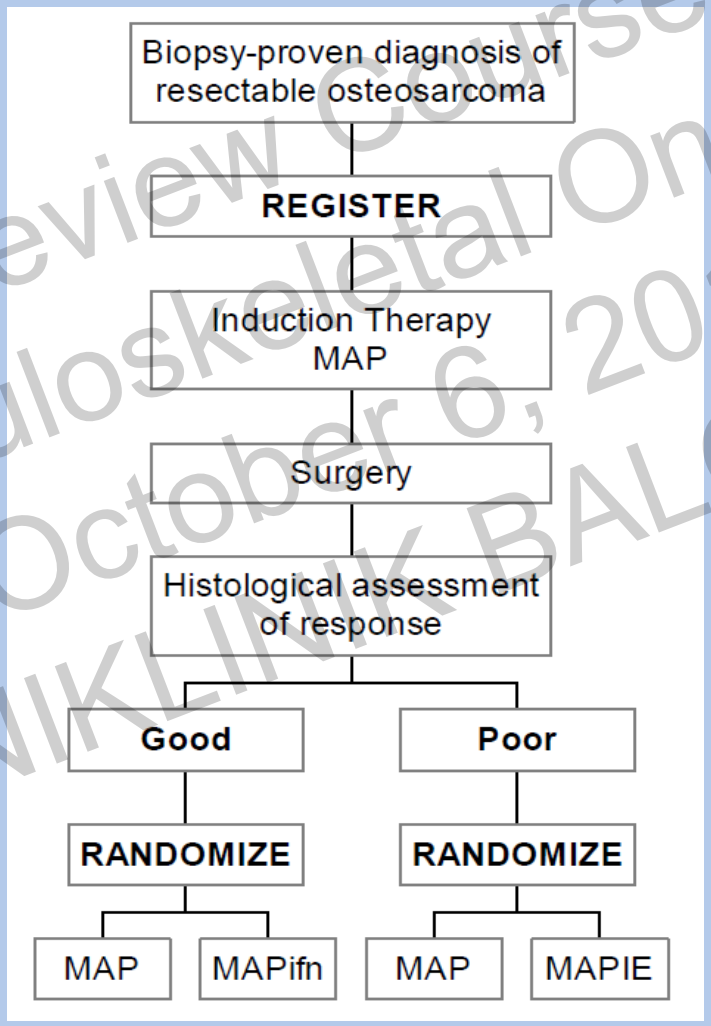
EURAMOS jüngere (5-40)

EURO - E.W.I.N.G.

Osteos.: disease-free survival rates (3yrs) of 60-70%
EWS : 50% 5JÜL (alle Stadien)

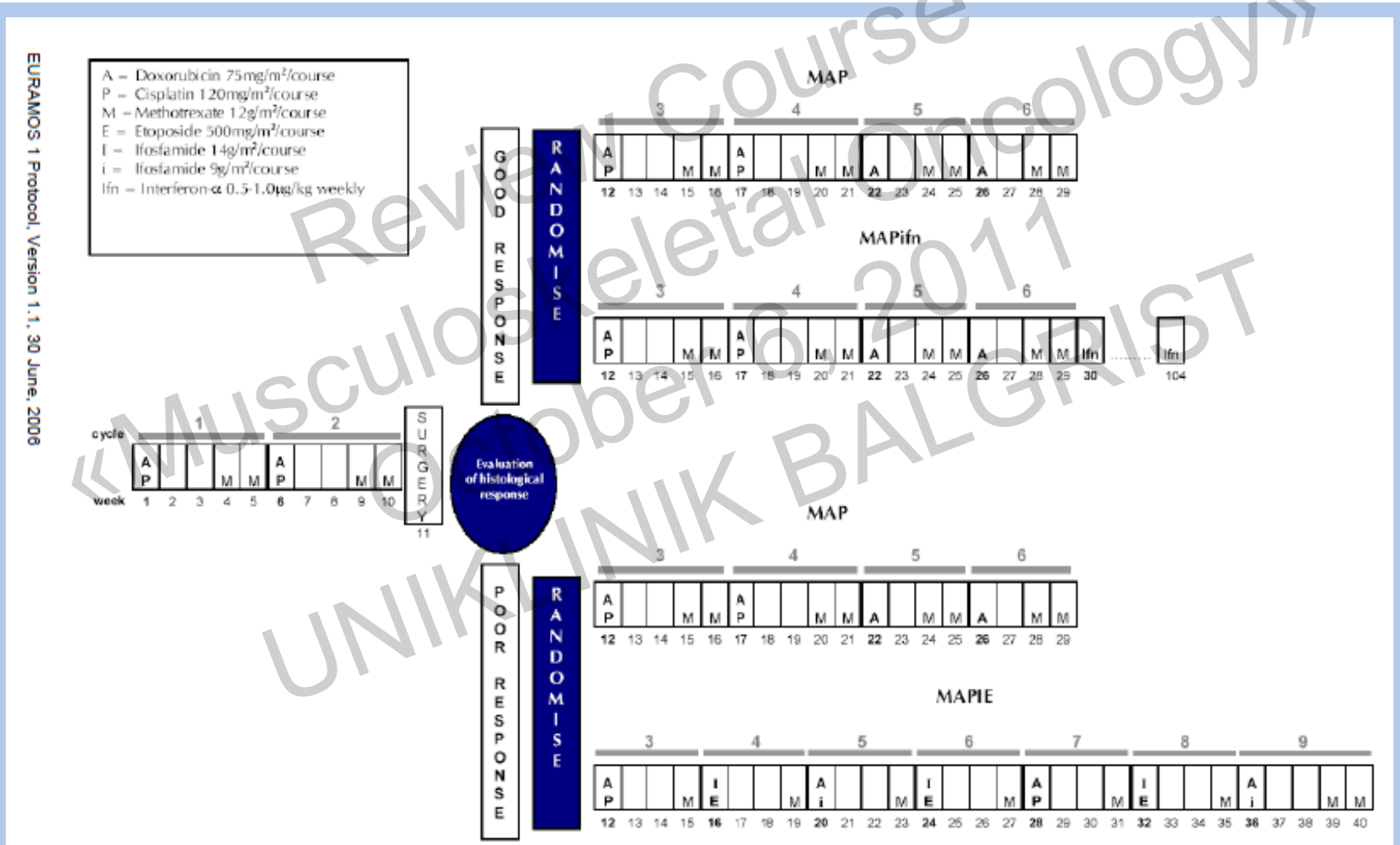
Osteosarkome

EURAMOS (for patients younger than 40 years 1st biopsy)



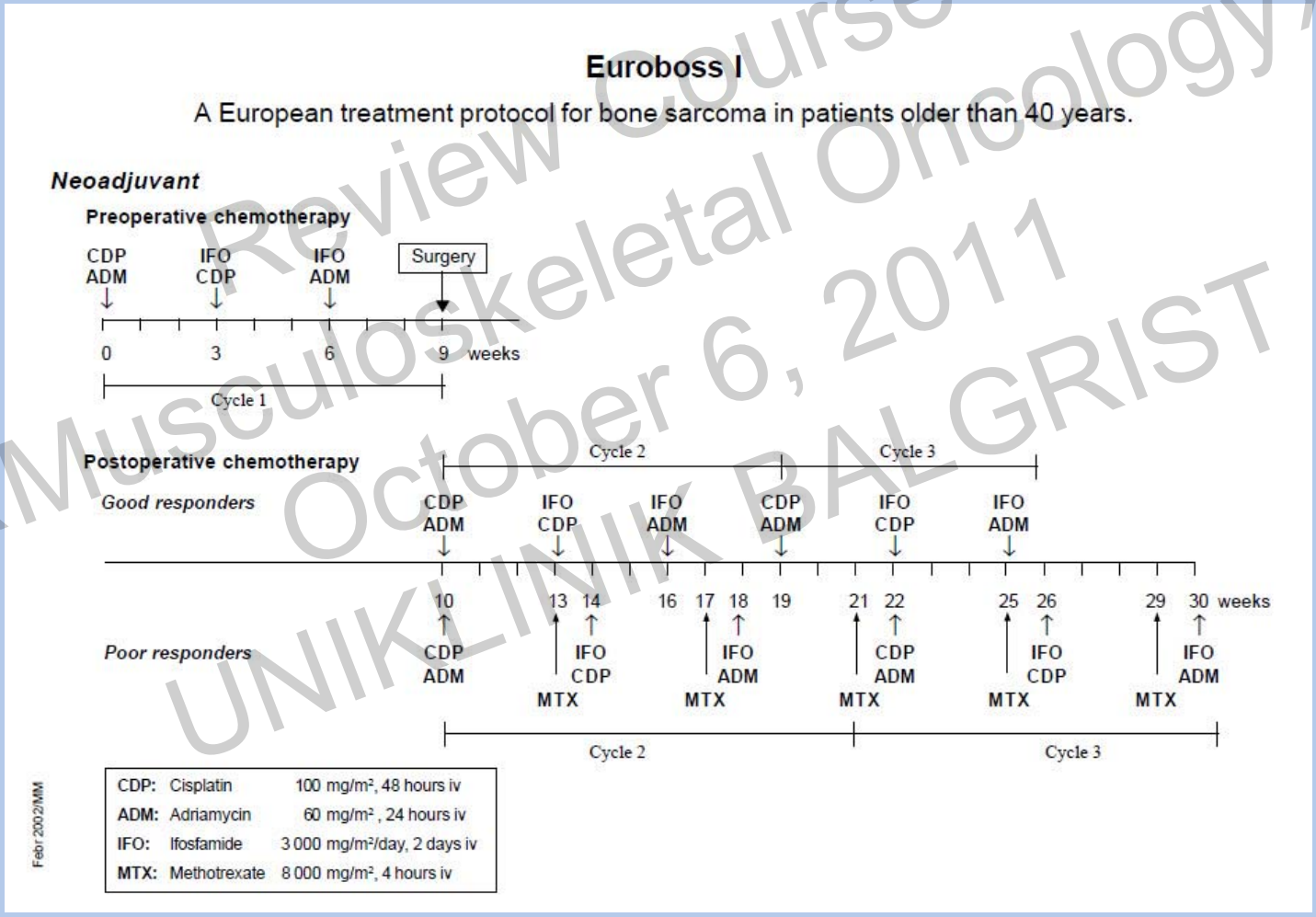
Osteosarkome

EURAMOS (for patients younger than 40 years 1st biopsy)

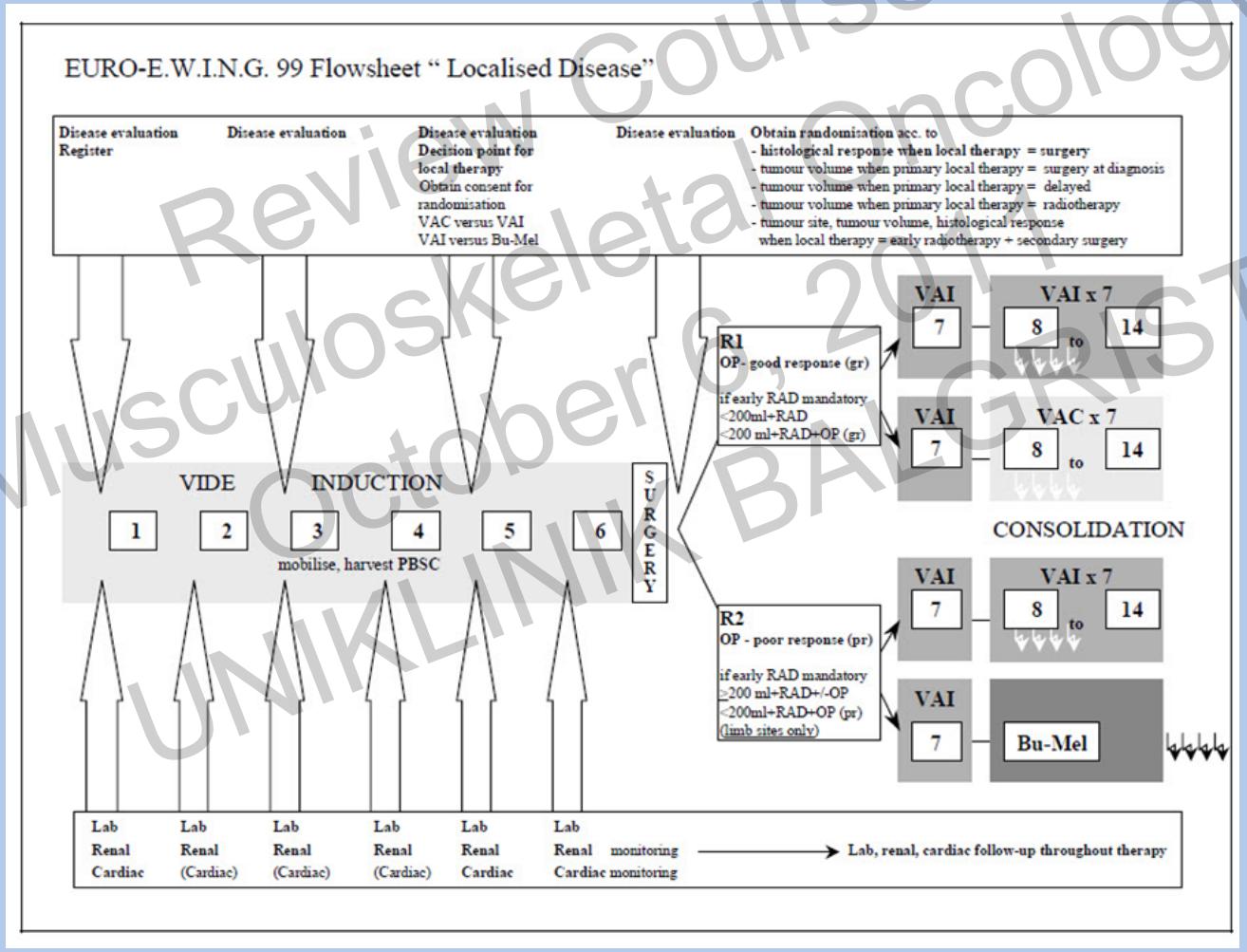


Osteosarkome

COSS, the interdisciplinary Cooperative German-Austrian-Swiss Osteosarcoma Study Group, was founded in 1977 and has since registered some 3,500 bone sarcoma patients from over 200 institutions.



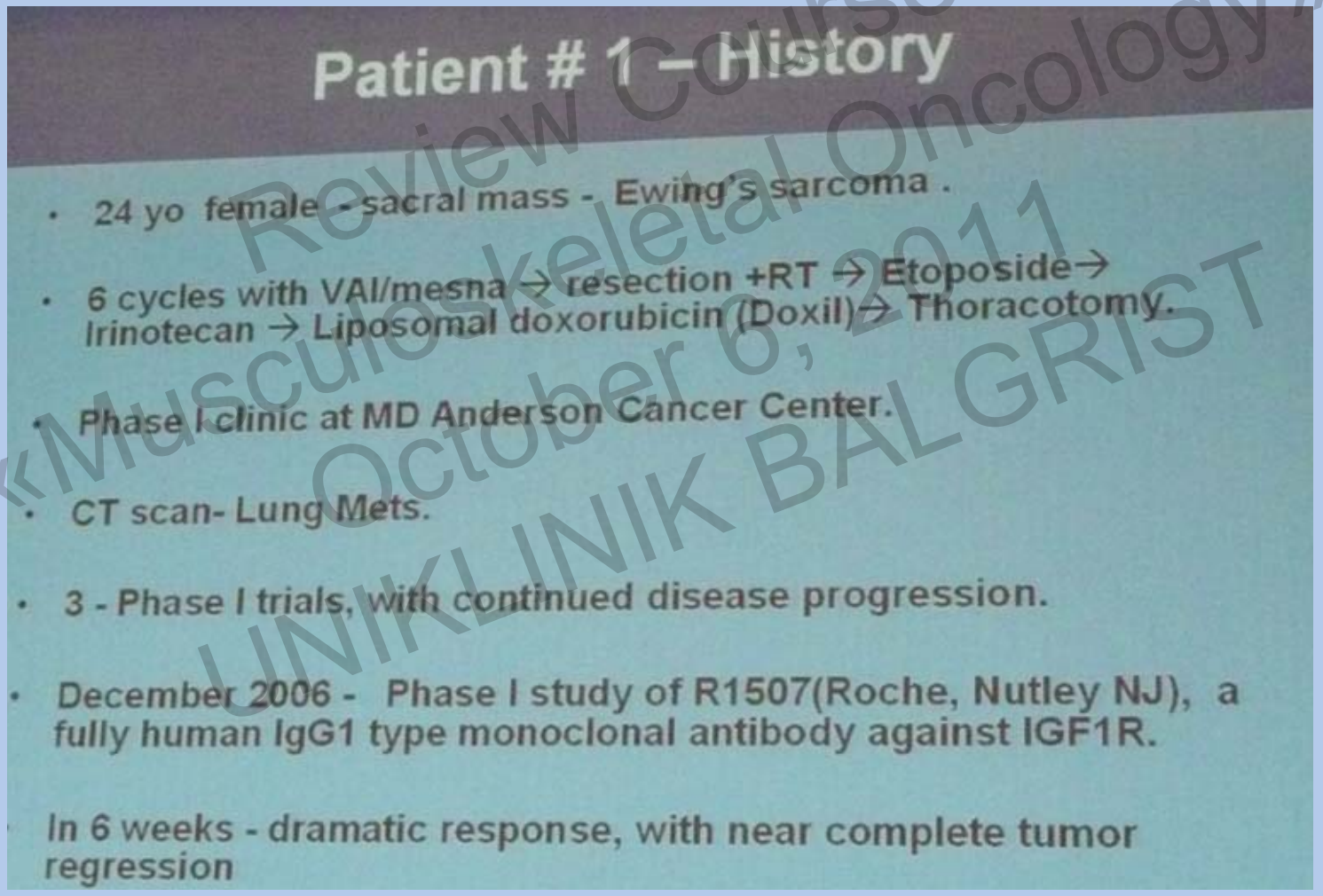
Ewing Sarkom



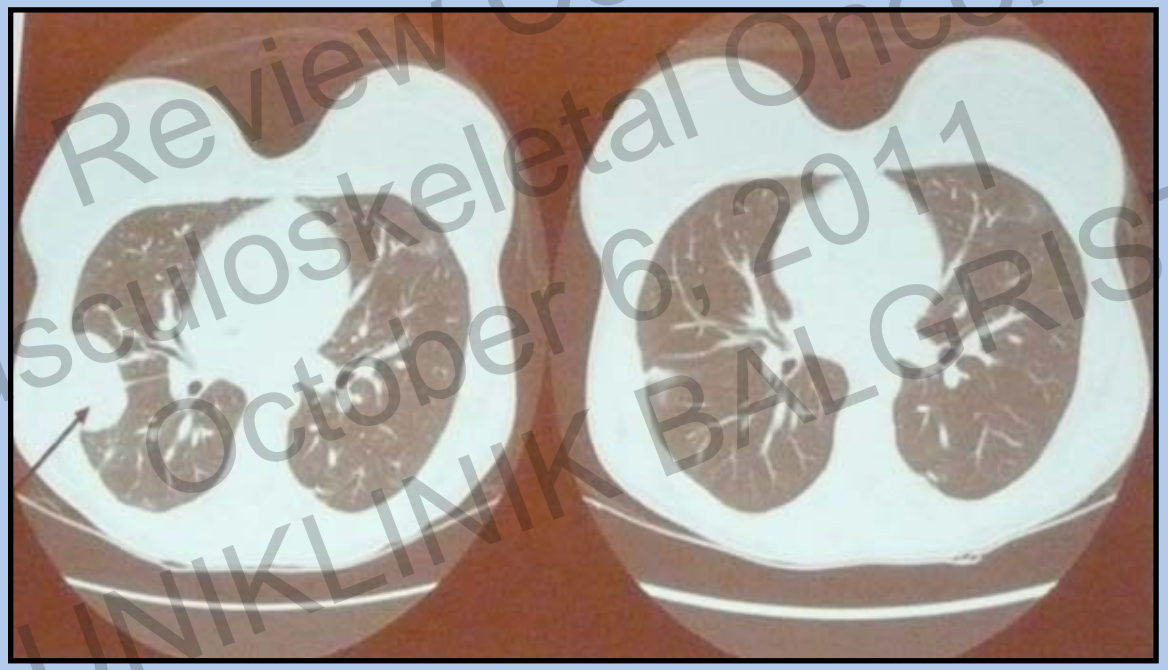
Nächste Generation Medikamente

mTor Inhibitoren +/- IGF-R Inhibition

Ewing Sarkom
IGF R1 (MD Andersen Experience)



Ewing Sarkom
IGF R1



Kurzrock R. et al Clin Cancer Res 16(8): 2458-65

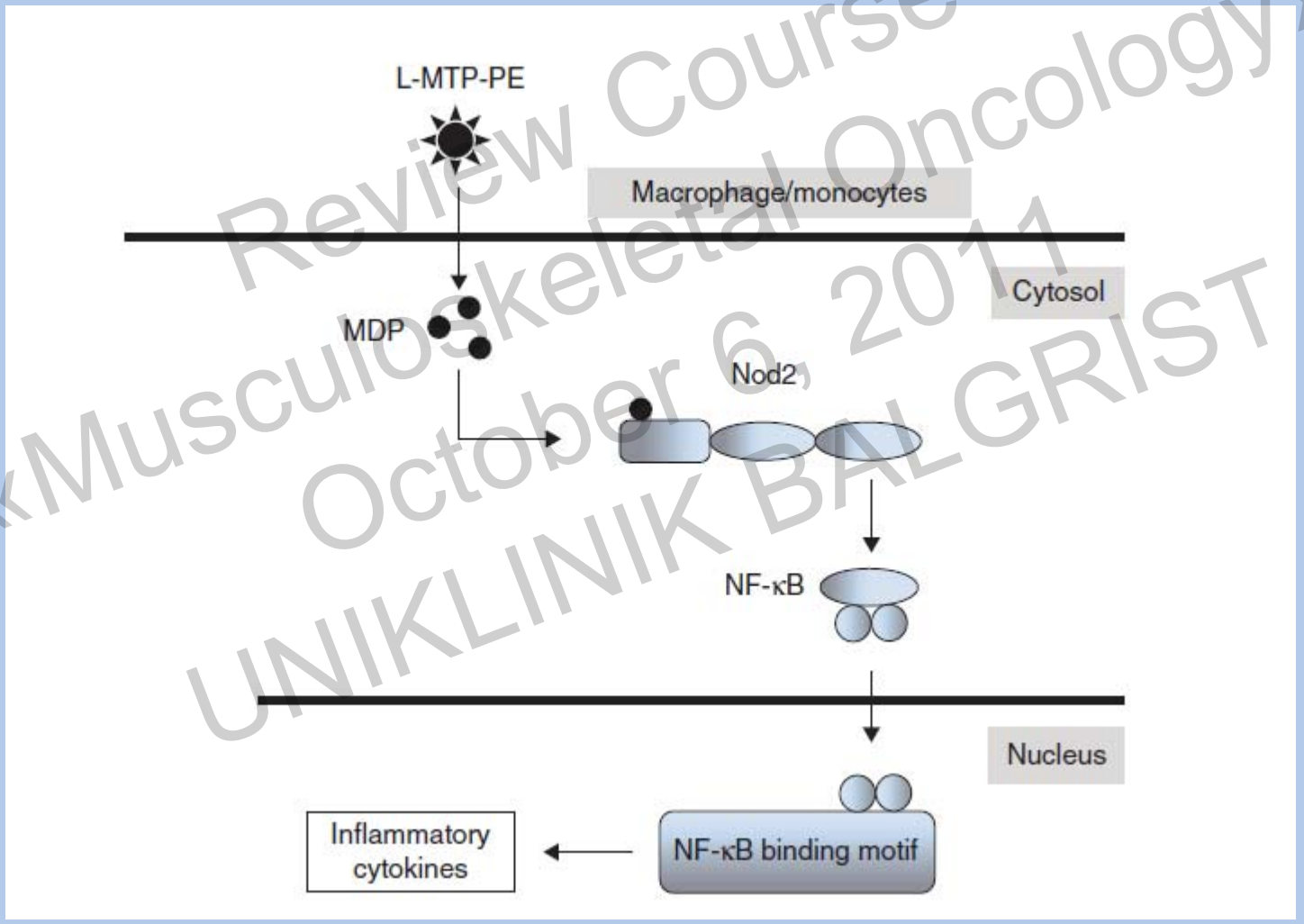
Universität Zürich

UniversitätsSpital Zürich

Danke für Ihre Aufmerksamkeit

Frank Stenner-Liewen
Klinik und Poliklinik für Onkologie,
UniversitätsSpital Zürich

Mifamurtide (MEPACT) in the treatment of patients with osteosarcoma



Mifamurtide (MEPACT) in the treatment of patients with osteosarcoma

In the phase III study INT 0133 reanalysis reported improved survival with the addition of L-MTP-PE to chemotherapy (pooled analysis) from 70% to 78% 6-year OS
(*P* = 0.03; relative risk, 0.73)

aber

in the cohort of patients with primary metastatic osteosarcoma, the addition of L-MTP-PE to chemotherapy did not achieve a statistically significant improvement in the outcome.

mifamurtide (MEPACT) in the treatment of patients with osteosarcoma

EMA Zulassung (FDA und NICE):
“postoperative treatment of patients (aged 2–30 years) with nonmetastatic high-grade resectable osteosarcoma after the complete macroscopic resection“

treatment of 1 patient (Germany):
€110,000,00 for children
€150,000,00 for adults

Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study

David Thomas, Robert Henshaw, Keith Skubitz, Sant Chawla, Arthur Staddon, Jean-Yves Blay, Martine Roudier, Judy Smith, Zhishen Ye, Winnie Sohn, Roger Dansey, Susie Jun

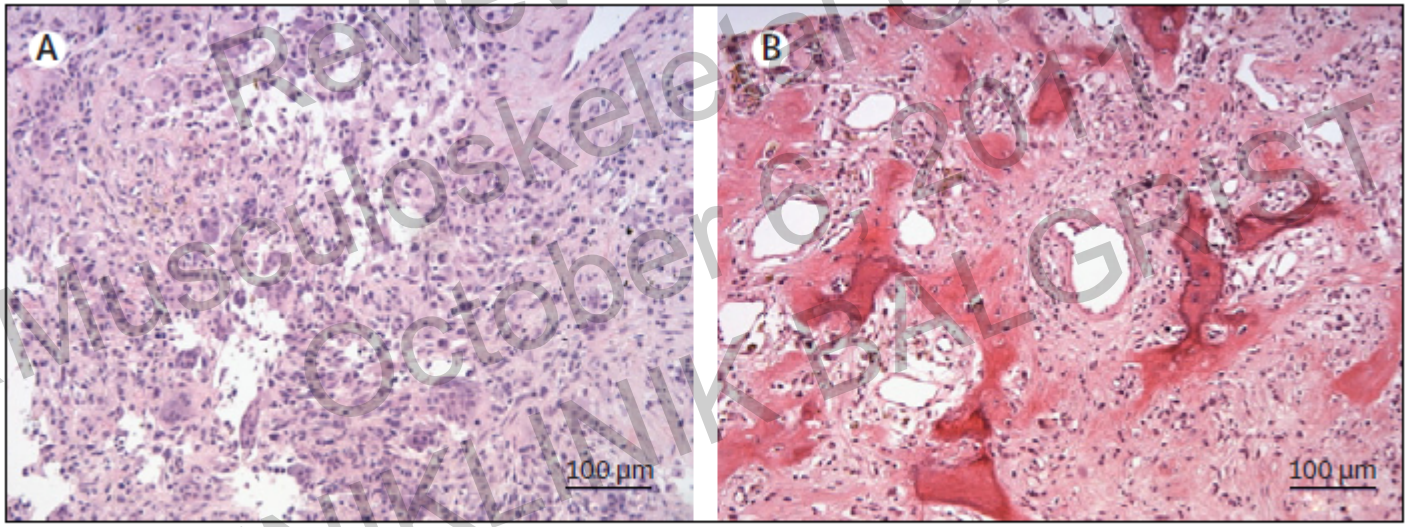


Figure 1: **Pretreatment (A) and week 13 post-treatment biopsy (B)**
Cells stained with haematoxylin and eosin.

Histological results showed near complete or complete elimination of giant cells in all patients for whom histology was