

# Multimodiale Therapien von lokal fortgeschrittenen Weichgewebesarkomen und Stellenwert der Hyperthermie

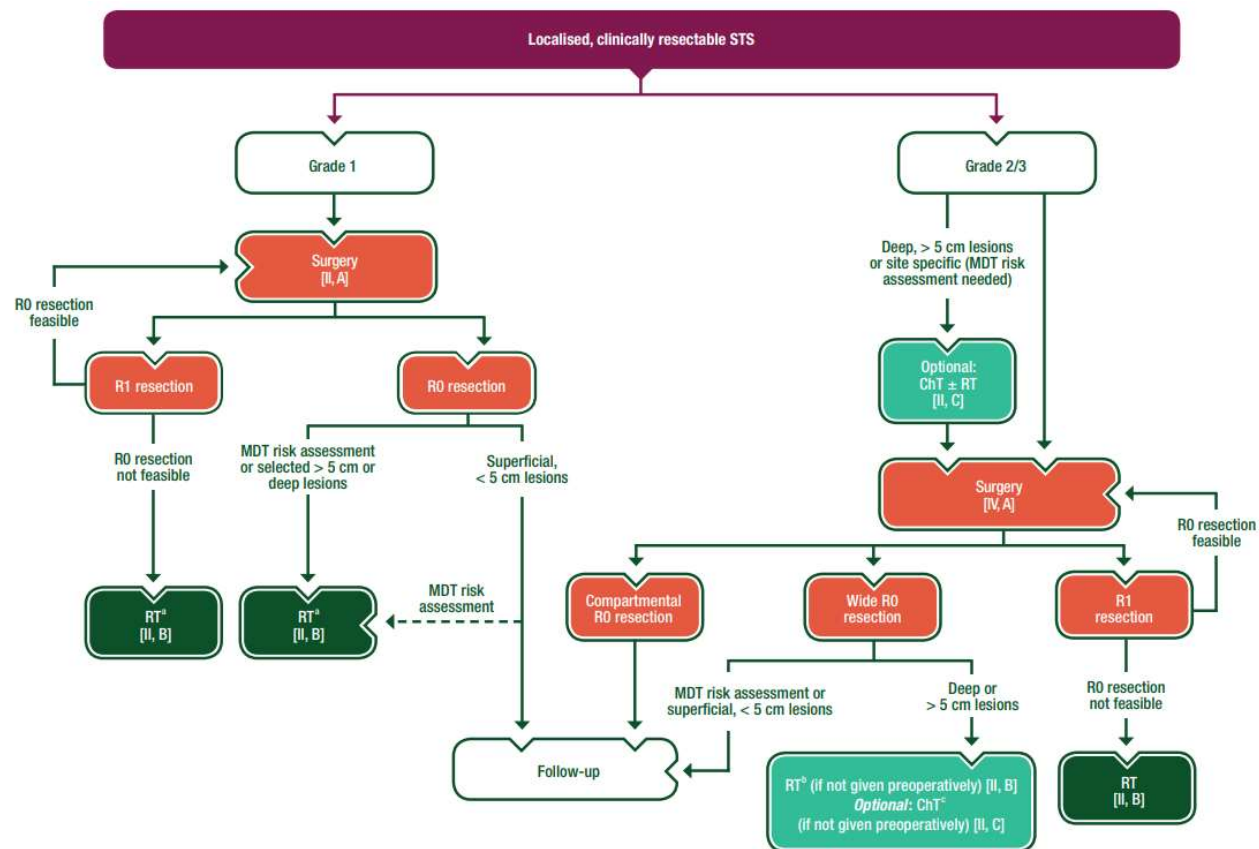
Zentrum für Knochen- und Weichteiltumoren (SarKUM)

08.10.2020 | Prof. L. Lindner



# ESMO-Leitlinie

## Lokalisiertes Weichgewebesarkom



## Sarkom

### Wo ist die neoadjuvante Systemtherapie bereits Standard?

- Ewing-Sarkom (VIDE bzw. VDC/IE)
  - High-grade Osteosarkom (MAP bzw. Dox/Ifo/Cis)
- Datenlage beim Weichgewebesarkom?

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**Articles****Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data**

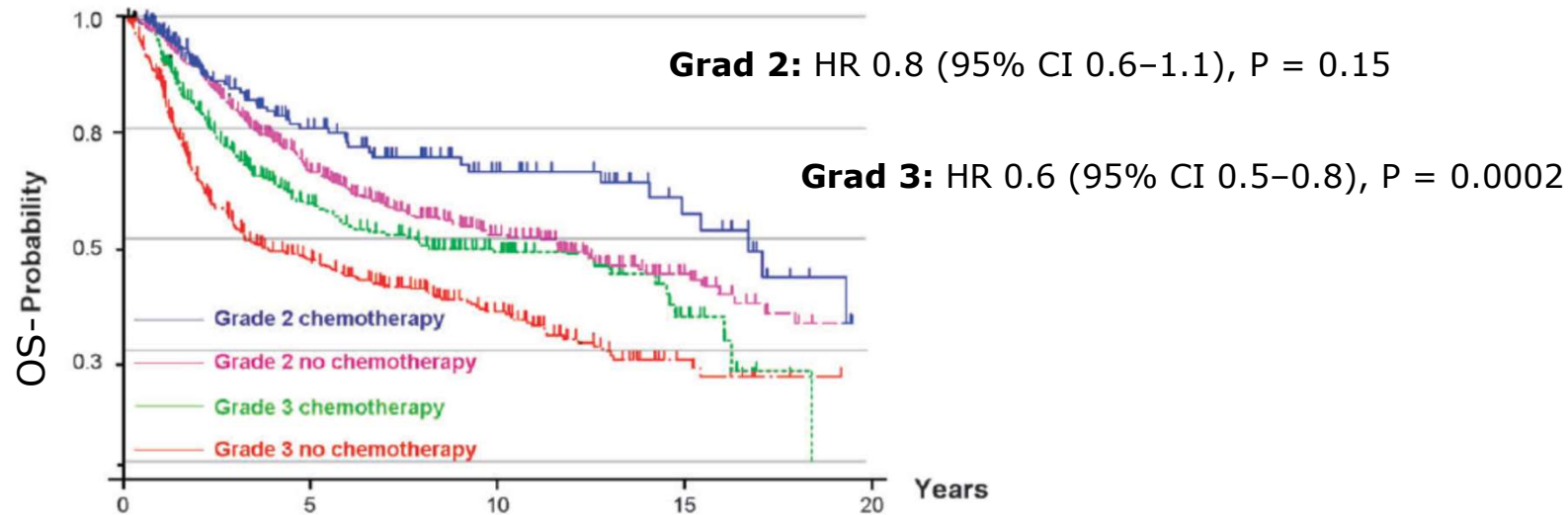
- 1568 Patienten aus 14 randomisierten Studien mit Doxorubicin-basierter Chemotherapie
- Mediane Nachbeobachtung: 9,4 Jahre
- Overall survival: HR 0,89 (0,76–1,03) nicht signifikant (p=0,12)

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

- 1953 Patienten aus 18 Studien  
(4 neue Studien aus den Jahren 2000 – 2002)
  
- Gesamtüberleben für **Doxorubicin + Ifosfamid**:  
HR 0,56 (0,36–0,85; p=0,01)

## Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database

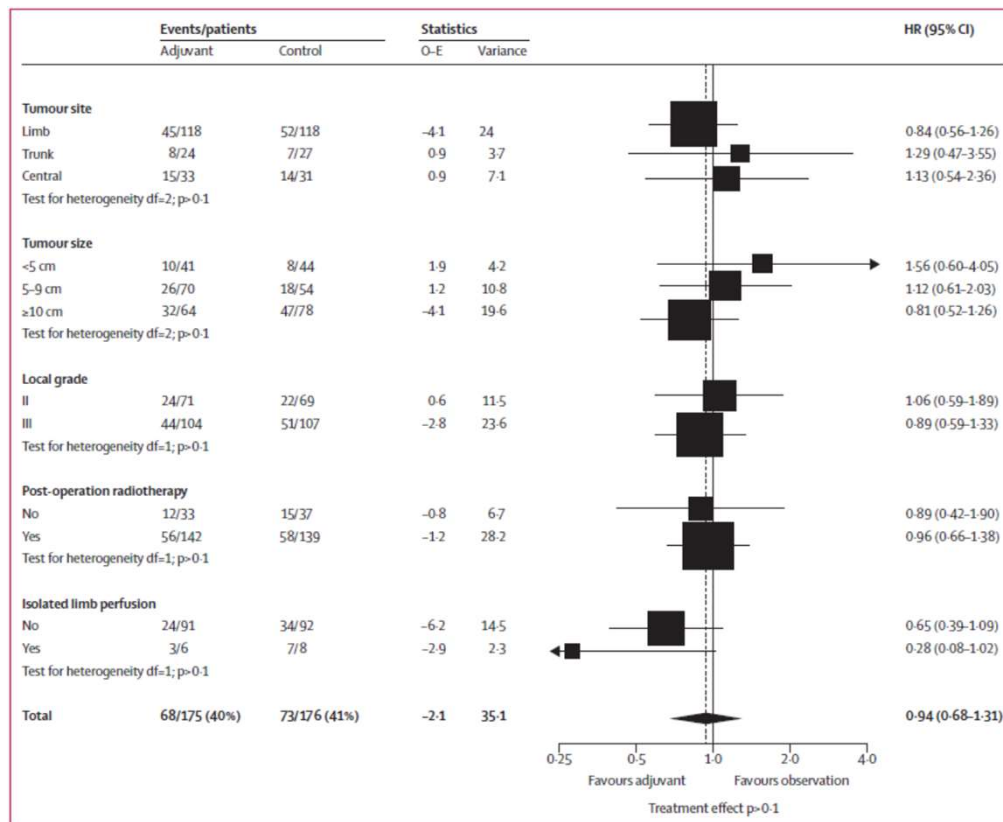
A. Italiano<sup>1\*</sup>, F. Delva<sup>2,3</sup>, S. Mathoulin-Pelissier<sup>2,3</sup>, A. Le Cesne<sup>4</sup>, S. Bonvalot<sup>5</sup>, P. Terrier<sup>6</sup>, M. Trassard<sup>7</sup>, J.-J. Michels<sup>8</sup>, J.-Y. Blay<sup>9</sup>, J.-M. Coindre<sup>10</sup> & B. Bui<sup>1</sup>



- Retrospektive Analyse
- Einheitliche histopathologische Begutachtung

# 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 and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee



5 x Doxo 75mg/m<sup>2</sup>  
+ Ifo 5 g/m<sup>2</sup>

Keine Verbesserung des PFS  
Keine Verbesserung des OS

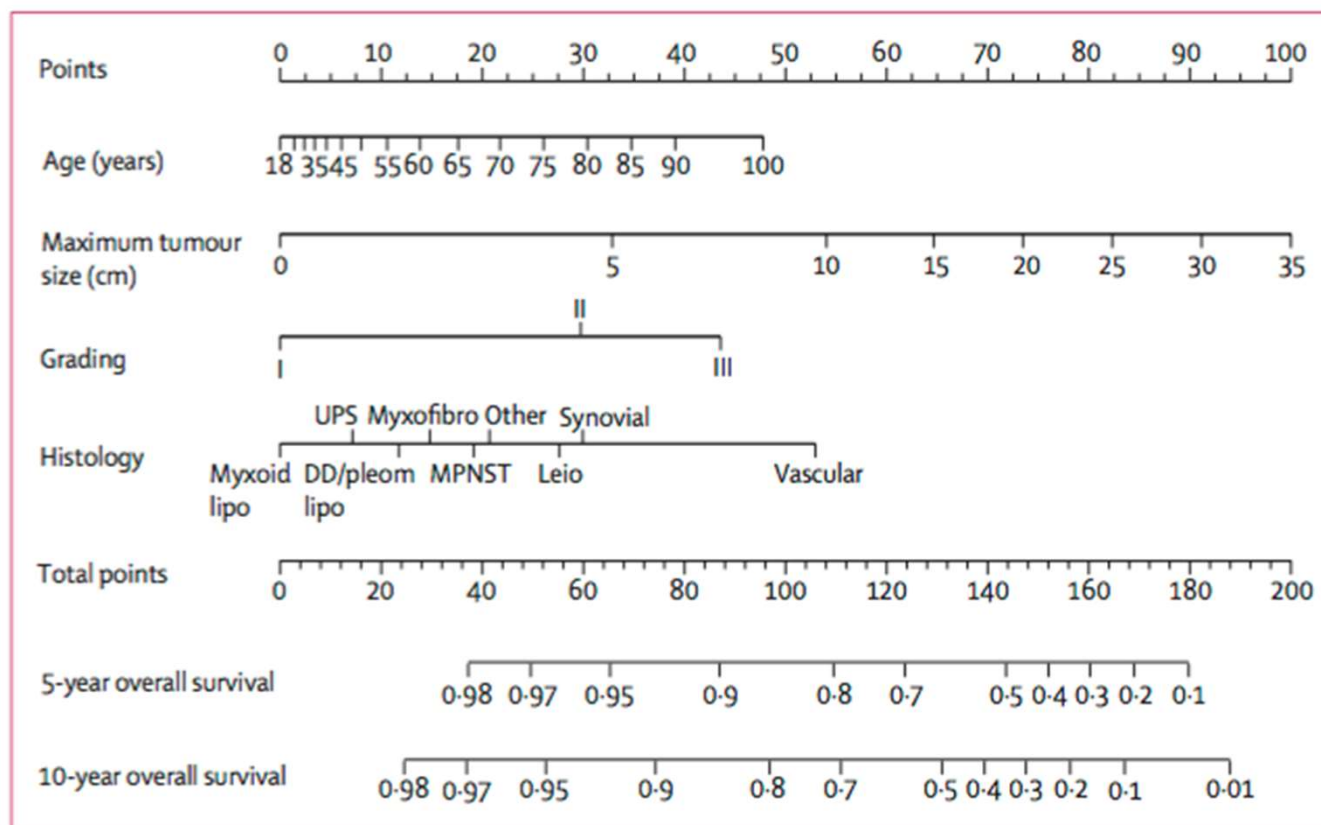
Trend für verbessertes OS:

- Große Tumoren (> 10 cm)
- G3
- Extremitäten-Lokalisation

56% ≠ G3-Sarkome!  
6% = G1 in  
Referenzpathologie!

# Nomogram

## Prognoseabschätzung bei Extremitätensarkomen

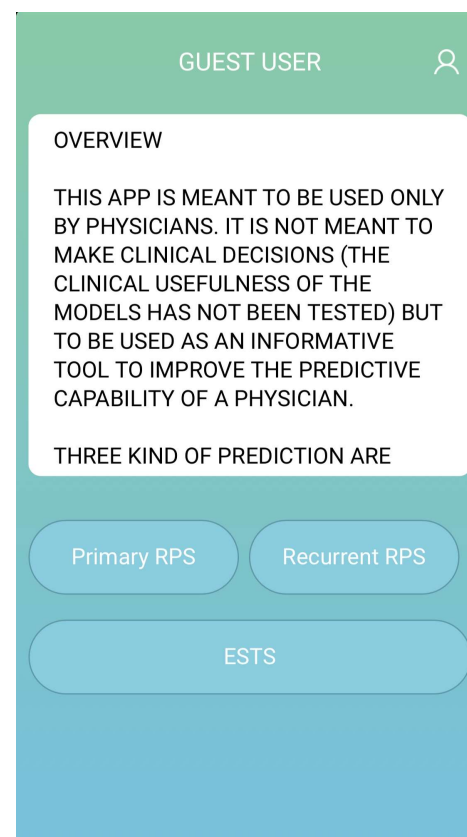
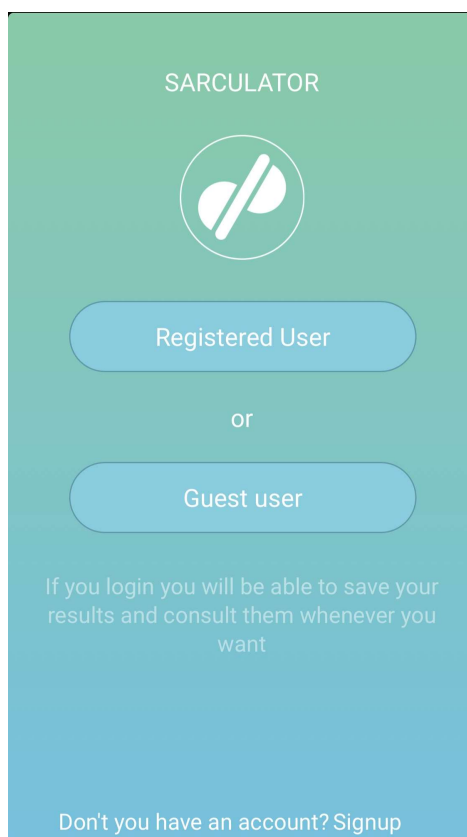


Callegaro D et al. Lancet Oncol 2016; 17: 671–80



# SARCULATOR APP

<https://www.sarculator.com>



# Beispiel

## Retroperitoneales Sarkom

AGE (10-90)

65

TUMOR SIZE (0-80 CM)

11

GRADE

3

HISTOLOGY

DD LPS

MULTIFOCALITY

N

COMPLETENESS OF RESECTION

COMPLETE

7-year OS



info

7-year DFS



info

# Beispiel

## Extremitätensarkom

AGE (18-100)

65

TUMOR SIZE (0-35 CM)

9

GRADE

3

HISTOLOGY

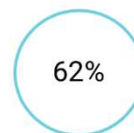
UPS

5-year OS



info

10-year OS



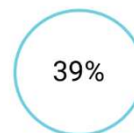
info

5-year DM



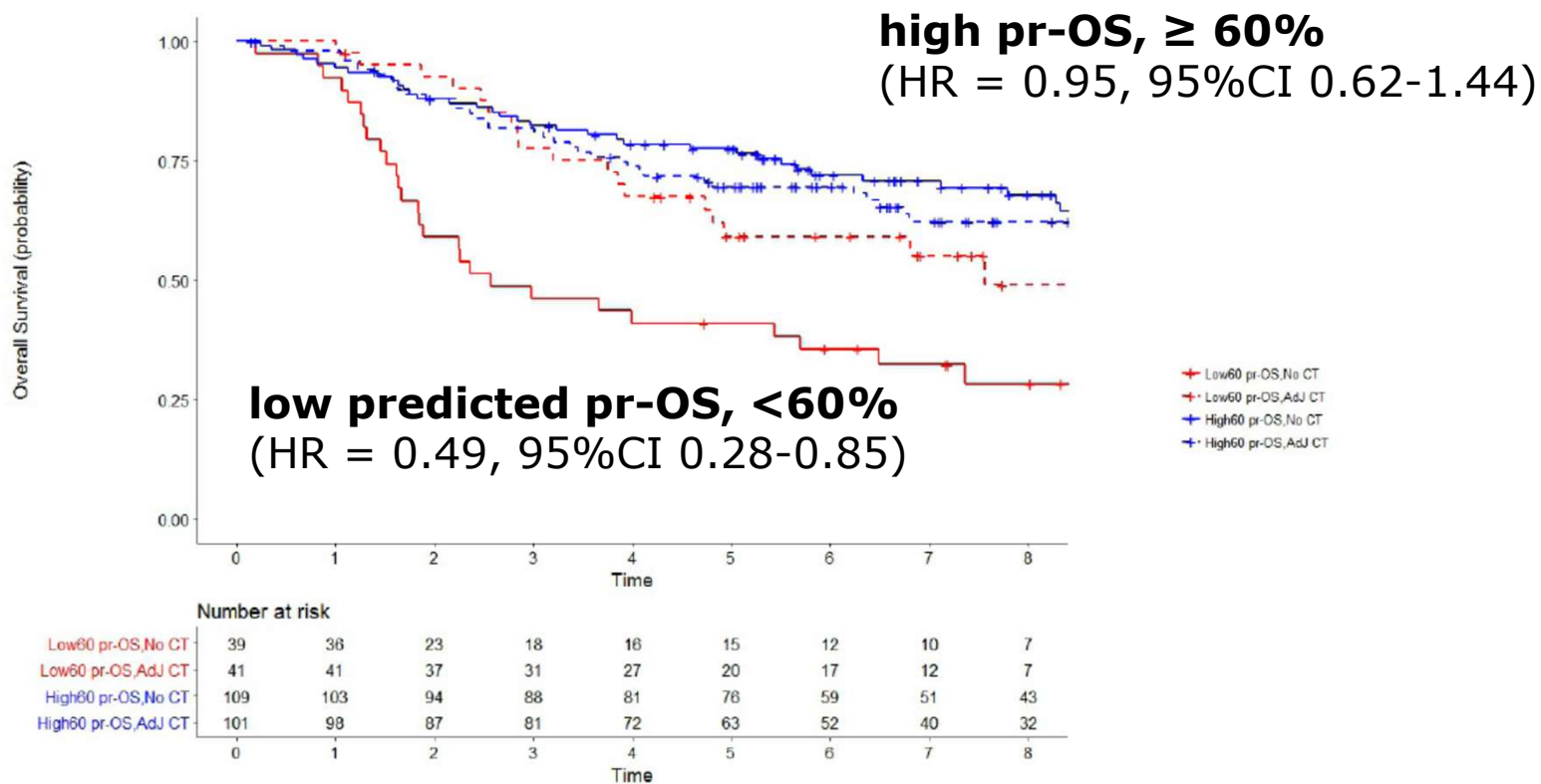
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10-year DM



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# Überlebensvorteil durch adjuvante Chemotherapie bei Patienten mit schlechter Prognose



# Neoadjuvante Chemotherapie

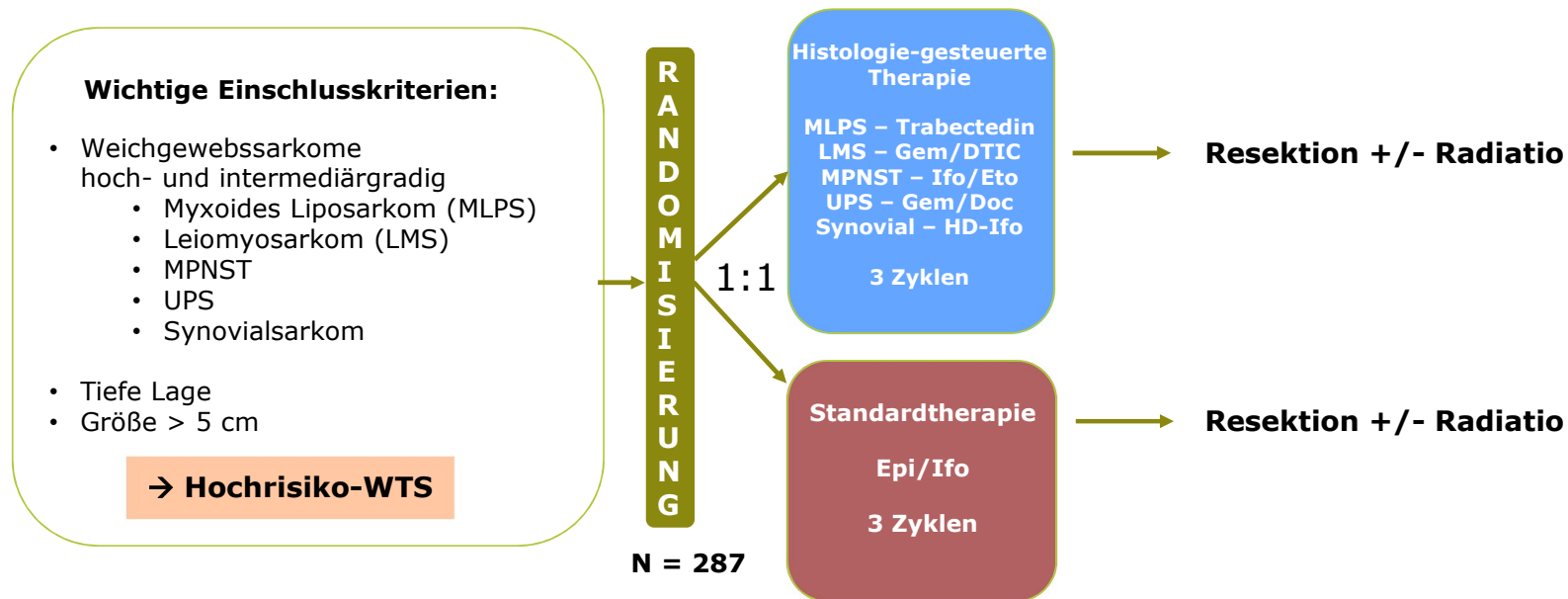
## Rationale

- Vereinfachung der Operation durch Tumorverkleinerung  
> mehr organerhaltenden Operationen
- Sofortige Therapie von Mikrometastasen und/oder skip lesions
- Reduzierung des intraoperativen Disseminationsrisikos
- Neue prognostische Informationen durch das Ansprechen auf neoadjuvante Chemotherapie

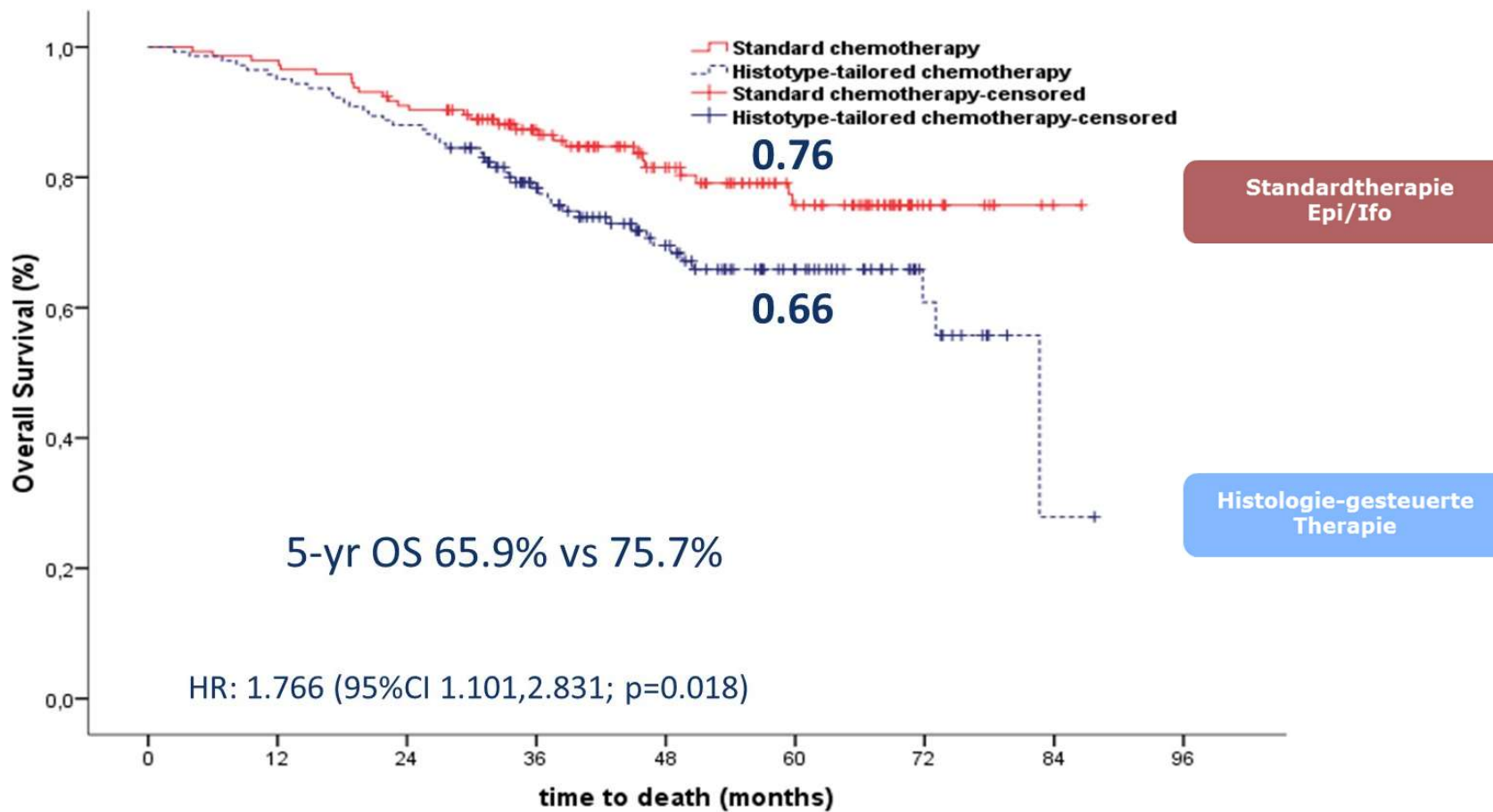
# Neoadjuvante Chemotherapie



Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial

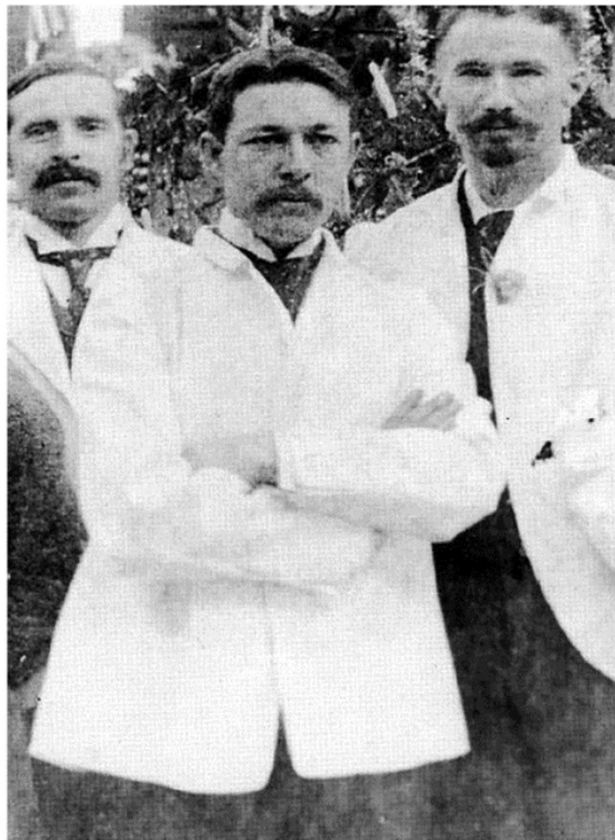


# Overall Survival



# Fieber-Induktion durch bakterielle Toxine

## Ursprung der Krebsimmuntherapie



New York Times - July 29, 1908

### ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed  
Toxins Makes One Disease  
Cast Out the Other.

MANY CASES CURED HERE

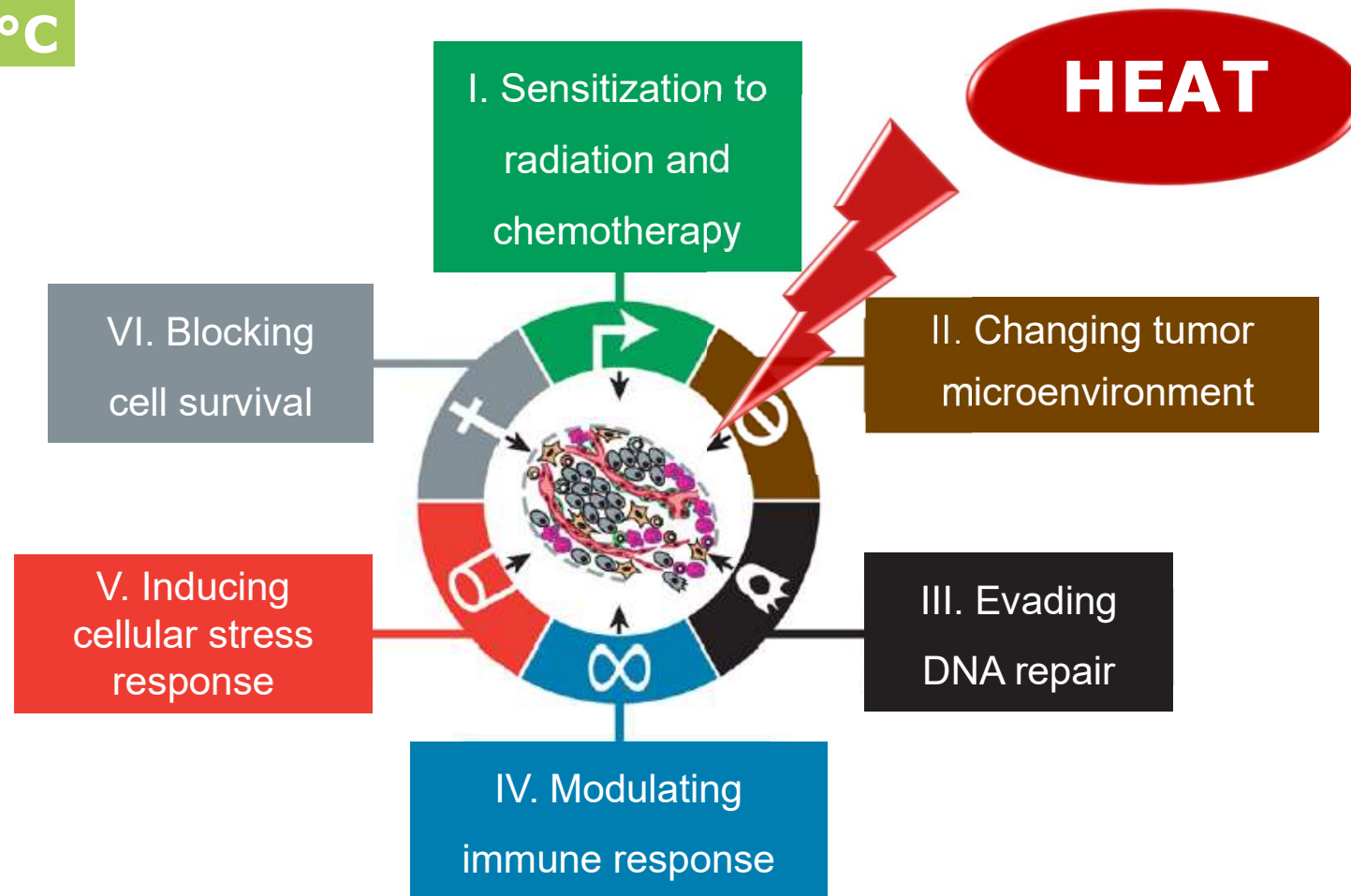
Physician Has Used the Cure for 15  
Years and Treated 430 Cases—  
Probably 150 Sure Cures.

Following news from St. Louis that  
two men have been cured of cancer in  
the City Hospital there by the use of  
a fluid discovered by Dr. William B.  
Coley of New York. It came out yester-



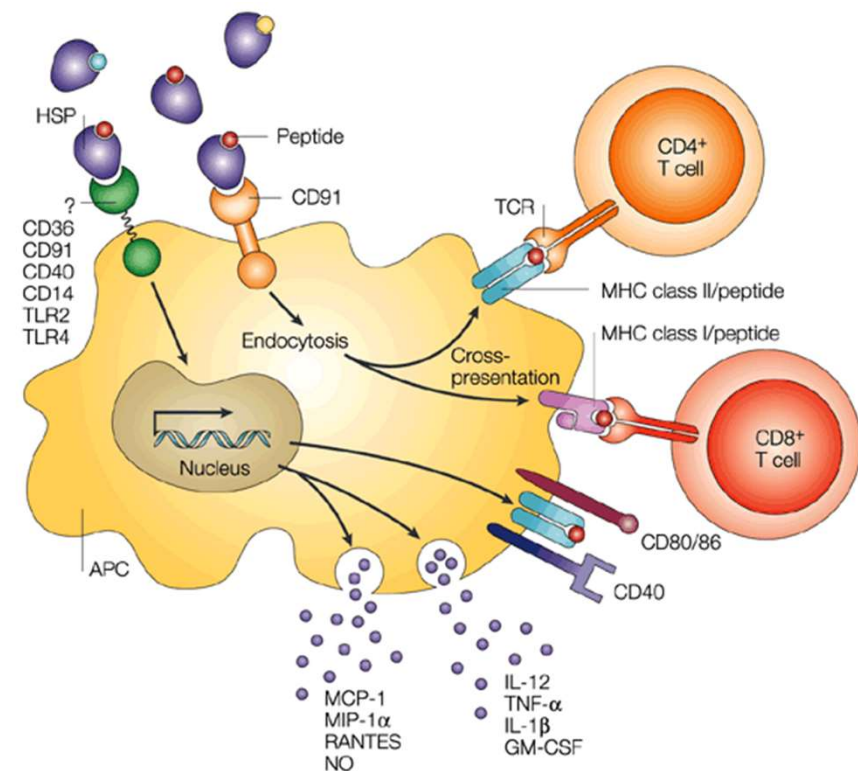
# Hallmarks of Hyperthermia

40°C - 43°C



# Local tumour hyperthermia as immunotherapy

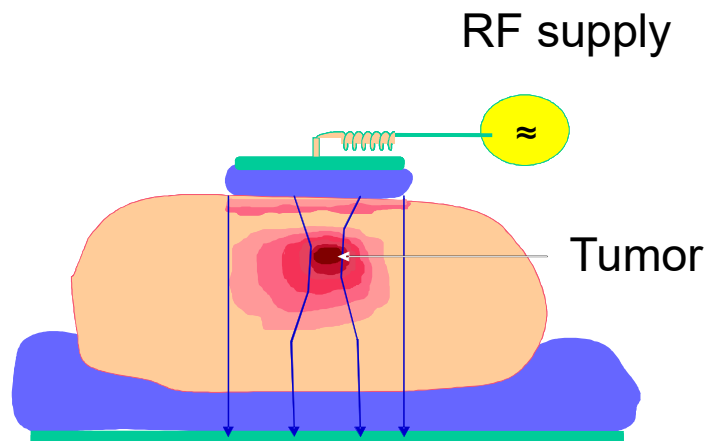
(A) Surface Molecules on Heated Tumor Cells	
<ul style="list-style-type: none"> <li>MICA ↑ (after 39.5°C, 6h)</li> <li>MHCI ↑ (after 43°C, 30min)</li> </ul>	
(B) Heat Shock Proteins	
<ul style="list-style-type: none"> <li>heated tumor cells release HSPs</li> <li>HSPs activate NK cells</li> <li>HSPs bind to TLR2 and TLR4 on APCs</li> <li>HSPs transfer potential tumor antigens to APCs</li> <li>APCs then cross present antigens to CD8+ T cells</li> </ul>	
(C) Exosomes	
<ul style="list-style-type: none"> <li>heated tumor cells release exosomes</li> <li>exosomes transfer potential tumor antigens to APCs</li> <li>APCs then cross present antigens to CD8+ T cells</li> <li>exosomes also contain chemokines</li> </ul>	
(D) Direct Effects on Immune Cells	
<ul style="list-style-type: none"> <li>NKG2D ↑ on NK cells (after 39.5°C, 6h)</li> <li>CD8+ T cell activity ↑ (after 39.5°C, 6h)</li> <li>activate DCs (after 39.5-41°C, 6-24h)</li> </ul>	
(E) Tumor Vasculature	
<ul style="list-style-type: none"> <li>improve tumor perfusion (after 42°C, 1h)</li> <li>may increase adhesion molecule expression</li> <li>may facilitate better immune trafficking between tumors and dLN</li> </ul>	



Nature Reviews | Immunology

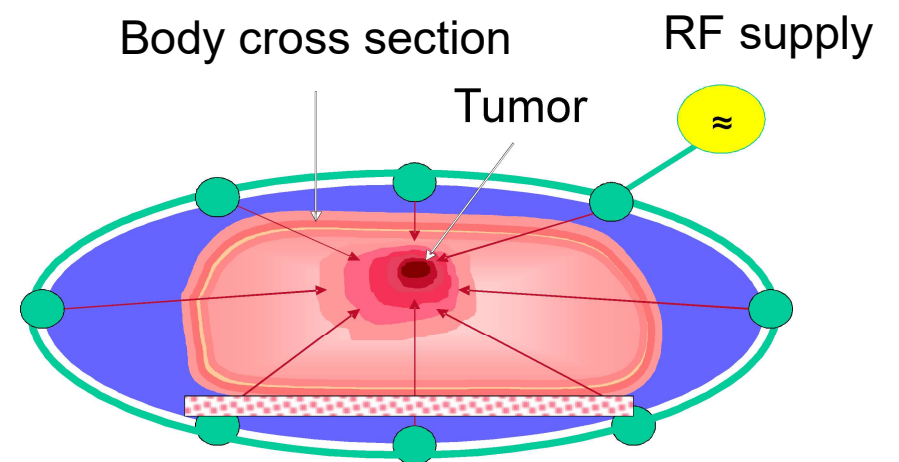
# Hyperthermie - Techniken

## Kapazitive-Hyperthermie



≠

## Antennen-Hyperthermie



# Hyperthermie - Applikatoren

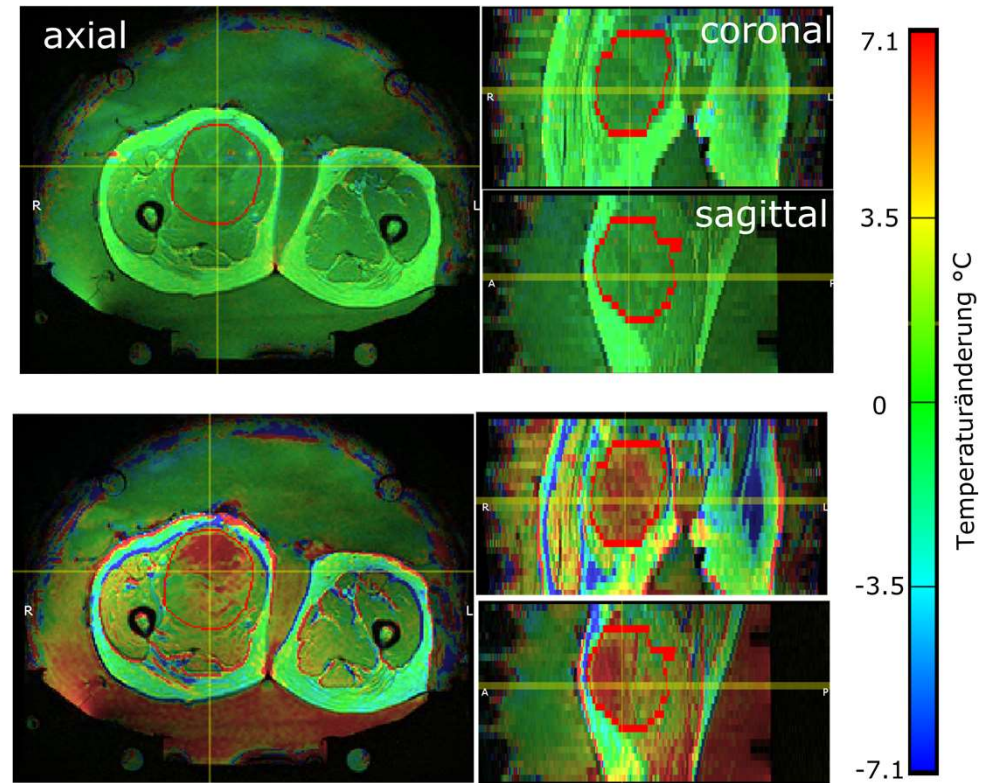
## Tiefenhyperthermie



## Oberflächenhyperthermie

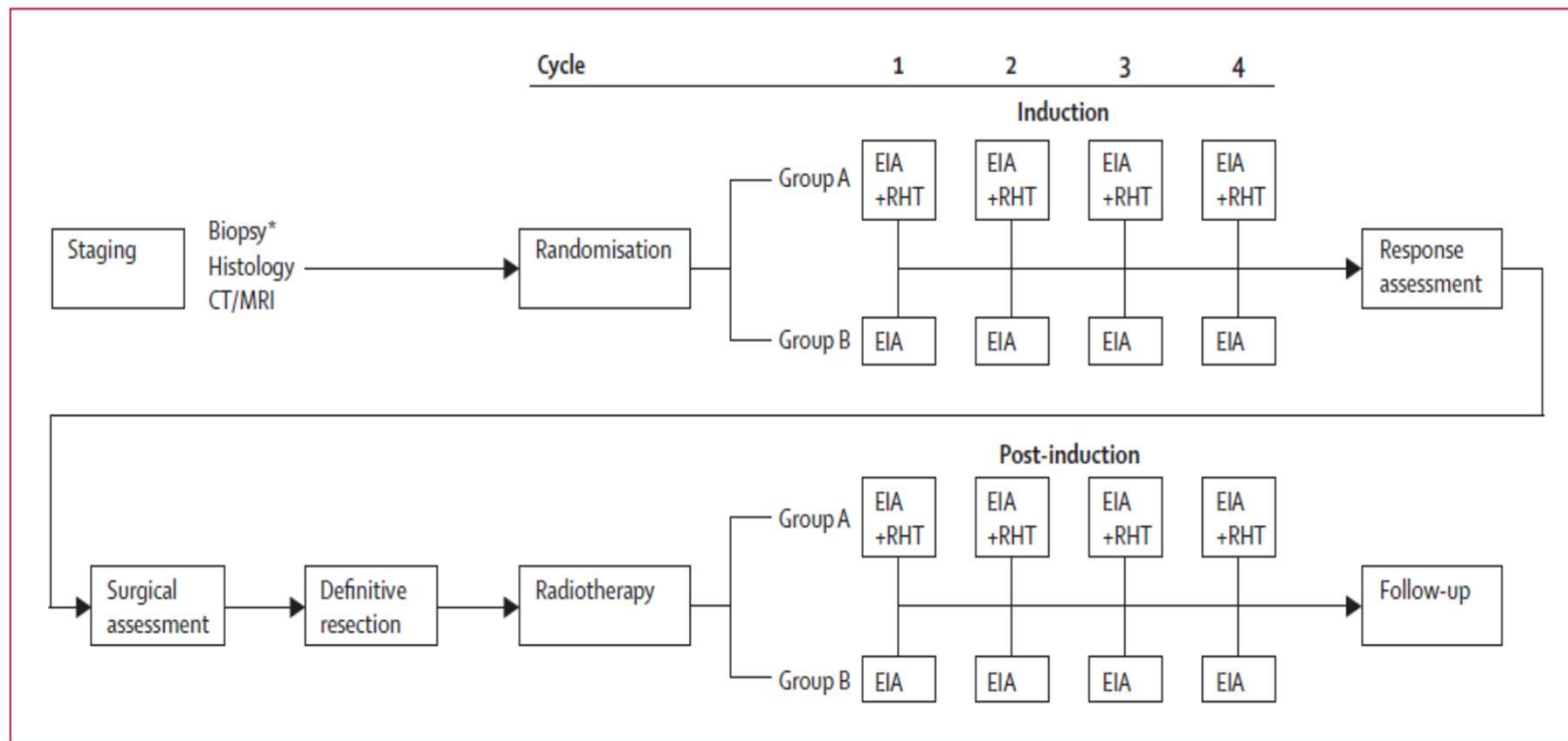


# MR-Hyperthermie Hybridsystem



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

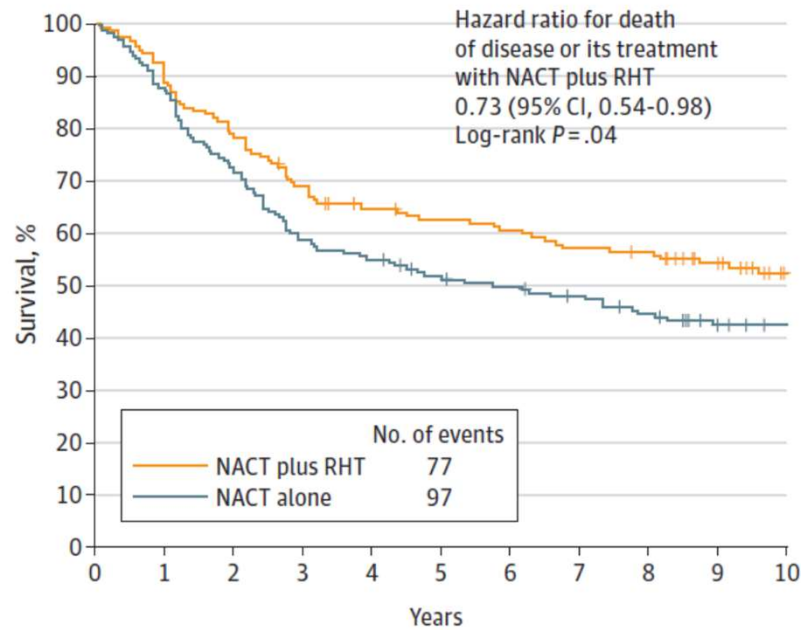
Rolf D Issels\*, Lars H Lindner\*, Jaap Verweij, Peter Wust, Peter Reichardt, Baard-Christian Schem, Sultan Abdel-Rahman, Soeren Daugaard, Christoph Salat, Clemens-Martin Wendtner, Zeljko Vujaskovic, Rüdiger Wessalowski, Karl-Walter Jauch, Hans Roland Dürr, Ferdinand Ploner, Andrea Baur-Melnyk, Ulrich 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)



# Kaplan-Meier Überlebenskurven

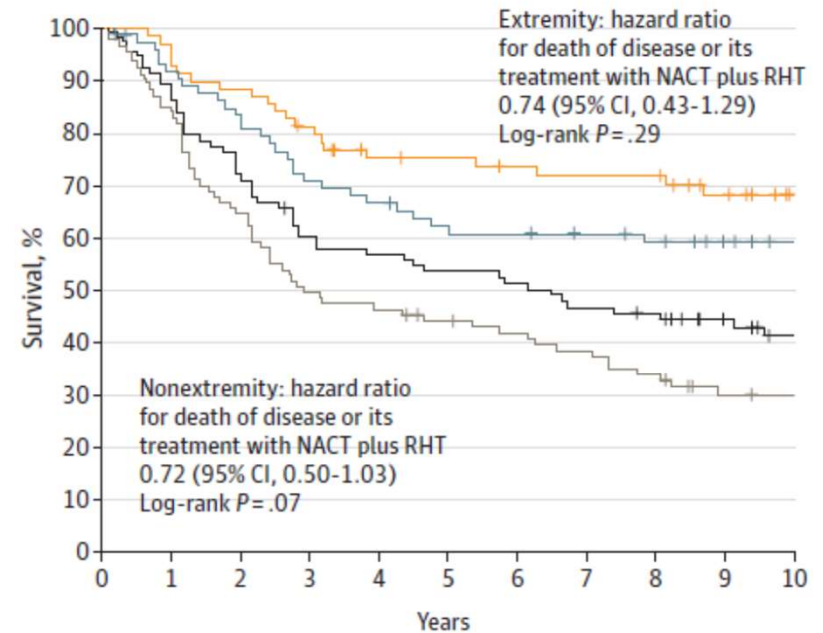
## Nach Langzeit-Follow-Up

**C** Median survival



No. at risk	0	1	2	3	4	5	6	7	8	9	10
NACT plus RHT	162	150	128	110	98	94	89	84	82	68	54
NACT alone	167	145	118	96	90	82	78	73	67	56	51

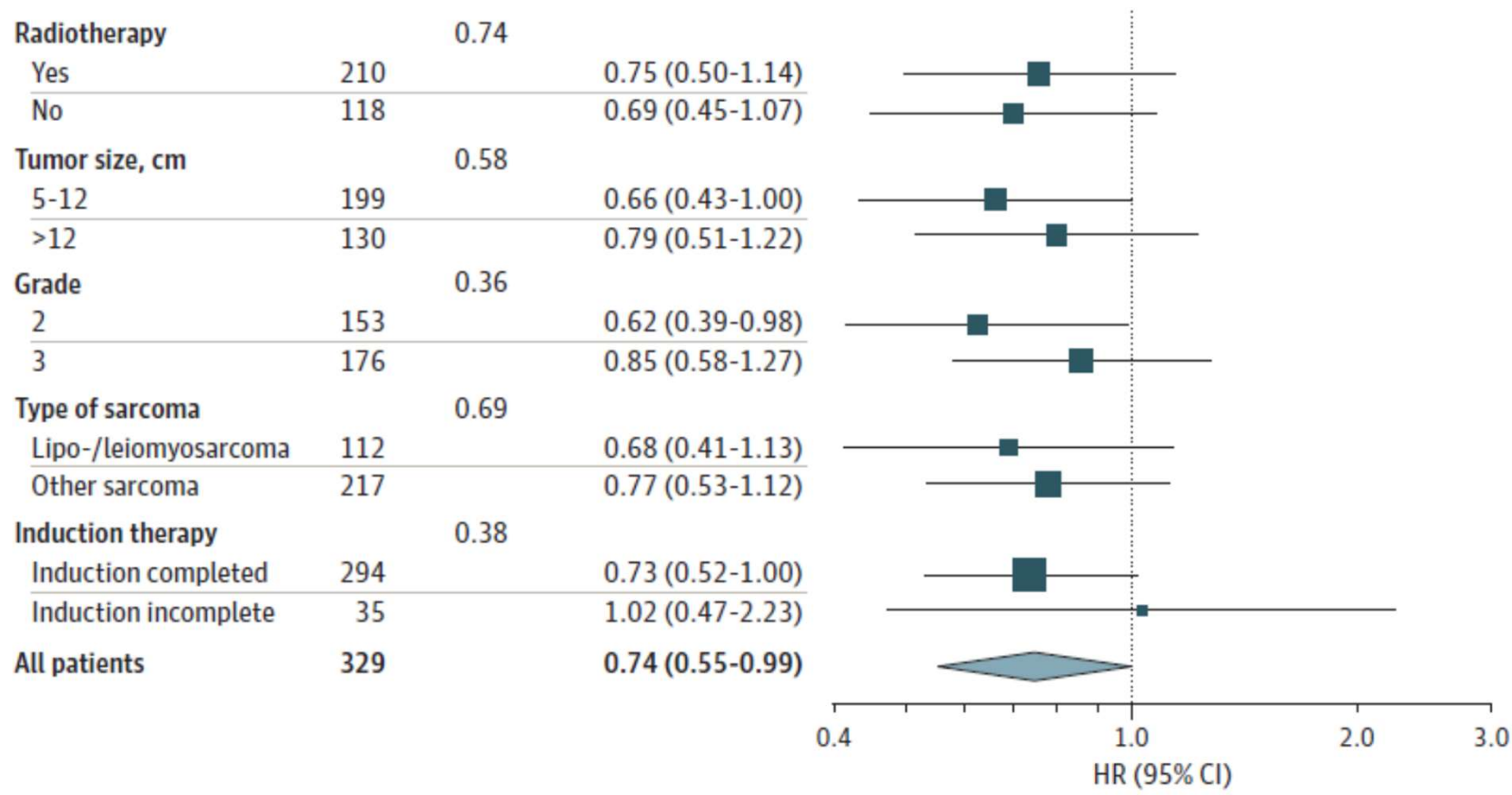
**D** Extremity vs nonextremity



No. at risk	0	1	2	3	4	5	6	7	8	9	10
NACT plus RHT extremity	69	67	61	55	47	46	44	43	43	36	30
NACT alone extremity	74	66	58	50	47	43	42	40	38	35	31
NACT plus RHT nonextremity	93	83	67	55	51	48	45	41	39	32	24
NACT alone nonextremity	93	79	60	46	43	39	36	33	29	21	20

	No. of events
NACT plus RHT extremity	22
NACT alone extremity	31
NACT plus RHT nonextremity	55
NACT alone nonextremity	66

# Forest-Plot Überleben





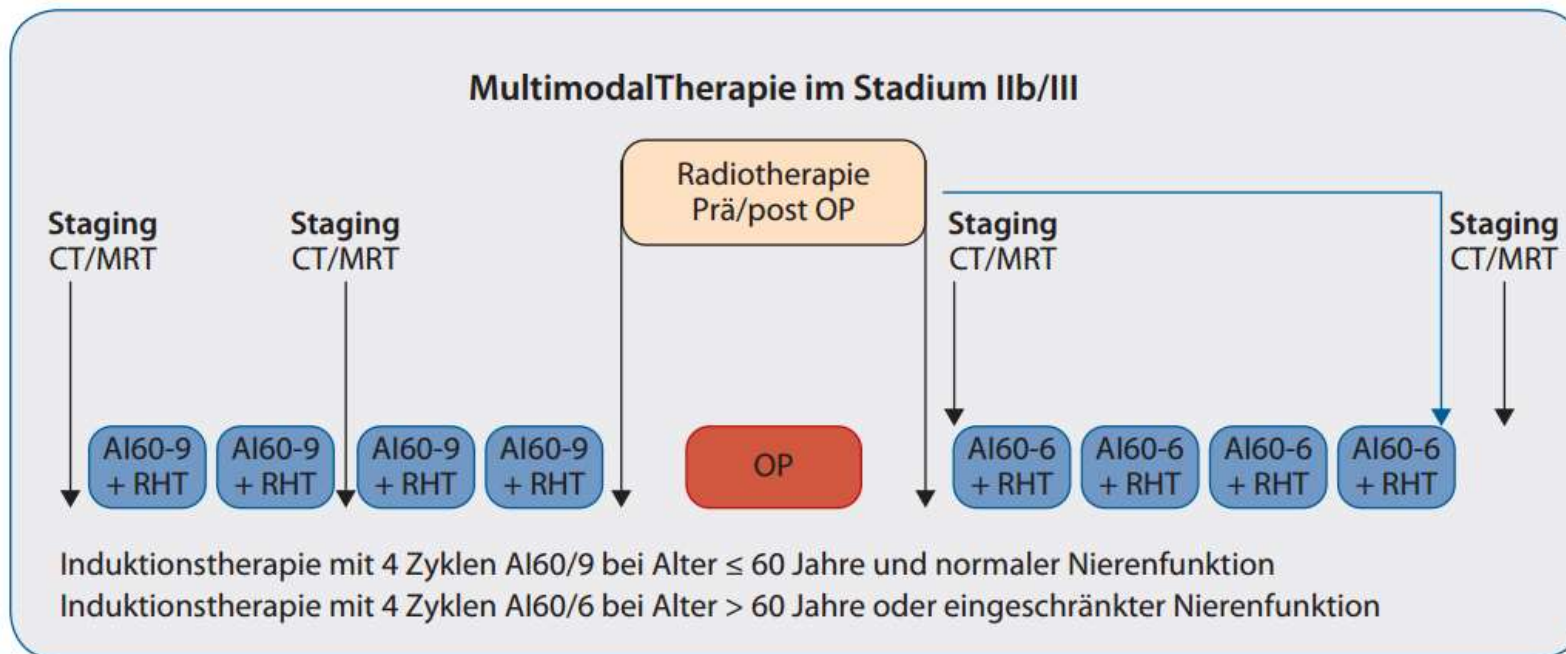
## Zusammenfassung

- Positive Studie für **Anthrazyklin + Ifosfamid** vs. andere Ctx
- Positive Studie für **Regionale Tiefenhyperthermie + anthrazyklin/ifosfamid-basierte Ctx** vs. anthrazyklin/ifosfamid-basierte Ctx

**Anthrazyklin + Ifosfamid-basierte neoadjuvante Chemotherapie in Kombination mit Tiefenhyperthermie als neuer Standard für Patienten mit lokalisiertem Hochrisikoweichteilsarkom (> 5cm, tief, G2-3)**

# Multimodales Therapiekonzept am SarKUM

## Hochrisikoweichteilsarkome



- AI60/9 = Doxorubicin 60 mg/m<sup>2</sup> + Ifosfamid 9 g/m<sup>2</sup>
- AI60/6 = Doxorubicin 60 mg/m<sup>2</sup> + Ifosfamid 6 g/m<sup>2</sup>

# **Preliminary results of a phase II study of neoadjuvant checkpoint blockade for surgically resectable undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated liposarcoma (DDLPS).**

Autoren:

Christina Lynn Roland, Emily Zhi-Yun Keung, Alexander J. Lazar, Keila E Torres, Wei-Lien Wang, Ashleigh Guadagnolo, Andrew Justin Bishop, Heather Y. Lin, Kelly Hunt, Barry W. Feig, Justin E. Bird, Valerae O. Lewis, Hussein Abdul-Hassan Tawbi, Ravin Ratan, Shreyaskumar Patel, Jennifer Ann Wargo, Neeta Somaiah

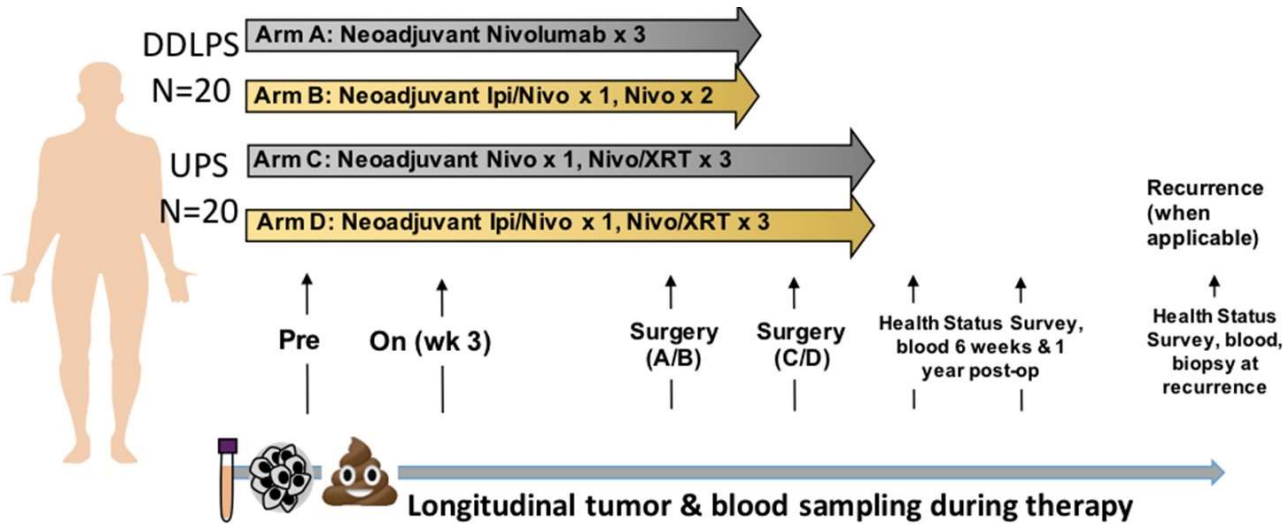
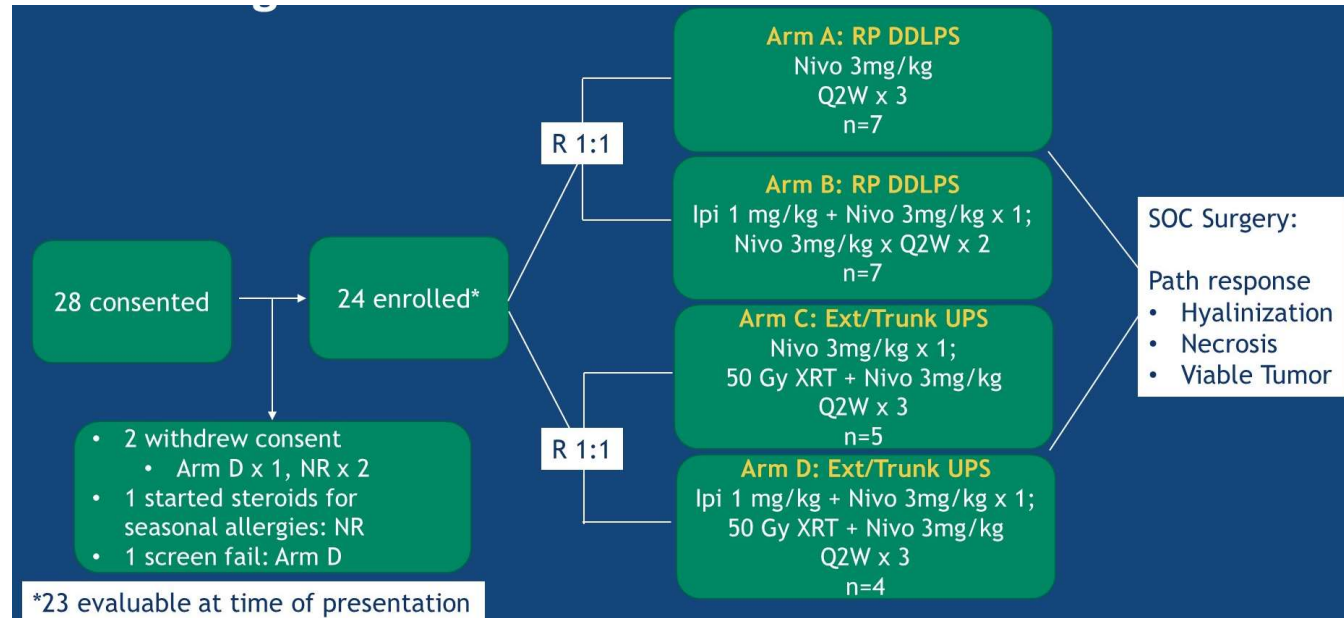
Roland, Abstract 11505

# NCT03307616

## Studiendesign

- Q2/W Dosierung: Nivolumab 3mg/kg  
Ipilimumab 1mg/kg\*
- Retroperitoneal: DDLPS
- Extremitäten / Rumpf: UPS
- Randomisierung 1:1
- 50 Gy Radiotherapie

\*(Dosisreduktion nach 7 Patienten)



### Primärer Endpunkt:

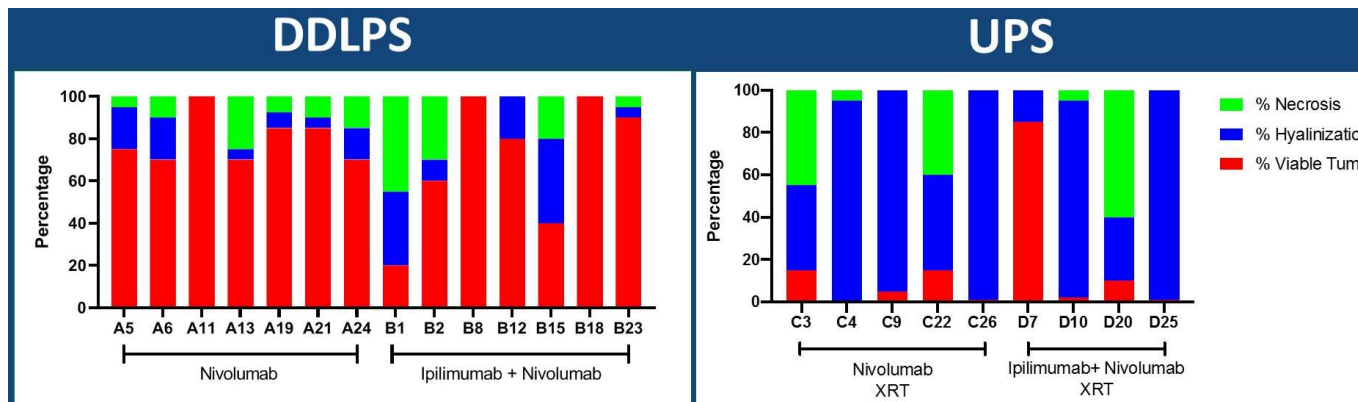
- pathologisches Ansprechen

### Sekundäre Endpunkte:

- ORR nach RECIST 1.1
- 12- und 24-Monats rezidivfreies Überleben
- Sicherheitsdaten
- Patientenberichte

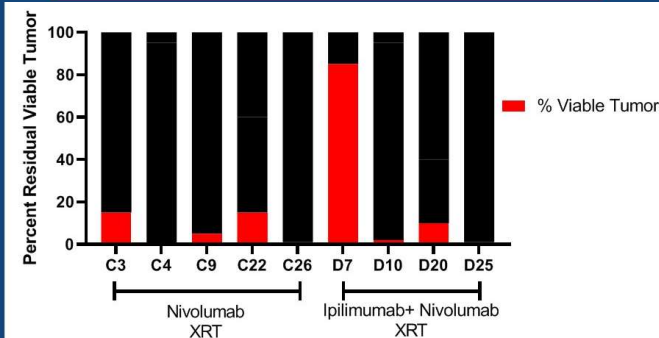
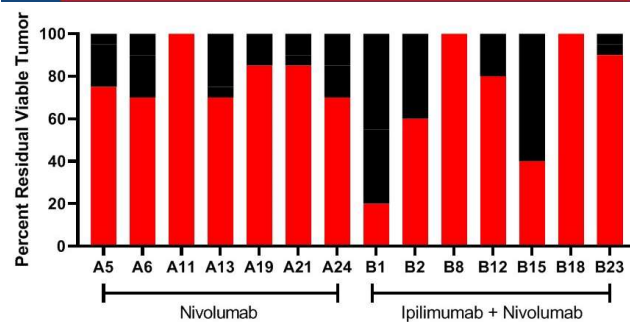
# NCT03307616

## Pathologisches Ansprechen



Median hyalinization: 8.75% (range 0-40)  
5/14 (35.7%) patients >20% hyalinization

Median hyalinization: 93% (range 15-99)  
5/9 (56%) patients >95% hyalinization



Residual viable tumor : 77.5% (range 20-100)

Residual viable tumor : 5% (range 0-85)  
8/9 (89%) patients <15% viable tumor

## Kasuistik

### Synovialsarkom

- 27-jährige Patientin, ED 05/2013



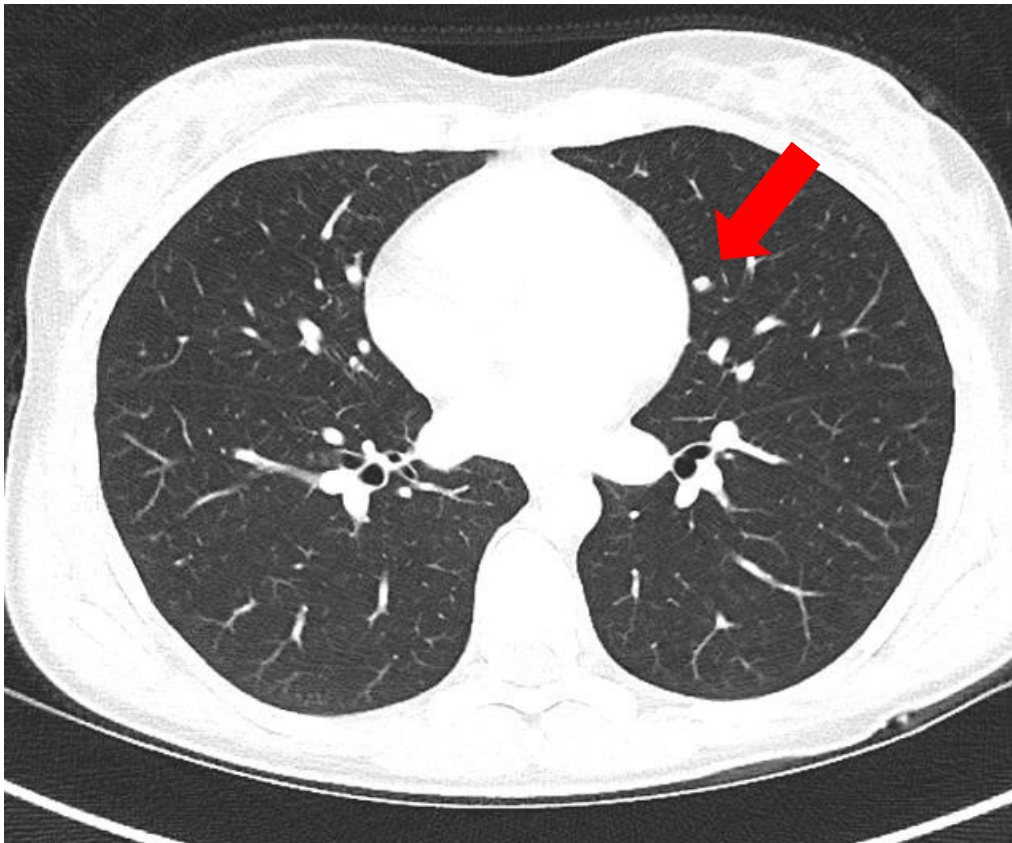
## Pat 05 (W, 27 Jahre): Synovialsarkom retroperitoneal

- 06/13-03/14 multimodale Therapie mit 4xAI60/9+RHT, neoadj. RT, R1-Resektion (<5% vitale Tumorzellen), 4xAI60/6+RHT



## Pat 05 (W, 27 Jahre): Synovialsarkom retroperitoneal

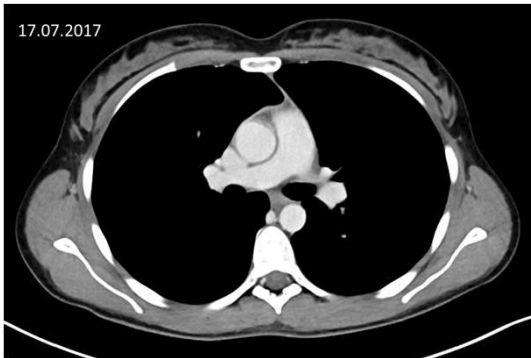
- 10/2016 Lungenmetastase linker OL, VATS



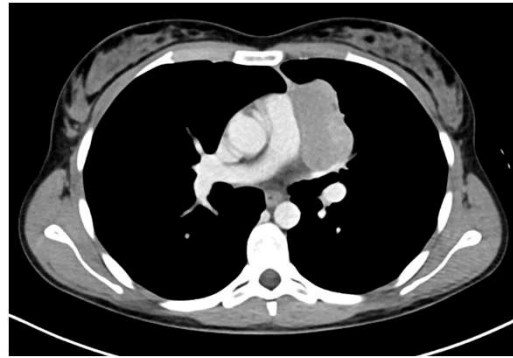


## Pat 05 (W, 27 Jahre): Synovialsarkom retroperitoneal

- 10/2017 pleurale/mediastinale Metastase



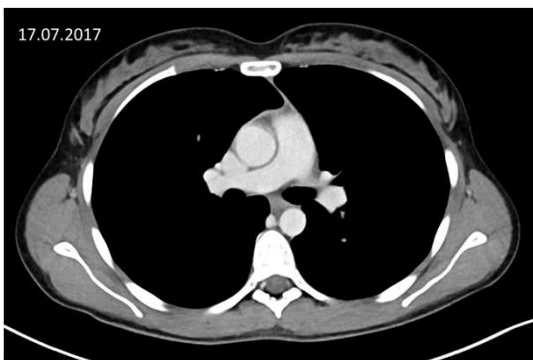
17.07.2017



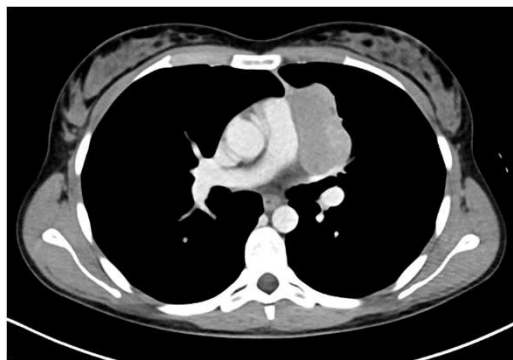
10.2017

## Pat 05 (W, 27 Jahre): Synovialsarkom retroperitoneal

- 10/2017 pleurale/mediastinale Metastase



17.07.2017



10.2017



12.2017



02.2018

- 10/17-01/18 4 Zyklen HD-Ifosfamid
- 01/2018 offene Resektion mit Perikardteilresektion

**Vielen Dank**

**für Ihre Aufmerksamkeit!**

Bei weiteren Fragen wenden Sie sich bitte an Lars Lindner  
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Tel.: +49 89 4400-74768