

SYSTEMTHERAPIE BEI SARKOMEN UND GIST

**Winterthurer
Ärztefortbildung**

28. November 2024

Ralph Zachariah
Leitender Arzt
Medizinische Onkologie



Welche Onkologie im Kampf gegen Sarkome und GIST?

Traditionell und altbewährt, aber doch sehr unspezifisch?



Oder zielgerichtet und/oder immuntherapeutisch? Stichwort Präzisionsonkologie?



**DAS
SOWOHL-
ALS-AUCH-
PRINZIP**

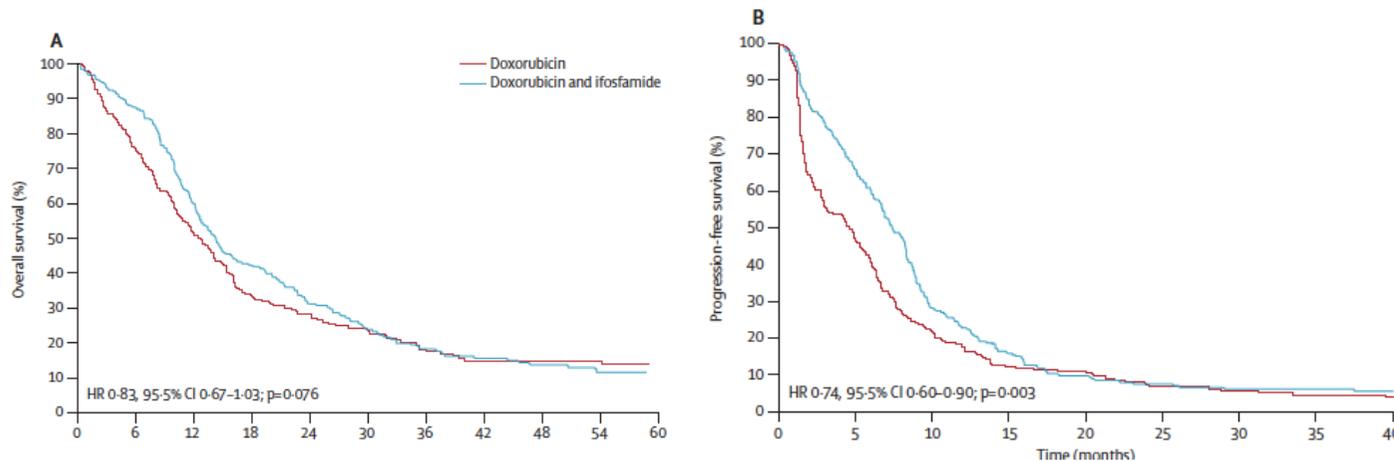


Klassische Zytostatika bleiben ein Eckpfeiler der Sarkombehandlung

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 WHogendoorn, 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 Oncol 2014



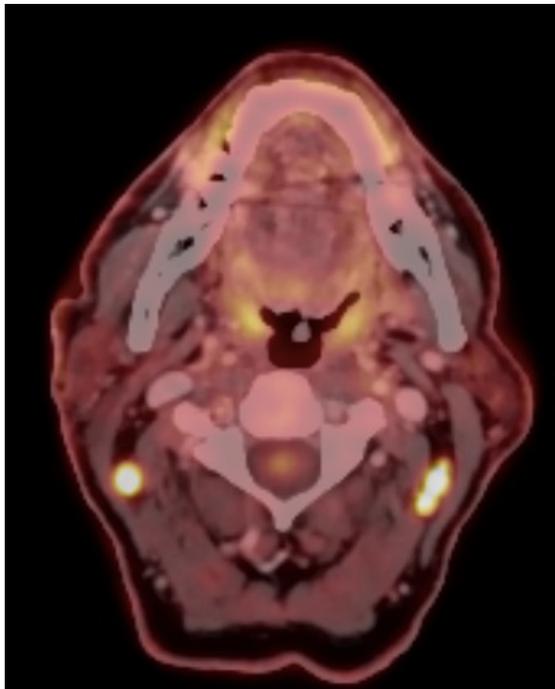
	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
Complete response	1 (<1%)	4 (2%)
Partial response	30 (13%)	56 (25%)
Stable disease	105 (46%)	114 (50%)
Progressive disease	74 (32%)	30 (13%)
Early death (progression)	4 (2%)	5 (2%)
Early death (other cause)	3 (1%)	2 (1%)
Not evaluable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

Data are n (%).

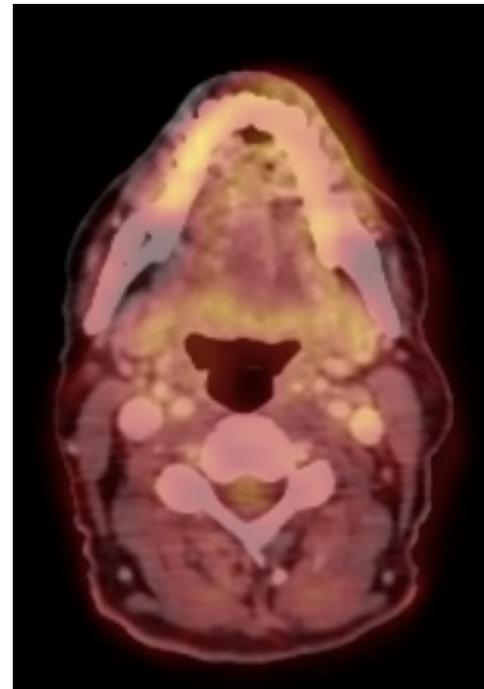
Table 3: Responses to treatment

85j Patient mit pleomorphem dermale Sarkom der Kopfhaut

Baseline PET-CT



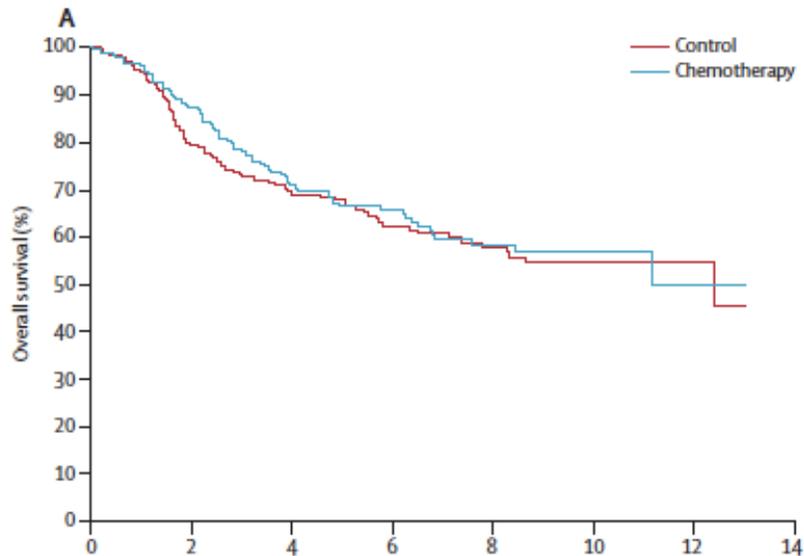
Nach 2 Zyklen Doxorubicin mono



Kann eine (neo)adjuvante Chemotherapie die Prognose bei Sarkomen verbessern?

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 CW 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 *Lancet Oncol* 2012; 13: 1045–54



Kritik an der Studie

- **Zu heterogene Population: auch kleine low-grade Sarkome wurden eingeschlossen.**
- **Die Ifosfamidosis von 5g/m² ist zu tief (wir geben heute 9g/m²).**

Soll eine Risiko-adaptierte Strategie verfolgt werden?

The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: revisiting the results of the EORTC-STBSG 62931 randomised trial

Sandro Pasquali ^{a,*}, Sara Pizzamiglio ^b, Nathan Touati ^c, Saskia Litier ^c, Sandrine Marreaud ^c, Bernd Kasper ^d, Hans Gelderblom ^e, Silvia Stacchiotti ^f, Ian Judson ^g, Angelo P. Dei Tos ^{h,i}, Paolo Verderio ^b, Paolo G. Casali ^{f,g,h,i,j}, Penella J. Woll ^k, Alessandro Gronchi ^{a,**} on behalf of the EORTC – Soft Tissue and Bone Sarcoma Group

European Journal of Cancer 109 (2019) 51–60

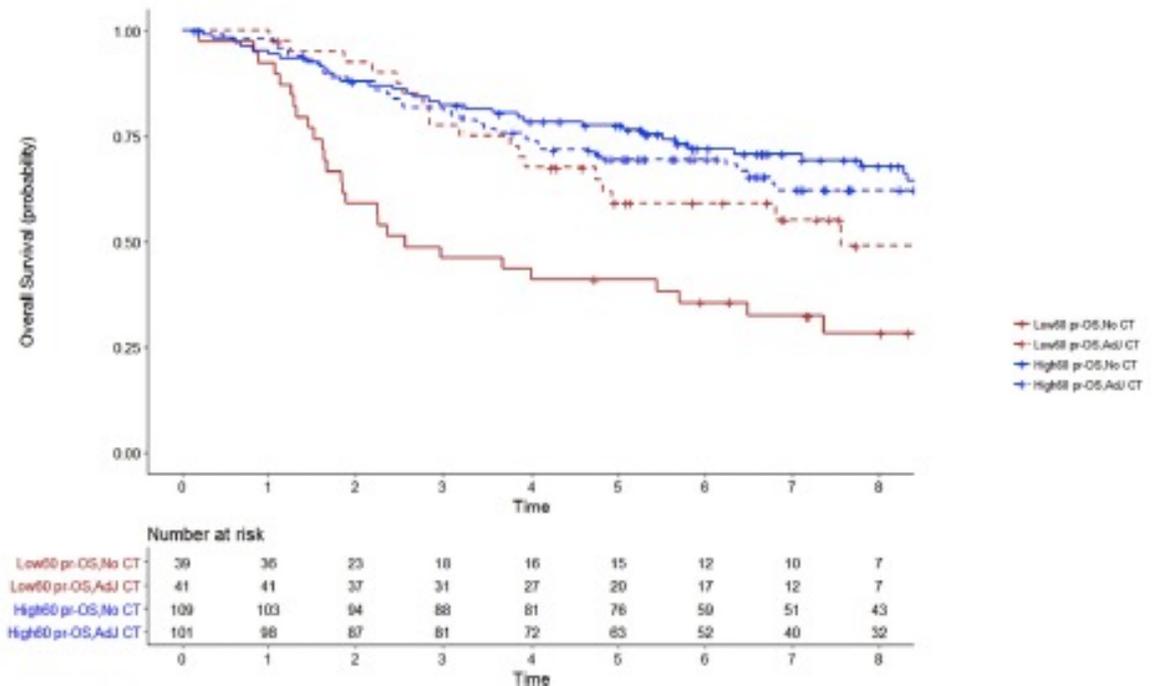


Fig. 2. Overall survival according to two categories according to the median survival value (10-year predicted OS: 60%) of a previous study [24] and the EORTC-STBSG 62931 study treatment arms. OS, overall survival.

Sarculator

Sarculator

Primary RPS

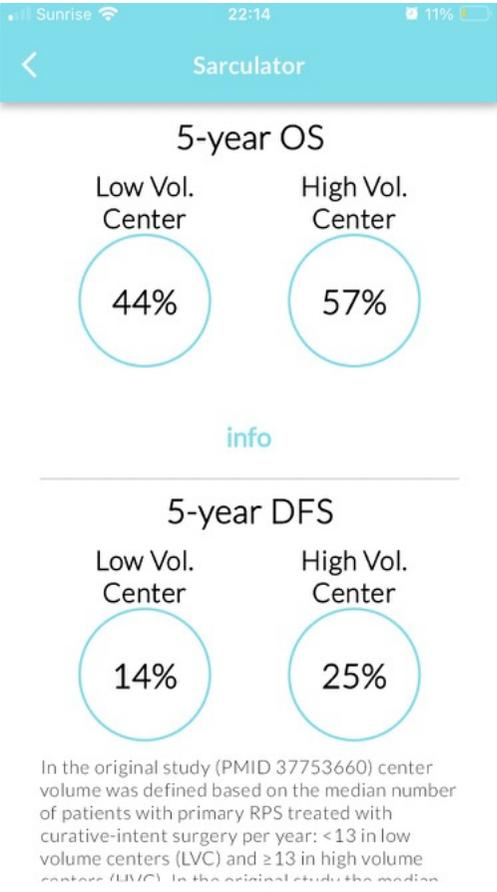
Age
55

Tumor Size
14

FNCLCC GRADE
3

Histology
LMS

Multifocality
no



GEHT ES DENN NICHT EIN BISSCHEN PRÄZISER?

GIST als Prototyp der Präzisionsonkologie

Historisch gesehen ist der metastasierte gastrointestinale Stromatumor (GIST) eine schreckliche Krankheit, bei der klassische Zytostatika unwirksam sind.

The New England Journal of Medicine

EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

GEORGE D. DEMETRI, M.D., MARGARET VON MEHREN, M.D., CHARLES D. BLANKE, M.D.,
ANNICK D. VAN DEN ABEELE, M.D., BURTON EISENBERG, M.D., PETER J. ROBERTS, M.D., MICHAEL C. HEINRICH, M.D.,
DAVID A. TUVESON, M.D., PH.D., SAMUEL SINGER, M.D., MILOS JANICEK, M.D., PH.D., JONATHAN A. FLETCHER, M.D.,
STUART G. SILVERMAN, M.D., SANDRA L. SILBERMAN, M.D., PH.D., RENAUD CAPDEVILLE, M.D., BEATE KIESE, M.Sc.,
BIN PENG, M.D., PH.D., SASA DIMITRIJEVIC, PH.D., BRIAN J. DRUKER, M.D., CHRISTOPHER CORLESS, M.D.,
CHRISTOPHER D.M. FLETCHER, M.D., AND HEIKKI JOENSUU, M.D.

2002

GIST als Prototyp der Präzisionsonkologie

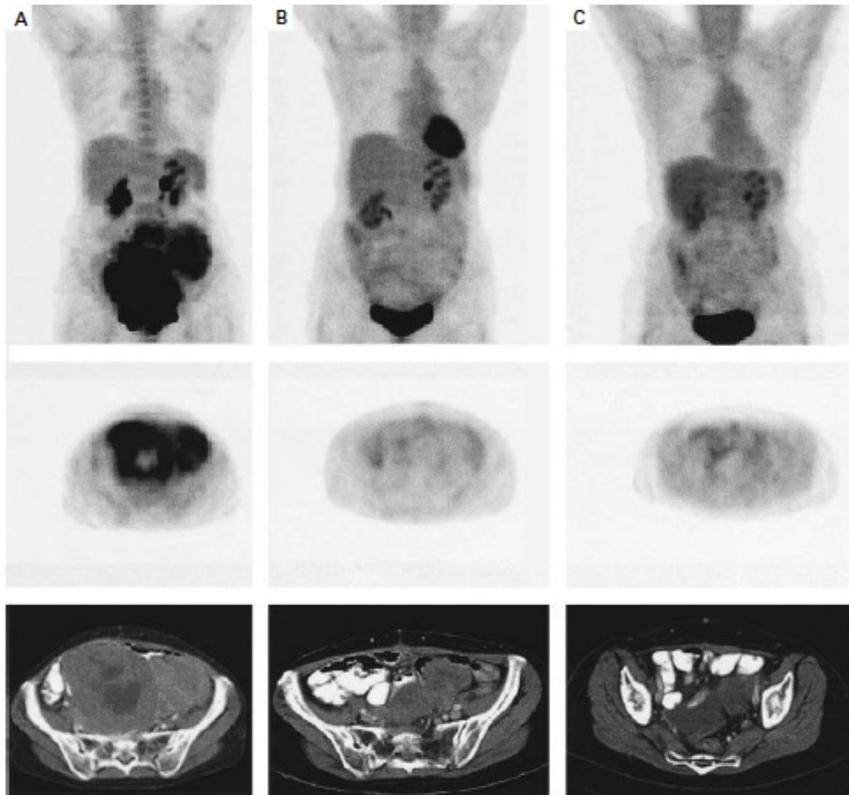


Figure 2. Sequential PET Scans Obtained in the Same Patient at Base Line (before Treatment, Panel A), 1 Month after Imatinib Treatment Began (Panel B), and after 16 Months of Continuous Treatment (Panel C).

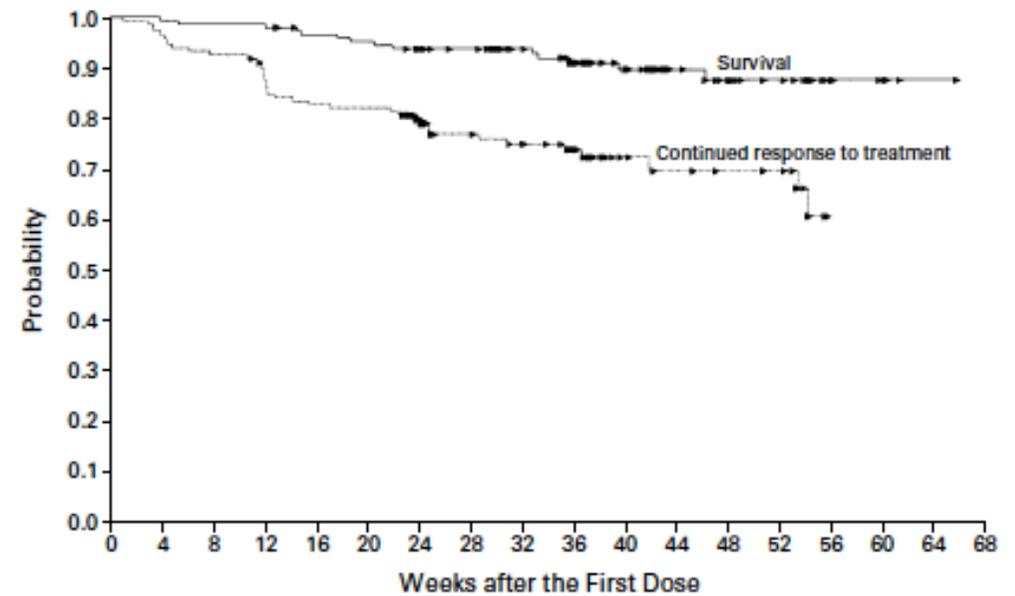


Figure 1. Kaplan-Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient's data were censored.

Demetri, NEJM 2002

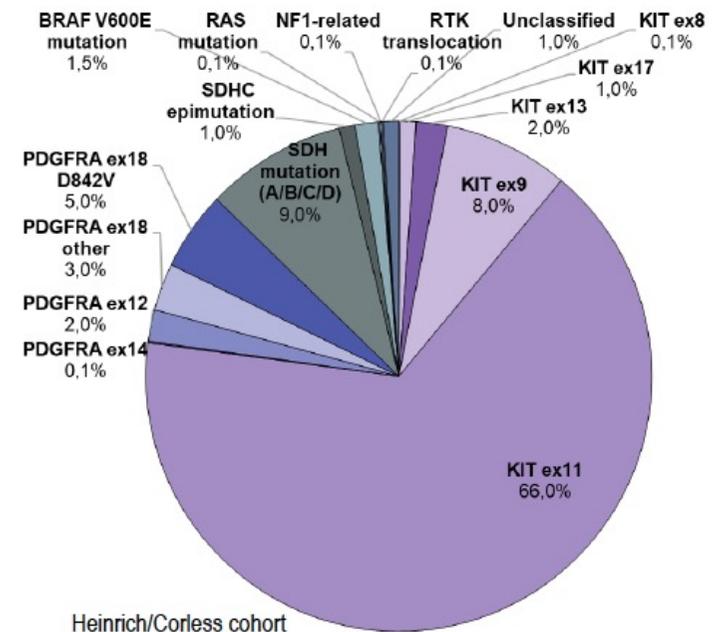
GIST: Risikostratifizierung und Mutationsanalyse

Risikostratifizierung für adjuvante Therapie mit Imatinib

Risikostratifizierung von primären GIST unter Berücksichtigung der Lokalisation nach Miettinen⁷

MITOSERATE	TUMOR-GRÖSSE (CM)	MAGEN	JEJUNUM-ODER ILEUM	DUODENUM	REKTUM
≤ 5/50 HPF	≤ 2	0%	0%	0%	0%
	> 2 ≤ 5	1.9%	4.3%	8.3%	8.5%
	> 5 ≤ 10	3.6%	24%	34%*	57%*
	> 10	12%	52%		
> 5/50 HPF	≤ 2	0%*	50%*	N/A ^b	54%
	> 2 ≤ 5	16%	73%	50%	52%
	> 5 ≤ 10	55%	85%		
	> 10	86%	90%	86%*	71%*

HPF = high power field. 50 HPF entsprechen 5 mm^{2,3}



Sebastian Bauer, ESMO Sarcoma 2020

Präzisionsonkologie abgesehen von GIST

Viele Sarkome weisen spezifische molekulare Alterationen auf

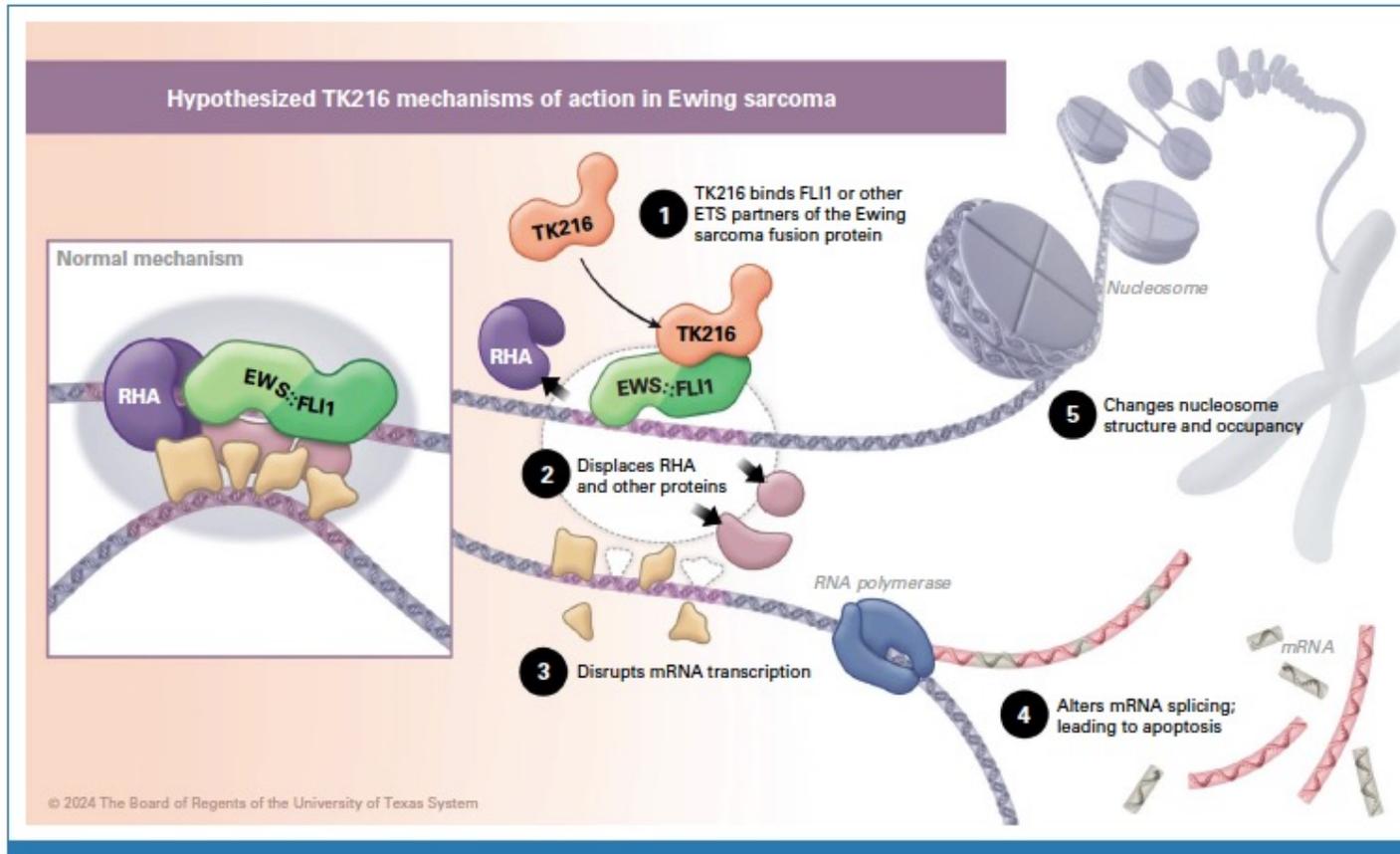
- Alveoläres Rhabdomyosarkom PAX3:FOXO1 Translokation
- Ewing-Sarkom EWSR:FLI1 Translokation
- Dedifferenziertes Liposarkom MDM2-Amplifikation
- Chondrosarkom IDH1-Mutation
- Verschiedene Sarkome NTRK-Fusion

Ist es denn nicht möglich, diese Alterationen zielgerichtet anzugreifen?

Alveoläres Rhabdomyosarkom > PAX3:FOXO1 Translokation



Ewing Sarkom > EWSR:FLI1 Translokation



Meyers, JCO 2024

Ewing Sarkom > EWSR:FLI1 Translokation

- 3 Patienten wiesen ein ausserordentlich gutes und langes Ansprechen auf.
- Bezogen auf die gesamte Studienpopulation ist das Ansprechen aber enttäuschend
- Wir verstehen noch nicht den ganzen Wirkmechanismus der EWSR:FLI1 Translokation

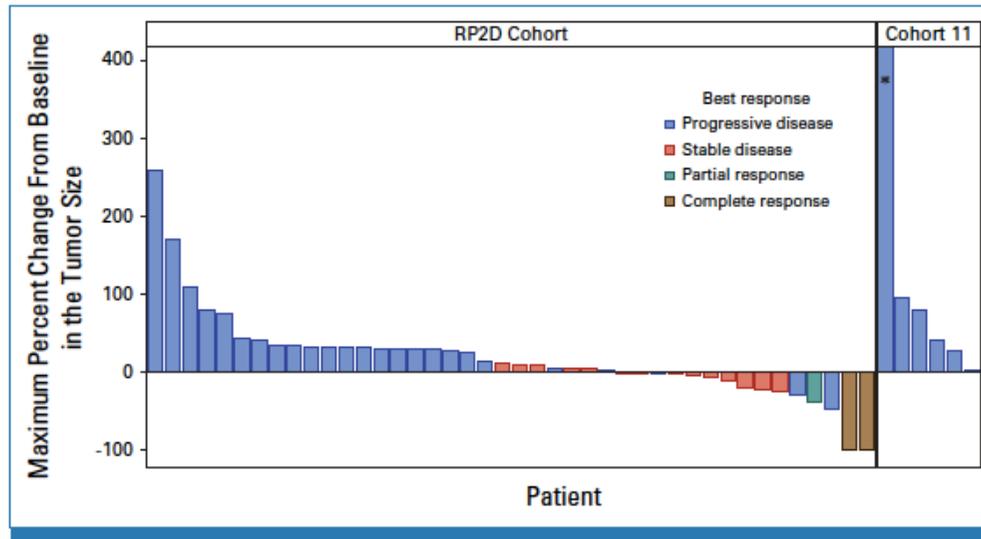


FIG3. Waterfall plot. Each bar represents one patient in the study, with maximum percent change in tumor size from baseline on the y axis, sorted from largest positive to most negative change from baseline. The color of the bars indicates the best objective tumor response. RP2D, recommended phase II dose.

Meyers, JCO 2024

Dedifferenziertes Liposarkom > MDM2 Amplifikation

- p53 ist das wichtigste Tumorsuppressor Protein des Menschen: Wächter des Genoms
- Ein Funktionsverlust von p53 ist onkogen, d.h. führt zur Tumorentstehung
- MDM2 ist ein negativer Regulator von p53, dh. eine übermässige Aktivierung von MDM2 bei dedifferenzierten Liposarkomen führt zur Ausschaltung von p53.
- Eine pharmakologische Unterdrückung von MDM2 stellt die p53 Funktion wieder her
- Das dedifferenzierte Liposarkom ist ein sehr häufiges Sarkom



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BRIGIMADLIN VERSUS STANDARD-OF-CARE DOXORUBICIN AS FIRST-LINE TREATMENT IN PATIENTS WITH ADVANCED DEDIFFERENTIATED LIPOSARCOMA: BRIGHTLINE-1

P. Schöffski,¹ R. Sanfilippo,² J. Martin-Broto,³ A. Kawai,⁴ J. Desai,⁵ P. LoRusso,⁶ R.G. Maki,⁷ R.L. Jones,⁸ J.Y. Blay,⁹ A. Smrke,¹⁰ A. Abdul Razak,¹¹ A. Italiano,¹² A. Sebio,¹³ R. Bahleda,¹⁴ Y.C. Lee,¹⁵ W. van der Graaf,¹⁶ X. Zhang,¹⁷ M. Lahmar,¹⁸ M. Teufel,¹⁹ A.J. Wagner²⁰

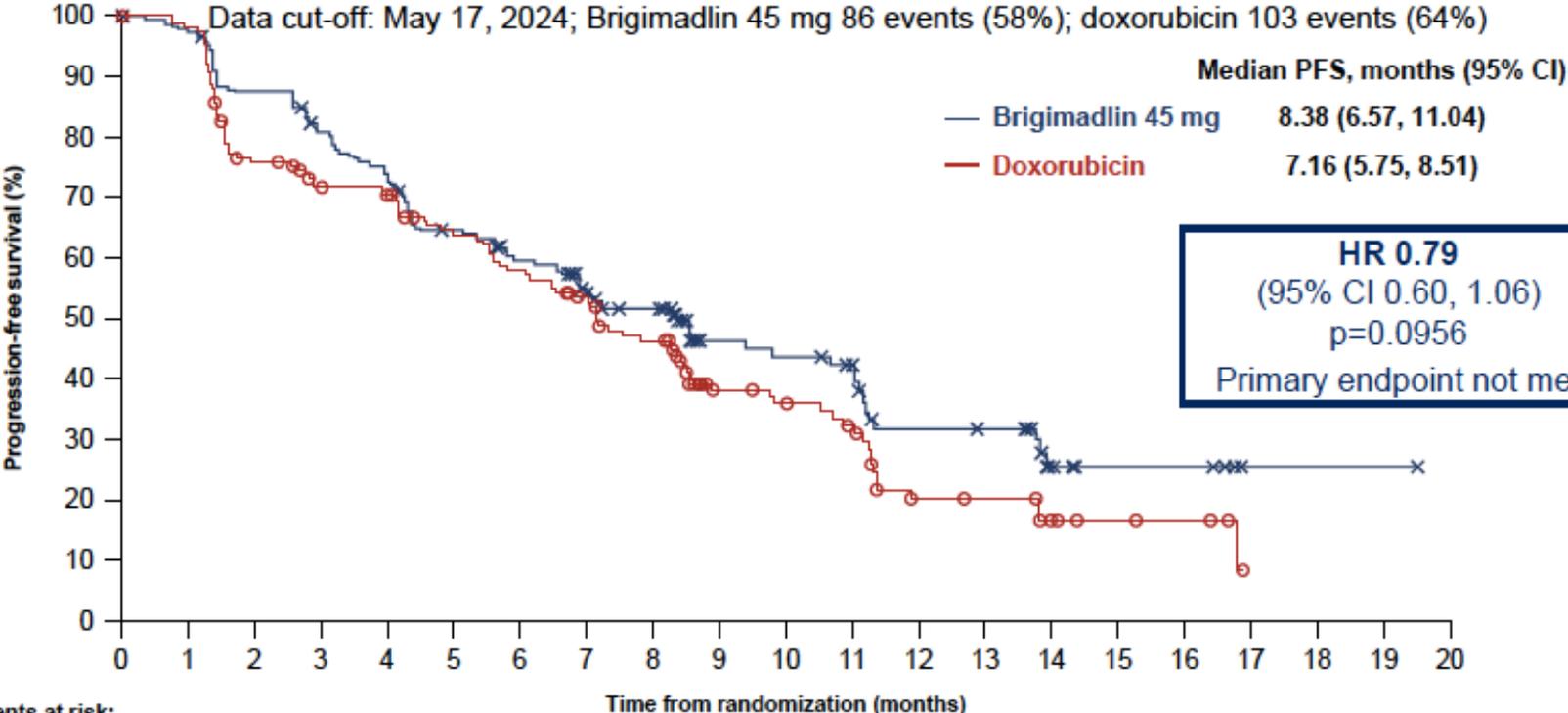
¹Department of General Medical Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven; ²Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; ³Hospital Universitario Fundación Jiménez Díaz, Madrid; ⁴National Cancer Center Hospital, Tokyo; ⁵Peter MacCallum Cancer Center, Melbourne; ⁶Yale University School of Medicine, Yale Cancer Center, New Haven; ⁷Memorial Sloan-Kettering Cancer Center, New York; ⁸The Royal Marsden Hospital and Institute of Cancer Research, London; ⁹Centre Léon Bérard, Lyon; ¹⁰BC Canada, Vancouver, British Columbia; ¹¹Princess Margaret Cancer Center, Toronto, Ontario; ¹²Institut Bergonié, Bordeaux; ¹³Hospital de la Santa Creu i Sant Pau, Barcelona; ¹⁴Institut Gustave Roussy, Villejuif; ¹⁵Prince of Wales Hospital, Randwick, NSW; ¹⁶Netherlands Cancer Institute, Amsterdam; ¹⁷Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong Province; ¹⁸Boehringer Ingelheim International GmbH, Ingelheim am Rhein; ¹⁹Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield; ²⁰Dana-Farber Cancer Institute, Boston

2024
ANNUAL MEETING

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Presented by: Patrick Schöffski

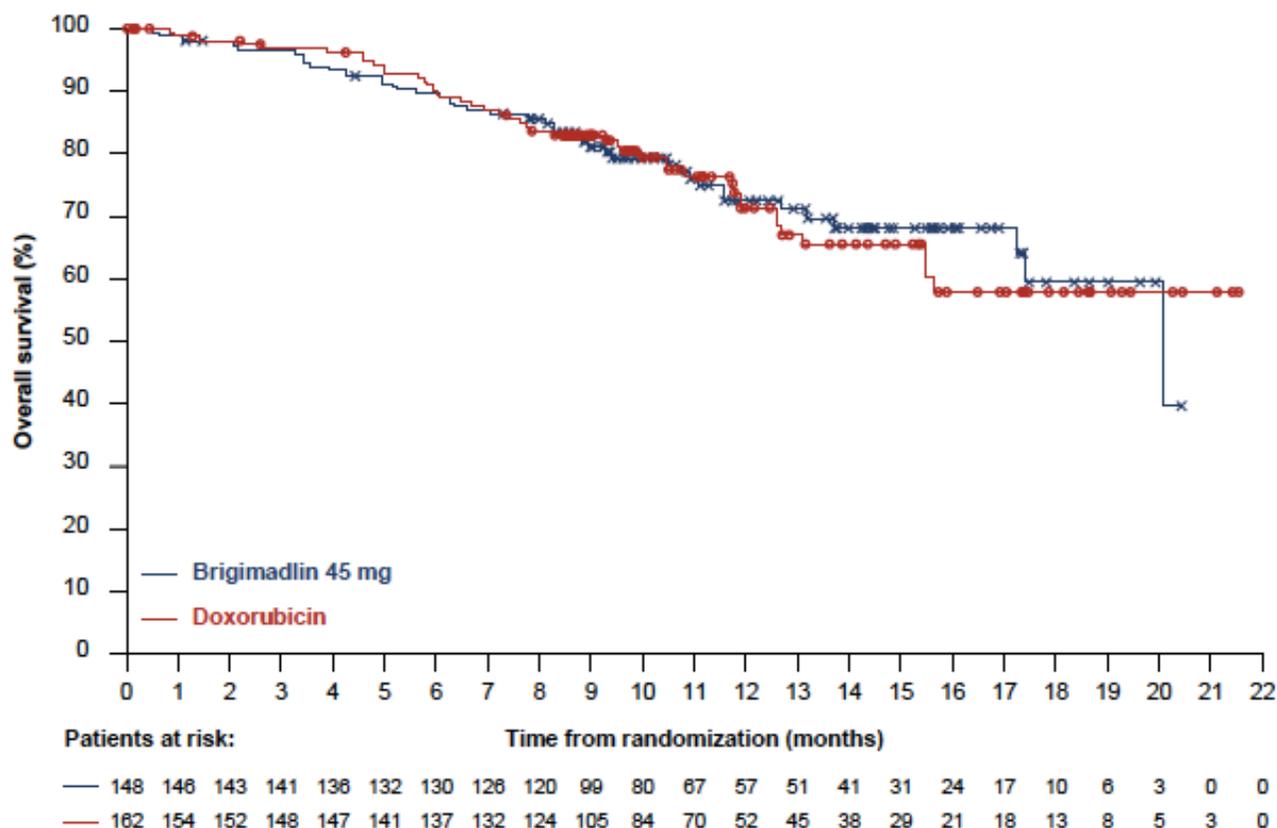
PRIMARY ENDPOINT: PFS BY BLINDED INDEPENDENT CENTRAL REVIEW



Patients at risk:		Time from randomization (months)																				
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Brigimadlin	148	143	128	116	107	90	81	64	58	35	33	30	20	19	9	6	6	1	1	1	0	
Doxorubicin	162	151	114	104	100	87	79	70	58	34	31	26	13	12	7	5	4	0	0	0	0	

OVERALL SURVIVAL (BICR)

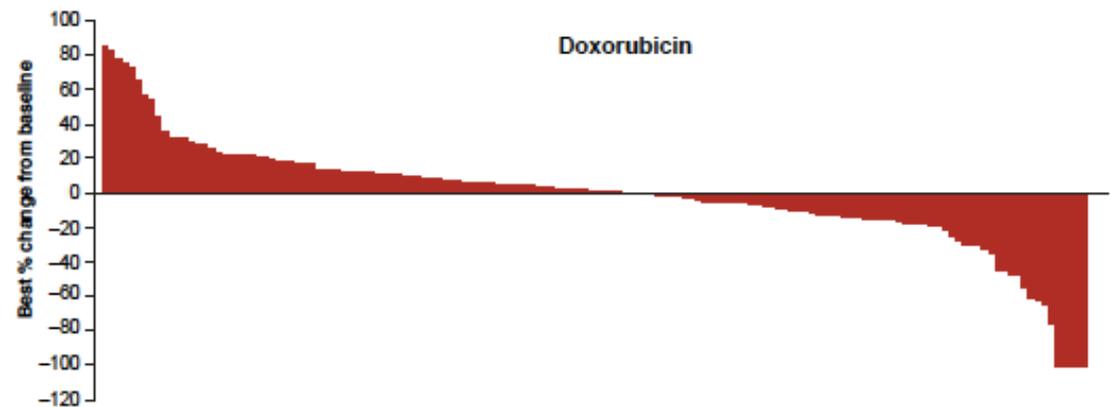
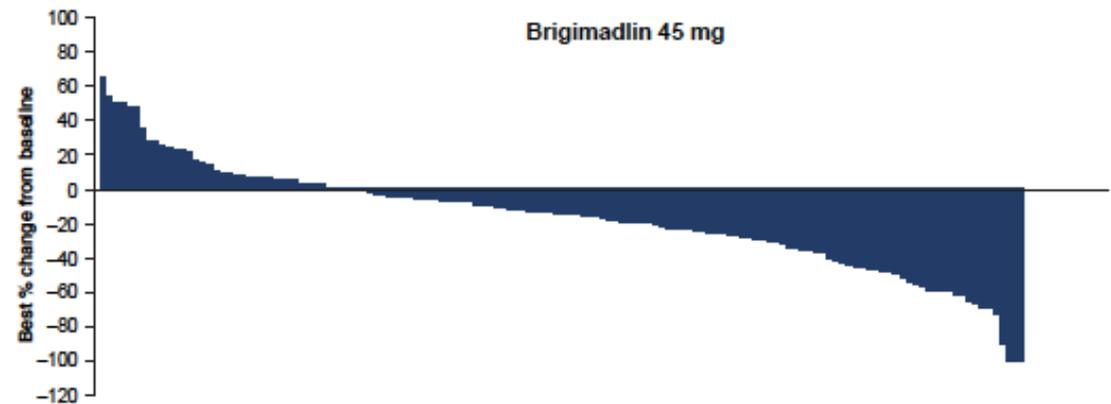
- Overall survival data remain immature:
 - Low event rate of ~27%
 - At data cut-off (May 17, 2024), 77 (47.5%) doxorubicin patients had crossed over to receive brigimadlin



OBJECTIVE RESPONSE (BICR) AND ASSESSMENT OF TARGET LESIONS

Response, n (%)	Brigimadlin 45 mg (n=148)	Doxorubicin (n=162)
Objective response	33 (22.3)	14 (8.6)
Complete response	2 (1.4)	2 (1.2)
Partial response	31 (20.9)	12 (7.4)
Disease control	128 (86.5)	117 (72.2)

- The objective response and disease control rates were numerically superior with brigimadlin vs doxorubicin
 - Response endpoint not formally met due to hierarchical ranking of endpoints



OVERALL SAFETY PROFILE

- Most common AEs with brigimadlin 45 mg were nausea, fatigue, neutropenia and thrombocytopenia
- Higher rates of AEs leading to dose modification with brigimadlin 45 mg vs doxorubicin

n (%)	Brigimadlin 45 mg (n=147)		Doxorubicin (n=154)	
Any AE	146 (99.3)		153 (99.4)	
Any drug-related* AEs	144 (98.0)		150 (97.4)	
Any serious AEs	57 (38.8)		42 (27.3)	
Any drug-related* serious AEs	30 (20.4)		25 (16.2)	
Fatal AEs	2 (1.4)		1 (0.6)	
AEs leading to discontinuation	33 (22.4)		9 (5.8)	
AEs leading to dose reduction	71 (48.3)		52 (33.8)	
AEs leading to dose delay	92 (62.6)		48 (31.2)	
Most common AEs	Any-grade	Grade ≥3	Any-grade	Grade ≥3
Nausea	112 (76.2)	3 (2.0)	90 (58.4)	1 (0.6)
Fatigue	111 (75.5)	13 (8.8)	104 (67.5)	12 (7.8)
Neutropenia	87 (59.2)	54 (36.7)	84 (54.5)	70 (45.5)
Thrombocytopenia	83 (56.5)	41 (27.9)	24 (15.6)	7 (4.5)
Decreased appetite	68 (46.3)	5 (3.4)	41 (26.6)	2 (1.3)
Diarrhea	60 (40.8)	1 (0.7)	42 (27.3)	2 (1.3)
Vomiting	55 (37.4)	1 (0.7)	28 (18.2)	0
Anemia	53 (36.1)	19 (12.9)	63 (40.9)	18 (11.7)



Chondrosarkom > IDH1 Mutation

- IDH1 (Isocitrat-Dehydrogenase 1) Mutationen sind häufig bei Chondrosarkomen
- Sie führen zu einer Akkumulation des Onkometaboliten D-2-Hydroxyglutarat
- Ivosidenib ist ein oraler IDH1 Inhibitor

Patient mit Chondrosarkom des Beckens

- Mehrfach operiert, Radiotherapie und Kryoblation ausgeschöpft wegen den Tumorerläsionen in direkter Nachbarschaft zum Rektum und zum N. ischiadicus
- Seit ... unter Therapie mit Ivosidenib
- Partielle Remission und kaum noch Schmerzen
- Keine Nebenwirkungen

Und was ist mit Immuntherapie?

Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial

Hussein A Tawbi, Melissa Burgess, Vanessa Bolejack, Brian A Van Tine, Scott M Schuetze, James Hu, Sandra D'Angelo, Steven Attia, Richard F Riedel, Dennis A Priebat, Sujana Movva, Lara E Davis, Scott H Okuno, Damon R Reed, John Crowley, Lisa H Butterfield, Ruth Salazar, Jaime Rodriguez-Canales, Alexander J Lazar, Ignacio I Wistuba, Laurence H Baker, Robert G Maki, Denise Reinke, Shreyaskumar Patel

**Lancet Oncol 2017;
18: 1493-1501**

SARC028 Pembrolizumab

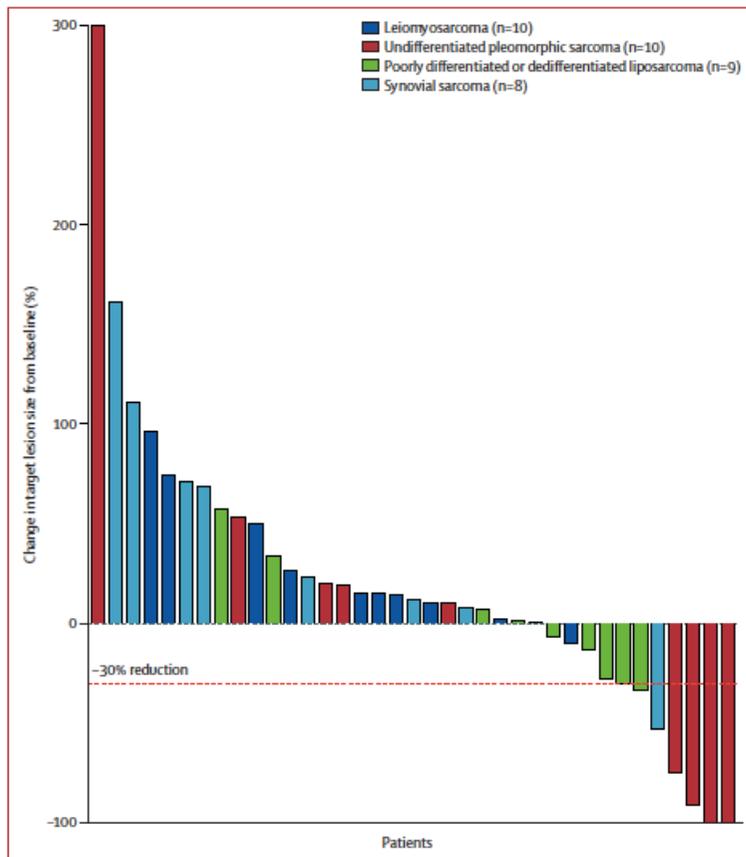


Figure 2: Best percentage change from baseline in size of target lesions in patients with soft-tissue sarcoma. Tumour sizes were calculated as the sum of target lesion diameters. Data for two patients with synovial sarcoma and one patient with liposarcoma are not shown because they did not have a second scan.

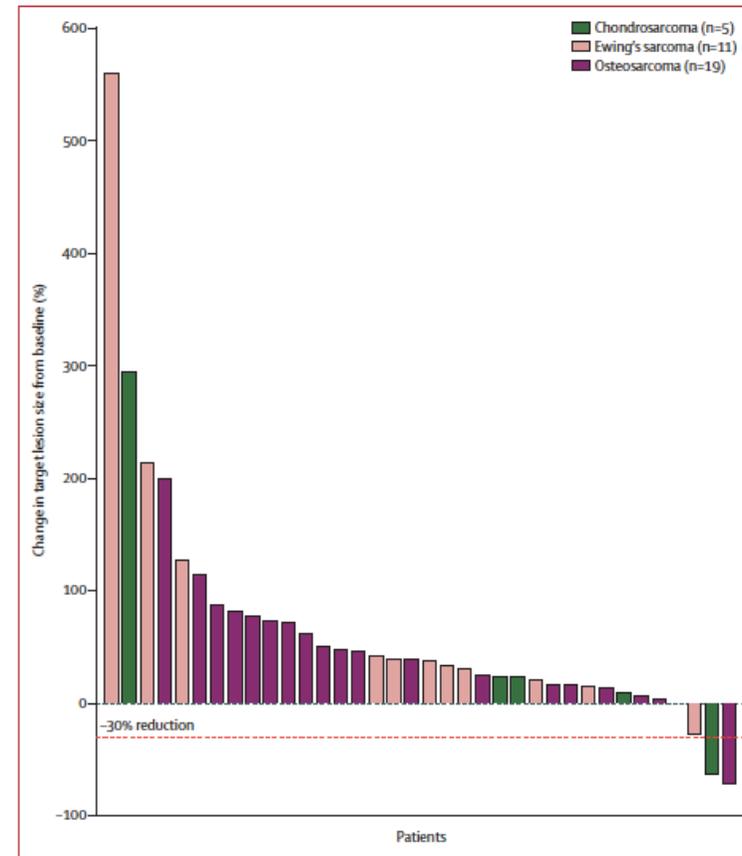


Figure 4: Best percentage change from baseline in size of target lesions in patients with bone sarcoma. Tumour sizes were calculated as the sum of target lesion diameters. Data for two patients with Ewing's sarcoma and three patients with osteosarcoma are not shown because they did not have a second scan.

Zelluläre Immuntherapie

Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial

Lancet 2024; 403: 1460-71

Sandra P D'Angelo, Dejka M Araujo, Albiruni R Abdul Razak, Mark Agulnik, Steven Attia, Jean-Yves Blay, Irene Carrasco Garcia, John A Charlson, Edwin Choy, George D Demetri, Mihaela Druta, Edouard Forcade, Kristen N Ganjoo, John Glod, Vicki L Keedy, Axel Le Cesne, David A Lieber, Victor Moreno, Seth M Pollack, Scott M Schuetz, Gary K Schwartz, Sandra J Strauss, William D Tap, Fiona Thistle, Claudia Maria Valverde Morales, Michael J Wagner, Breezlyn A Wilky, Cheryl McAlpine, Laura Hudson, Jean-Marc L Stawos Rafaël, Ruoxi Wang, Amy Sun, Lilliam Fernandes, Erin Van Winkle, Erica Elefant, Colin Lunt, Elliot Norry, I Swethajit Biswas, Brian A Van Tine

- Afami-Cel (afamitresgene autoleucel) ist eine MAGE-A4-gerichtete T-Zell-Immuntherapie bei Synovialsarkom
- Die erste zelluläre Immuntherapie bei soliden Tumoren
- Soeben FDA-zugelassen
- Medianes OS 15.4 Monate
- Ca. 40% "Langzeit" Überleben

