Gemeinschaftsklinikum Mittelrhein

ASCO 2024 Highlights - Sarkome

Ausgewählte Themen

- Neoadjuvante/perioperative Therapie bei high risk Weichteilsarkomen
- Neues zu Kombinationen mit immuntherapeutischen Ansätzen beim Weichteilsarkomen
- Zelluläre immuntherapeutische Therapieansätze bei Weichteilsarkomen

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2024 ASCO ANNUAL MEETING

SU2C-SARC032: A Randomized Trial of Neoadjuvant Radiotherapy and Surgery with or without Pembrolizumab for Soft Tissue Sarcoma

Mowery YM, Ballman K, Hong AM, Schuetze SM, Wagner AJ, Monga V, Heise RS, Attia S, Choy E, Burgess MA, Bae S, Pryor D, Van Tine BA, Tinoco G, Chmielowski B, Freeman C, van de Rijn M, Brigman BE, Riedel RF, Kirsch DG

David Kirsch, MD, PhD

Princess Margaret Cancer Centre UHN

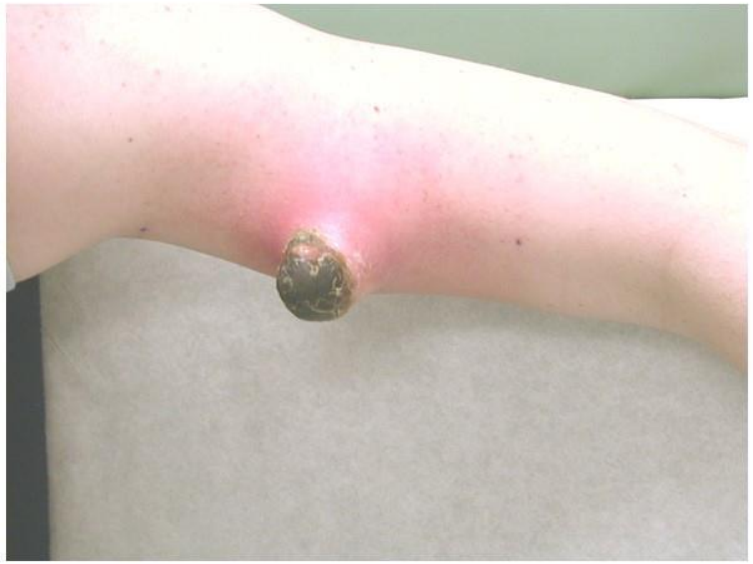
RMP Radiation Medicine Program

TORONTO SARCOMA

Radiation Oncology UNIVERSITY OF TORONTO

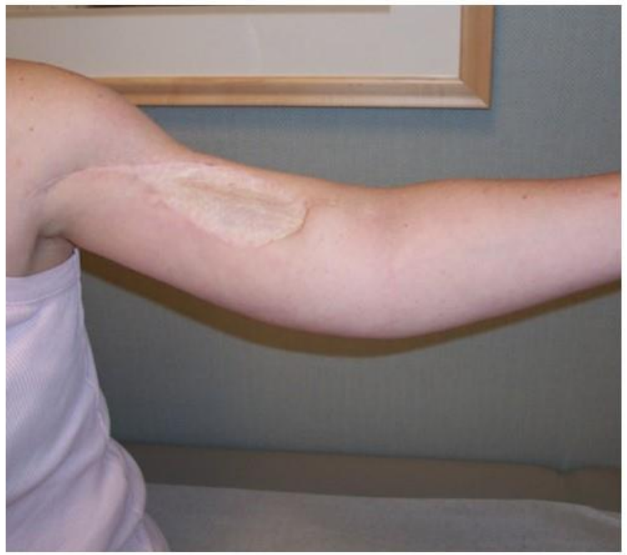
PRESENTED BY: David Kirsch, MD, PhD

Standard Therapy for Extremity Soft Tissue Sarcoma (STS)



RT

Surgery

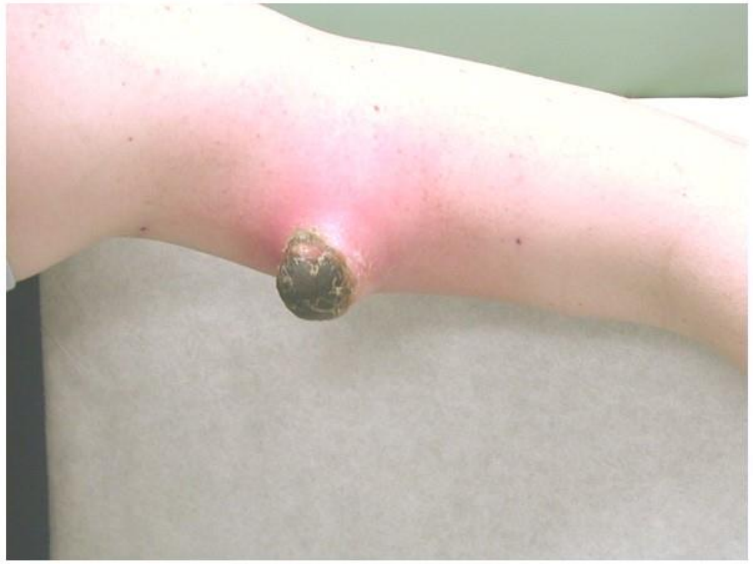


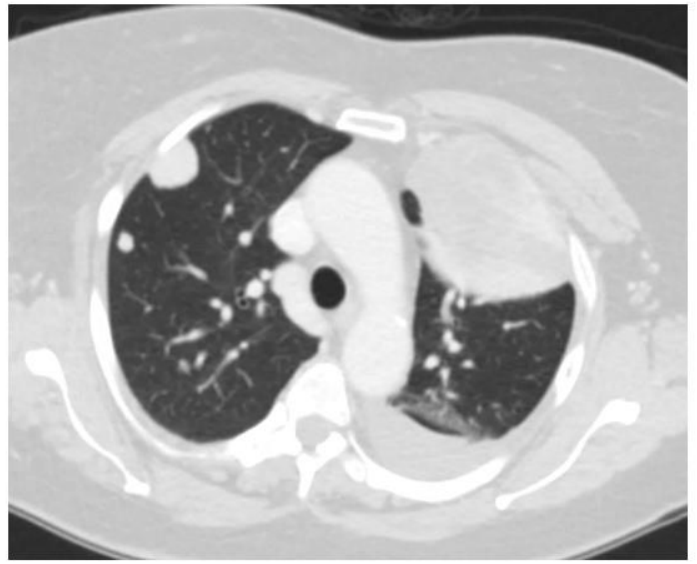
Local Control: 90%

O'Sullivan et al, *Lancet* 2002

Wang et al, *JCO* 2015

Risk of Developing Distant Metastases





~50% for large, high-grade disease

K. Winters, Personal Communication (RTOG 0630)

SARC028 Results

- Multicenter phase II study of **pembrolizumab** for advanced STS
  - n = 40 patients (10/subtype) & expansion to 40 patients for UPS and LPS

	Complete response	Partial response	Stable disease	Progressive disease
Soft-tissue sarcomas (n=40)	1 (3%)	6 (15%)	15 (38%)	18 (45%)
Leiomyosarcoma (n=10)	0 (0%)	0 (0%)	6 (60%)	4 (40%)
Undifferentiated pleomorphic sarcoma (n=10)	1 (10%)	3 (30%)	3 (30%)	3 (30%)
Liposarcoma (n=10)	0 (0%)	2 (20%)	4 (40%)	4 (40%)
Synovial sarcoma (n=10)	0 (0%)	1 (10%)	2 (20%)	7 (70%)

Expansion Cohorts

UPS: 20% response

LPS: 8.7% response

Tawbi et al, *Lancet Oncology* 2017

Burgess et al, *ASCO* 2019

SARC028 Results

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Synovial sarc (n=10)	0 (0%)	1 (10%)	2 (20%)	7 (70%)

Geringe Wirksamkeit von Immuncheckpoint-Inhibitoren bei WTS

Expansion Cohorts

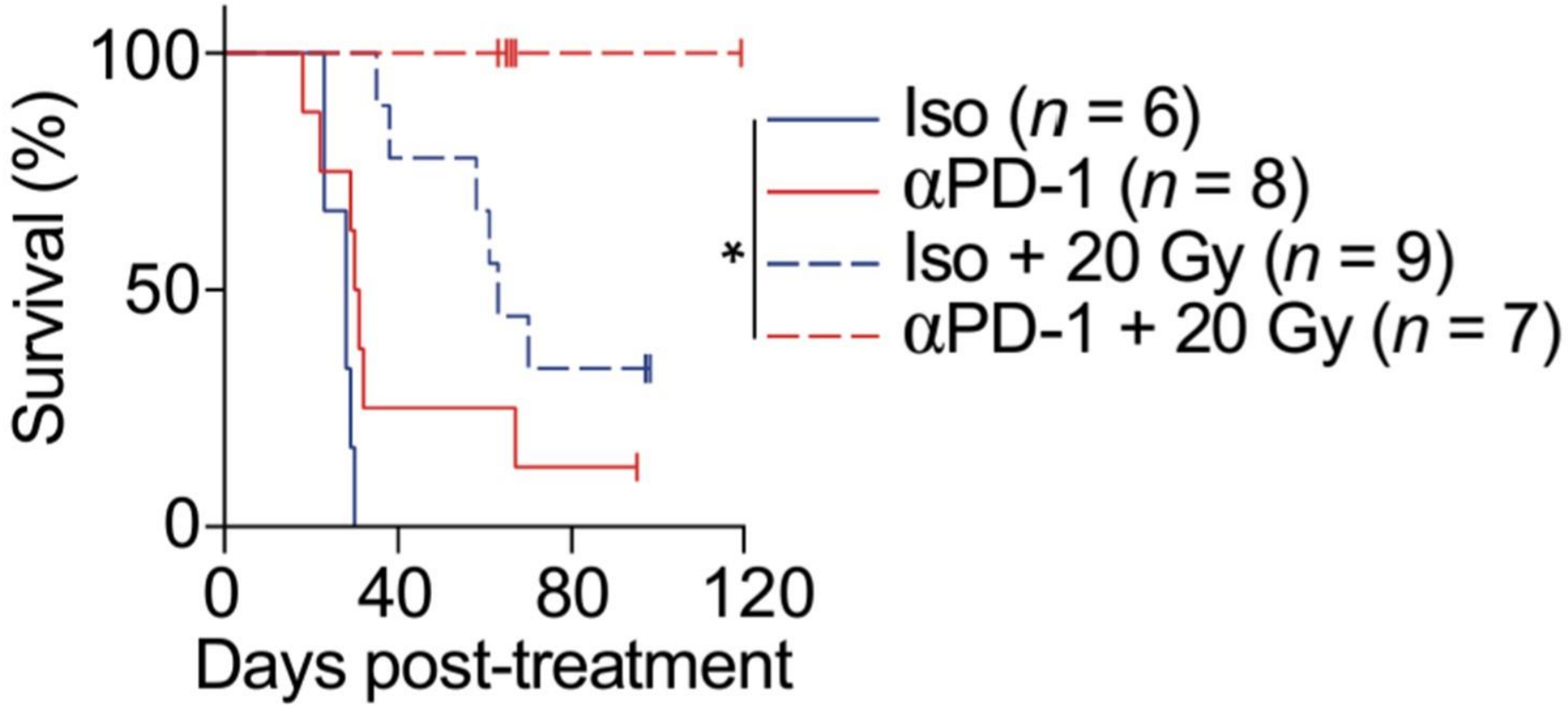
UPS: 20% response

LPS: 8.7% response

Tawbi et al, *Lancet Oncology* 2017

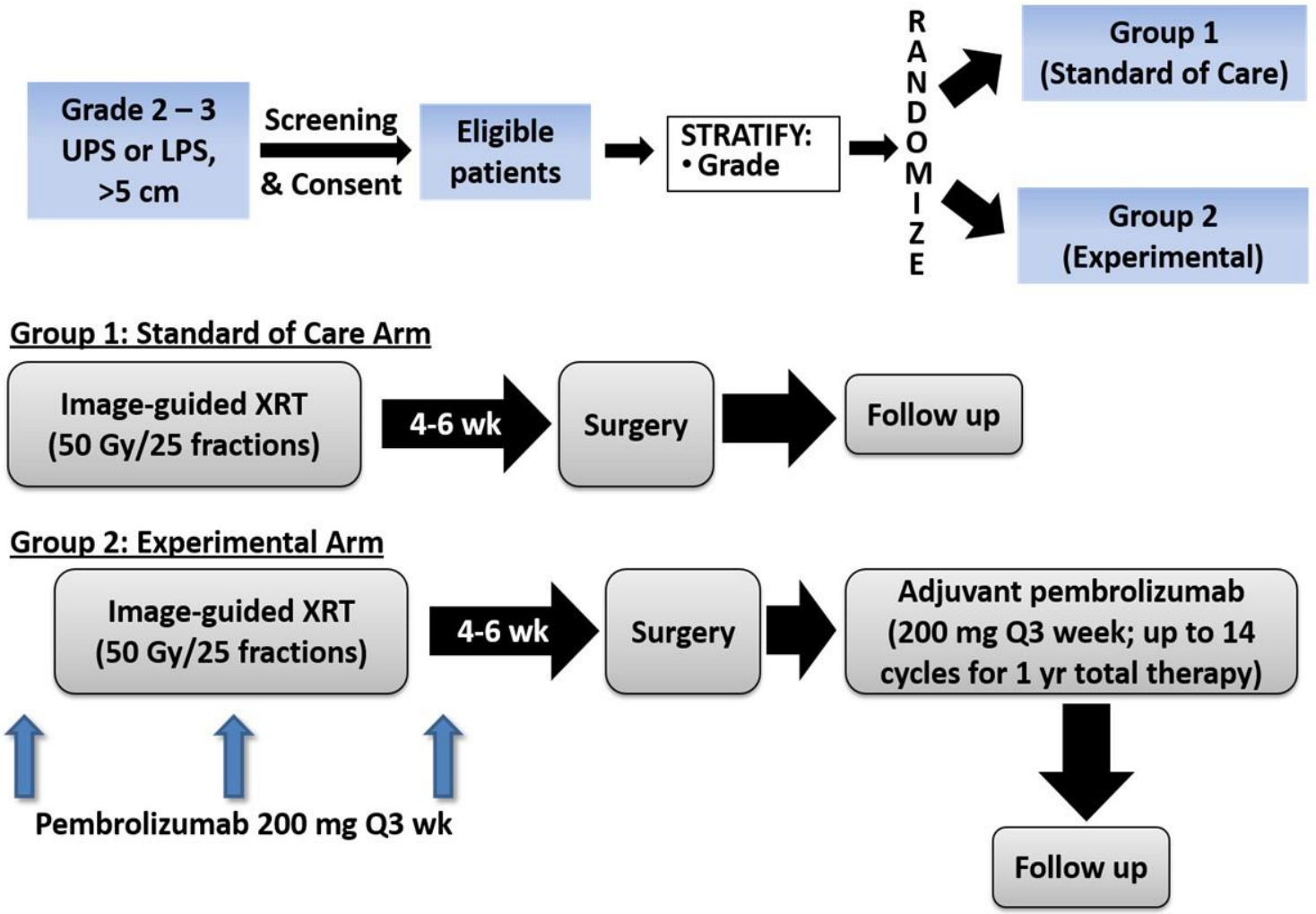
Burgess et al, *ASCO* 2019

RT + Immune Checkpoint Inhibitors: Synergy in p53/MCA Mouse Sarcoma (UPS) Model



Wisdom et al, *Nature Communications* 2020

SU2C-SARC032 (NCT03092323)



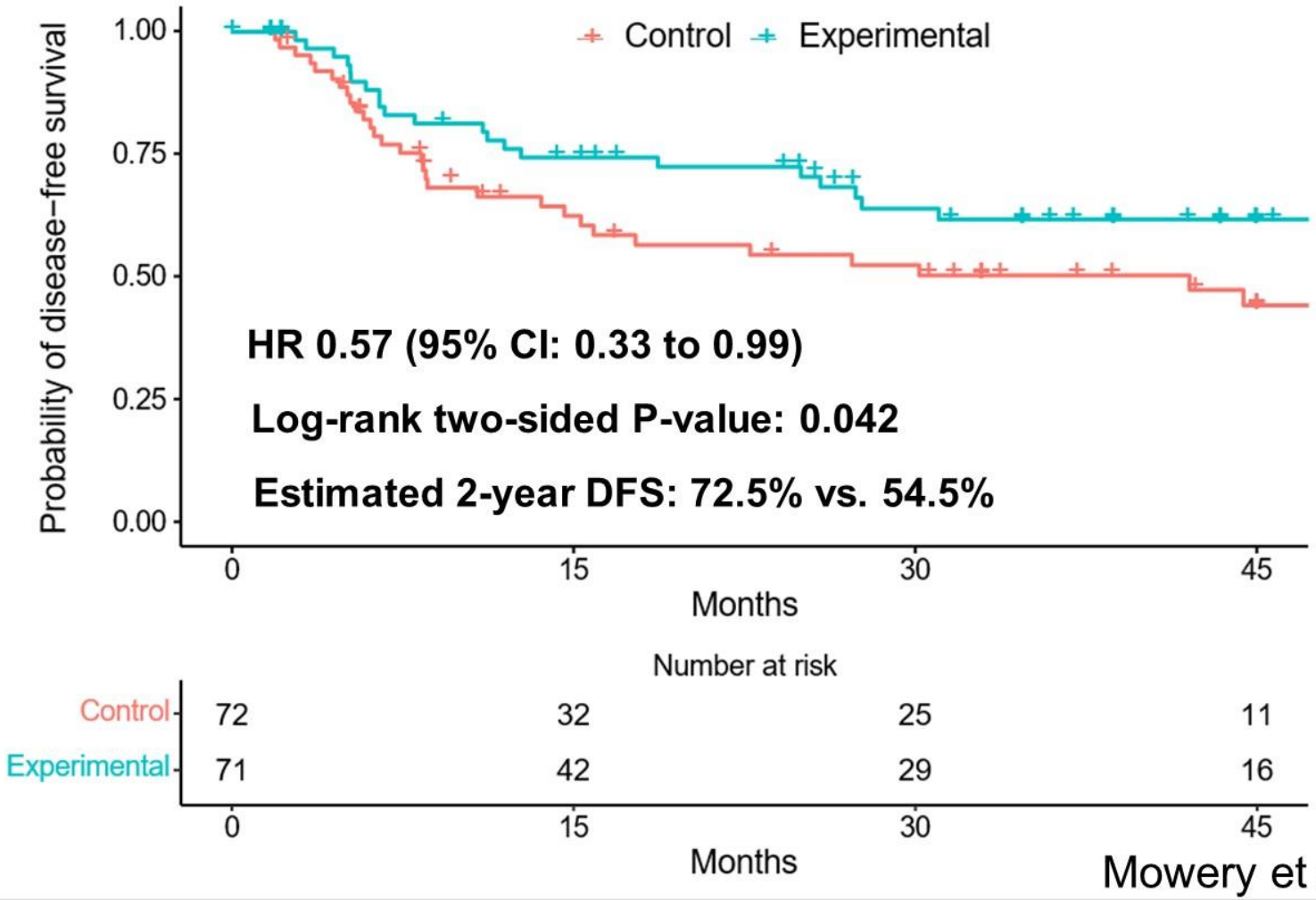
Patient Baseline Characteristics

	Control (N=72)	Experimental (N=71)
Sex	N (%)	N (%)
Female	26 (36%)	26 (37%)
Male	46 (64%)	45 (63%)
Grade		
2	25 (35%)	26 (37%)
3	47 (65%)	45 (63%)
Histology		
UPS	60 (83%)	63 (89%)
LPS	12 (15%)	8 (11%)

Mowery et al, *Under Review*

Adding Pembrolizumab to RT + Surgery Improves DFS

Intention to Treat Analysis

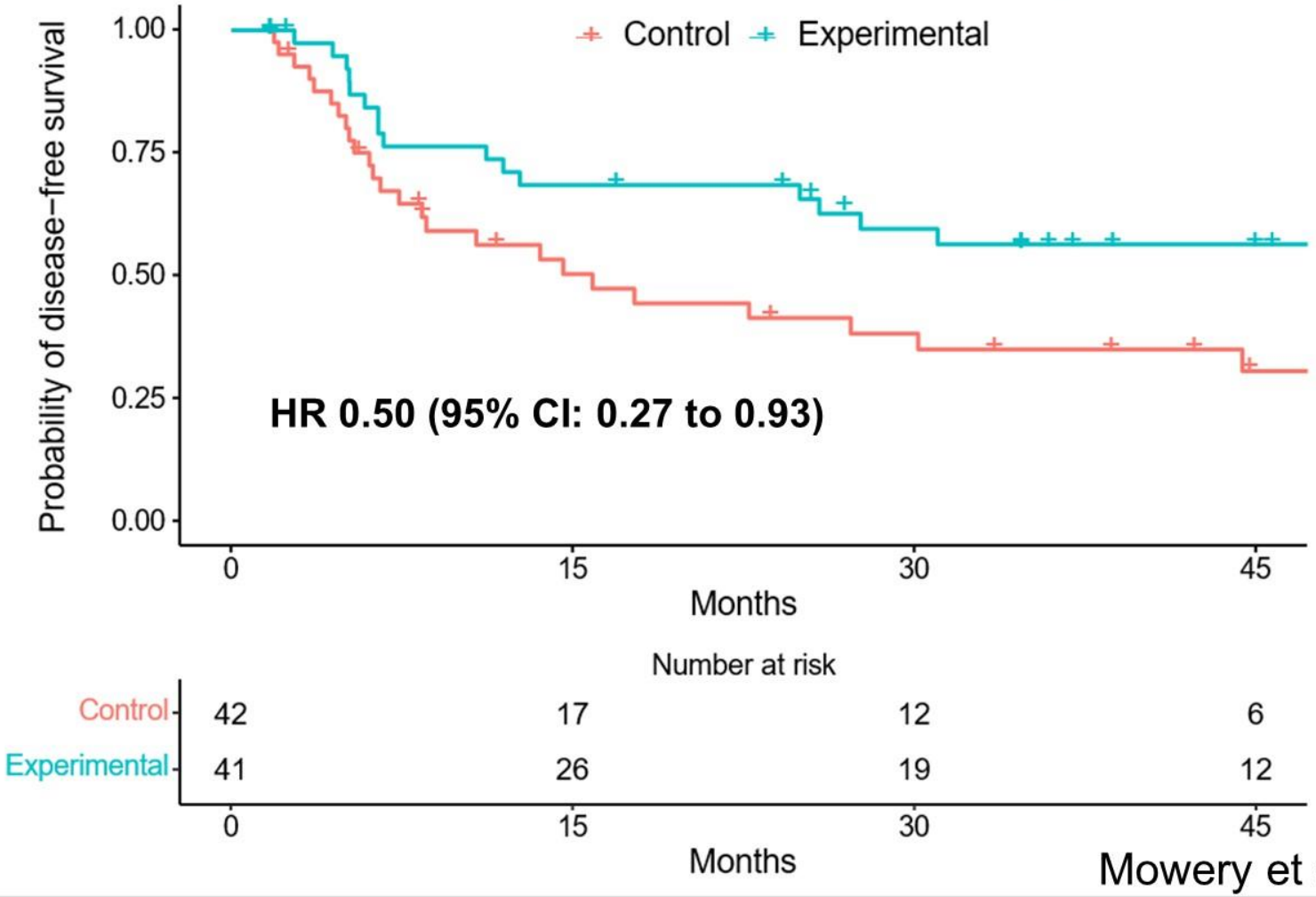


Mowery et al, *Under Review*

PRESENTED BY: David Kirsch, MD, PhD

Adding Pembrolizumab to RT + Surgery Improves DFS in Patients with Grade 3 STS

Evaluable Patients

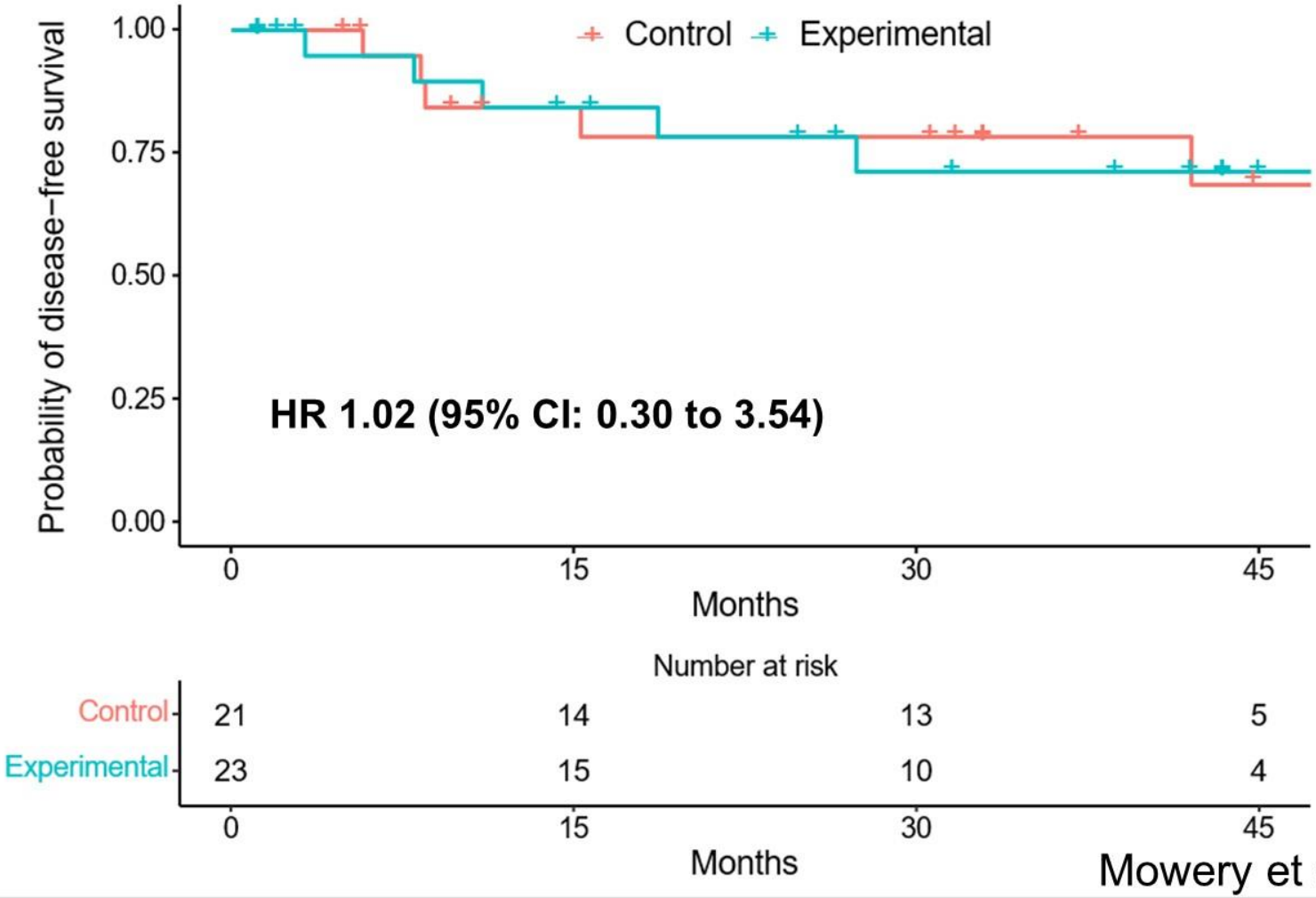


Mowery et al, *Under Review*

PRESENTED BY: David Kirsch, MD, PhD

No Observed Benefit from Pembrolizumab in Patients with Grade 2 STS

Evaluable Patients

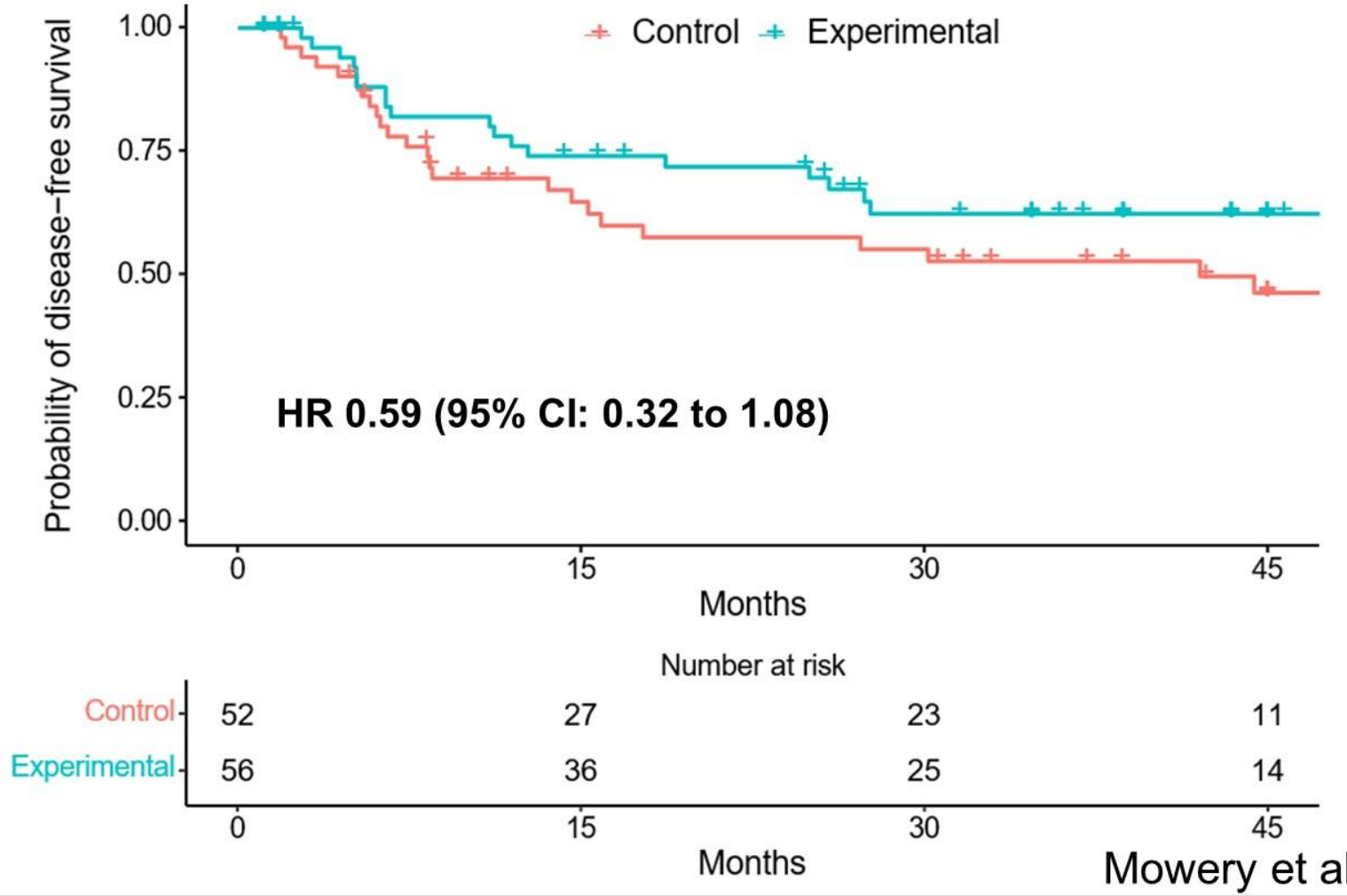


Mowery et al, *Under Review*

PRESENTED BY: David Kirsch, MD, PhD

DFS Benefit from Adding Pembrolizumab to RT + Surgery in Patients with UPS

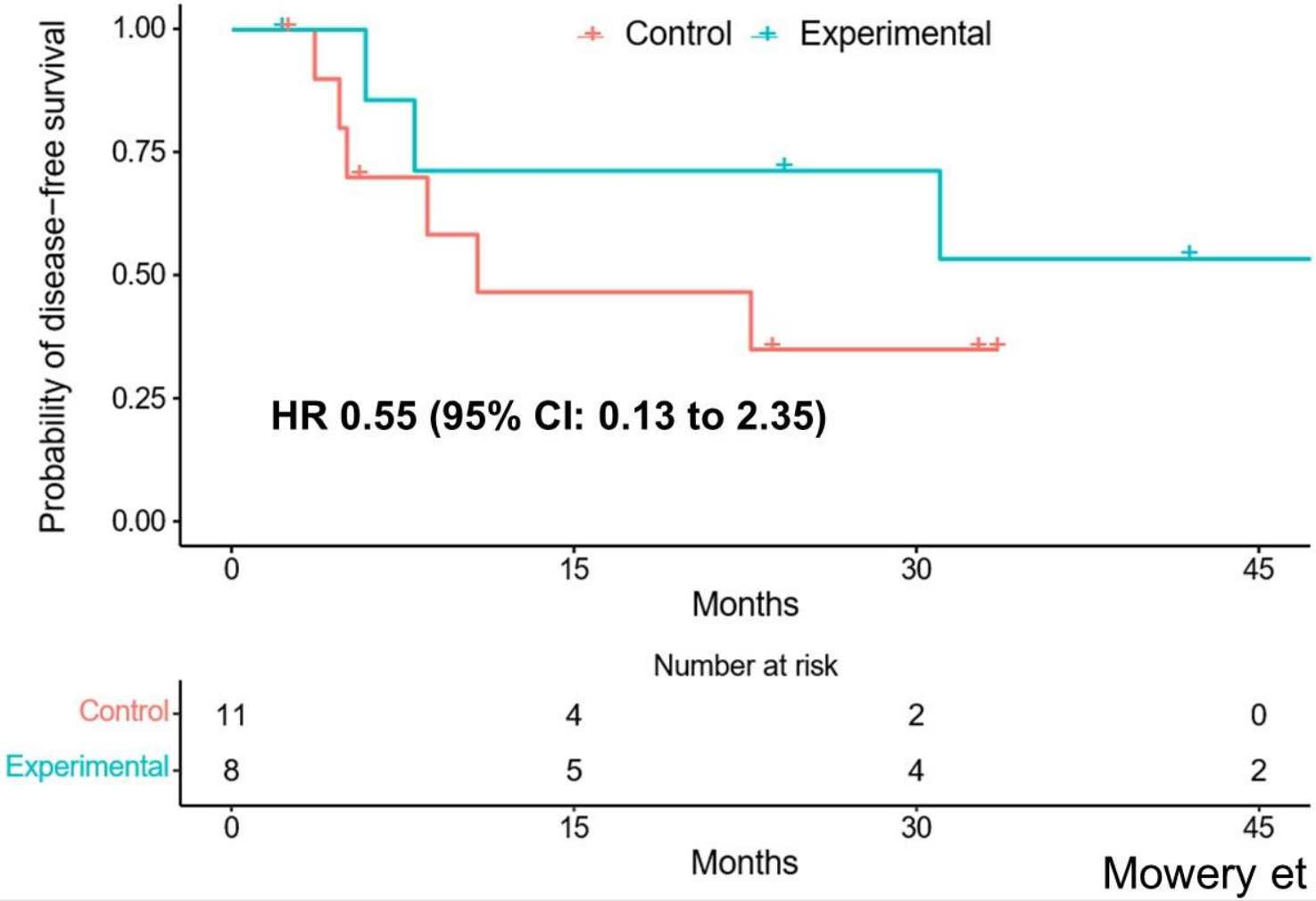
Evaluable Patients



Mowery et al, *Under Review*

DFS Benefit from Adding Pembrolizumab to RT + Surgery in Patients with LPS

Evaluable Patients



Mowery et al, *Under Review*

Safety

- Patients treated with pembrolizumab had more grade 3 or 4 adverse events (**no grade 5 AEs**)
  - Experimental: 37 of 70 patients (53%; 95% CI, 41% to 64%)
    - 52% had at least one AEs (any grade) related to pembrolizumab on central review
  - Control: 20 of 67 patients (30%; 95% CI, 20% to 42%)

- No difference in major surgical complications: 15 patients in Experimental group (21.4%) and 13 patients in Control group (19.4%)
  - Major surgical complications: ≥ G3 wound complications, hematoma, wound dehiscence/infection

Mowery et al, *Under Review*

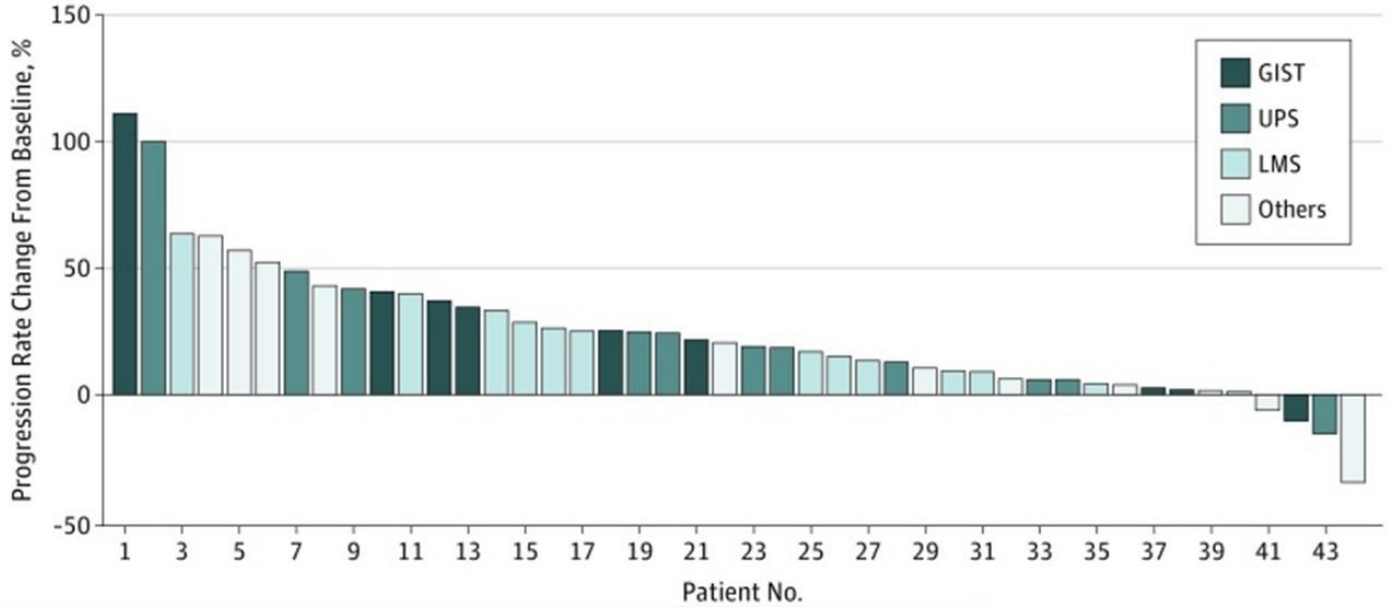
Conclusions

- In SU2C-SARC032, addition of anti-PD-1 therapy pembrolizumab to preoperative RT + surgery increases disease-free survival
- Highest benefit appears to be in grade 3, but the study is not powered for subset analysis
- Pembrolizumab increases grade 3-4 adverse events
- Correlative analyses of tumor and blood samples ongoing
- SU2C-SARC032 establishes addition of pembrolizumab to preoperative RT + surgery as a new treatment option for Stage 3 UPS and LPS of the extremity

Ausgewählte Themen

- Neoadjuvante/perioperative Therapie bei high risk Weichteilsarkomen
- Neues zu Kombinationen mit immuntherapeutischen Ansätzen beim Weichteilsarkomen
- Zelluläre immuntherapeutische Therapieansätze bei Weichteilsarkomen

Limitierte Wirksamkeit von anti-PD-1 Immuncheckpointblockade bei Patienten mit rezidivierten metastasierten Weichteilsarkomen

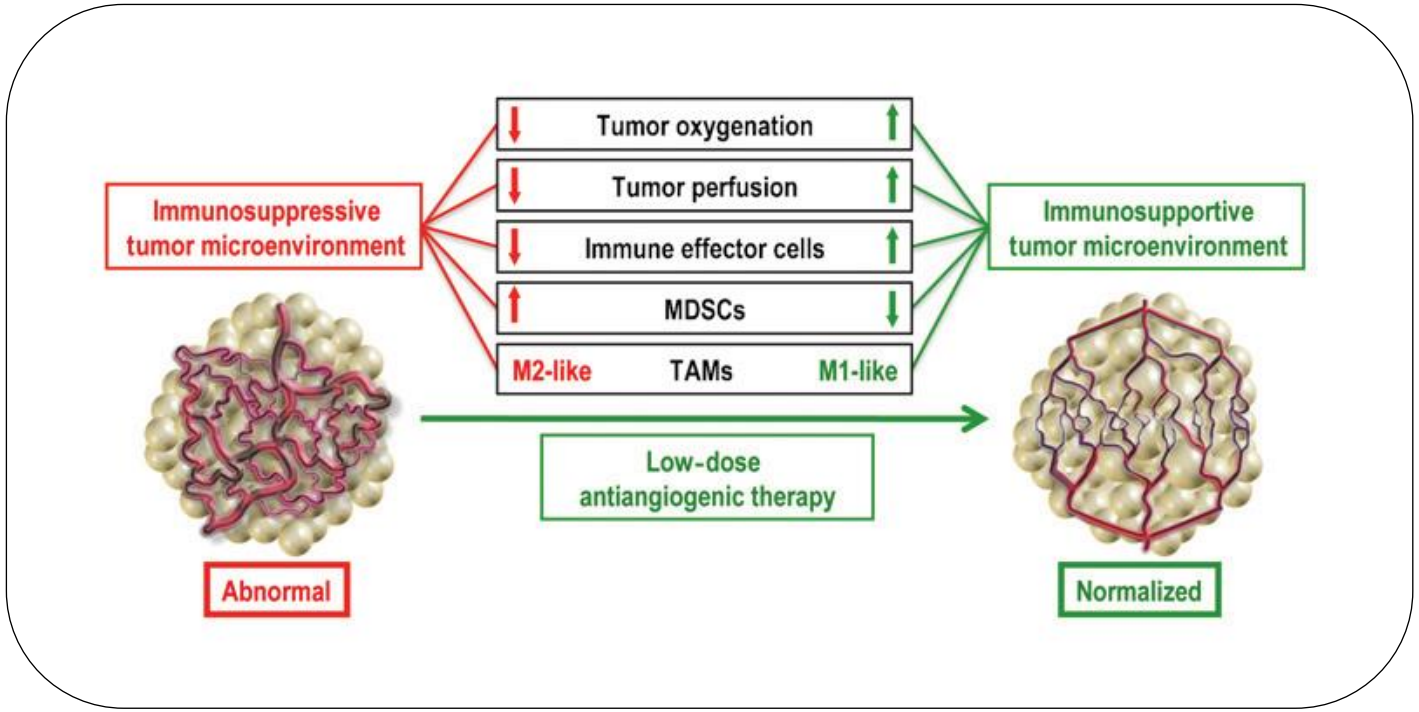


Ansätze zur Verbesserung der Ansprechraten einer Immuncheckpoint Therapie durch Kombinationstherapien?

Toulmonde, Jama Oncology, 2018

Gemeinschaftsklinikum Mittelrhein

„Reshaping“ eines immun-*kalten* in ein immun-*heisses* Tumormikromilieu durch anti-angiogene Therapie



Huang et al, Cancer Research, 2013

2024 ASCO® ANNUAL MEETING

A Phase II Study of Anlotinib and an Anti-PDL1 Antibody in Patients with Alveolar Soft Part Sarcoma: Results of Expansion Cohorts.

Zhichao Tan[1]; Yan Wu[2]; Zhengfu Fan[1]; Tian Gao[1]; Wei Guo[3]; Chujie Bai[1]; Ruifeng Xue[1]; Shu Li[1]; Lu Zhang[1]; Xinyu Wang[1]; Ling Jia[2]; Jiayong Liu[1]

1. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital & Institute, Beijing, China.

2. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Pathology, Peking University Cancer Hospital & Institute, Beijing, China.

3. Musculoskeletal Tumor Center, Peking University People's Hospital, Beijing, China.

Jiayong Liu, MD, Peking University Cancer Hospital & Institute

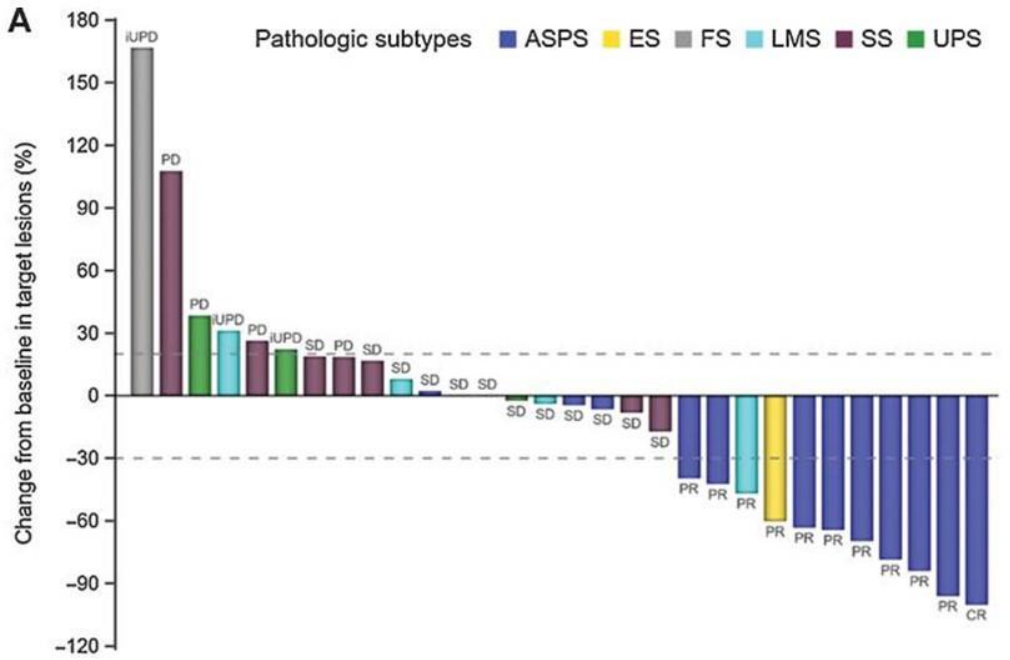
CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD

Sherwin Family Endowed Merit Award

*Supported by **Stephen A. Sherwin, MD***

Background

- Alveolar soft part sarcoma (ASPS) shows sensitivity to tyrosine kinase inhibitors (TKIs) and immune check point inhibitors (ICIs).
- The overall response rates (ORR) of anlotinib (TKI)[1] and atezolizumab (PD-L1)[2] monotherapy was 46% and 37%, respectively.
- Anlotinib and TQB2450 (a PD-L1 inhibitor) demonstrated promising efficacy in ASPS cohorts in a pan-sarcoma phase-II trial[3].



Best ORR in anlotinib plus TQB2450, n (ASPS)=12, ORR=75%

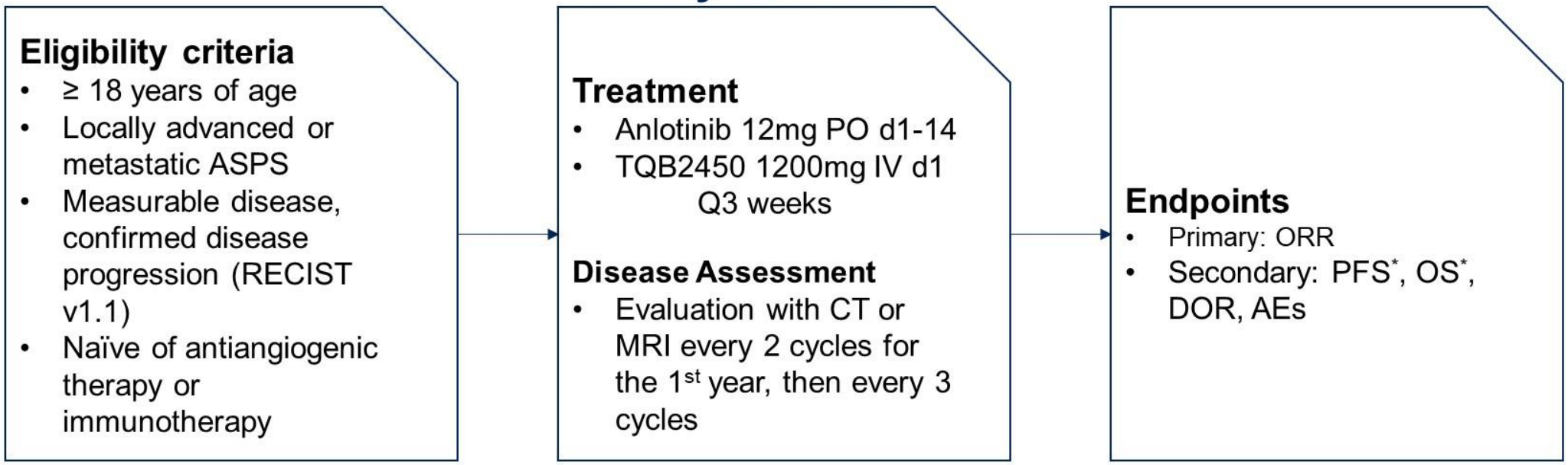
1. Chi Y, Fang Z, Hong X, et al. Safety and Efficacy of Anlotinib, a Multikinase Angiogenesis Inhibitor, in Patients with Refractory Metastatic Soft-Tissue Sarcoma. Clin Cancer Res. 2018;24(21):5233-5238. doi:10.1158/1078-0432.CCR-17-3766
2. Chen AP, Sharon E, O'Sullivan-Coyne G, et al. Atezolizumab for Advanced Alveolar Soft Part Sarcoma. N Engl J Med. 2023;389(10):911-921. doi:10.1056/NEJMoa2303383
3. Liu J, Gao T, Tan Z, et al. Phase II Study of TQB2450, a Novel PD-L1 Antibody, in Combination with Anlotinib in Patients with Locally Advanced or Metastatic Soft Tissue Sarcoma. *Clin Cancer Res*. 2022;28(16):3473-3479. doi:10.1158/1078-0432.CCR-22-0871

Methods

Hypothesis

- To prove that the addition of PD-L1 inhibitor would exert better effect than anlotinib monotherapy, we assumed the true incidence of response would reach 70% to reject a null hypothesis of an incidence of response of 40%
- The enrollment of 25 evaluable patients would provide 90% power with one-sided 5% significance level.

Study schema



* PFS was defined as the time from the first date of drug administration to the time of disease progression according to RECIST 1.1 or death due to any cause, whichever occurred first. OS was measured from the first date of drug administration to the date of death from any cause.

Results: characteristics

- Twenty-nine patients were enrolled in the phase II trial.
- The median age was 29 years (range: 19-46), with female 48.3%.
- Twenty-eight patients were evaluable for efficacy (one withdrew*).
- The ORR for evaluable patients reached 79.3%, characterized by 3 complete responses and 20 partial responses.

Table 1. Baseline Characteristics

Demographics	Study population (n=29)
Age, median (range)	29.0 (19-46)
Gender, no. (%)	
male	15 (51.7)
female	14 (48.3)
Previous chemotherapy, no. (%)	
yes	6 (20.7)
no	23 (79.3)
Disease stage	
locally advanced	0 (0)
metastatic	29 (100)
Metastatic site	
lung	29 (100)
Brain	1 (3.4)
liver	2 (6.8)
bone	3 (10.3)

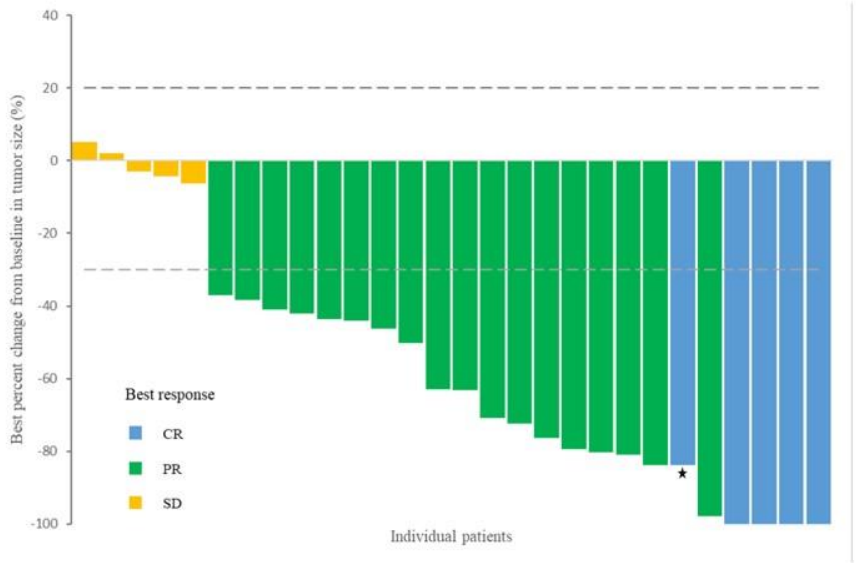


Figure 1. Best Target Lesion Response

* One patient withdrew from the study due to acute pancreatitis

Results: survival

- The median follow-up time was 23.9 months (95%CI: 19.6-30.1).
- The median PFS (months) was not reached (95%CI: 20.7, not-reached).
- The median DOR (months) for responders was not reached (95%CI: 18.0, not-reached).
- No mortalities occurred during the follow-up.

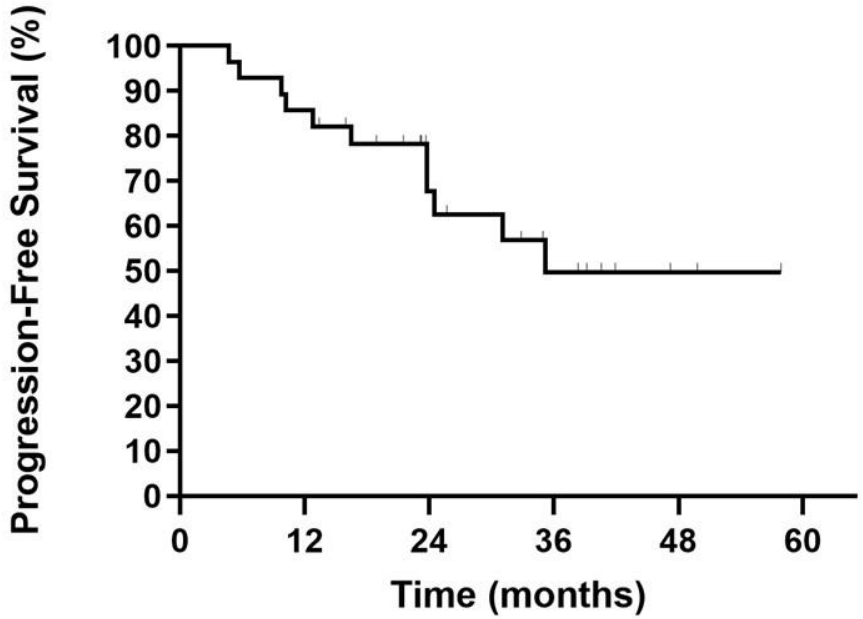


Figure 2. Kaplan-Meier Plot of Progression-free Survival

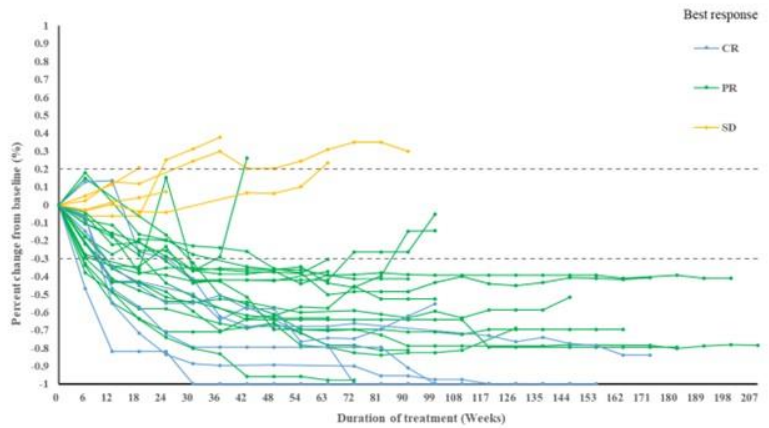


Figure 3. Spider Plot of Tumor Responses

Results: AEs

- AEs were predominantly grade 1 and 2.
- Grade ≥3 AEs: 13 (44.83%)
  - hypertriglyceridemia (13.79%)
  - lipase elevation (6.90%)
  - amylase elevation (3.45%)
  - hypertension (3.45%)
- Dose reduction of anlotinib: 3 (consecutive grade 2-3 proteinuria).
- TRAEs led to treatment termination of TQB2450: 1 (immune-related acute pancreatitis)

Lay Summary

- Alveolar soft part sarcoma is a very rare but highly malignant tumor
- Single agent of target or immune drugs: response <50%
- Combination of anlotinib plus TQB2450: response 79.3%
- Patients achieved long survival without impairment of life quality

Ausgewählte Themen

- Neoadjuvante/perioperative Therapie bei high risk Weichteilsarkomen
- Neues zu Kombinationen mit immuntherapeutischen Ansätzen beim Weichteilsarkomen
- Zelluläre immuntherapeutische Therapieansätze bei Weichteilsarkomen

Gemeinschaftsklinikum Mittelrhein

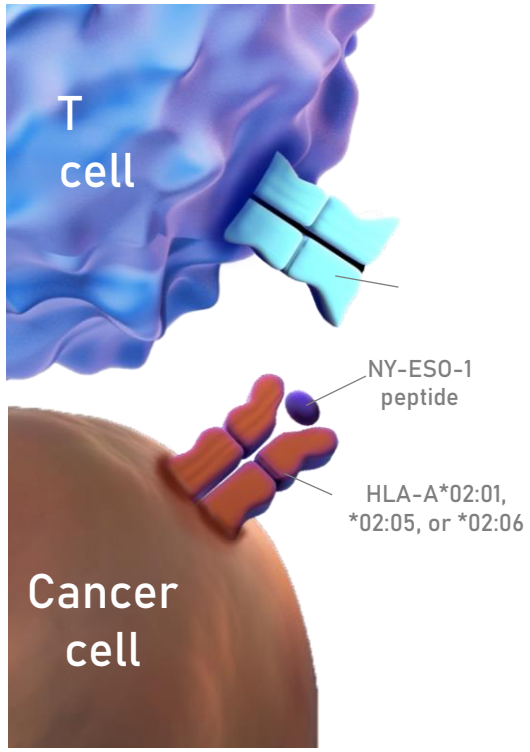
2024 ASCO® ANNUAL MEETING

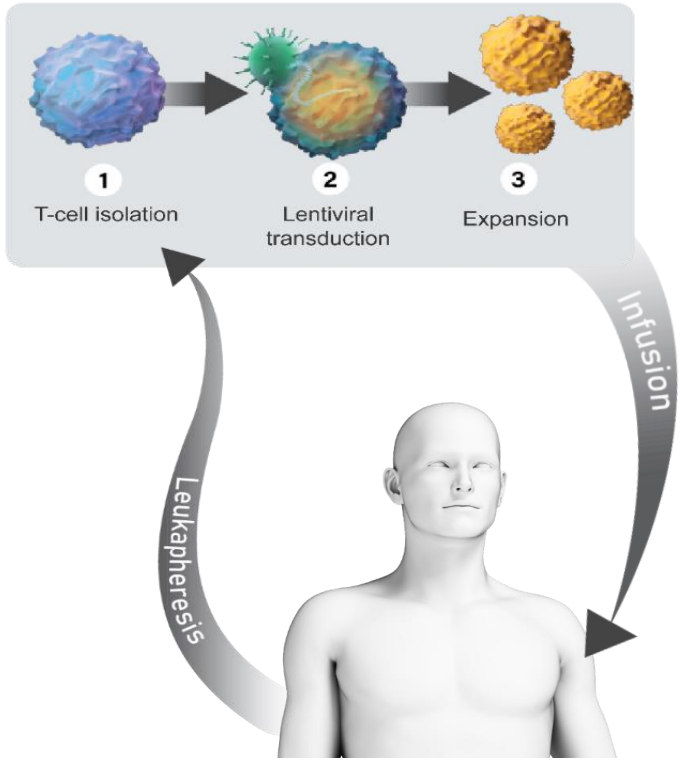
Lete-cel in Patients With Synovial Sarcoma or Myxoid/Round Cell Liposarcoma: Planned Interim Analysis of the Pivotal IGNYTE-ESO Trial

Sandra P. D'Angelo,[1] Andrew J. S. Furness,[2] Fiona Thistlethwaite,[3] Melissa A. Burgess,[4] Richard F. Riedel,[5] John Haanen,[6] Jonathan Noujaim,[7] Anna Weinberg Chalmers,[8] Antonio López Pousa,[9] Rashmi Chugh,[10] Lara E. Davis,[11] Edouard Forcade,[12] Mark Agulnik,[13] Dennis Williams,[14] Mary A. Woessner,[15] Thomas Faitg,[16] Beth Ireland,[17] Michael J. Nathenson,[14] Elliot Norry,[14] Albiruni R. Abdul Razak[18]

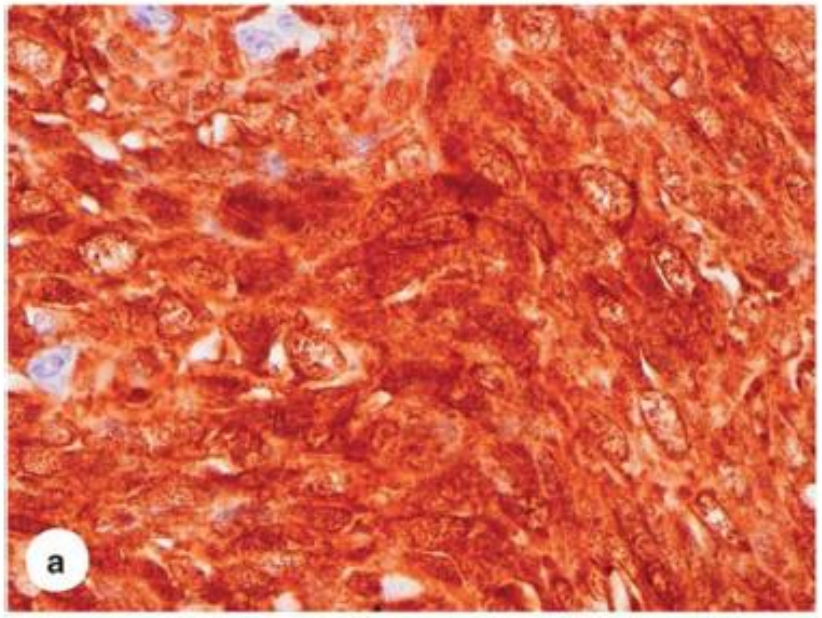
[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]The Royal Marsden NHS Foundation Trust, London, UK; [3]The Christie NHS Foundation Trust and University of Manchester, Manchester, UK; [4]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [5]Duke Cancer Institute, Durham, NC, USA; [6]Netherlands Cancer Institute, Amsterdam, Netherlands; [7]Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; [8]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [9]Hospital Santa Creu Y Sant Pau, Barcelona, Spain; [10]University of Michigan Rogel Comprehensive Cancer Center, Ann Arbor, MI, USA; [11]Oregon Health and Science University, Portland, OR, USA; [12]Centre Hospitalier Universitaire de Bordeaux – Hôpital Haut-Lévêque, Bordeaux, France; [13]City of Hope, Duarte, CA, USA; [14]Adaptimmune, Philadelphia, PA, USA; [15]GlaxoSmithKline, Durham, NC, USA; [16]GlaxoSmithKline, Philadelphia, PA, USA; [17]Adaptimmune, Abingdon, Oxfordshire, UK; [18]University Health Network – Princess Margaret Cancer Centre, Toronto, ON, Canada

IGNYTE-ESO TRIAL:
Personalisierte T-Cell Therapie gegen NY-ESO-1:HLA





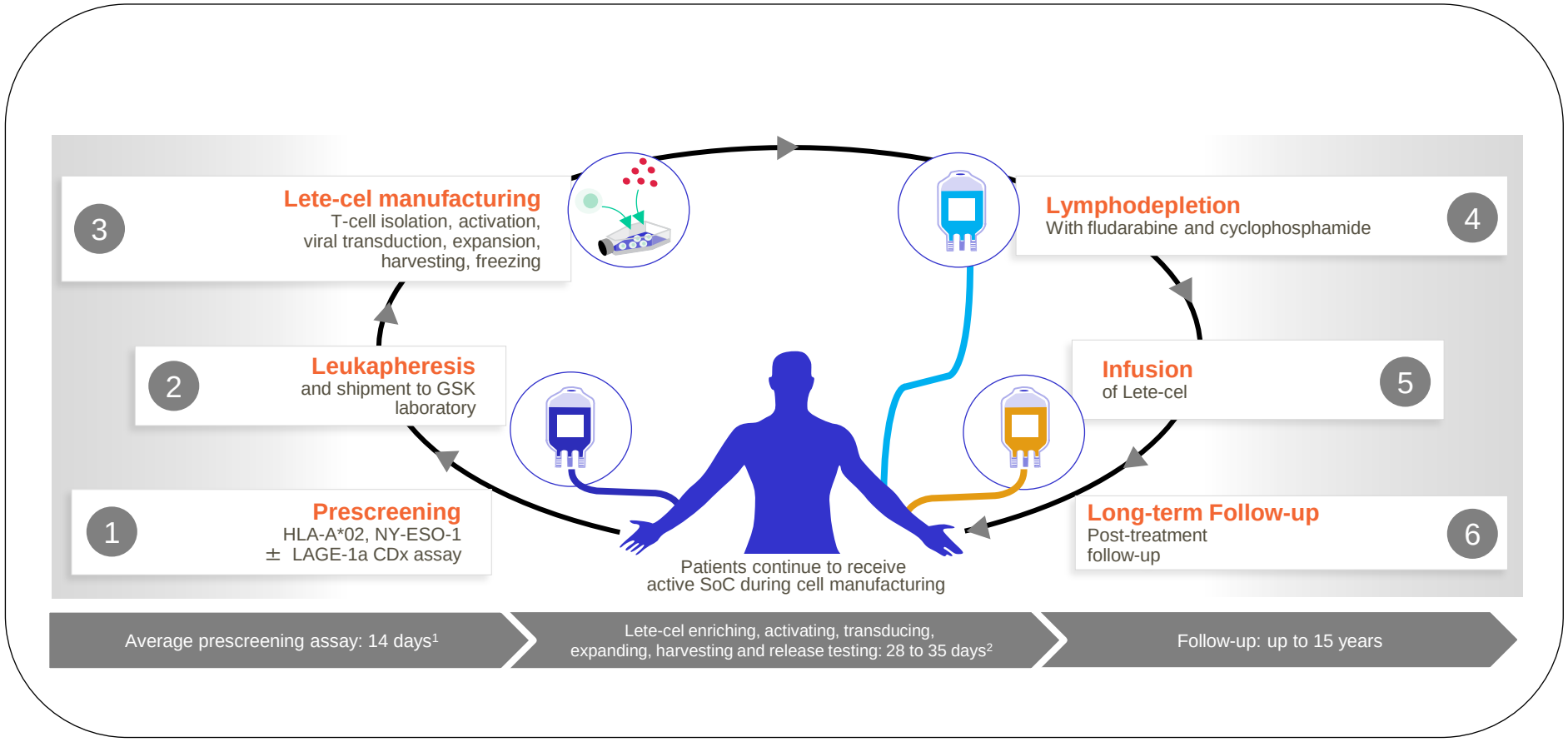
Hohe NY-ESO-1 Expression bei mehr als 80% der Patienten mit Synovialsarkomen



	N	*NY-ESO positive*	*NY-ESO negative*	
Synovial sarcomma	50	41 (82%)	9	
GISTs	155	2 (1%)	153	$P<0.0001$
Leiomyosarcoma	24	0 (0%)	24	$P<0.0001$
MPNST	34	1 (3%)	33	$P<0.0001$
SFT	40	0 (0%)	40	$P<0.0001$
Cellular schwannoma	17	0 (0%)	17	$P<0.0001$
DFSP	20	2 (10%)	18	$P<0.0001$
Angiosarcoma	20	2 (10%)	18	$P<0.0001$
Ewing sarcoma	18	0 (0%)	18	$P<0.0001$
Malignant mesothelioma	27	0 (0%)	27	$P<0.0001$
Other sarcomas[a]	12	3	9	$P=0.0003$

Lai et al, Mod Pathology, 2012

IGNYTE-ESO TRIAL bei Patienten mit NY-ESO-1:HLA positiven SS und MRCLS



- 1. D'Angelo SP, et al. Poster presented at SITC 2019; Poster P453 (Image adapted). 2. D'Angelo SP, et al. *Cancer Discov.* 2018;8:944-957.

IGNYTE-ESO TRIAL
Baseline Characteristics

March 2, 2023, interim analysis

Characteristic	N=45
SyS, n (%)	23 (51)
MRCLS, n (%)	22 (49)
Male, n (%)	25 (56)
Female, n (%)	20 (44)
Race, n (%)	
White	43 (96)
American Indian or Alaska Native	1 (2)
Asian	1 (2)
Age, years, median (min, max)	46 (18, 68)
Extent of disease at screening,[a] n (%)	
Local unresectable	3 (7)
Metastatic	41 (91)

Characteristic	N=45
Systemic therapy regimens before leukapheresis,[b] n (%)	
0	1 (2)
1	10 (22)
2	14 (31)
≥3	20 (44)
Received ifosfamide before leukapheresis, n (%)	34 (76)
Received any anthracycline before leukapheresis, n (%)	44 (98)[b]
Transduced cell dose, median (min, max)	$6.4x10^9$ (2.1, 11.3)
Continuation of supportive therapy between leukapheresis and lymphodepletion, n (%)	18 (40)
Received a new standard of care between leukapheresis and lymphodepletion, n (%)	5 (11)

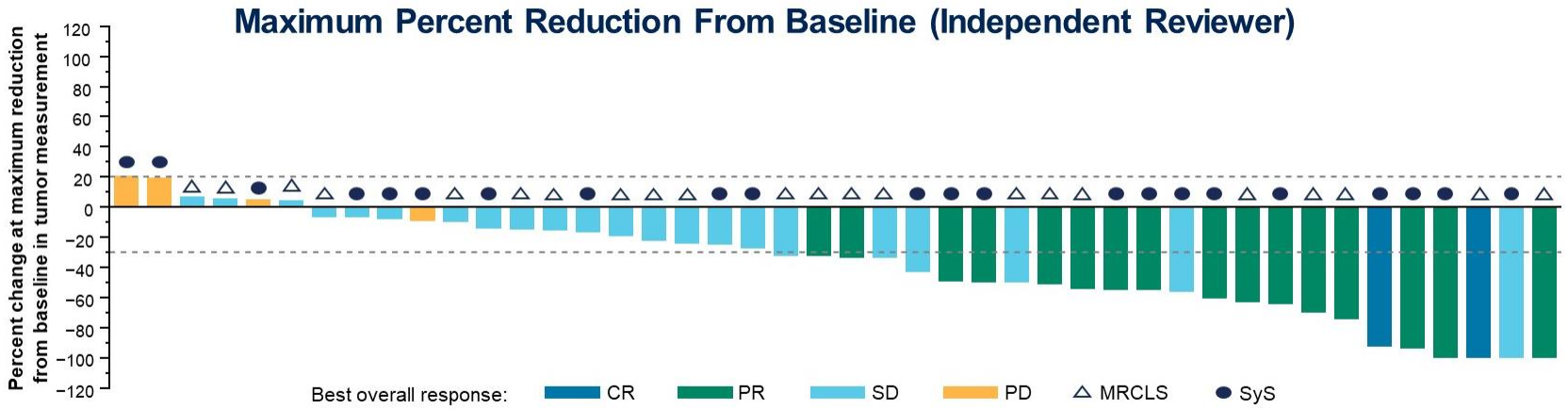
IGNYTE-ESO TRIAL
Adverse Events

Treatment-emergent lymphodepletion-related AEs of special interest or of any grade in ≥15% of participants (N=73)

Event	Any grade	Grade ≥3
Any event, n (%)	68 (93)	60 (82)
Neutropenia	47 (64)	46 (63)
Thrombocytopenia	40 (55)	31 (42)
Anemia	34 (47)	23 (32)
Leukopenia	33 (45)	32 (44)
Febrile neutropenia	19 (26)	18 (25)
Alopecia	15 (21)	–
Decreased appetite	15 (21)	2 (3)
Fatigue	14 (19)	2 (3)
Diarrhea	11 (15)	–
Hypokalemia	11 (15)	2 (3)
Rash/rash maculopapular	8 (11)	2 (3)
Lymphopenia	6 (8)	4 (5)

- Safety was assessed in the 73 participants who had received lete-cel
- All patients experienced an AE; 68 (93%) experienced a Grade ≥3 event
  - Grade ≥3 cytopenias occurred in 63 (86%) patients
- Two (3%) patients experienced Grade 5 events related to lymphodepletion:
  - Neutropenia was in the setting of pancytopenia, and led to a terminal pulmonary infection
  - Pulmonary alveolar hemorrhage was in the setting of pancytopenia, and a platelet count of 0 despite HLA-matched platelets and platelet-stimulating agents

IGNYTE-ESO TRIAL
Overall Response



IGNYTE-ESO TRIAL
Response

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- ORR: 18 of 45 (40%) patients by independent central review (multiplicity-adjusted 99.6% CI: 20.3–62.3%)

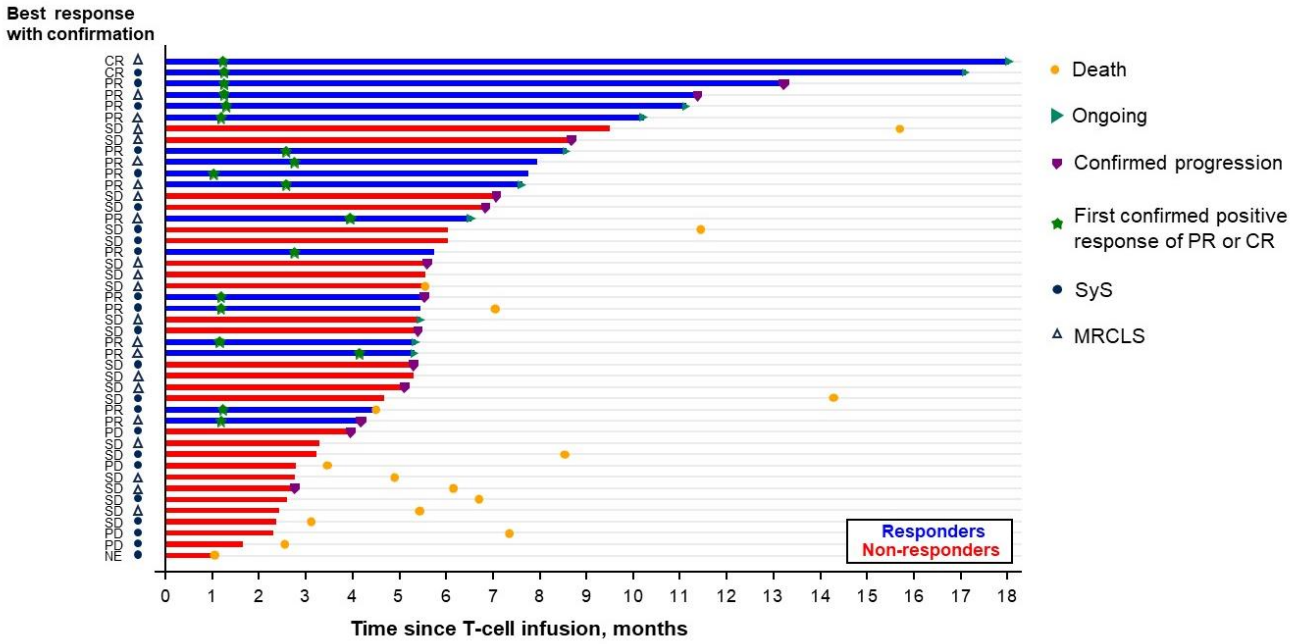
Best response, n (%)	Independent central review		
	Overall (N=45)	SyS (n=23)	MRCLS (n=22)
CR	2 (4)	1 (4)	1 (5)
PR	16 (36)	8 (35)	8 (36)
SD	22 (49)	9 (39)	13 (59)
PD	4 (9)	4 (17)	0
NE	1 (2)	1 (4)	0
ORR [95% CI]	18 (**40**) [25.7–55.7]	9 (**39**) [19.7–61.5]	9 (**41**) [20.7–63.6]

Fazit: Hohe Ansprechraten unter NYESO-gerichteter adoptiver T Zelltherapie bei r/r MRC-LC und Synovialsarkomen

IGNYTE-ESO TRIAL
Duration of Response

At the data cut (18/45 responses):

- 9 responses were ongoing
- Median duration of response: 10.6 months (95% CI: 3.3–**NE**)



Fazit: Dauerhafte Ansprechraten unter NYESO-gerichteter adoptiver T Zelltherapie

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Zusammenfassung

- Perioperative Pembrolizumab + RT bei lokalen „high risk“ WTS wirksam
- Hohe Wirksamkeit von Immuncheckpoint-Blockade mit anti-angiogener TKIs in der metastasierten Situation bei ausgewählten Entitäten
- Dauerhafte Ansprechraten unter NYESO-gerichteter adoptiver T Zelltherapie

Gemeinschaftsklinikum Mittelrhein gGmbH

Prof. Dr. med. Jens Chemnitz

Chefarzt Innere Medizin – Hämatologie/Onkologie, Palliativmedizin

Ev. Stift St. Martin

Telefon: 0261 137-1070

E-Mail: jensmarcus.chemnitz@gk.de