CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

# Aderhautmelanom

13.10.2024

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***Hematology, Oncology and Tumor Immunology***

***Comprehensive Cancer Center***

.

# Intereressenkonflikte

***Unterstützung Forschung:***

Bayer, **SirTex**

***Beratungshonorare:***

**Immunocore, DelCath, Ideaya, Replimmune,** MSD, BMS, Merck, Janssen, Pfizer, Ipsen, AstraZeneca

***Reiseunterstützung:***

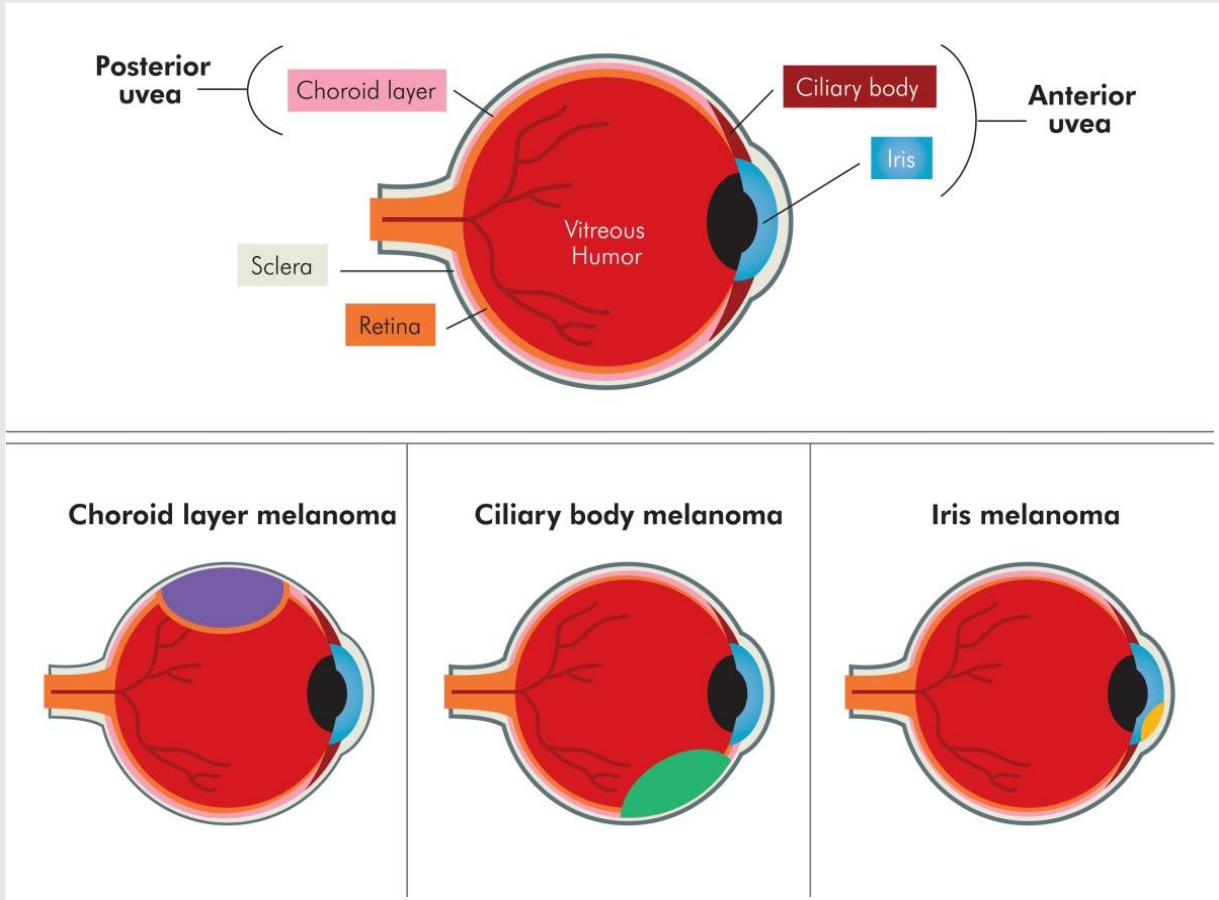
Merck, Ipsen, Janssen

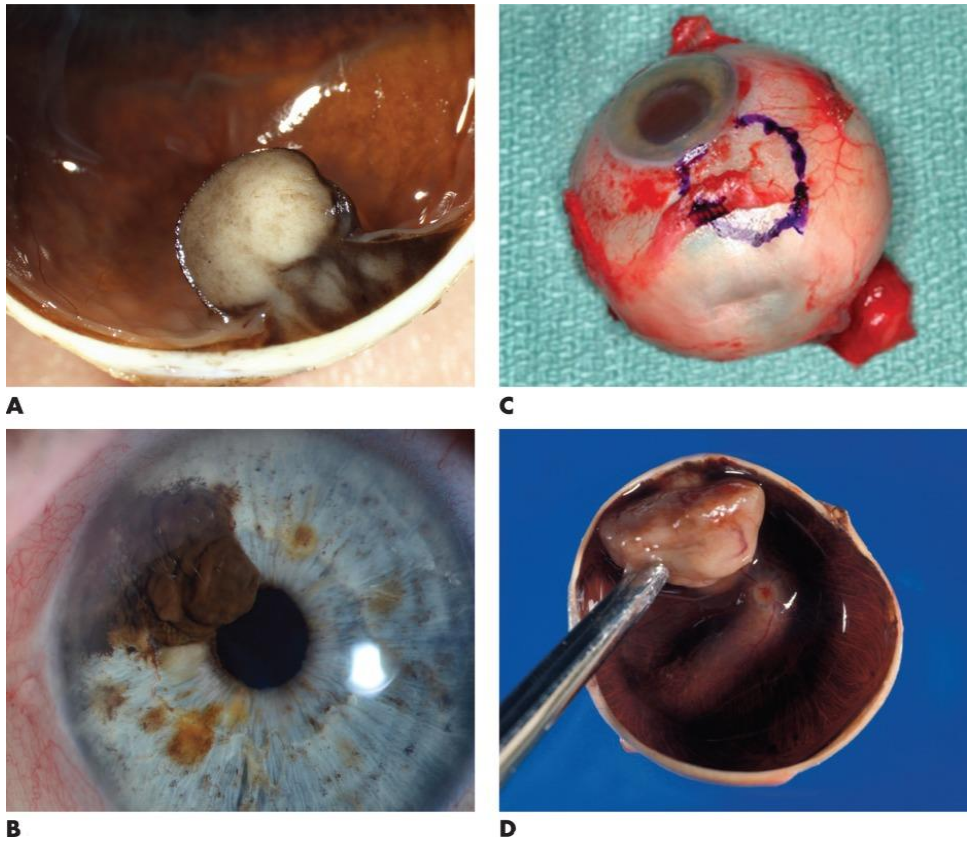
***Patente:***

CCNA1 als T-Zell target bei mailgnen tumoren (FHCRC, Seattle, WA)

# Hintergrund: Aderhautmelanom

- Häufigster maligner Tumor des Auges, insgesamt sehr selten (2-8/1 000 000/Jahr)



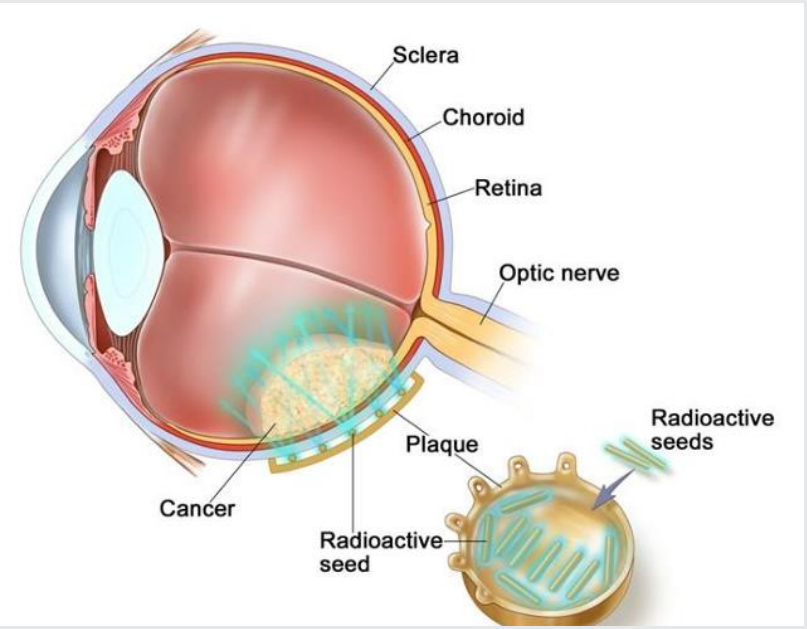




A Choriodales Melanom, B Iris-Melanom, C/D Ziliarkörper-Melanom

# Hintergrund: Primärbehandlung

- Je nach Größe und Lage OP (Enukleation / Eviszeration), Protonenbestrahlung oder Brachytherapie
- Hohe lokale Kontrollraten

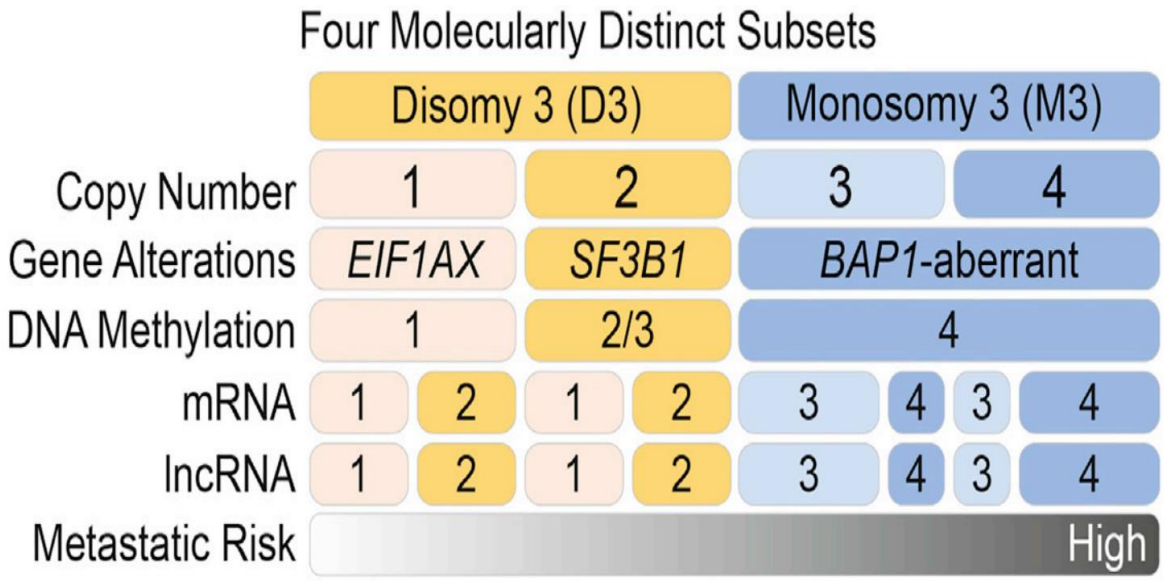
Zyklotron mit Bestrahlungsplatz



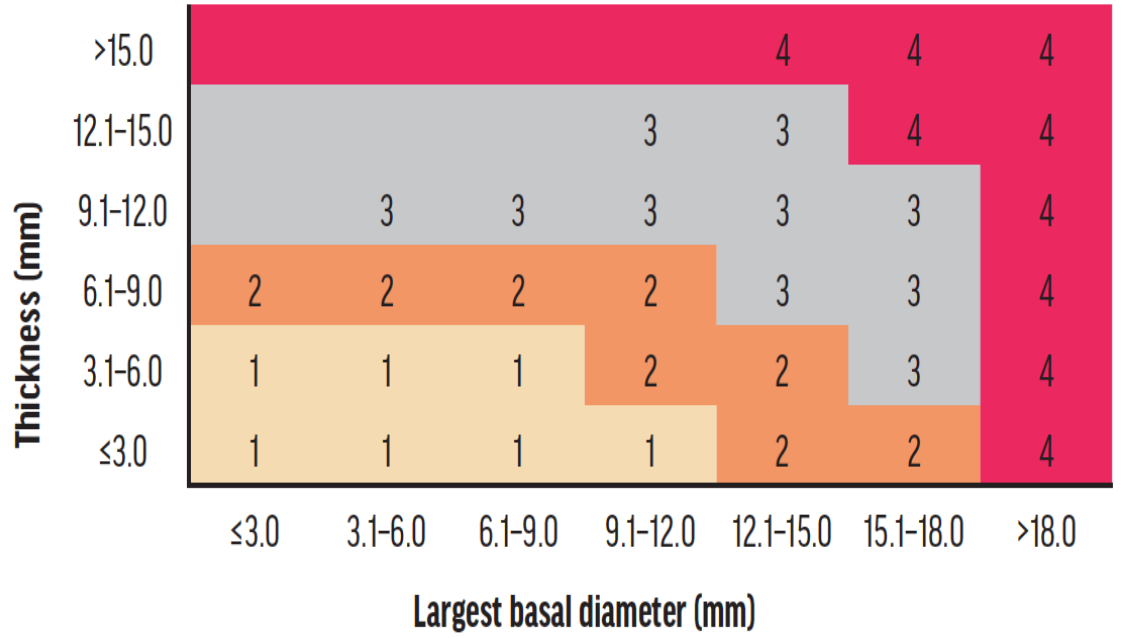

Ruthenium-Plaque

# Hintergrund: Metastasierung

- Fernmetastasierung in 50% (20-80%)
- Wahrscheinlichkeit hängt ab von molekularem Subtyp und Stadium




Spezifische Treibermutationen und chromosomale und genetische Veränderungen



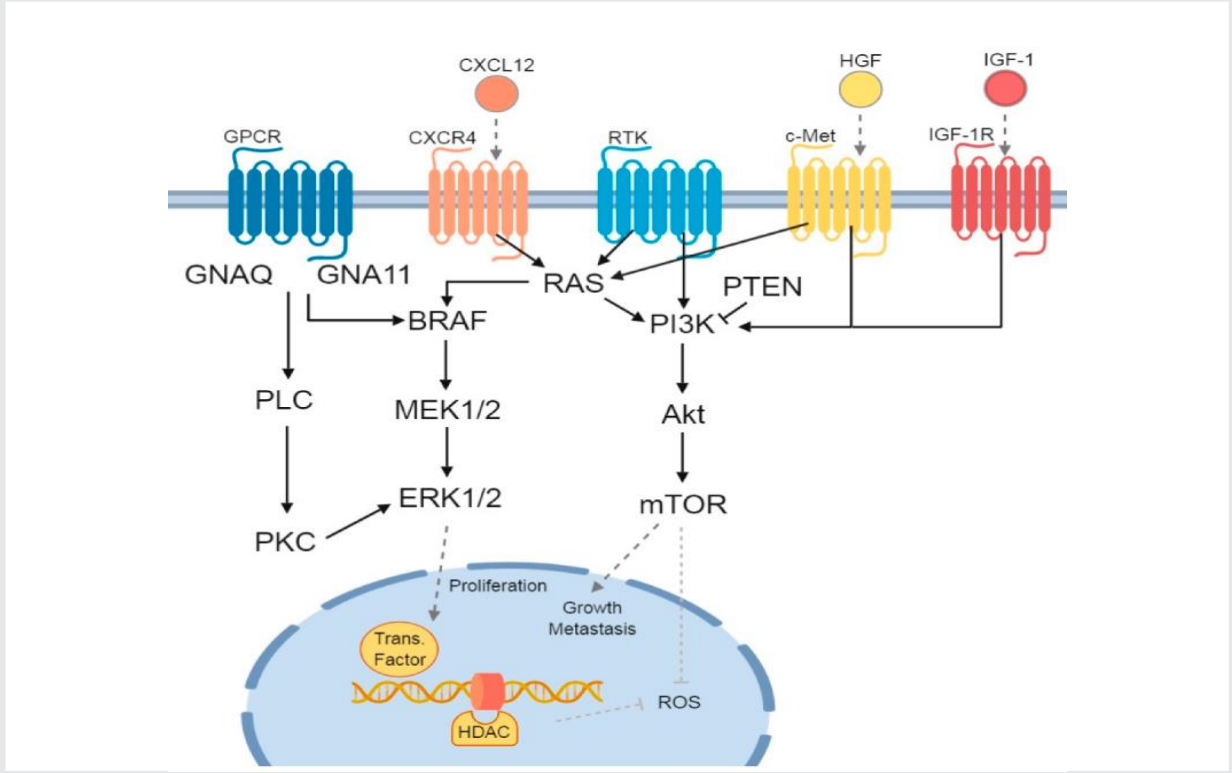

Klinische Stadien (nur T, N gibt es nicht beim UM)



Van der Kooji et al, Cancers 2019; Robertson et al, Cancer Cell 2017; Yarchoan NEJM 2017

# Hintergrund: Tumorbiologie

- Tumorbiologie grundlegend anders als beim kutanen Melanom
- Ansprechraten auf systemische Therapien gering

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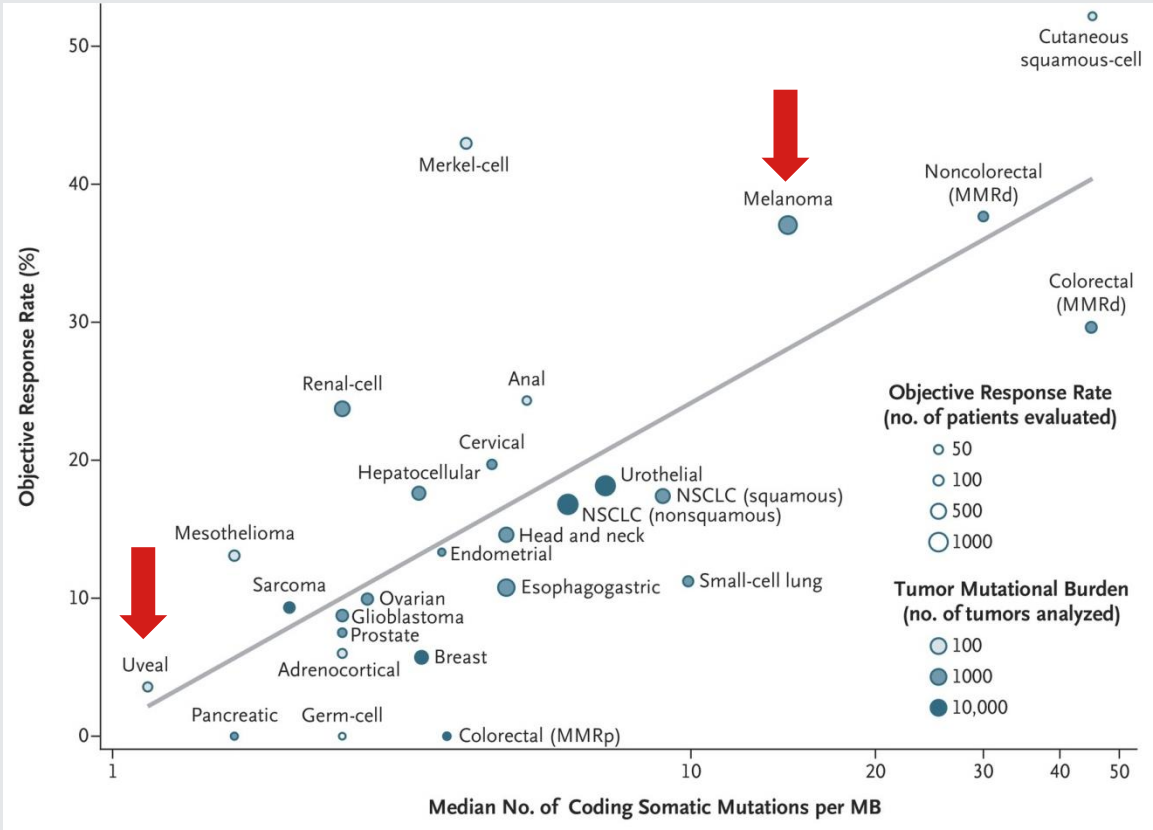



Extrem geringe Mutationslast



Van der Kooji et al, Cancers 2019; Robertson et al, Cancer Cell 2017; Yarchoan NEJM 2017

# Adjuvante Therapien

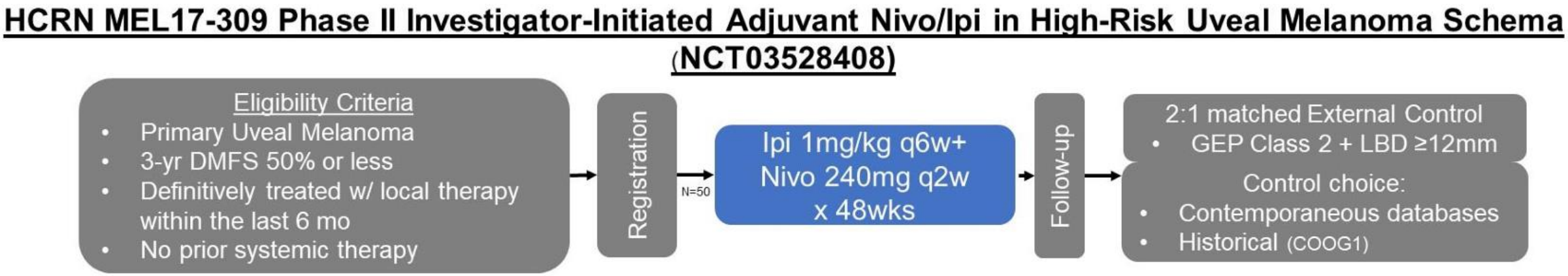
Studien extrem schwer durchzuführen, da

- zum Teil  sehr späte Rezidive,
- Inzidenz extrem niedrig,
- davon nur *high risk*-Patienten elegibel

Nicht bewiesen *beneficial* (auch nicht in high risk Population):

- Interferon
- Fotemustin
- Crizotinib
- Dendritische Zellen
- Melatonin
- U. v. m.

# Adjuvante Therapien: aktuell Ipi/Nivo?

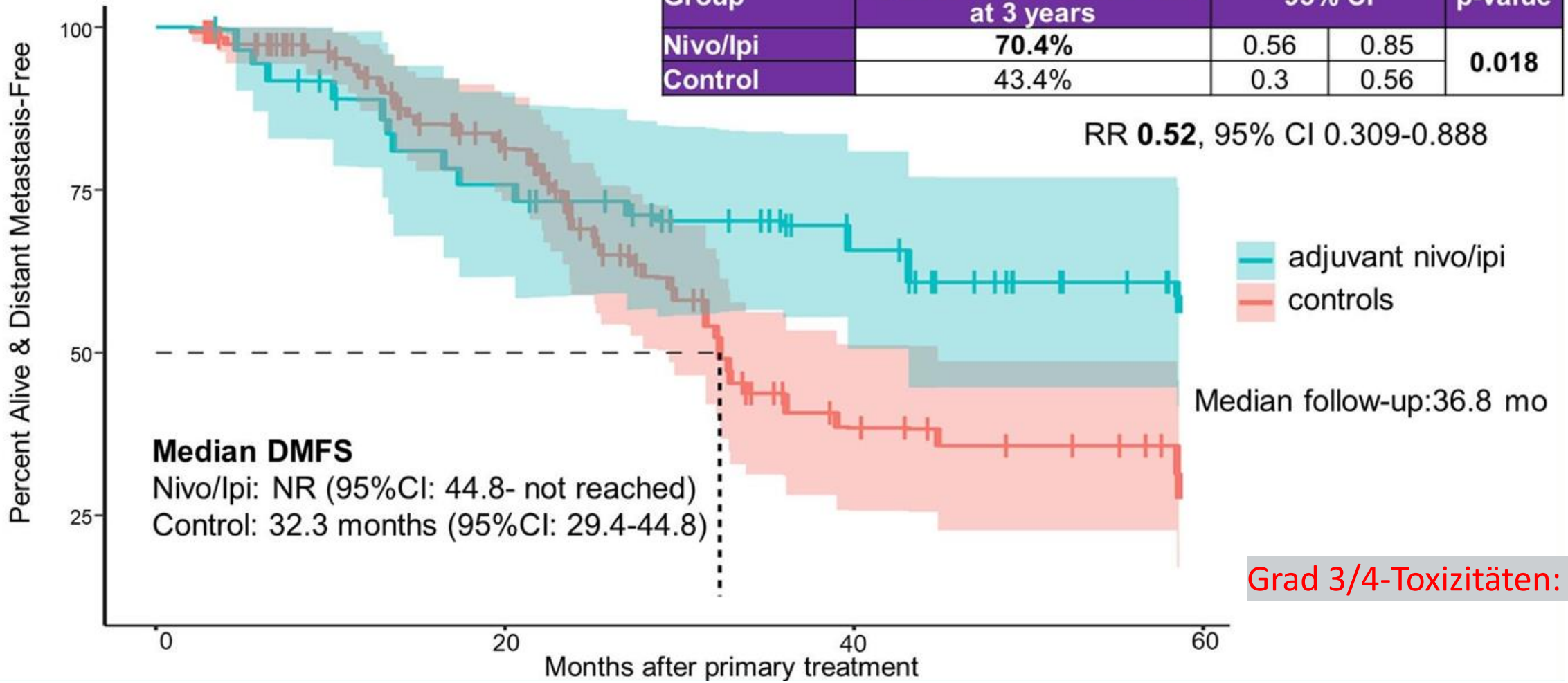



High risk-Patienten, n=50, historische Kontrolle

Primärer Endpunkt: Fernmetastasen-freies Überleben

# Adjuvante Therapien: aktuell Ipi/Nivo?

| Group | Adjusted DMFS probability at 3 years | 95% CI | | p-value |
|---|---|---|---|---|
| Nivo/Ipi | **70.4%** | 0.56 | 0.85 | **0.018** |
| Control | 43.4% | 0.3 | 0.56 | |

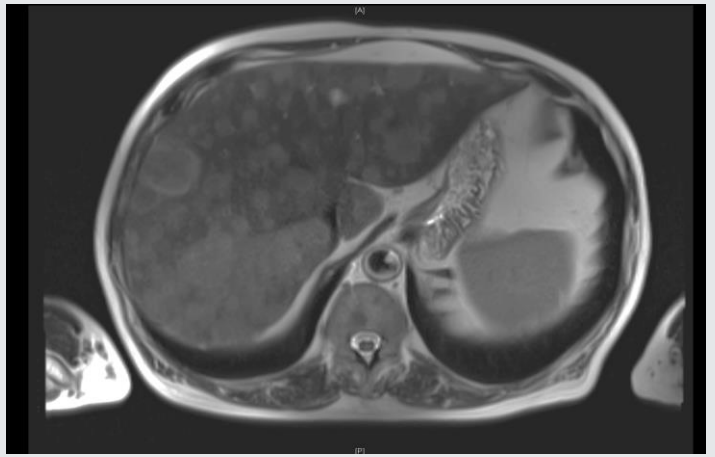



Grad 3/4-Toxizitäten: 48%

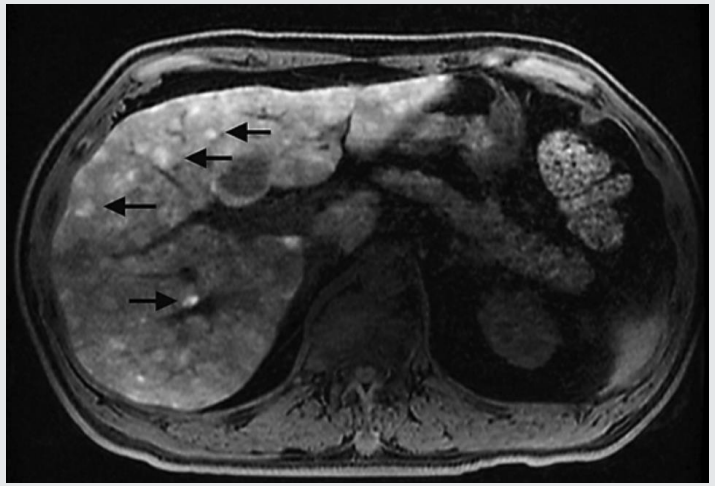
# Hintergrund: Metastasierte Erkrankung

- Uveale Melanome metastasieren inital fast immer in die Leber
- Hepatische Metastasen zeigen häufig die schnellste Dynamik

→Kontrolle der hepatische Metastasierung definiert Morbidität und Mortalität



Hepatotropismus



Hyperintense Läsionen in T1

# Aktuelle Situation

**Diverse lokal-ablative Therapieoptionen (TACE, SIRT, Perkutane Leber-Perfusion)**

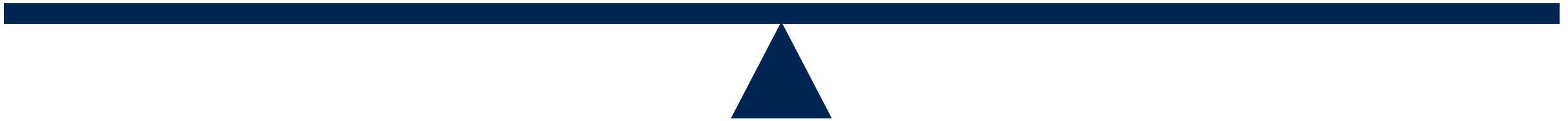
Abhängig von

- Metastasierungsmuster
- Gefäßverhältnissen
- Kardiovaskulärer Fitness

**Diverse systemische Therapieoptionen**

Abhängig von

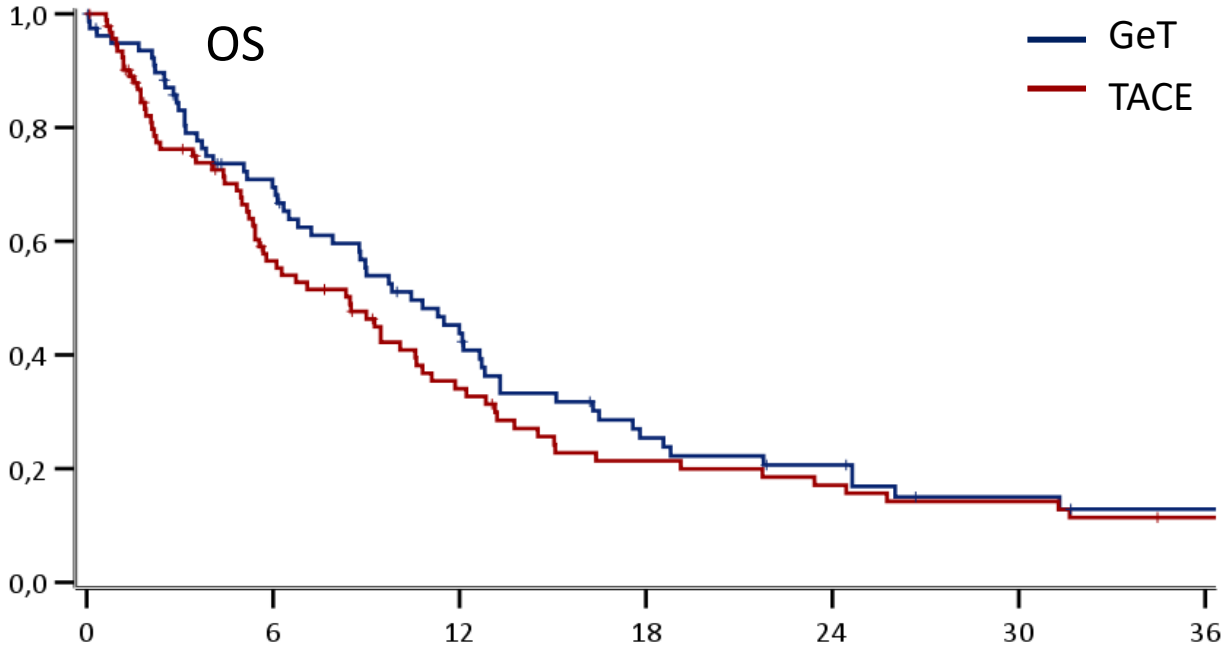
- HLA A*02:01-Status
- Allgemeinzustand
- Organfunktion



**Keine** klinisch gut wirksamen Therapieoptionen
**Wenige** prospektive Daten / **viele** individuelle Therapieentscheidungen

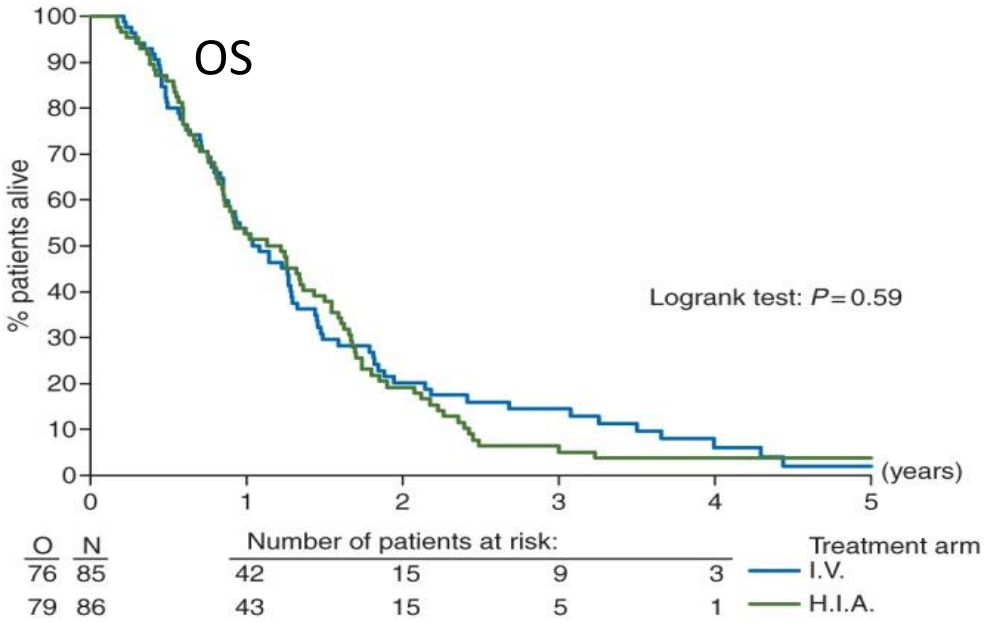
# Systemtherapie: Chemotherapie

**Gemcitabine/Treosulfan**
D1/d8, alle 4 Wochen




**Fotemustin**
D1 d8 d15, nach 5 Wochen Erhaltung

N=171, i. v. vs intraarteriell / hepatisch (HIA)

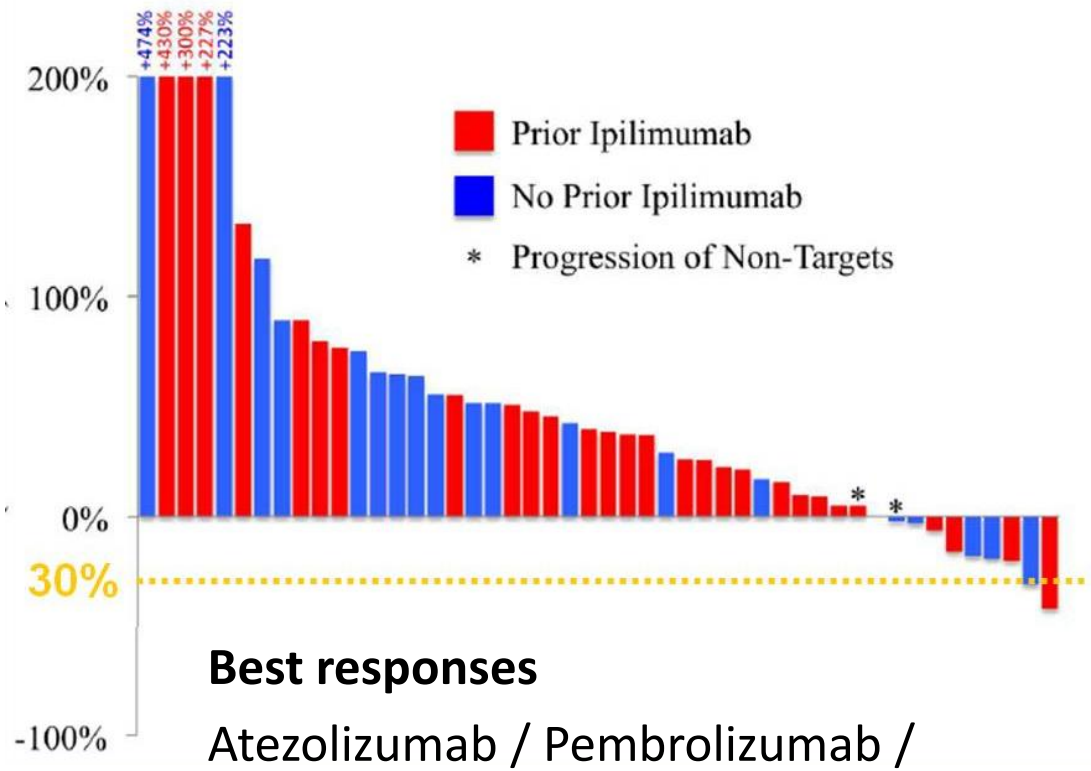





Peuker et al. ESMO 2019, Leyvraz et al. Ann Oncol 2014

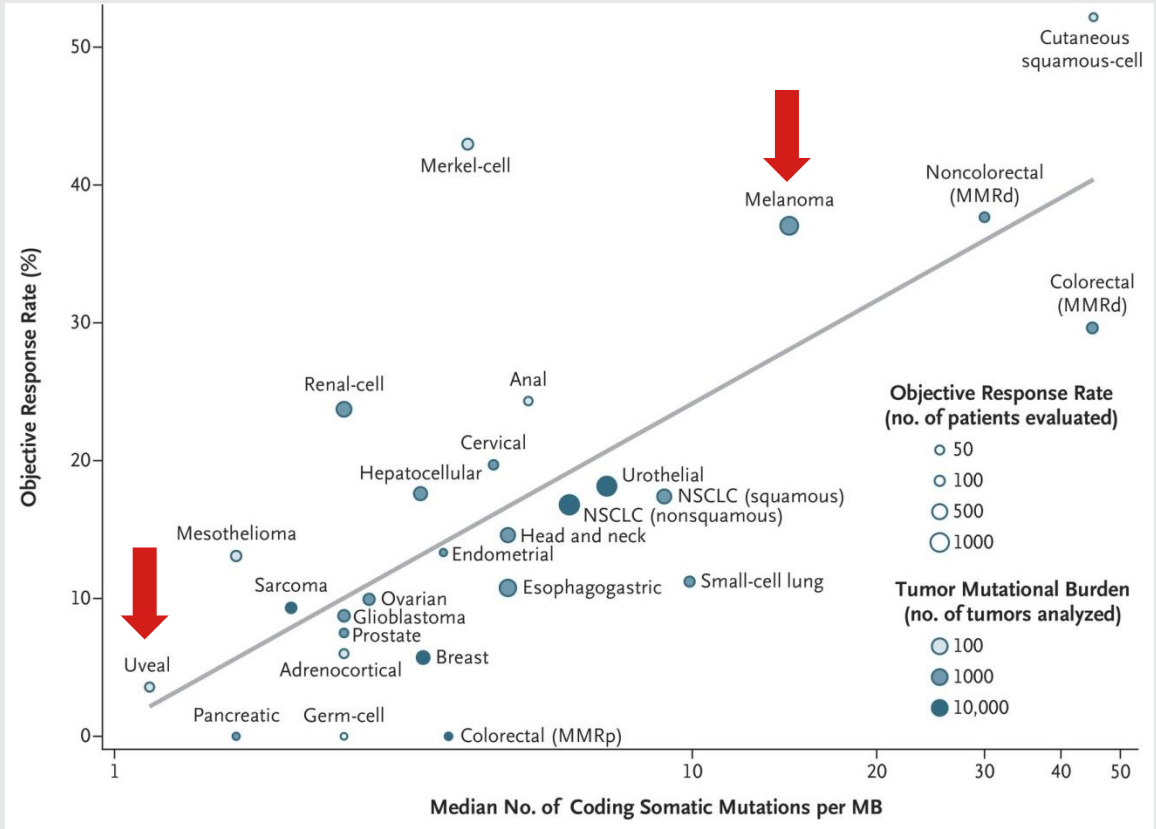
# Systemtherapie: Checkpoint-Inhibition

## PD1-/PD-L1-Inhibition




**Best responses**

Atezolizumab / Pembrolizumab / Nivolumab bei Aderhautmelanomen (n=58)




Extrem geringe Mutationslast



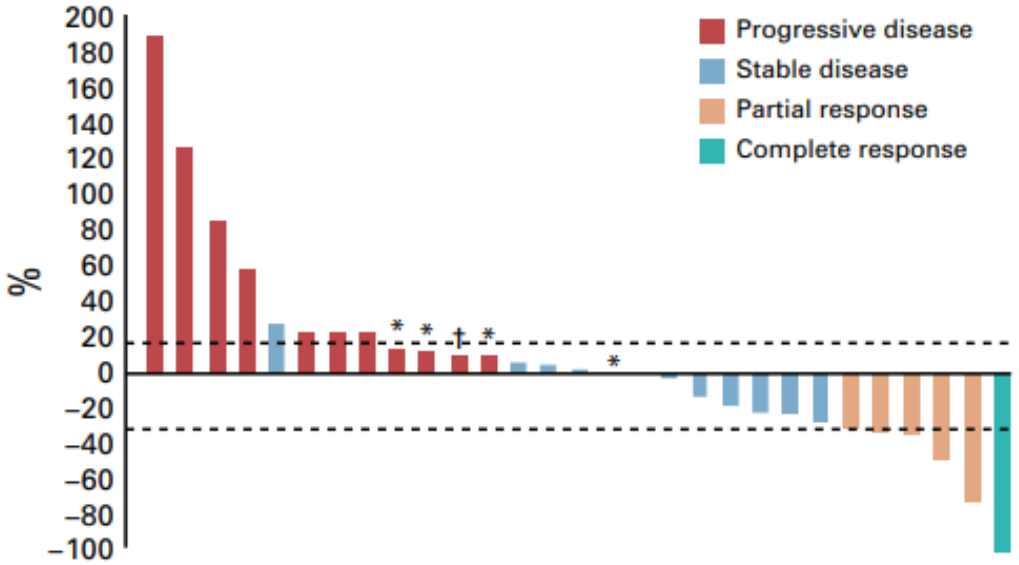
K. Tsai et al. ASCO 2016, Yarchoan NEJM 2017

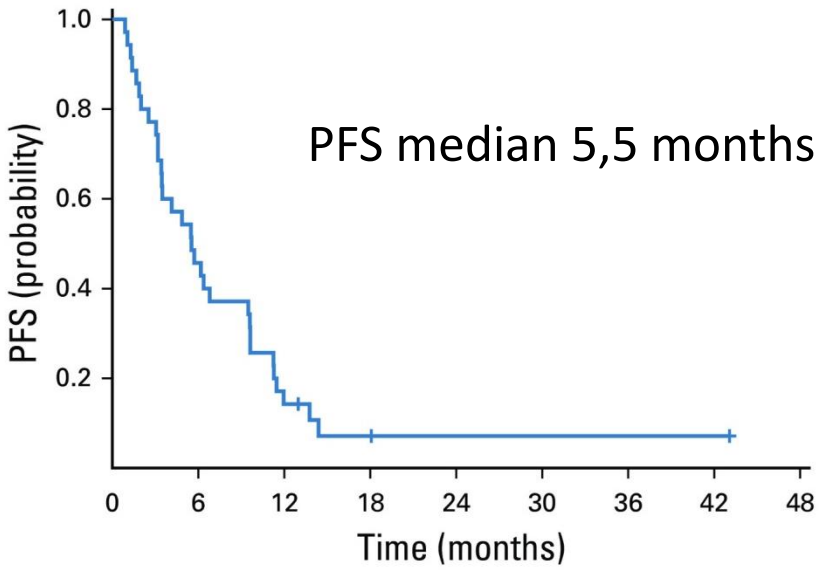
# Systemtherapie: Checkpoint-Inhibition

## Ipilimumab/Nivolumab 1.-3. Therapielinie (Phase II)

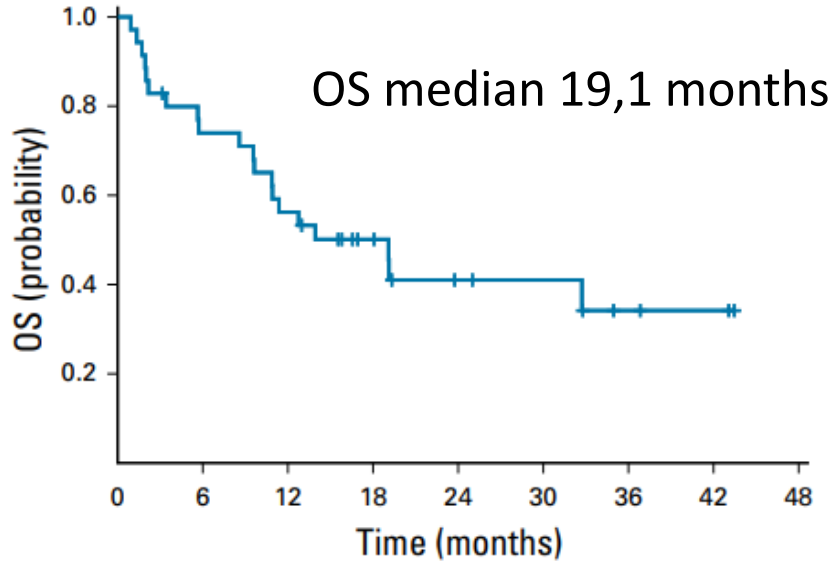
- N=33 (auswertbar)
- 31 % hepatic, 20% extrahepatic, 49% both
- 43% LDH>ULN
- 57% *1st line*

ORR 18%



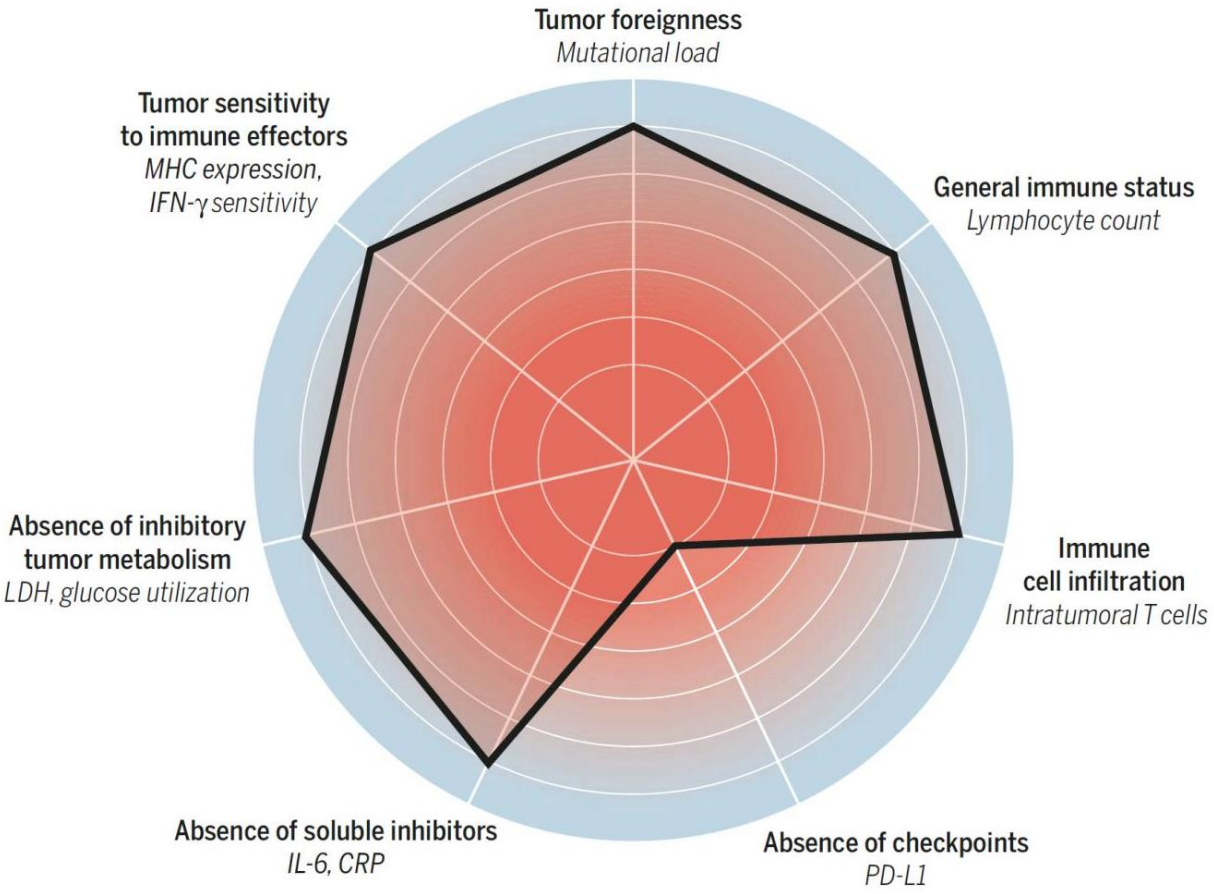

PFS median 5,5 months

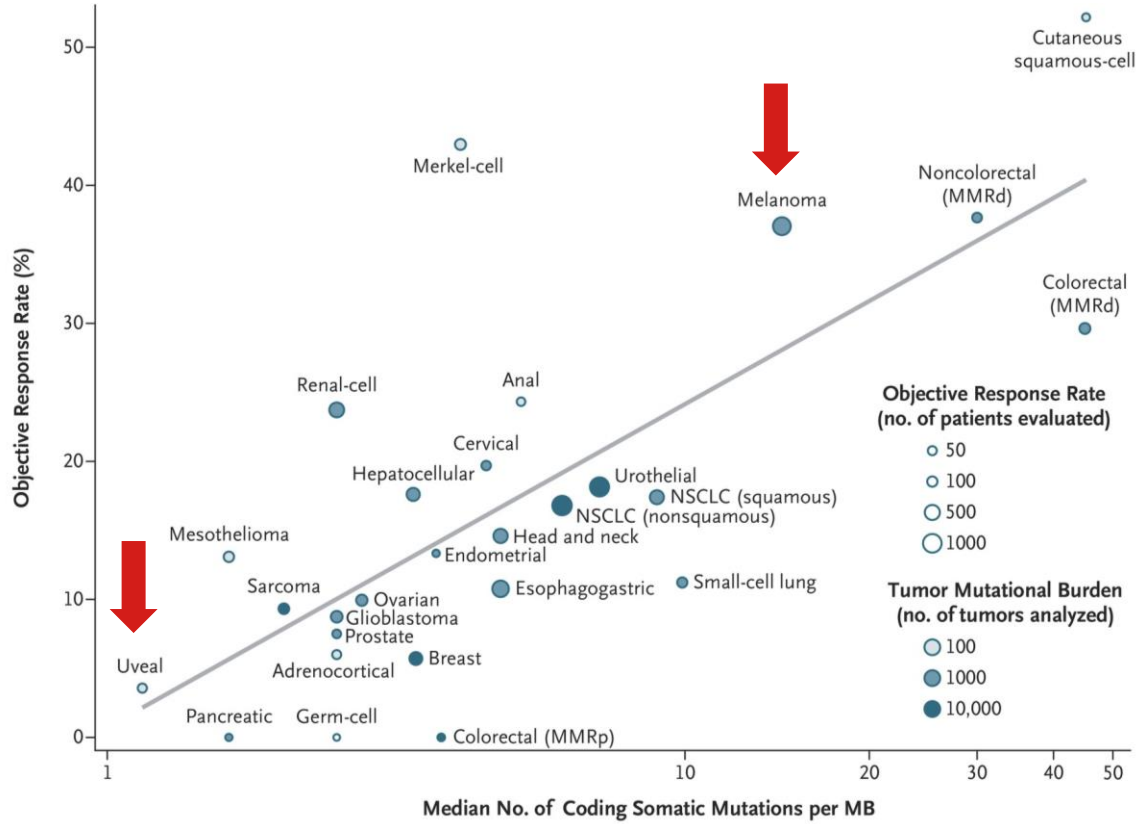



OS median 19,1 months

Pelster et al JCO 2021

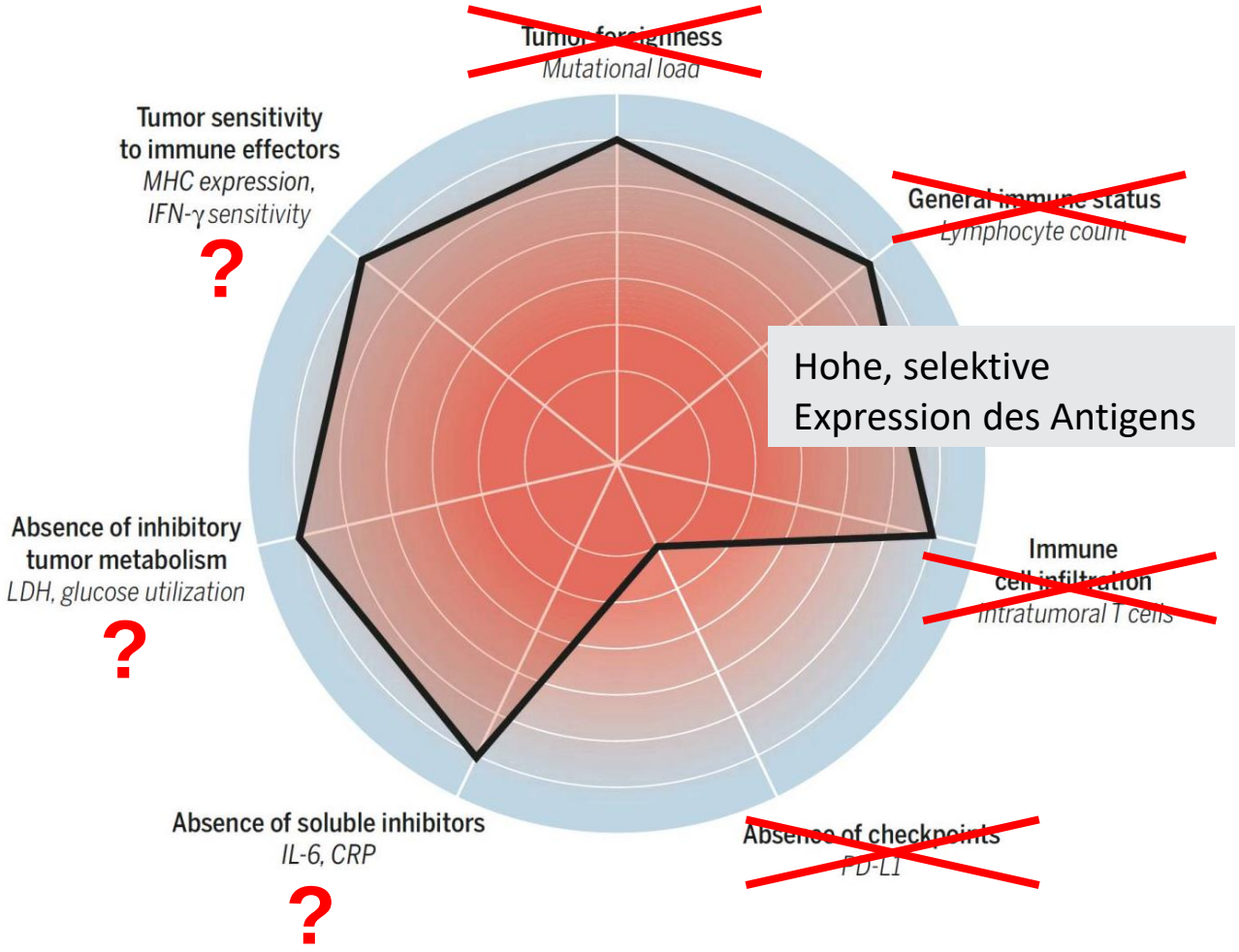
# Prädiktive Faktoren: Checkpoint-Inhibition



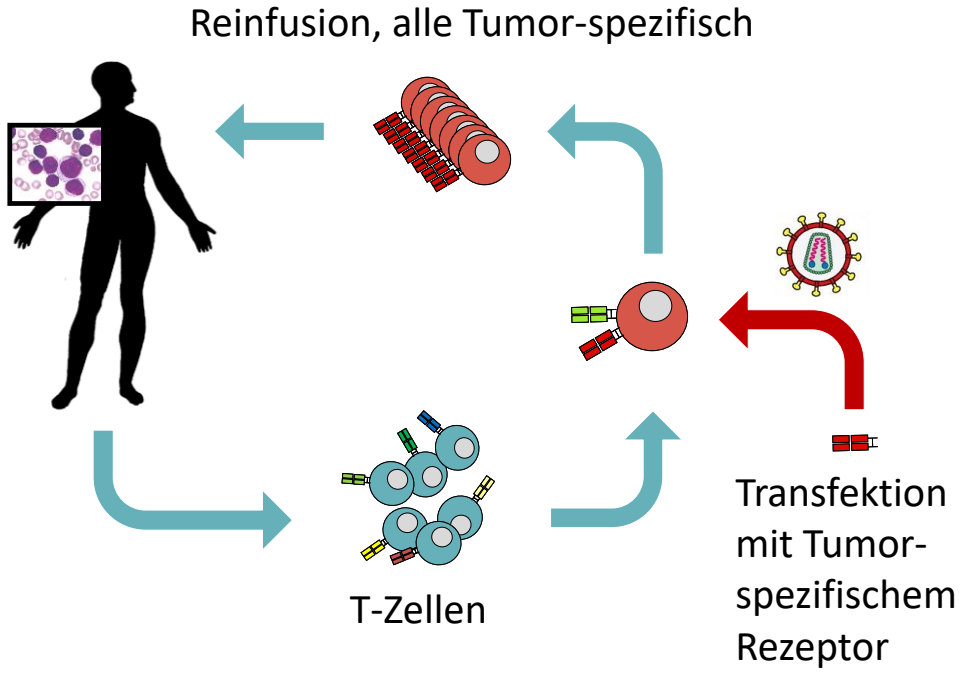




Blank, Haanen et al. Science, 2016; Yarchoan et al., NEJM, 2017

# Prädiktive Faktoren: gerichtete T-Zelltherapie



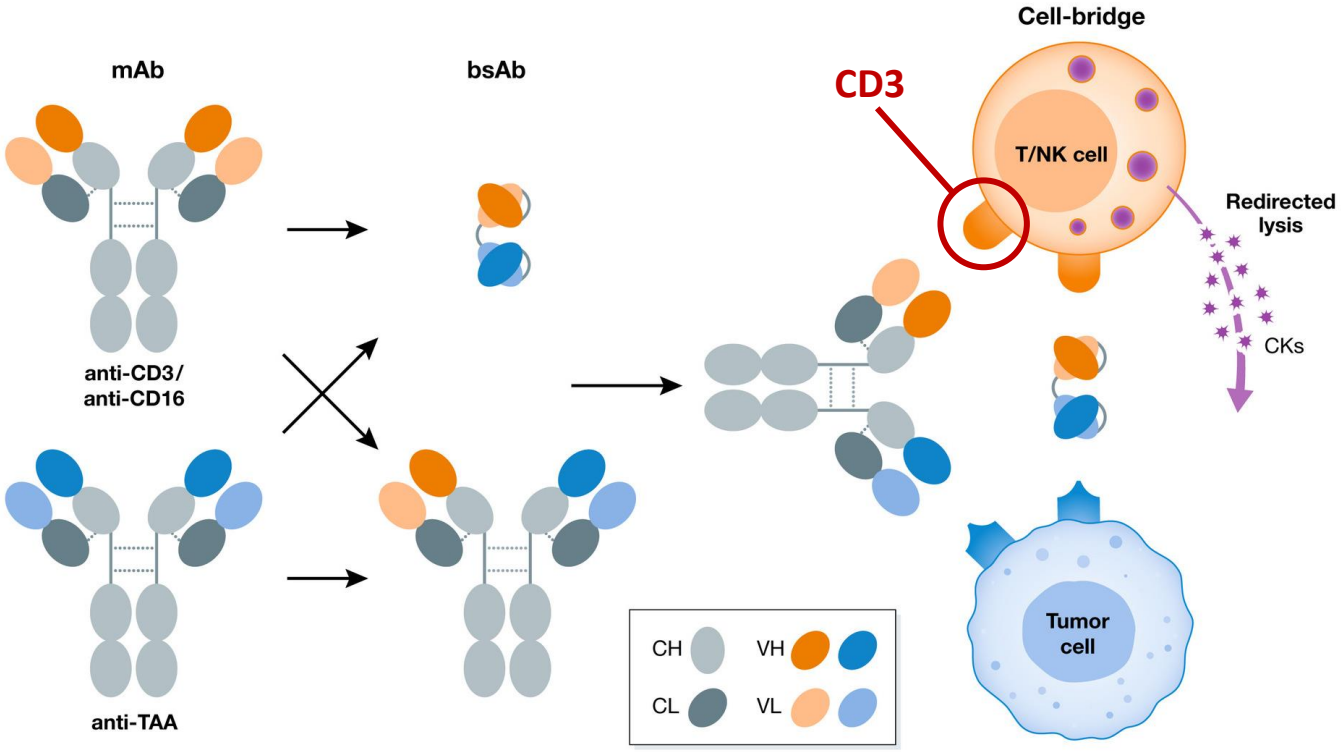

## Adoptive (gerichtete) T-Zelltherapie



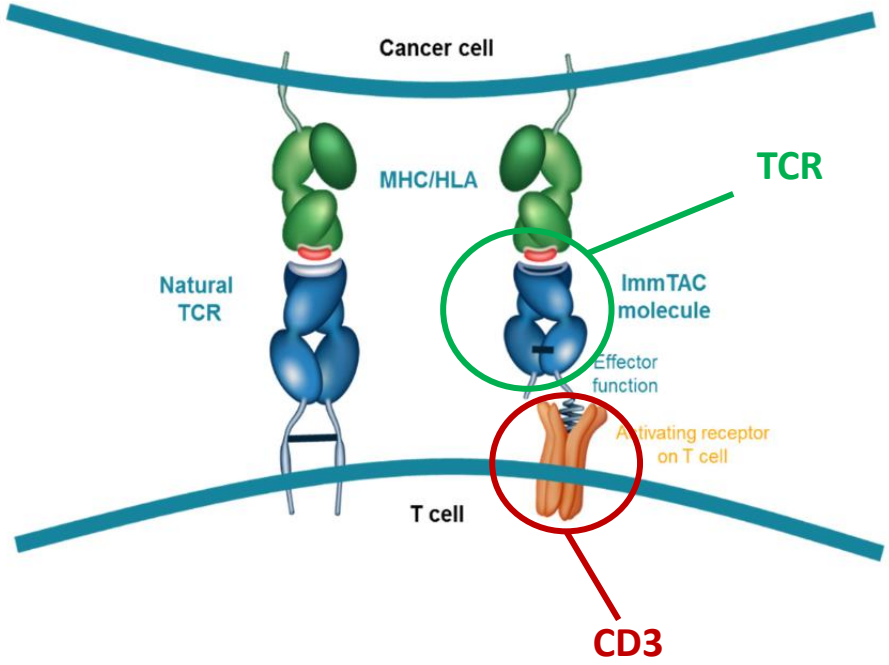

Blank, Haanen et al. Science, 2016

# *Bispecific T-cell engager*: Formate

## mAb-basiert



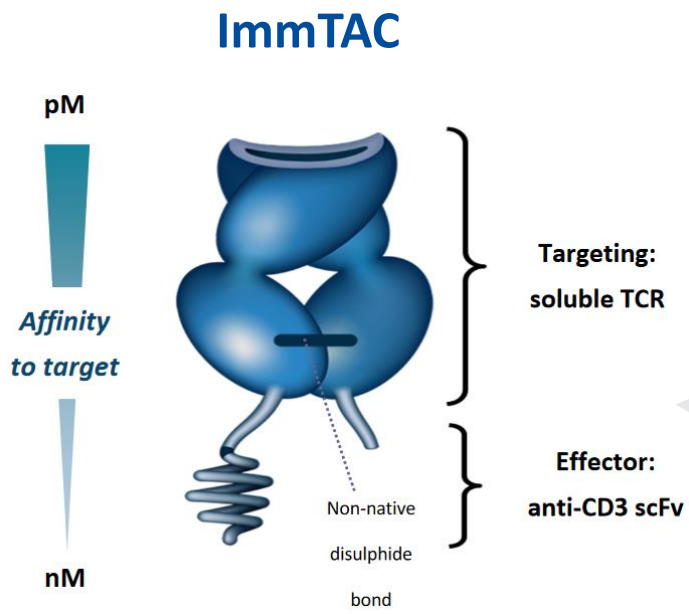

## TCR-basiert

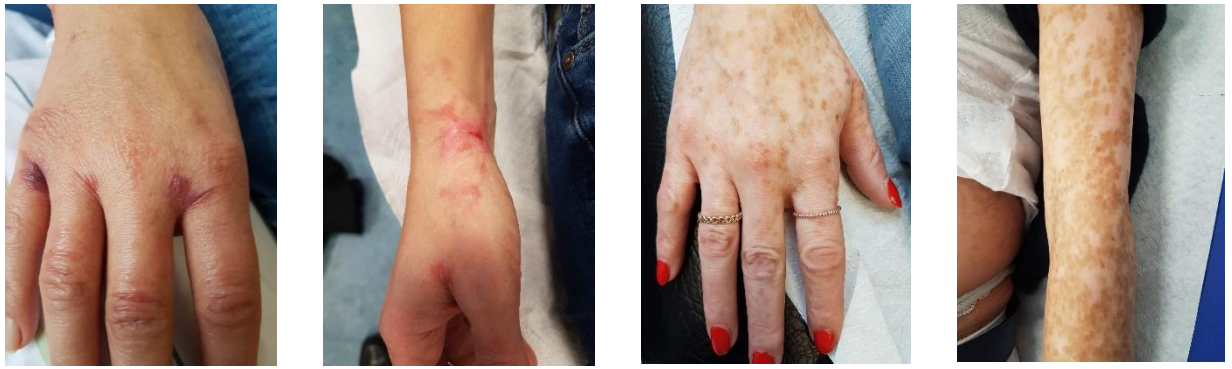





Zhang, Zhang, Wan, J, Hematol Oncol 2023

# Tebentafusp



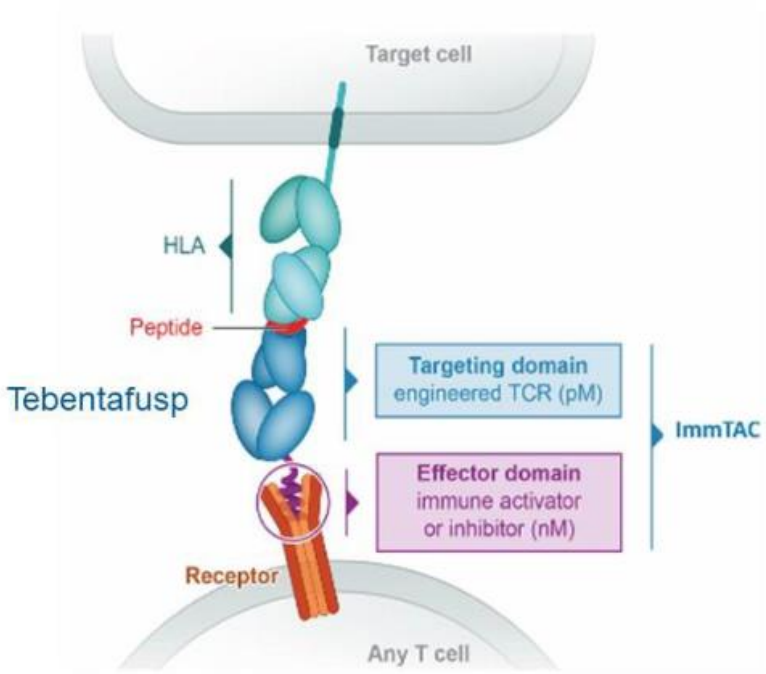
Toxizität: CRS, Dermatitis (*on target/off tumor* Toxizität)

- Bispezifischer T-Zellaktivator
- Spezifisch für gp100-Epitop im Kontext mit HLA A*02:01
- Wöchentlich Dosierung bis zum Progress



Fotos: S. Leyvraz, Charité

# Tebentafusp




## Phase 3 Study (IMCgp100-202)

**Advanced UM:**
- HLA-A*0201+
- No prior systemic therapy in the advanced setting
- No prior liver-directed therapy, except surgery
- Any LDH

Randomized 2:1

Stratification by LDH level (>ULN vs ≤ULN)

**Tebentafusp (N=252):**
- 20 mcg C1D1
- 30 mcg C1D8
- 68 mcg C1D15+

**Investigator's Choice (IC; N=126):**
- Pembrolizumab 2 mg/kg Q3W (82%)
- Ipilimumab 3 mg/kg Q3W (12%)
- Dacarbazine 1000 mg/m² Q3W (6%)

### Co-primary endpoints

- OS in randomized patients to tebentafusp vs IC treatment (ITT)
- OS in randomized patients to tebentafusp with rash during Wk 1 vs IC treatment

### Key secondary endpoints

- ORR and PFS by investigator assessment

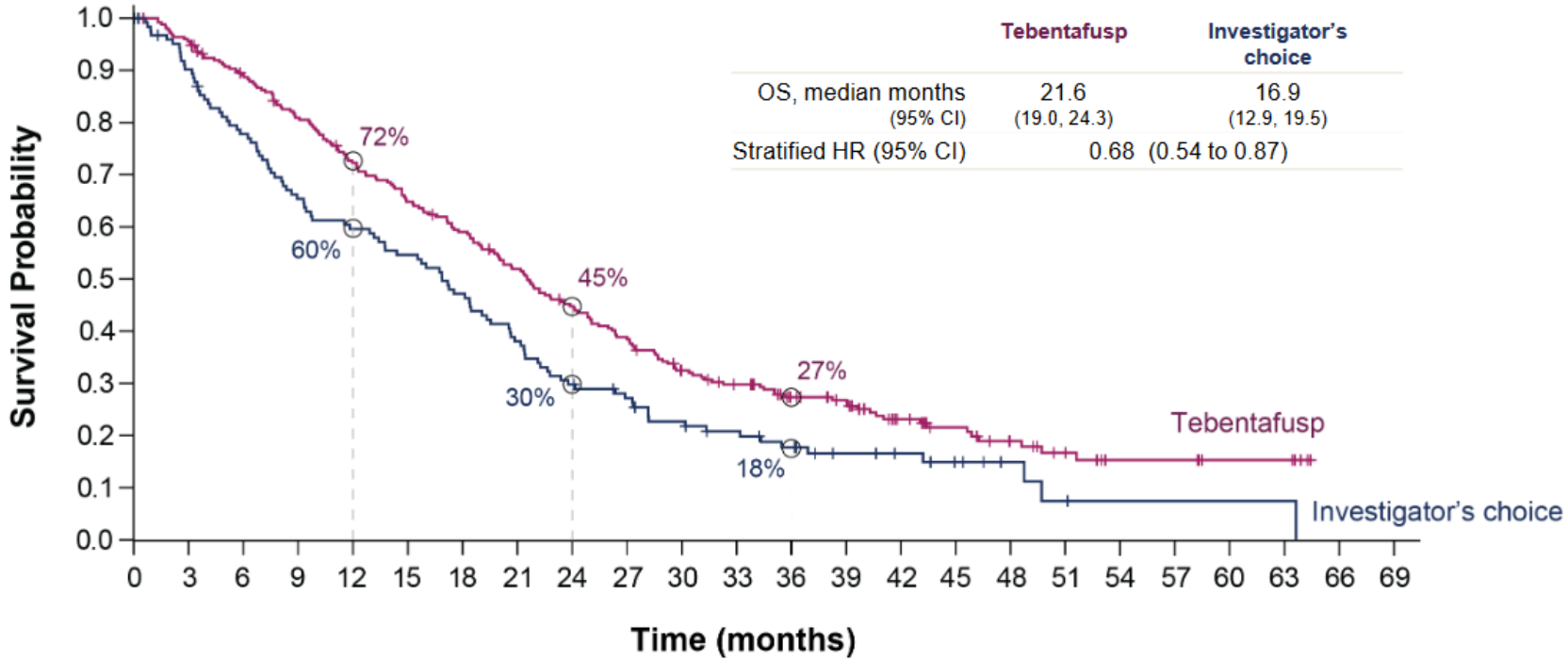


Nathan, Hassel, …, Ochsenreither, et al., NEJM 2021

# Tebentafusp

## 3-year update: OS in ITT

### OS benefit of tebentafusp vs IC maintained at 3-year follow-up, HR 0.68




| | Tebentafusp | Investigator's choice |
|---|---|---|
| OS, median months (95% CI) | 21.6 (19.0, 24.3) | 16.9 (12.9, 19.5) |
| Stratified HR (95% CI) | 0.68 (0.54 to 0.87) | |

**No. at risk**

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tebentafusp | 252 | 239 | 218 | 197 | 175 | 157 | 142 | 124 | 106 | 92 | 73 | 64 | 53 | 47 | 32 | 25 | 18 | 13 | 8 | 8 | 5 | 5 | 0 |
| IC | 126 | 110 | 94 | 79 | 72 | 66 | 57 | 46 | 36 | 31 | 25 | 21 | 17 | 12 | 10 | 7 | 4 | 2 | 1 | 1 | 1 | 1 | 0 |

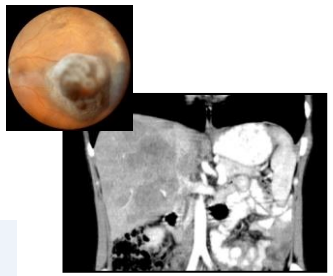


Hassel, …, Ochsenreither, et al., NEJM 2023

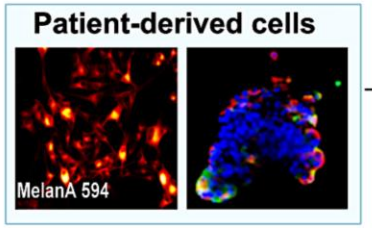
# Systemtherapie: Präzisionsonkologie

## TREAT20+: Precision oncology for uveal melanoma

Primärer Endpunkt: *feasibility*
Sekundäre Endpunkte: OS, PFS, *growth modulation index (GMI)*



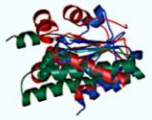
Biopsy of metastasis




**Data generation**

Next generation sequencing (WGS, exome, RNA-seq)

Methylome analysis (Illumina Human Methylation450k)

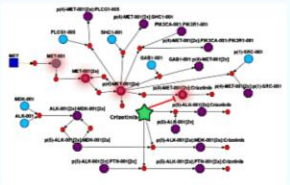


Proteome analysis (Thermo Orbitrap, Sciex 6500 QTrap Helios Fluidigm)

**Data mass storage**

**Bioinformatics data analysis**

**Prediction of drug response**



**Treatment of patient**

**Treatment recommendations**

**Precision Medicine Tumor Board**

**Clinical Managment**

ALACRIS Theranostics GmbH

Max Planck Institute for Molecular Genetics

CHARITÉ Comprehensive Cancer Center Universitätstumorzentrum

TREAT20



Leyvraz, …, Ochsenreither, et al., Eur J Cancer 2022

# Systemtherapie: Präzisionsonkologie

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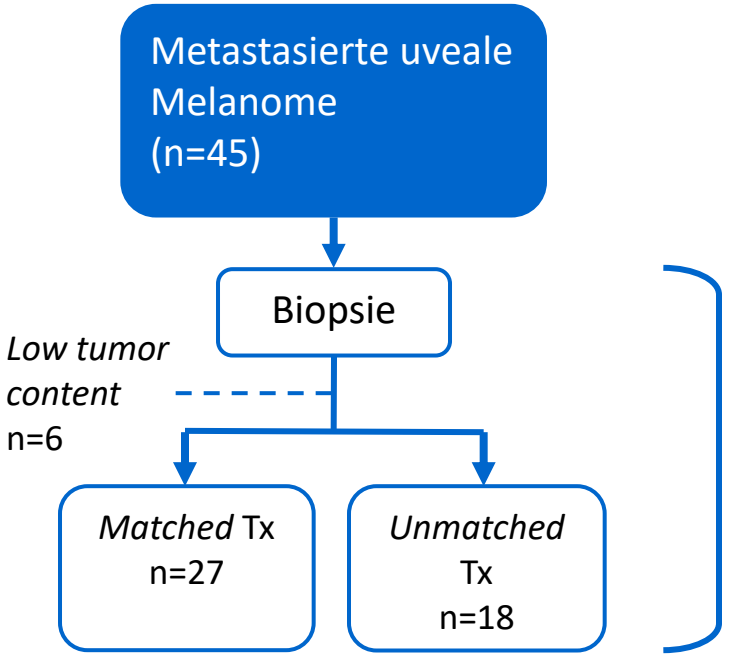
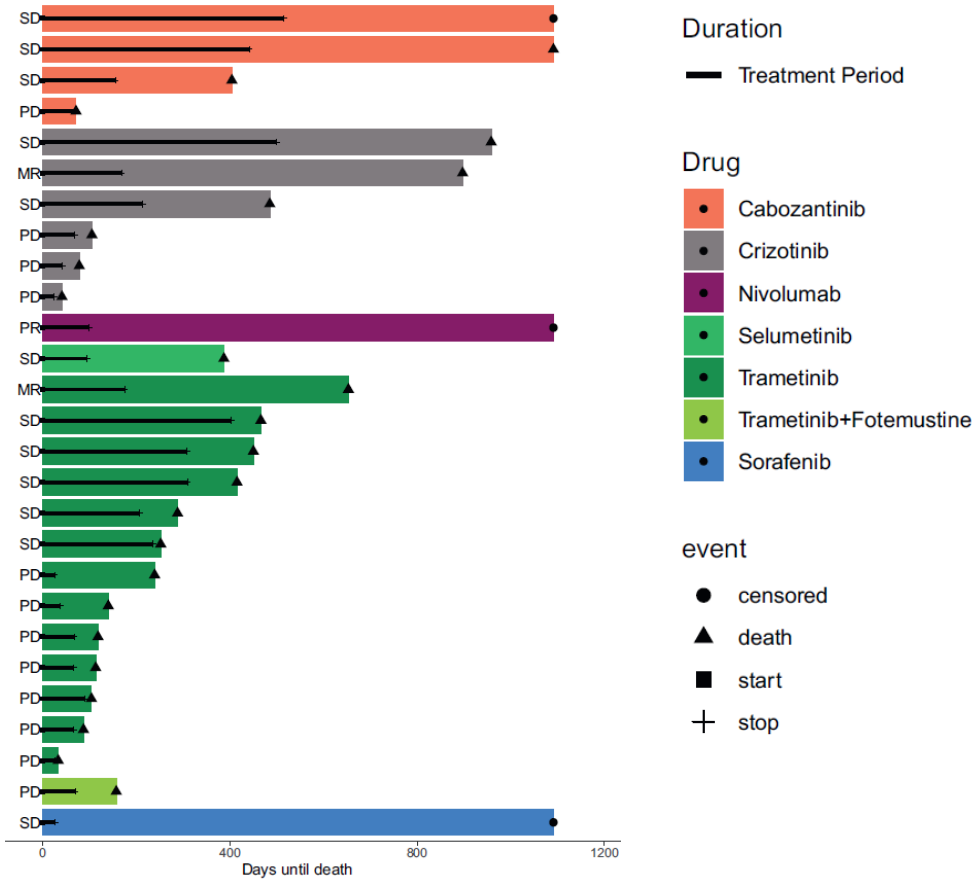



*Biopsy to Tx time*: median 58 d

→ *Feasibility*: *matched treated*: 60%

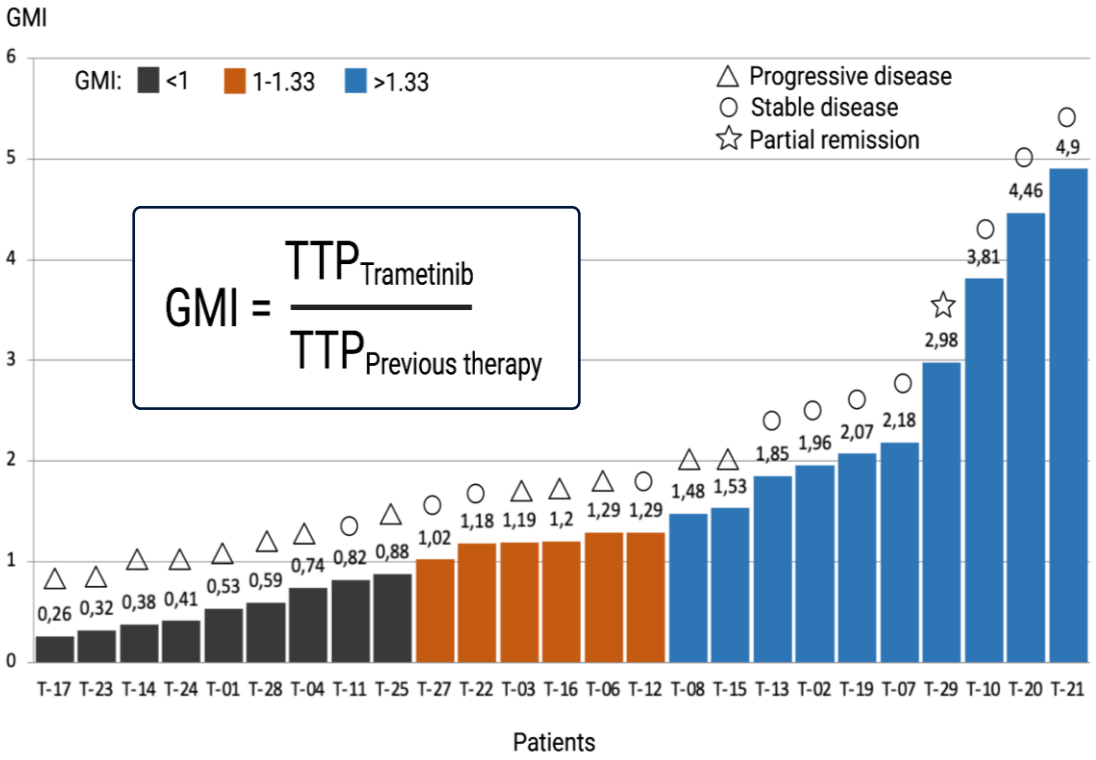
→ GMI :1,23

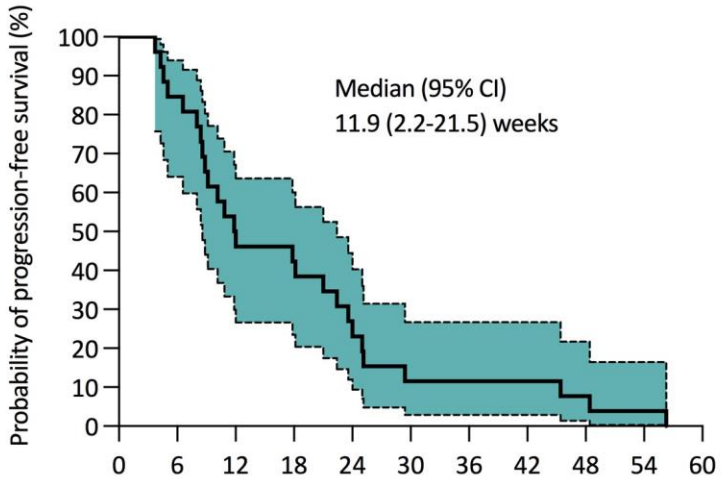


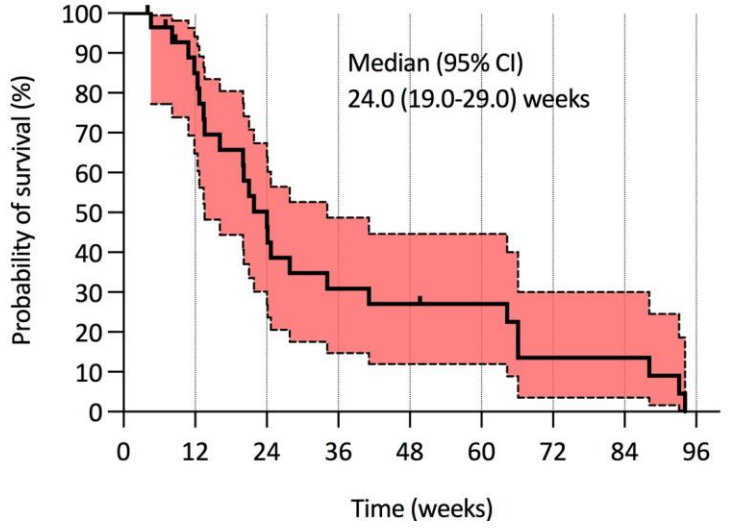

Leyvraz, …, Ochsenreither, et al., Eur J Cancer 2022

# Systemtherapie: Trametinib

Retrospektive Analyse einer unselektierten Patientenkohorte
n=29
Vortherapien median 3 (1-10)
LDH erhöht 86%, >2 x ULN 41%






Rittig, Ochsenreither, …, Peuker, DGHO 2022, *in prep*, GMI: Von Hoff DD Clin Can Res 1998

# Systemtherapie: Selumetinib

**SelPac-Studie**

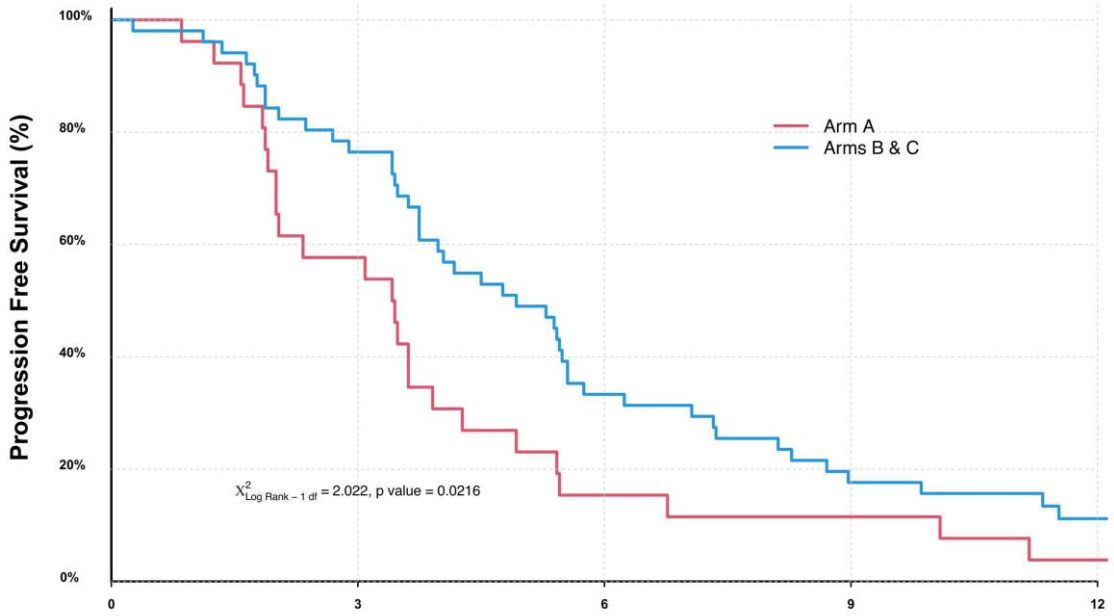
Prospektiv randomisierte Studie, n=77

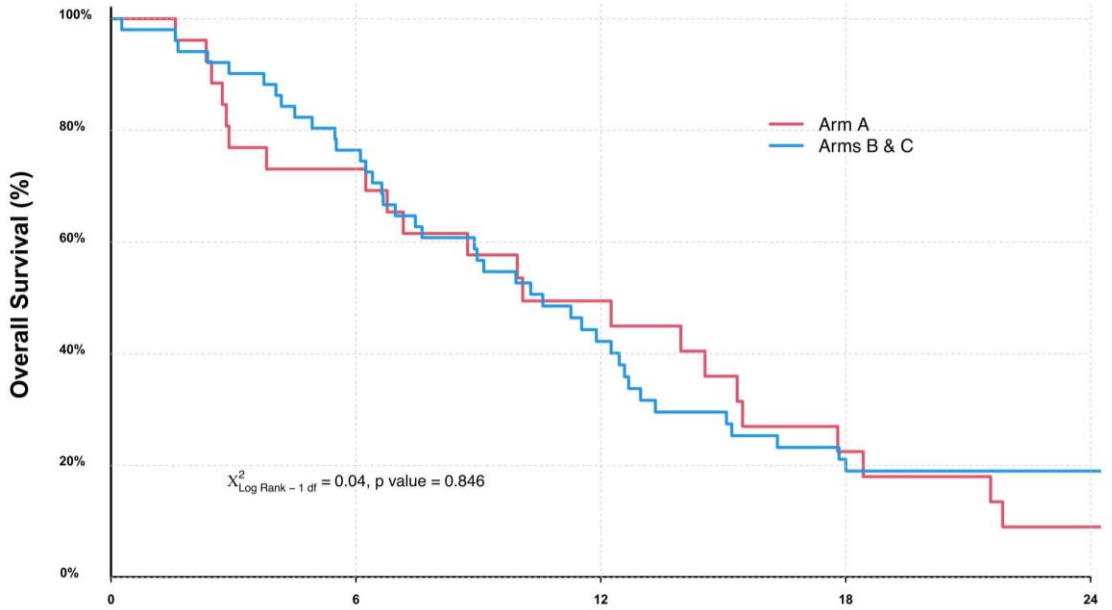
A Selumetinib cont

B Selumetinib cont. / Paclitaxel d1, 8, 15

C Selumetinib intermit. / Paclitaxel d1, 8, 15

Grad 3/4-Toxizität: 77% (Arm A), 53% (Arm B/C)

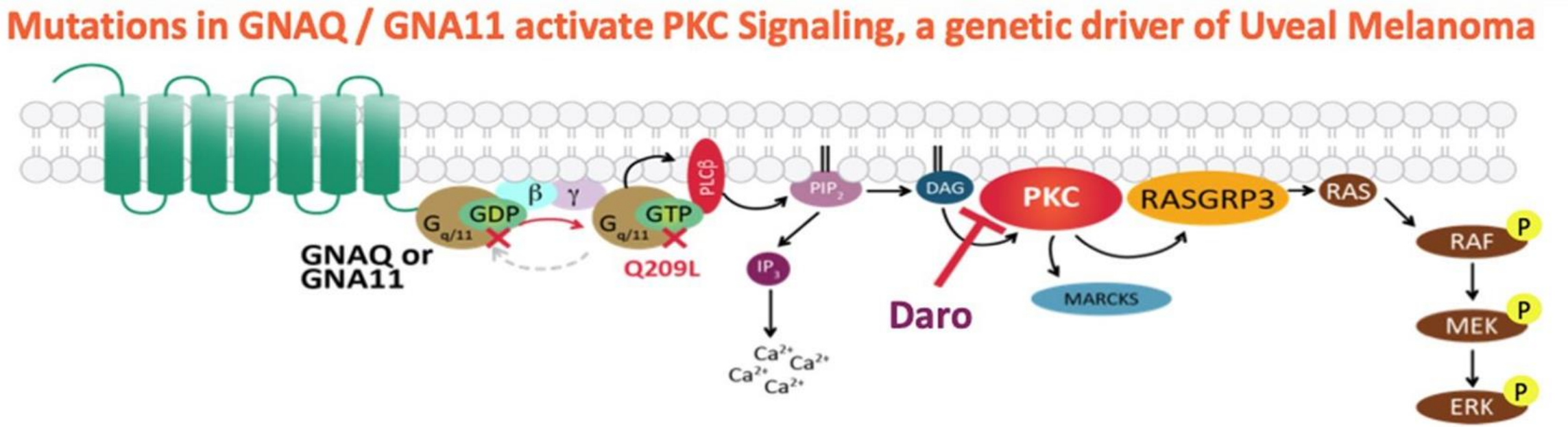



Sacco, …, Ochsenreither, et al., Eur J Cancer 2024

# Die Zukunft: präzisere molekulare Therapie

**Darovasertib:** Effektiver Protein Kinase C-Inhibitor



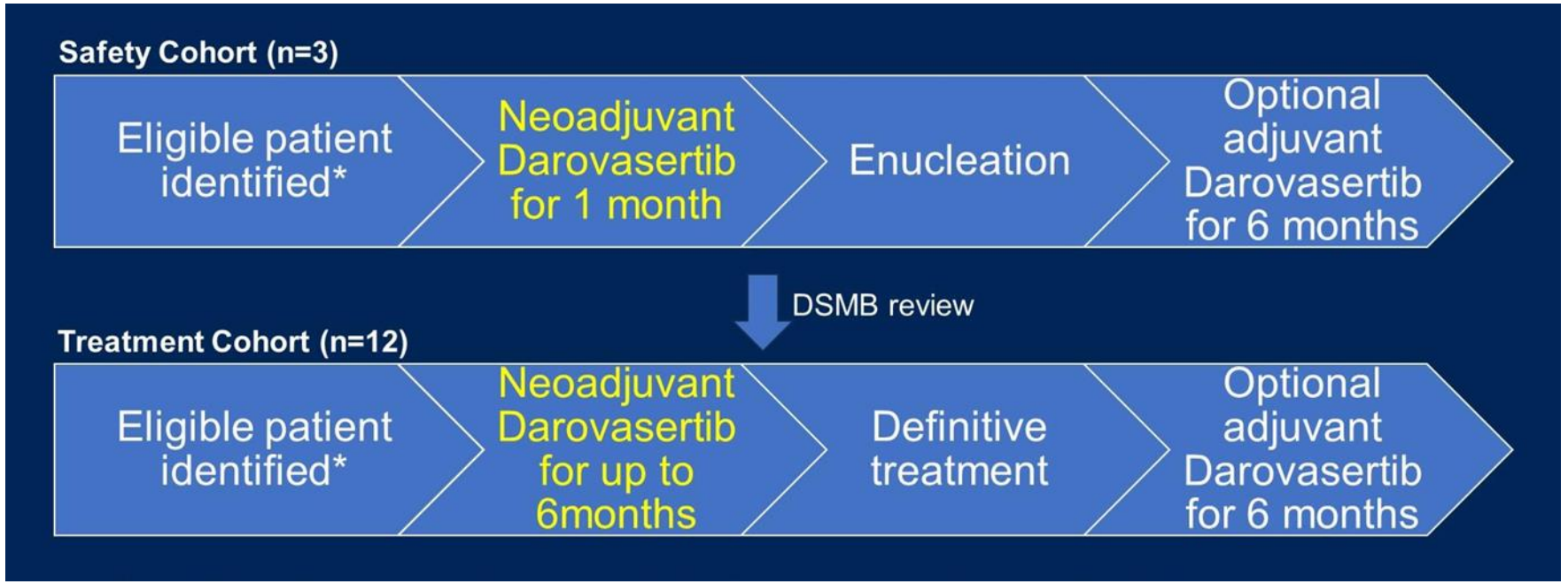



Joshua et al., ASCO 2024

# Die Zukunft: Darovasertib

**Darovasertib:** Effektiver Protein Kinase C-Inhibitor

**Phase I-Studie:** Darovasterib neoadjuvant vor/nach Brachytherapie

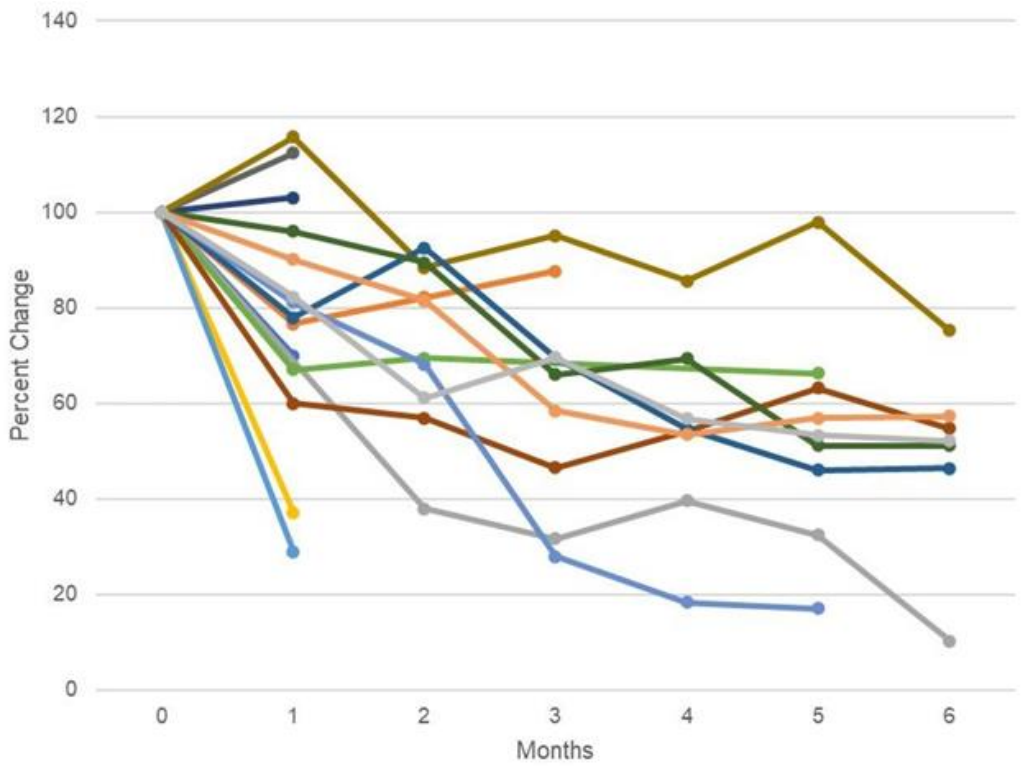




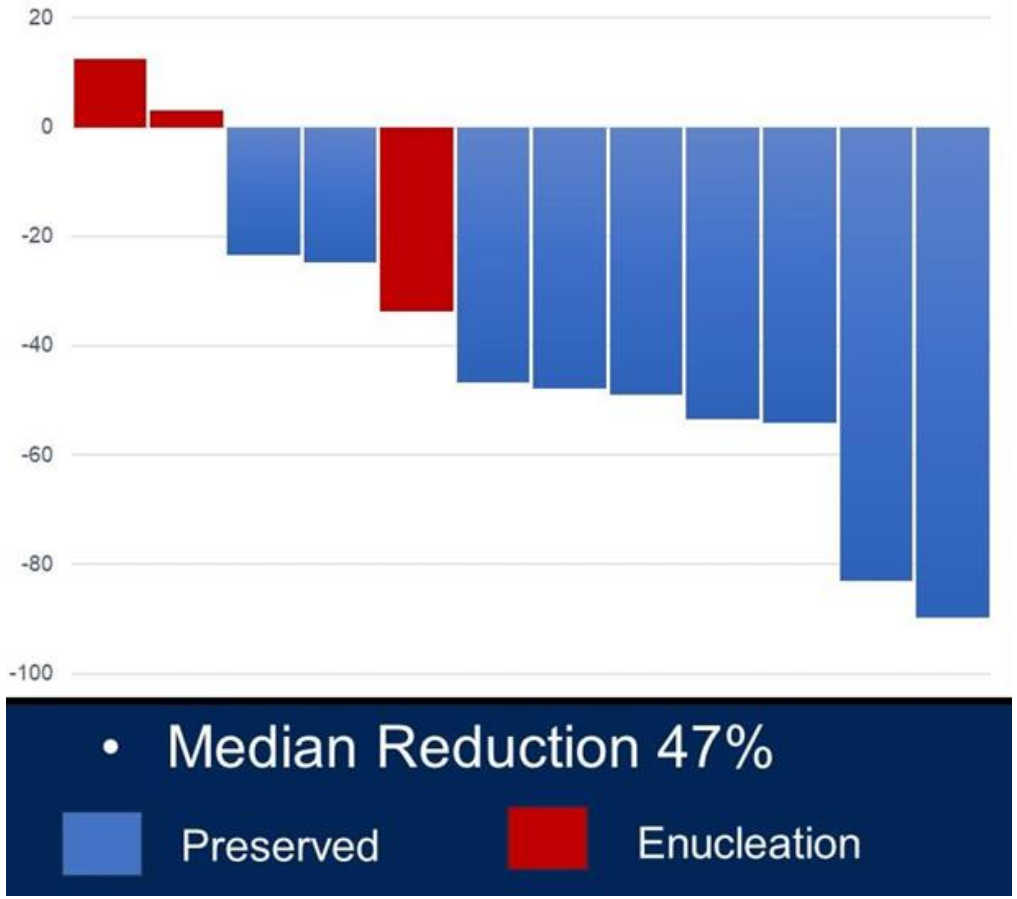

Joshua et al., ASCO 2024

# Die Zukunft: Darovasertib

Volumen-Reduktion (incl *safety cohort*) über Zeit

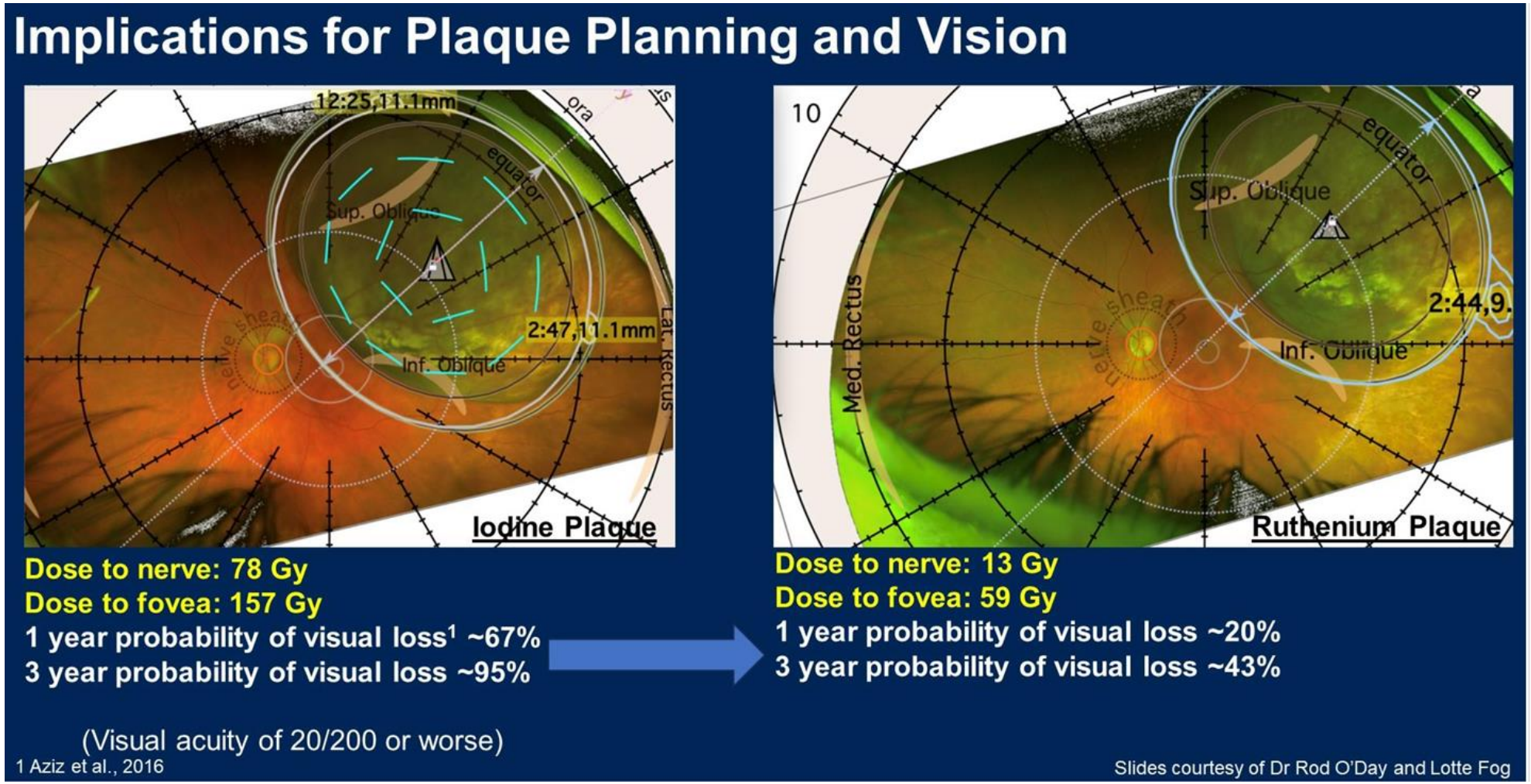



Maximales Ansprechen (Volumen)




Joshua et al., ASCO 2024

# Die Zukunft: Darovasertib




Joshua et al., ASCO 2024

# Die Zukunft: Darovasertib

**(Neo)Adjuvant IDE196 (Darovasertib) in Patients With Localized Ocular Melanoma**

Phase II, Open label
Primärer Endpunkt: Rezidivfreies Überleben

**Rekrutiert**

PI: Antonia Joussen

**IDE196 (Darovasertib) in Combination with Crizotinib As First-line Therapy in Metastatic Uveal Melanoma**

Phase II/III, Prospektiv, randomisiert gegen investigators choice
Primärer Endpunkt: PFS

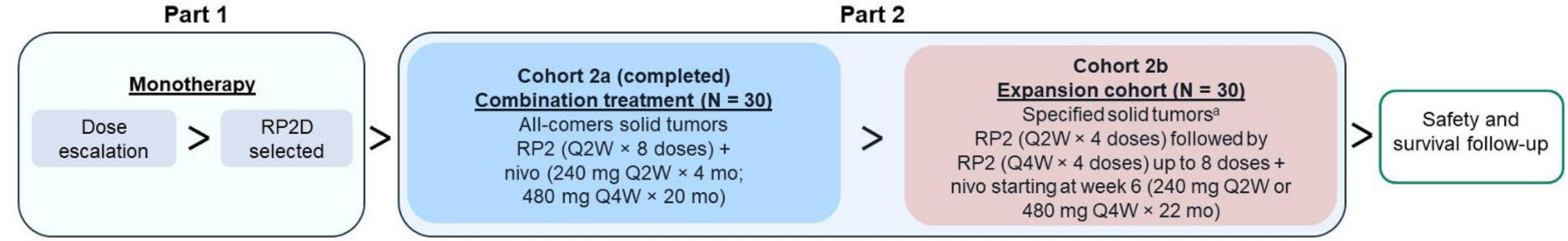
**In Vorbereitung**

PI: Caroline Peuker

# Die Zukunft: kombinierte unspezifische Immuntherapie

**Phase I-Studie**

RP2 intratumoral +/- Nivolumab




**RP2 administration**

RP2 is administered via direct intratumoral injection into:

- Superficial/subcutaneous lesions, or
- Deep/visceral lesions using image guidance (eg, ultrasound or CT)

**Key eligibility criteria**

**Inclusion**

- Age ≥18 years
- Advanced or metastatic non-neurological solid tumors **(including uveal melanoma)**
- Progressed on or cannot tolerate standard therapy
- At least 1 measurable and injectable tumor ≥1 cm
- ECOG PS 0–1

**Exclusion**

- Prior treatment with OI
- History of HBV, HCV, or HIV infection
- Active significant herpetic infections/ prior complications of HSV-1 infection
- Active CNS metastases and/or carcinomatous meningitis
- Major surgery ≤2 weeks prior to starting study drug[b]

**Key endpoints**

**Primary**

- Safety/tolerability of RP2 ± nivo (TEAEs, SAEs)
- ORR with RP2 ± nivo

**Secondary**

- DOR, CR rate, DCR, and PFS
- One- and 2-year OS

**Exploratory**

- Biomarker analyses

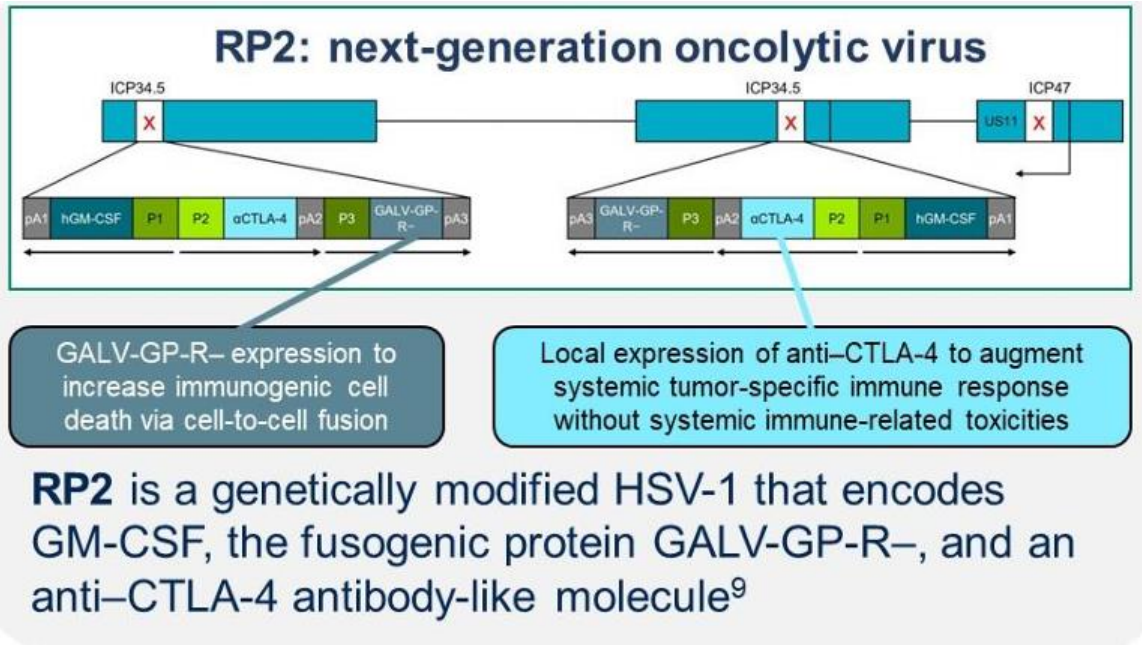


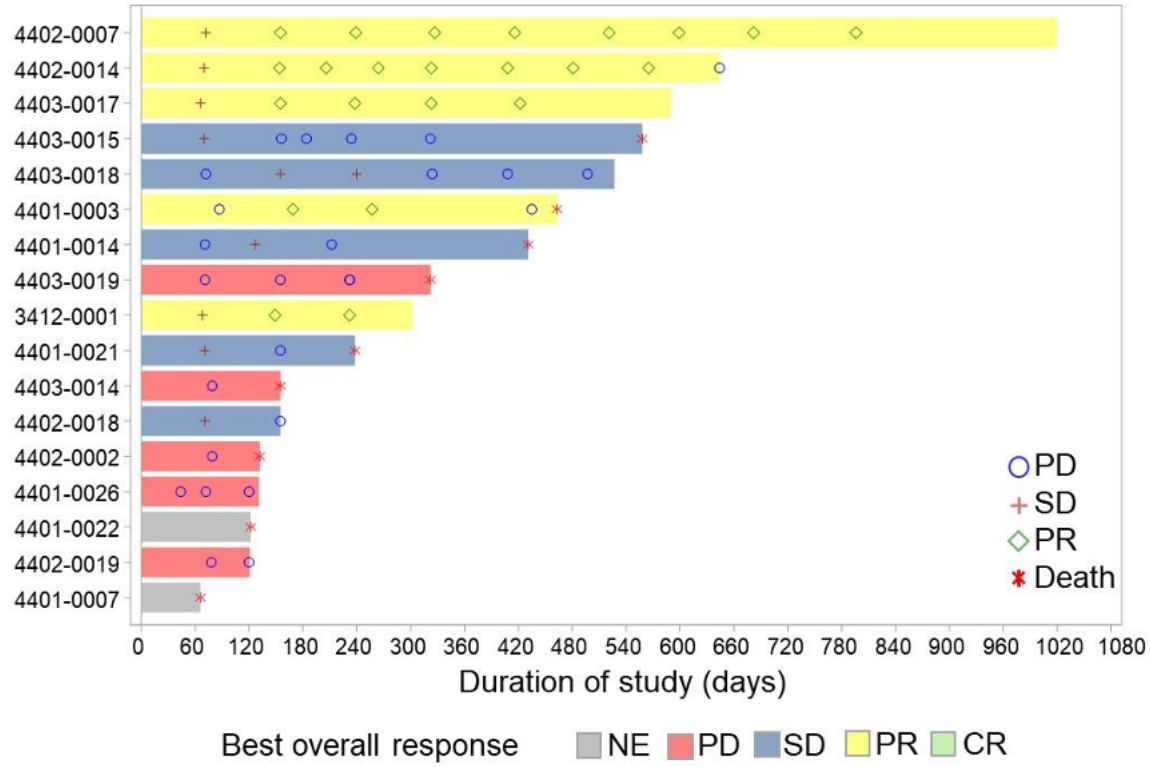
Sacco et al ASCO 2024

# Die Zukunft: kombinierte unspezifische Immuntherapie

**Phase I-Studie**
RP2 intratumoral +/- Nivolumab (3 mono, 14 kombi)

N=17 (uveale Melanome)
ORR: 29,4 %
DCR: 58,8%



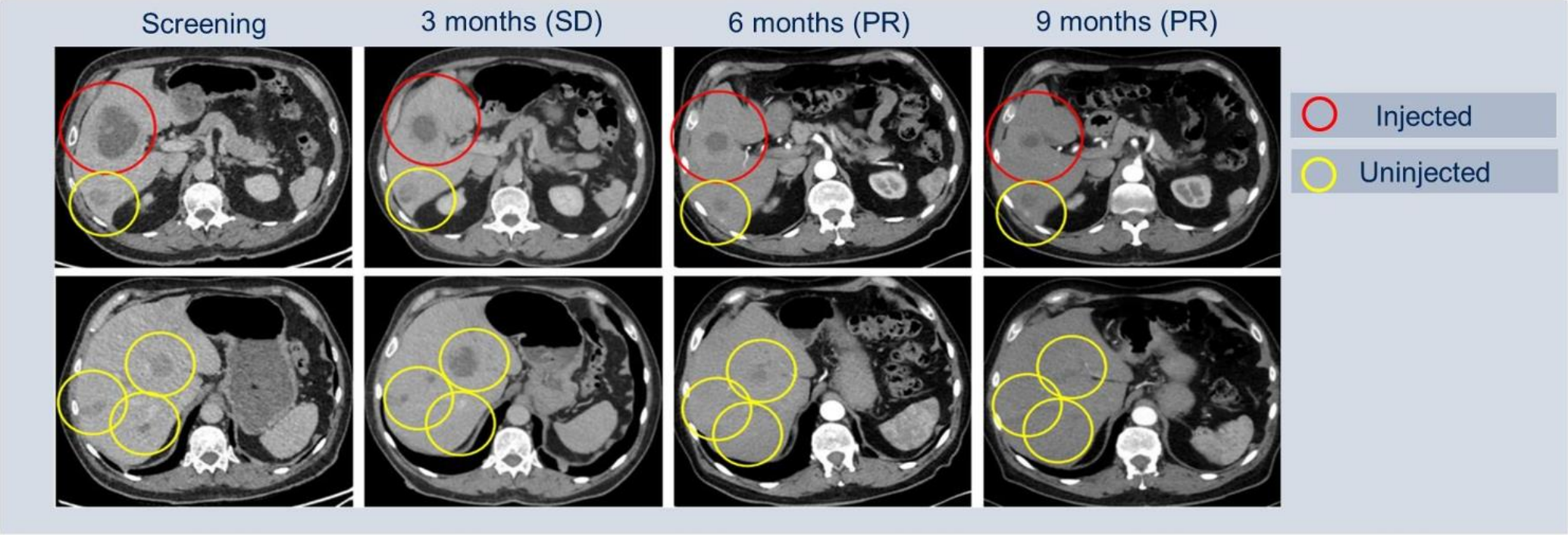




Sacco et al ASCO 2024

# Die Zukunft: kombinierte unspezifische Immuntherapie

## Results: Patient with liver metastases who progressed on prior ipilimumab and nivolumab and received RP2 monotherapy

- **Patient 4401-0003**: PR

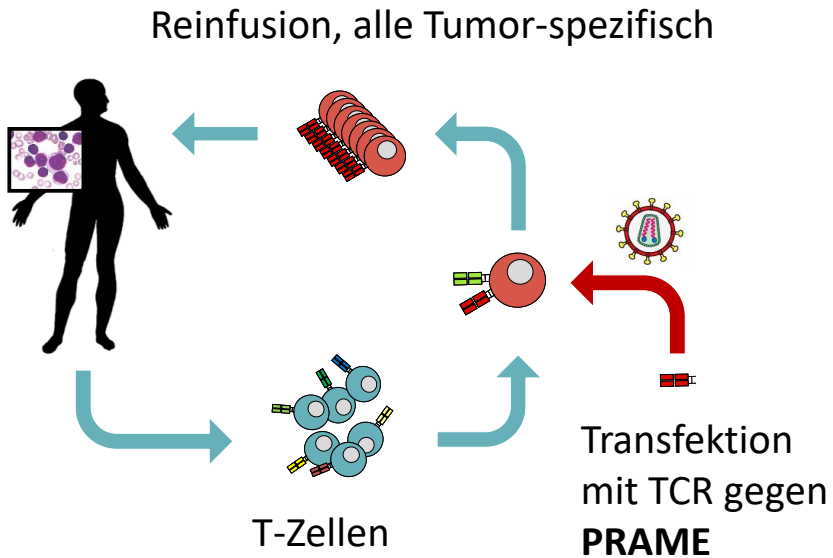


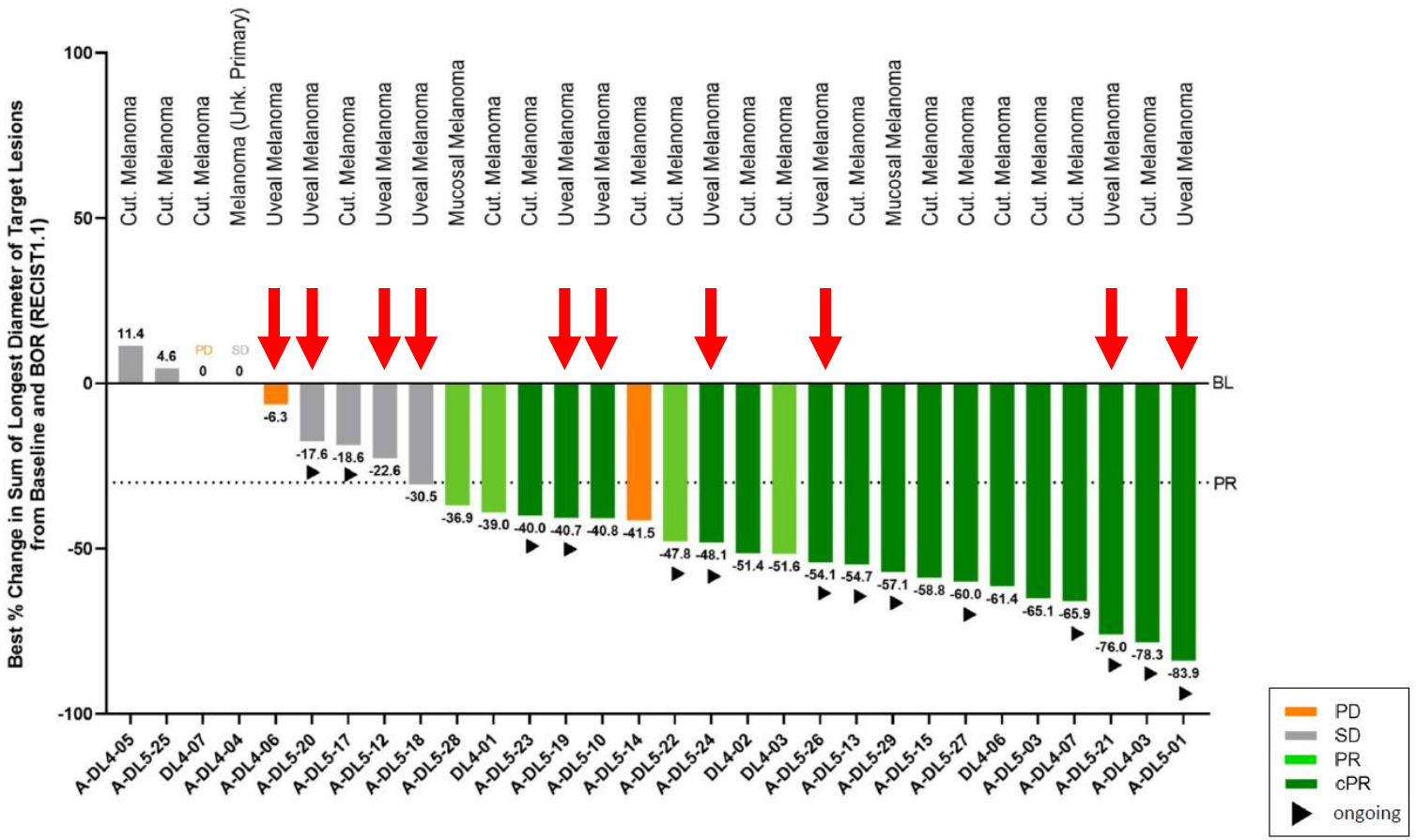



Sacco et al ASCO 2024

# Die Zukunft: gerichtete T-Zelltherapie

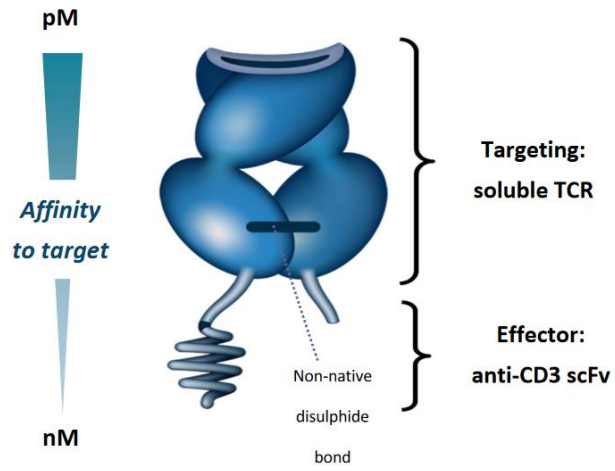
**IMA203:** Adoptive T-Zelltherapie gegen PRAME / HLA A*02:01



# Die Zukunft: gerichtete T-Zelltherapie

## Adjuvant Tebentafusp (ATOM-Trial)



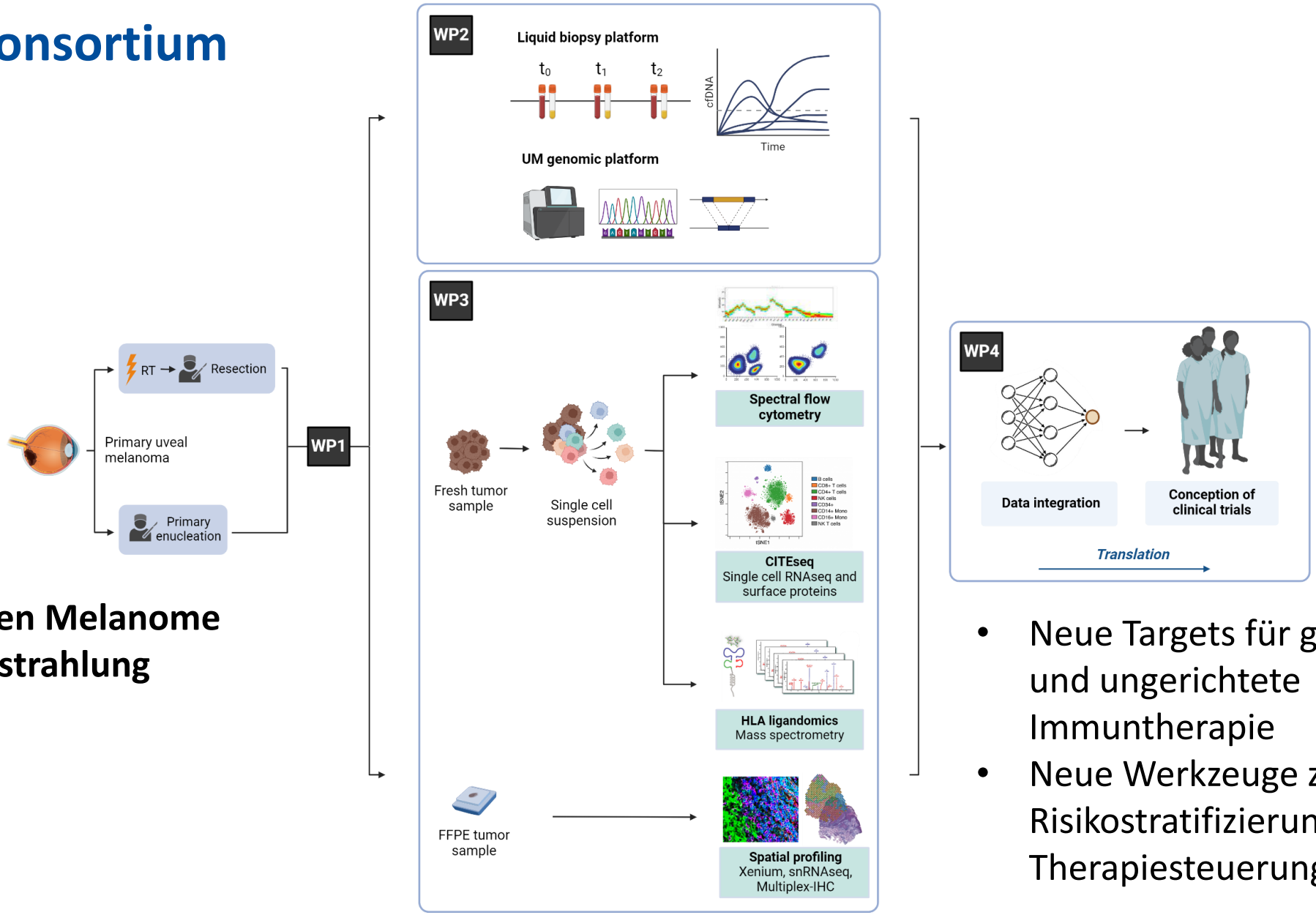

**Tebentafusp adjuvant (hoch Risiko)**

Prospektiv, randomisiert gegen w/w
Primärer Endpunkt: Rezidiv-freies Überleben

**Initiierung 11/2024**


PI: Caroline Peuker

# Decode-UM-Konsortium




**Primären uvealen Melanome**
**+/- Protonenbestrahlung**

- Neue Targets für gerichtete und ungerichtete Immuntherapie
- Neue Werkzeuge zur Risikostratifizierung und Therapiesteuerung

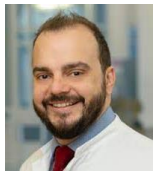
# Decode-UM-Konsortium

Human Genetics, Essen University

**Michael Zeschnigk**
UM genetics
Liquid biopsy

Ophthalmology, Essen University Hospital

**Claudia Le Guin**
Ocular oncology
Liquid biopsy

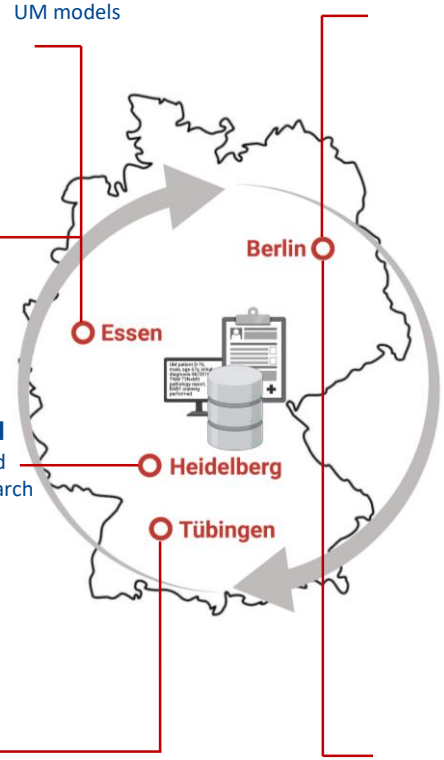


**Miltiadis Fiorentzis**
Ocular oncology
UM models

Experimental Tumor Therapy, University Essen

**Smiths Lueong**
Translational Oncology
Liquid biopsy

**Jens Siveke**
Cancer biology
Early trials
Liquid biopsy




Computational Oncology
NCT Heidelberg

**Daniel Hübschmann**
Bioinformatics
Multi-omics integration

Translational Oncology
NCT Heidelberg

**Stefan Fröhling**
Cancer Multi-omics
Precision oncology

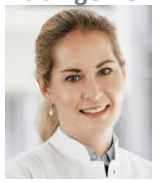
Dermatooncology
NCT Heidelberg

**Jessica Hassel**
Translational and clinical UM research

Translational Immunology
Tübingen University

**Hemut Salih**
Development of novel immunotherapeutics

Peptid-based Immunotherapy
Tübingen University



**Juliane Walz**
Mass spectrometric-based immunopeptidomics

Hematology, Oncology and Cancer Immunology, Charité Berlin

**Ulrich Keller**
**Consortium coordinator**
Biomarker-informed therapies
Adoptive T-cell therapies

**Caroline Peuker**
UM IIT trials,
Tumor immunology

**Sebastian Ochsenreither**
Cancer immunotherapy
Early clinical trials

Radiooncology, Charité Berlin
Helmholtz-Zentrum Berlin

**Johannes Gollrad**
Ocular radiation oncology

Ophthalmology, Charité Berlin

**Antonia Joussen**
Ocular oncology
Angiogenesis and inflammation

Single-cell omics
Charité Berlin, MDC and BIH

**Simon Haas**
Single-cell and spatial technologies
Systems immunology

Pathology
Charité Berlin

**Stefan Florian**
Multiplexed tissue imaging
Biomarker discovery

# BERLIN UVEAMELANOM SYMPOSIUM

**8. NOVEMBER 2024**
**10:00 - 19:00 UHR**

**HARNACK-HAUS DER MAX-PLANCK-GESELLSCHAFT, BERLIN**

VERANSTALTER

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM | DKTK Deutsches Konsortium für Translationale Krebsforschung

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14195 BERLIN

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Ophthalmo-Oncology WorkingGroup

***Hematology, Oncology and Tumor Immunology***

***Comprehensive Cancer Center***.

# Herzlichen Dank!


Sebastian Ochsenreither


Caroline Peuker


Susanne Rittig


Serge Leyvraz


Ulrich Keilholz


Maximilian de Bucourt


Holger Amthauer

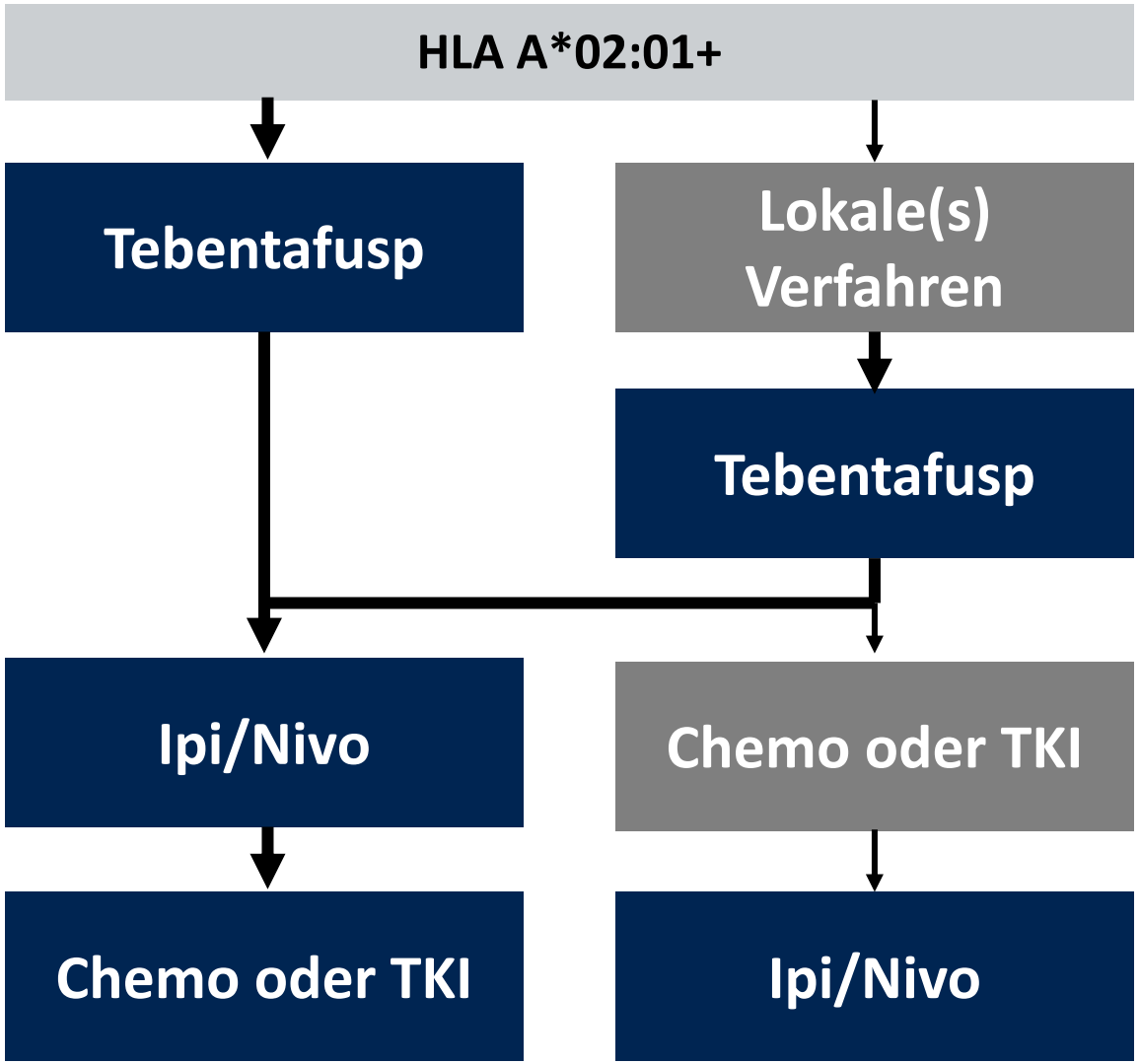

Bernhard Gebauer

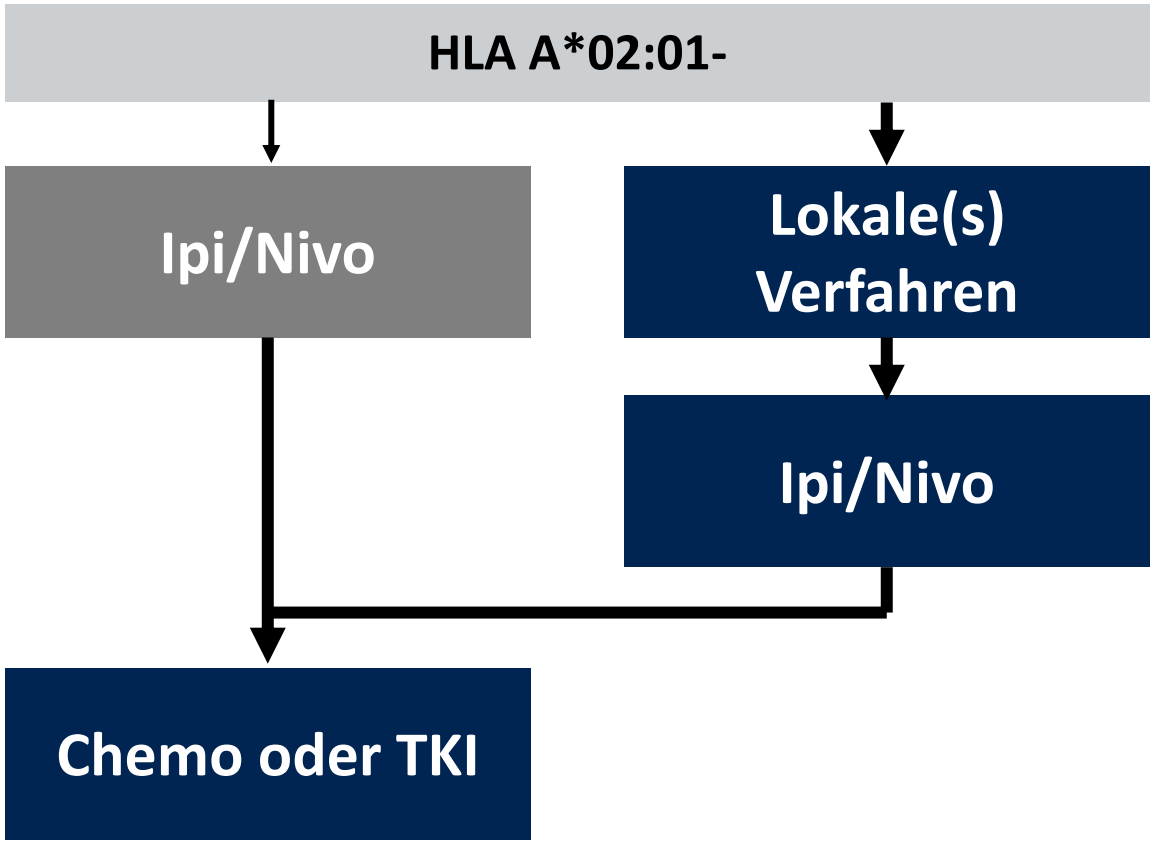

Kai Lehmann


Johannes Gollrad


Antonia Joussen

# Therapiealgorithmus (Vorschlag)




Studienoptionen immer präferieren (jede Linie)
Z. B. IMA-203 (PRAME-spezifische ACT, HLA A*02:01-restringiert)