Tumorale Heterogenität – SATURN-3

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Philipps Universität Marburg

2.- 3. März 2023

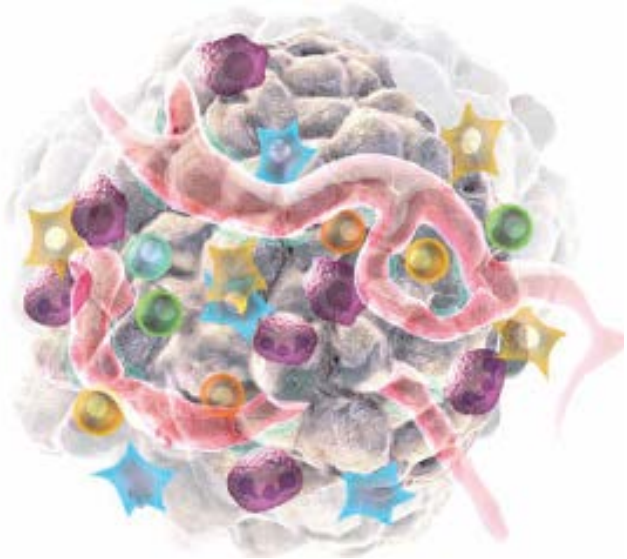
GBG Jahrestreffen

20 YEARS ANNIVERSARY

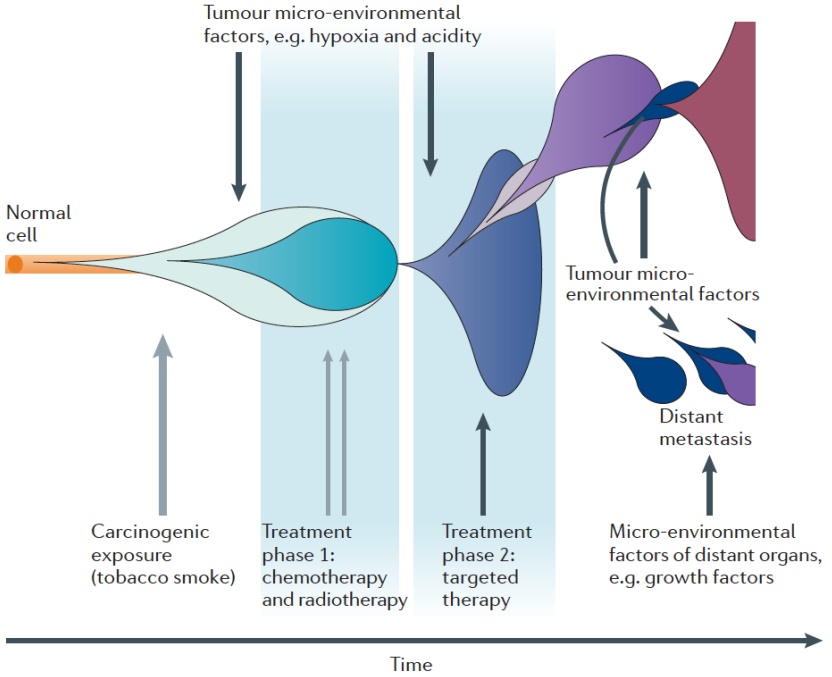
Conflict of Interest

- Advisory board, honoraria: Teva, Novartis, Molecular Health, Pfizer, Roche, Amgen, MSD, Daiichi Sankyo, Astra Zeneca
- Licensing fees: VMscope digital pathology software
- Research funding: Myriad

Heterogenität von Tumoren als Herausforderung für die Therapie



räumlich



zeitlich

Hanahan Cancer Disc 2022

Yates Campbell, Nature Reviews Genetics 2012

Spatial and Temporal Intratumoral Heterogeneity in 3 hard-to-treat Cancers

Koordinatoren

Jens Siveke, University Hospital Essen
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Gesamtbudget: 18 Mio Euro
Antragstellung seit 2020

Clinical therapeutic

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DKFZ, Heidelberg
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DKFZ, Heidelberg
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Mechanisms

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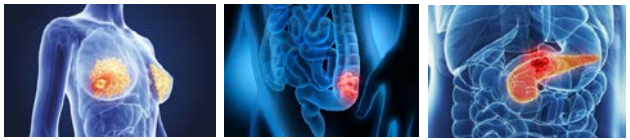
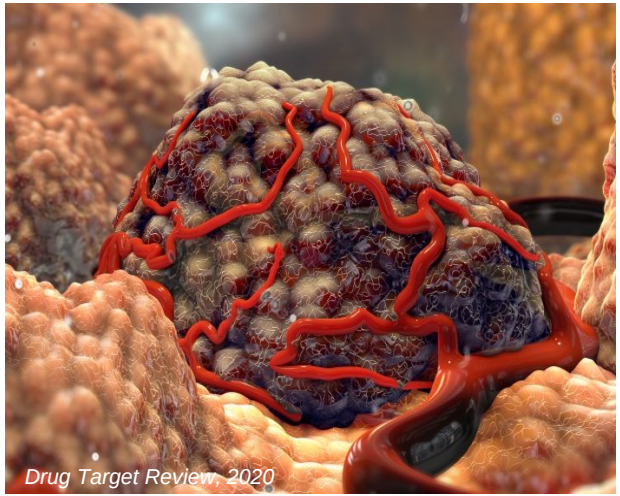
DKFZ, Heidelberg

Rationale



Hard - To - Treat SATURN³ Cancers



Challenge

Therapy Resistance and **Metastasis** remain the major problems in cancer treatment.

Major clinical need:

- Breast Cancer (Luminal B, Triple Negative)
- Colorectal cancer (CRC, non-MSI)
- Pancreatic cancer (PDAC)

Resistance to: radiotherapy, chemotherapy, targeted concepts (if available) and immune-checkpoint blockade

Problem: Intra-tumour heterogeneity (ITH):

→ Interplay of cellular, genetic and epigenetic processes that change dynamically during disease progression, metastasis, and therapy pressure.

Das dieser Präsentation zugrunde liegende Vorhaben wurde mit Mitteln des Bundesministeriums für Bildung und Forschung unter dem Förderkennzeichen 01KD2206M gefördert.
Die Verantwortung für den Inhalt dieser Veröffentlichung liegt bei der Autorin/beim Autor.

SATURN³

NATIONALE DEKADE GEGEN KREBS

SERIAL MULTI-REGION SAMPLING

Therapies: CTx, RTx, ICI, PARPi, CDK4/6i, VEGFRi; EGFRi

SP1

SP2

SP3

Postmortem Biopsy Program

BIOMATERIAL

SP1 SP2 SP3

Primary (single) cells (vital frozen)

Liquid Biopsies

Organoids (surgical, biopsies, CTCs)

Cohorts

SC-OMICS & BIOINFORMATICS

SP4

Transcriptome
ScRNA-seq, snRNA-seq

Chromatin activity
ScRNA-seq, snRNA-seq

Genome
targeted scDNA-seq

Cell surface markers
CITE-seq

T cell receptor
TCR-seq

Spatial „omics"
transcriptome & histology

Liquid biopsy
cell-free DNA/RNA, CTC

SP5

Cell subtypes

Gene regulation

Tumor subclones

Environment & immune repertoire

Cell-cell interactions

Clonal evolution

MECHANISMS

SP6

Cell type plasticity

Reprogramming of microenvironment

Immune escape

Metastasis

TRANSLATION

SP7

NOVEL ITH BIOMARKERS

- Validation in multiple trial cohorts
- Cross entity evaluation
- Response and ITH monitoring
- Biomarkers

NOVEL THERAPEUTIC STRATEGIES

- Novel treatment schemes
- Targeting of ITH
- Clinical trial protocols for each entity

SP8 SAMPLE & DATA MANAGEMENT

Heterogenität von Tumoren – klinische und translationale Studien

- **intertumorale Heterogenität**
  - verschiedene Tumor-Subtypen
  - Tumoren verhalten sich unterschiedlich

Klinische Strategie

- **Subtypen-spezifische klinische Studien**
- **ausreichend große klinische Studienkohorten**

- **zeitliche intratumorale Heterogenität**
  - Tumoren verändern sich unter der Therapie

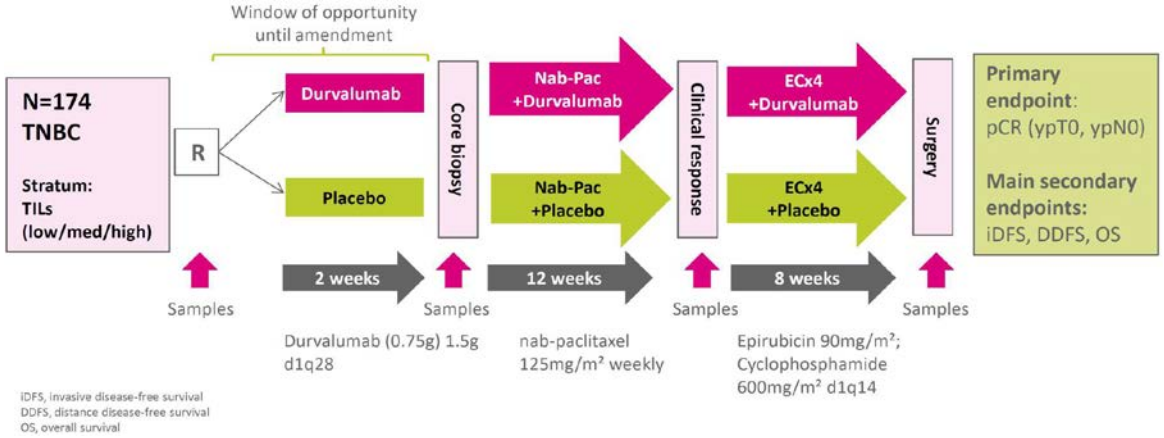
- **Vergleich von Tumorproben im Verlauf**
- **liquid biopsies**

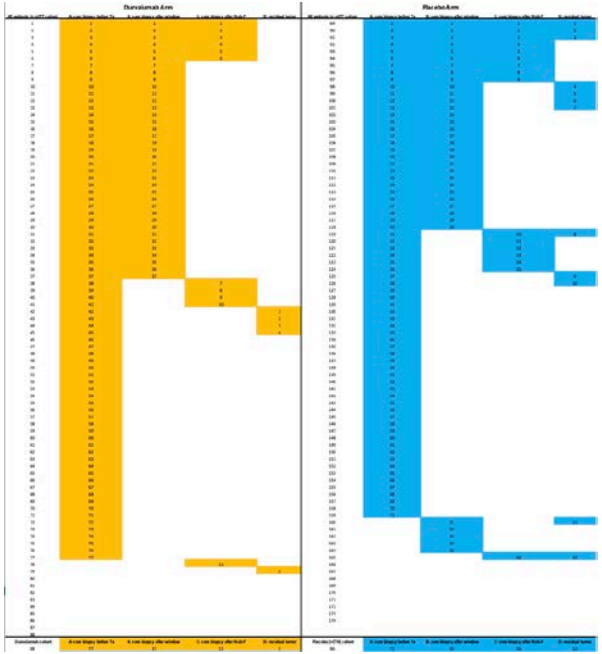
- **räumliche intratumorale Heterogenität**
  Tumoren bestehen aus verschiedenen Zelltypen
  - Immunzellen; Bindegewebszellen; Tumorzellen

- **Analyse von verschiedenen Zelltypen**
- **Analyse von verschiedenen Regionen im Tumor**

GeparNuevo neoadjuvant trial – longitudinal gene expression

Durvalumab cohort	**A: core biopsy before Tx**	**B: core biopsy after window**	**C: core biopsy after Nab-P**	**D: residual tumor**
88	77	37	11	5
Placebo (=CTX) cohort	**A: core biopsy before Tx**	**B: core biopsy after window**	**C: core biopsy after Nab-P**	**D: residual tumor**
86	71	35	16	12





45% two paired samples
10% three longitudinal samples
0.6% four longitudinal samples

GeparNuevo neoadjuvant trial

Durvalumab cohort	**A: core biopsy before Tx**	**B: core biopsy after window**	**C: core biopsy after Nab-P**	**D: residual tumor**
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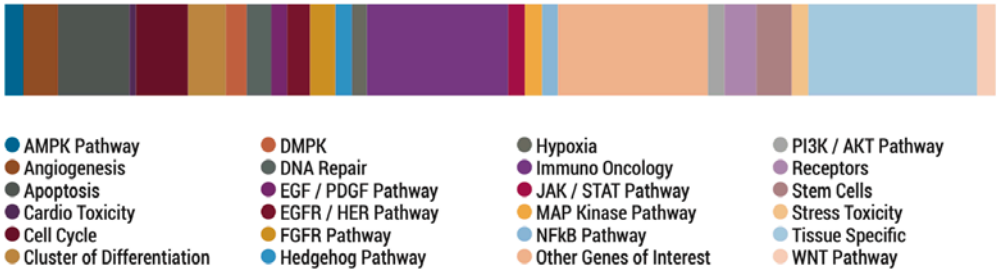

- HTG oncology biomarker panel (2449 genes) – linked to 24 pathways

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FFPE samples analyzed in Marburg:

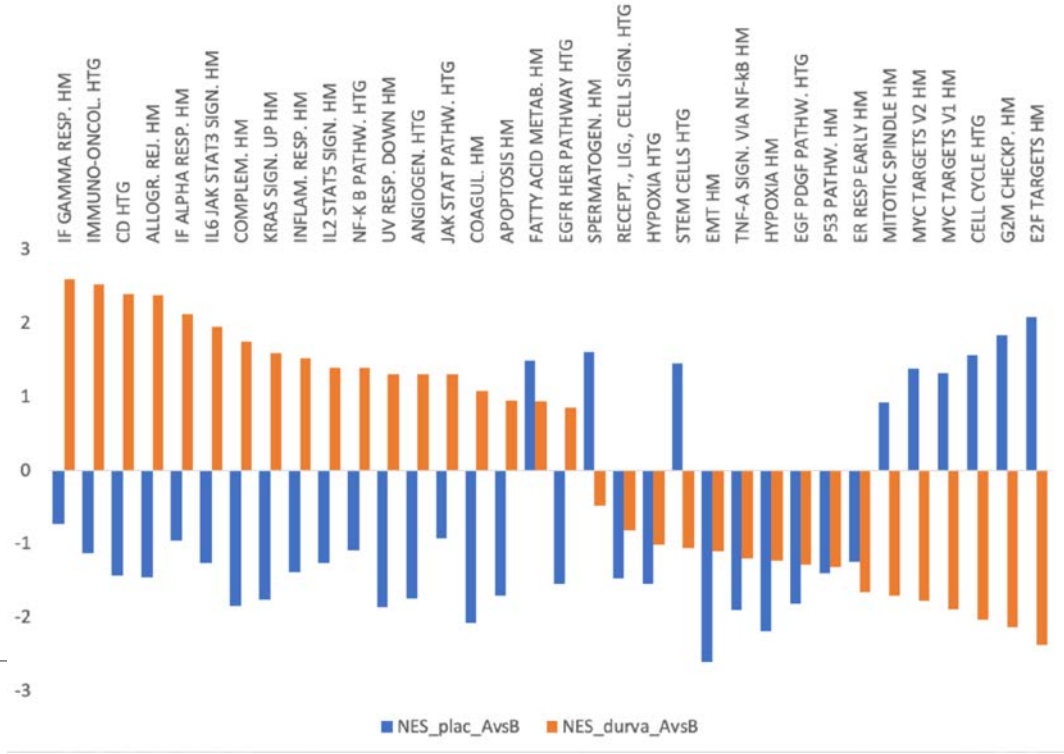
GBG GeparNuevo: 264 samples
GBG Penelope: 1700 samples
GBG GeparDouze: 470 samples
Pancreatic cancer: 200 samples

GeparNuevo trial – alterations induced by durvalumab alone

Durvalumab cohort 88	**A: core biopsy before Tx** 77	**B: core biopsy after window** 37
Placebo (=CTX) cohort 86	**A: core biopsy before Tx** 71	**B: core biopsy after window** 35

window duration: 2 weeks
= one dose of durvalumab (no CTX)
compared to placebo (just the biopsy)

IF GAMMA RESP. HM
IMMUNO-ONCOL. HTG
CD HTG
ALLOGR. REJ. HM
IF ALPHA RESP. HM
IL6 JAK STAT3 SIGN. HM
COMPLEM. HM
KRAS SIGN. UP HM
INFLAM. RESP. HM



MITOTIC SPINDLE HM
MYC TARGETS V2 HM
MYC TARGETS V1 HM
CELL CYCLE HTG
G2M CHECKP. HM
E2F TARGETS HM

GeparNuevo trial – durvalumab/CTX vs CTX alone

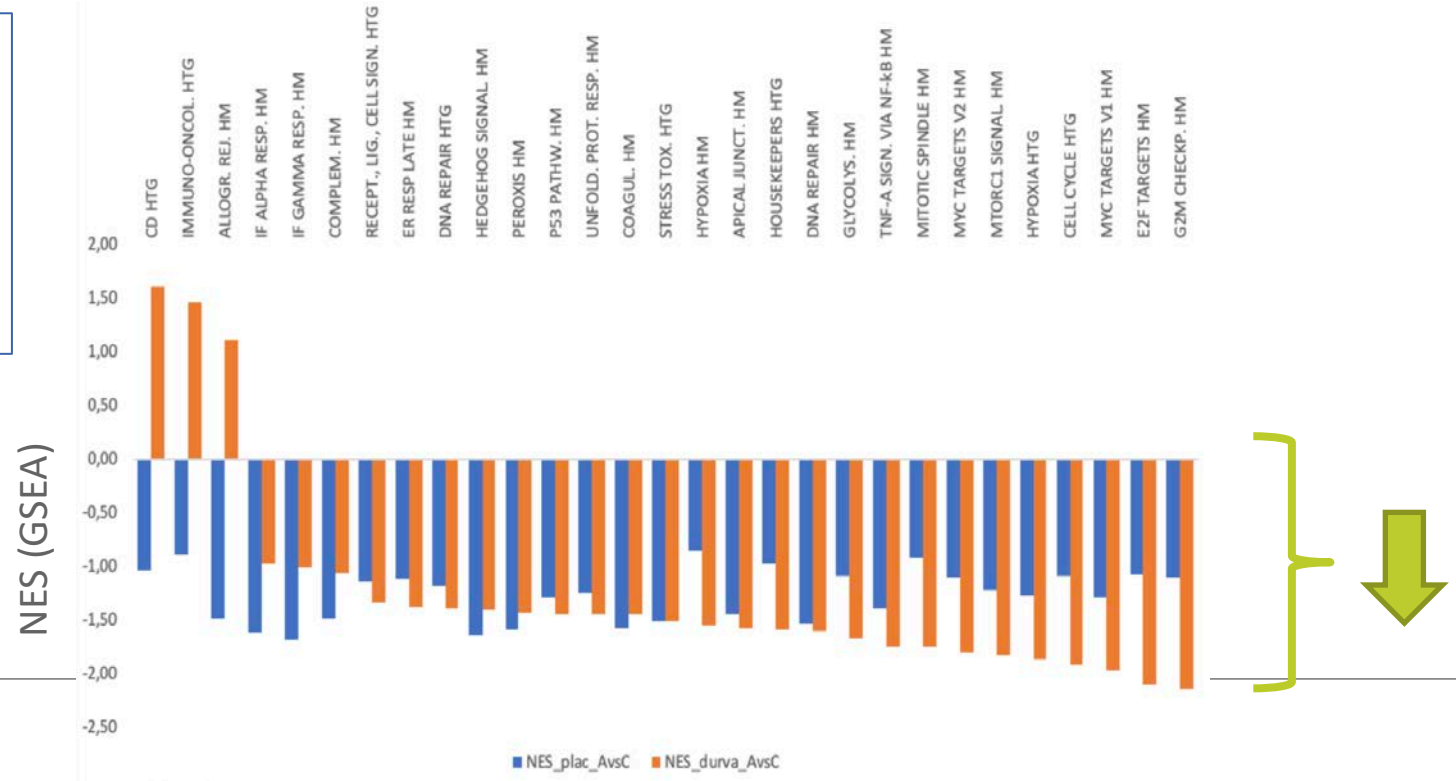
Durvalumab cohort
88
Placebo (=CTX) cohort
86

A: core biopsy before Tx	77
A: core biopsy before Tx	71

12 weeks
Nab Paclitaxel

C: core biopsy after Nab-P	11
C: core biopsy after Nab-P	16

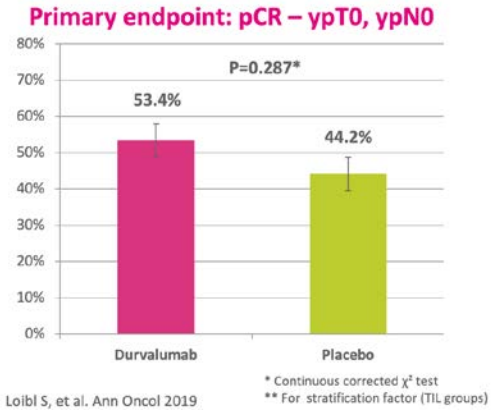
CD HTG
IMMUNO-ONCOL. HTG
ALLOGR. REJ. HM

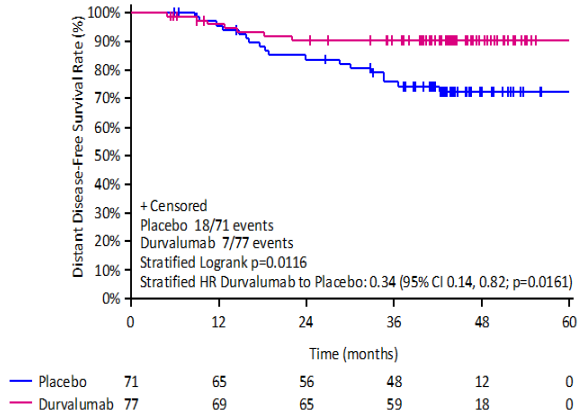


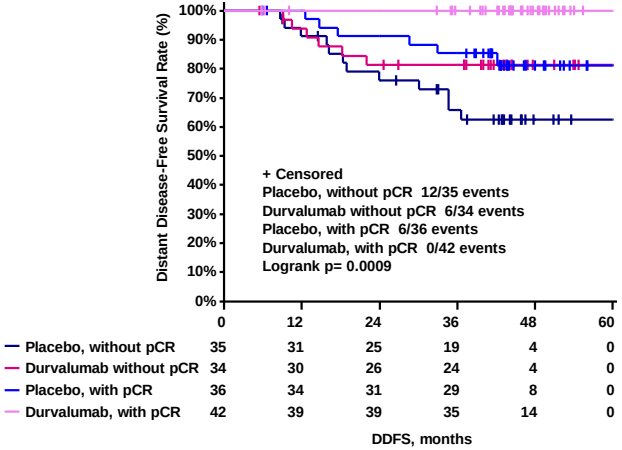
GeparNuevo trial – durvalumab/CTX vs CTX alone

Durvalumab cohort	**A: core biopsy before Tx**
88	77
Placebo (=CTX) cohort	**A: core biopsy before Tx**
86	71

two different endpoints:
pCR and DDFS



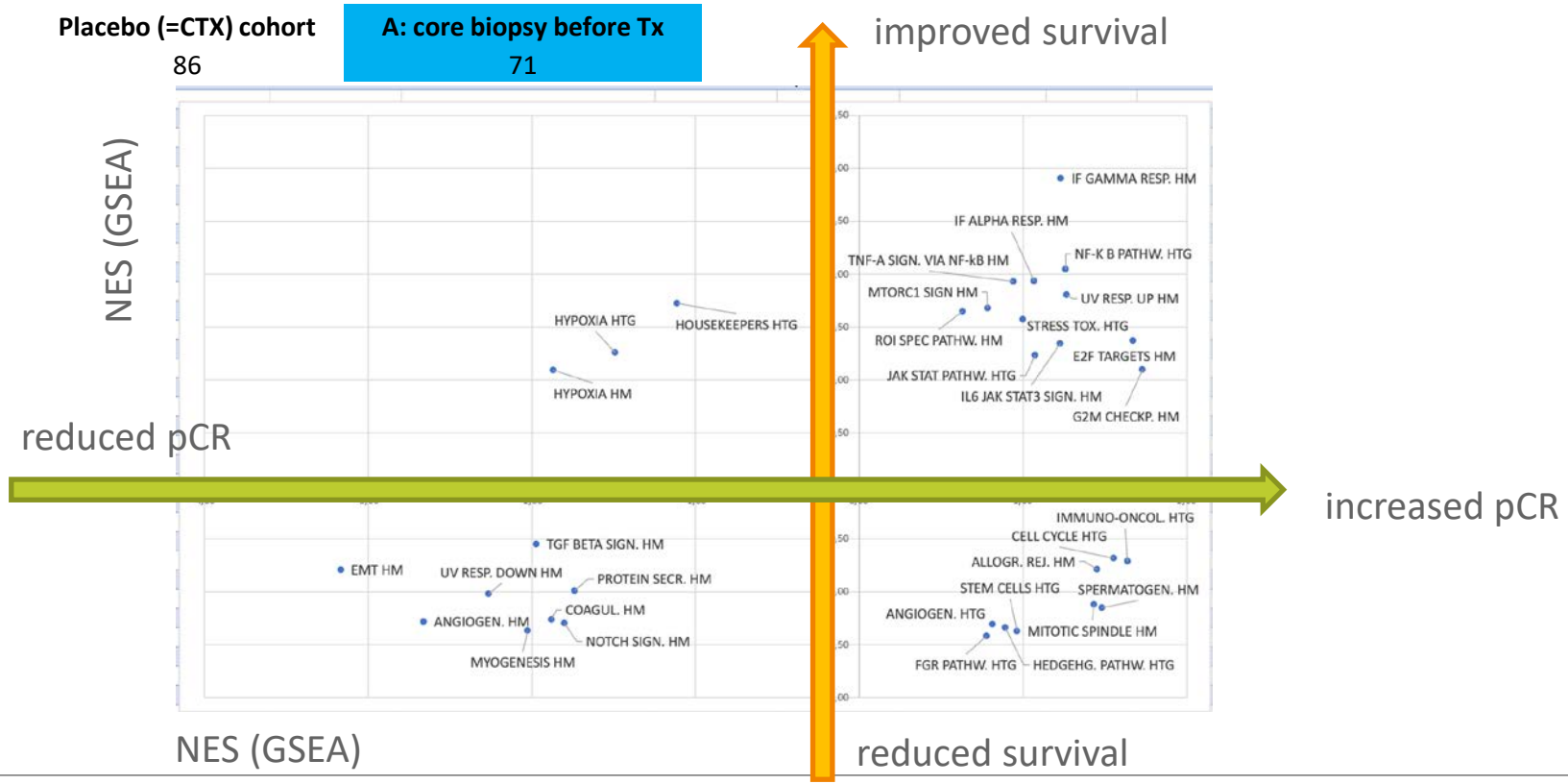




Placebo (=CTX) arm– prognostic vs predictive signatures

Placebo (=CTX) cohort
86

A: core biopsy before Tx
71



Placebo (=CTX) arm– prognostic vs predictive signatures

Placebo (=CTX) cohort
86

A: core biopsy before Tx
71

improved survival

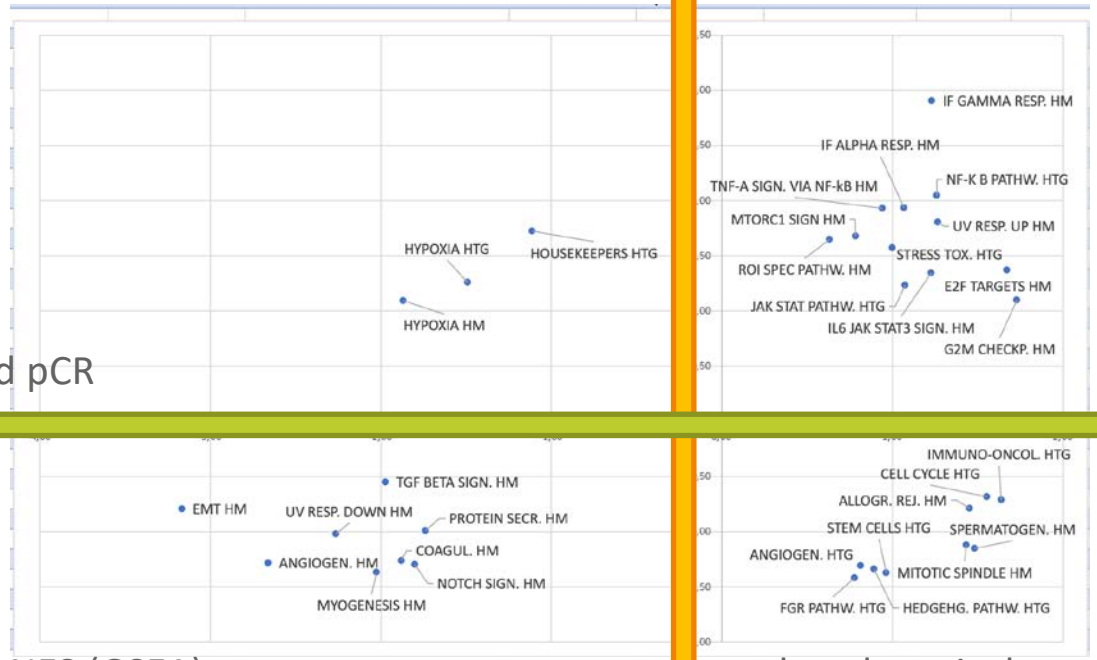
NES (GSEA)

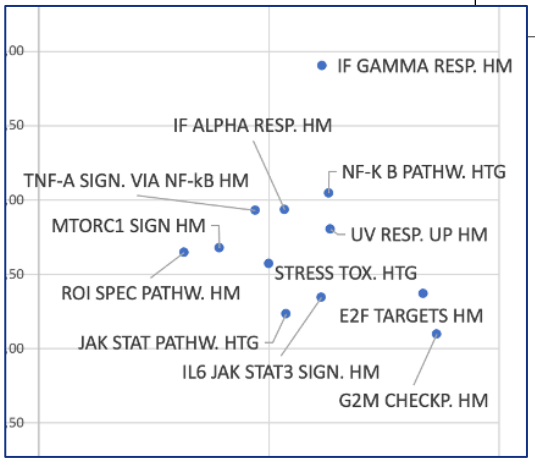
reduced pCR

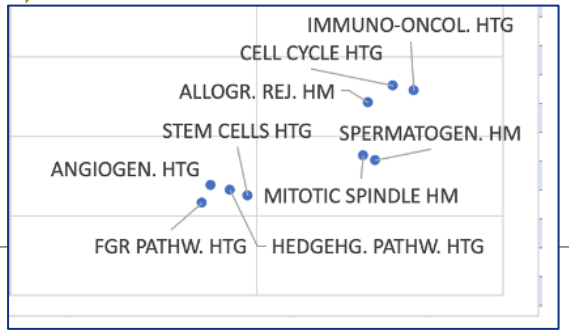
increased pCR

NES (GSEA)

reduced survival

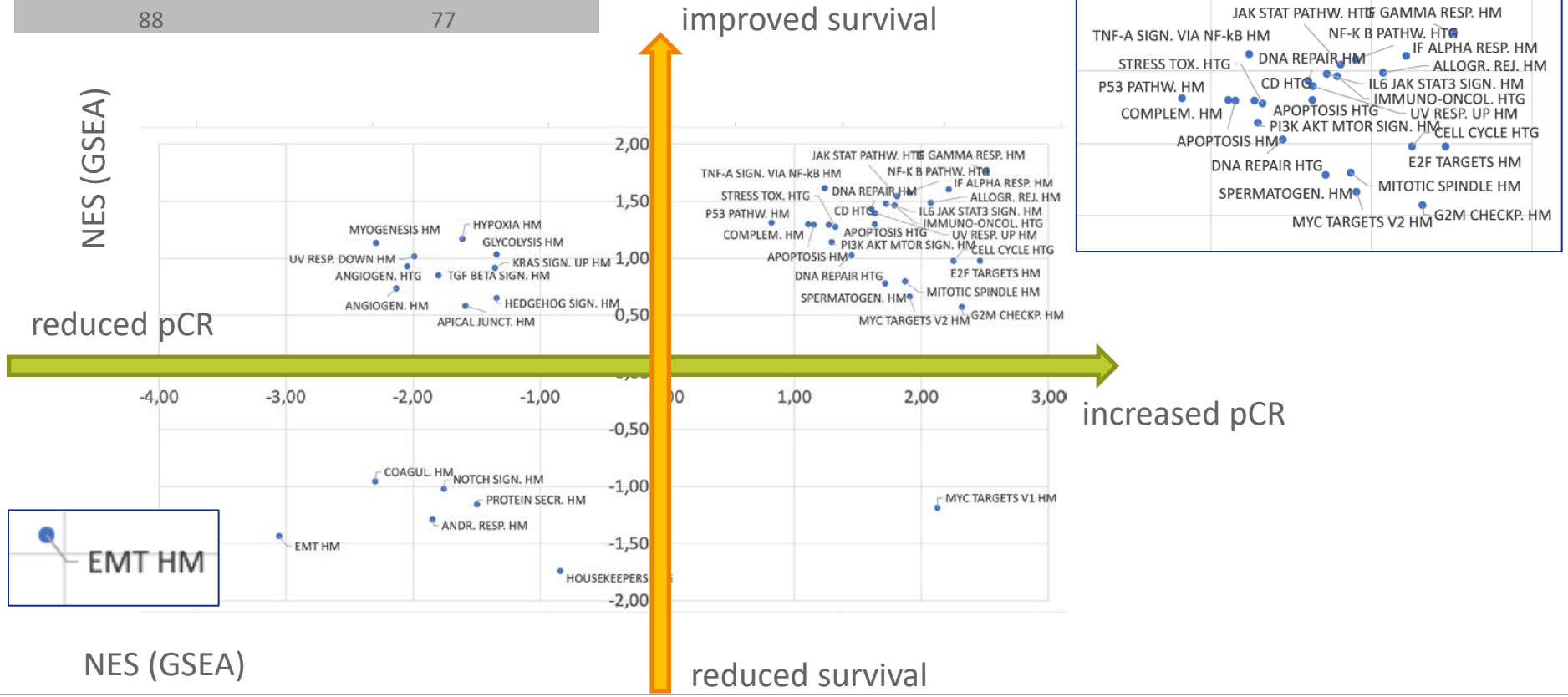




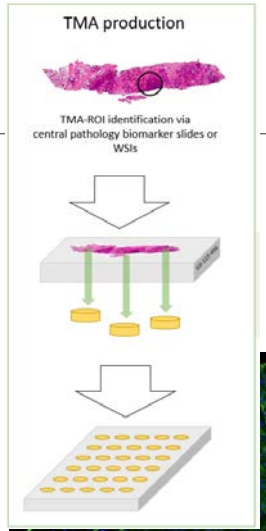


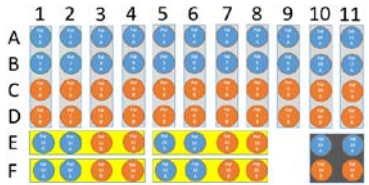
Durvalumab (+CTX) arm– prognostic vs predictive signatures

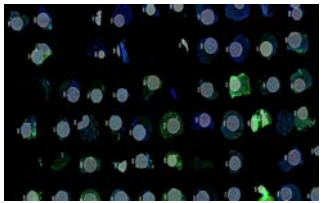
Durvalumab cohort	A: core biopsy before Tx
88	77

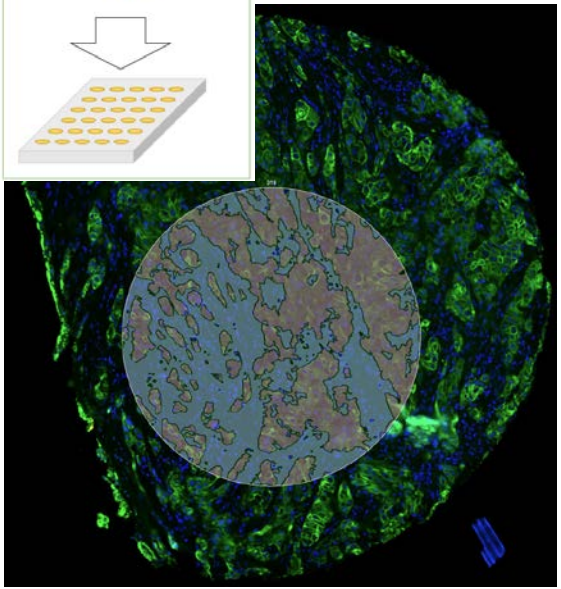


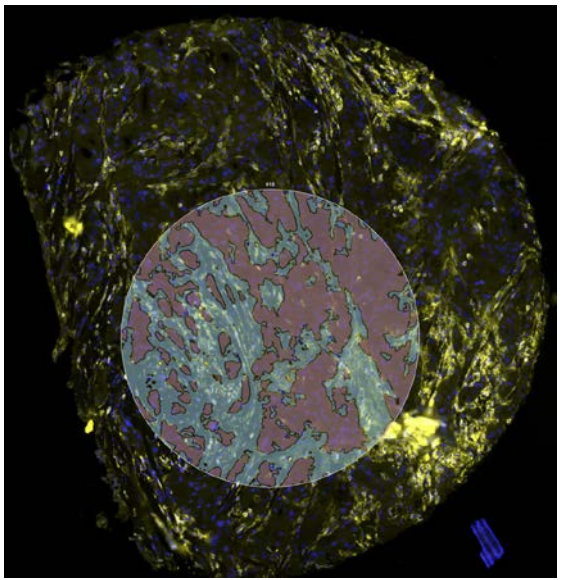
Nanostring GeoMx spatial profiling in the GeparNuevo trial



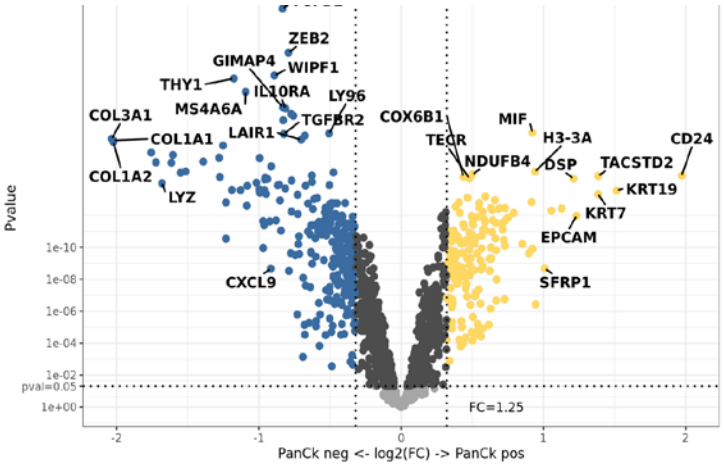








Spatial heterogeneity in tumor regions:
Tumor cell areas vs. stromal areas (GeoMx spatial RNA analysis)

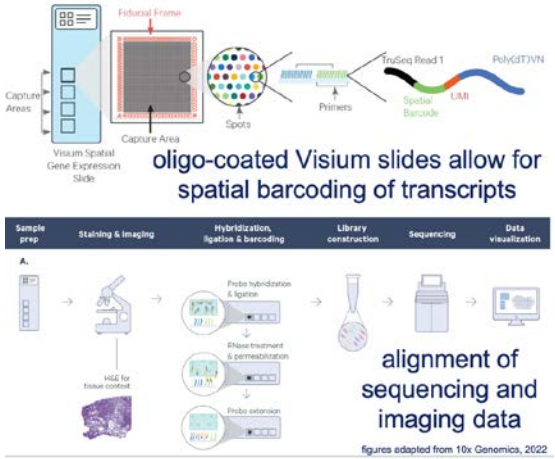


Paul Jank, Thomas Karn, Akira Hattesohl

Technologies to evaluate tumor heterogeneity in FFPE tissue

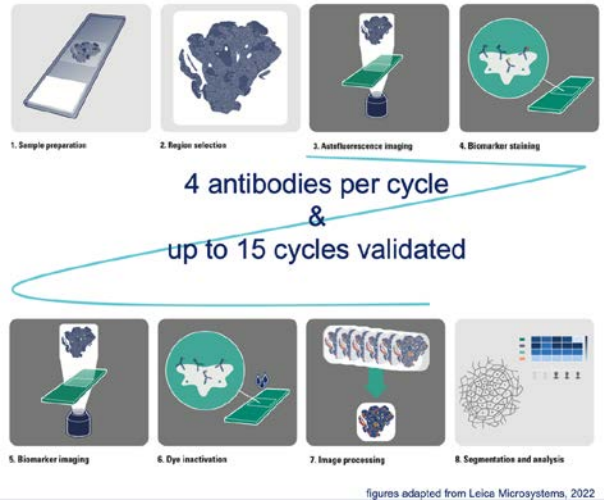
Visium 10x spatial RNA profiling in FFPE tissue from clinical trials

(Julia Teply-Szymanski)



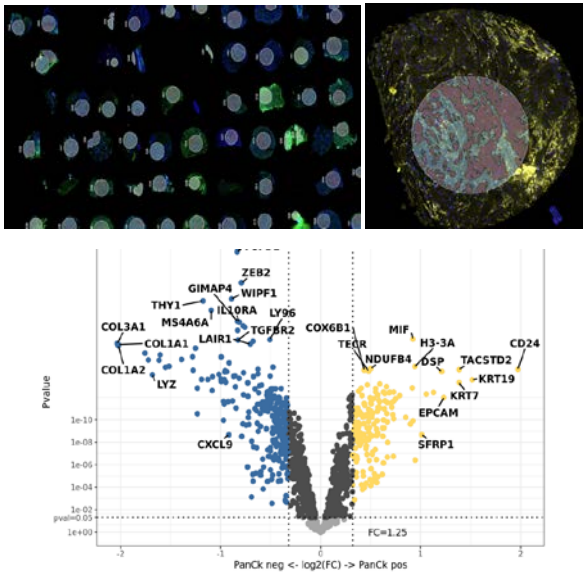
Leica CellDive multiplex imaging up to 60 antibodies

(Paul Jank, Maxime Schmitt, Moritz Jesinghaus)



Nanostring GeoMx spatial sequencing

(Paul Jank, Akira Hattesohl)



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Die Verantwortung für den Inhalt dieser Veröffentlichung liegt bei der Autorin/beim Autor.

Tumorheterogenität - GBG translationale Forschung

longitudinale und räumliche Heterogenität

- **Penelope:**
  - Vergleich von Stanze und Resektat
- **GeparNuevo:**
  - Vergleich von Stanzen vor und nach dem Window
  - Vergleich von Stanzen vor und nach der Chemotherapie
  - Vergleich von verschiedenen Regionen im Tumor
- **Klassifikation der molekularen Response im Residualtumor**

Methoden

- **HTG EdgeSeq Genexpressionsanalyse**
  - 2500 Gene in einem Schnitt
  - geeignet für kleine Proben
  - keine räumliche Auflösung
  - >2500 GBG Proben gemessen
- **Räumliche Auflösung**
  - Nanostring GeoMx
  - 10X Visium
  - Leica CellDive

Vielen Dank an das Team der Zentralpathologie Marburg

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Zentral-pathologie/ Forschungs-labor

- Paul Jank
- Ina Halbig
- Marion Kalden
- Regina Maxeiner-Walter
- Mareike Meier
- Viktoria Wischmann

Immun-histologisches Labor

- Manuela Gerber
- Johanna Grass
- Cosima Weinert

Befundung / translationale Forschung

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- Moritz Gleitsmann
- Marvin Görg
- Albert Grass
- Anne-Sophie Litmeyer
- Sabrina Müller
- Maxime Schmitt

Befundung Zentral-pathologie

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- Corinna Keber
- Anette Ramaswamy
- Fiona Rodepeter
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- Susanne von Gerlach
- Anika Pehl
- Christina Westhoff

Sequenzierung Molekular-pathologie

- Laura Frömel
- Akira Hattesohl
- Tanja Rausch
- Marcel Romey
- Julia Schreiner
- Julia Teply-Szymanski

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- Tanja Kastorf
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GBG

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Stefanie Lettkemann

Krishna Rachkonda

Valentina Vladimirova

Subboard Trafo of GBG

Kooperationsprojekte: Trafo Subboard der GBG

Team der Pathologie – Philipps Universität Marburg

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Christos Sotiriou

Fabrice André

Roberto Salgado

Andrew Tutt

Wilko Weichert

TIL working group

ONCOBIOME

Microbiota against cancer

International research program

European Commission

H2020

Deutsche Krebshilfe

HELFEN. FORSCHEN. INFORMIEREN.

INTEGRATE TN

BREAST CANCER

BIGPICTURE

Central Repository for Digital Pathology

imi innovative medicines initiative

RAD51 predict

#ERAPerMed

Philipps Universität Marburg

Institute of Pathology